EXHIBIT 45

Plaintiffs' Rebuttal Expert Report of
Craig Walter Hendrix, M.D.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

RICHARD ROE, ET AL.,
 	
     Plaintiffs,
  v.
 	
PATRICK M. SHANAHAN, ET AL.,
 	
     Defendants.
	CIVIL ACTION NO. 1:18-cv-01565

NICHOLAS HARRISON, ET AL.,
 	
     PLAINTIFFS,
  V.
 	
PATRICK M. SHANAHAN, ET AL.,
 	
     DEFENDANTS.
	CIVIL ACTION NO. 1:18-CV-00641

PLAINTIFFS' REBUTTAL EXPERT REPORT OF CRAIG W. HENDRIX, M.D.

1.   I am the same Craig W. Hendrix, M.D. who submitted an expert report on March 22, 2019. My credentials are set forth in that expert report, along with the other disclosures required by the Federal Rules of Civil Procedure.

2.   I have been asked to provide testimony rebutting the testimony expected from Colonel Clinton K. Murray, M.D., and Sheila Peel, M.D., who the Defendants have disclosed as non-retained expert witnesses in this case. To provide this rebuttal testimony, I have reviewed the expert disclosures regarding Colonel Clinton K. Murray, M.D. and Sheila Peel, MSPH, Ph.D., the deposition transcripts of Colonel Clinton K. Murray and Sheila Peel, and the materials referenced in the bibliography. I base my testimony on my education, professional experiences, and the materials cited to in this report and in my bibliography.

3.   The risk of adverse effects on organs or body systems due to HIV medications —

e.g., renal impairment, increased cardiovascular risk and changes in the lipid profile, or

increased liver enzymes — has progressively both shifted in type and diminished in overall

frequency as the new categories of drugs, particularly with introduction of integrase

inhibitors and replacement of an older formulation of tenofovir (tenofovir disoproxil

fumarate [TDF]) with a new formulation (tenofovir alafenamide [TAF]).[1] As current HIV

treatment guidelines recommend a combination of integrase inhibitors, TAF, and

emtricitabine (which has an excellent safety profile), the rate of side effects should decline

further.[2] More important for purposes of the potential deployment of service members living

with HIV, numerous studies of ARV use in the real world (outside of randomized controlled

trials) consistently demonstrate reduced side effects with time on treatment. These studies

demonstrate both: (1) reduced side effect-related drug discontinuations year over year after

starting ARVs; and (2) dramatically decreasing rates of side effect-related discontinuation

rates, correlated with evolution of the most commonly recommended ARVs over larger time

periods and populations—from 30% discontinuation rates in the first year (when boosted

protease inhibitors were most common) down to less than 5% with current, first-line

recommended integrase regimens.[3] The categories of side effects described above most often

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[1] AIDSInfo, *Side Effects of HIV Medicines*, (Aug. 29, 2018),
https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/22/63/hiv-medicines-and-side-effects
("[N]ewer HIV regimens cause fewer side effects than regimens used in the past. As HIV
treatment options continue to improve, people are less likely to experience side effects from their
HIV medicines.").
[2] Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV,
AIDSInfo (Oct. 25, 2018), https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0.
[3] *See, e.g.*, Alejandro Gonzalez-Serna et al., *Temporal trends in the discontinuation of first-line
antiretroviral therapy*, 69 J. Antimicrob. Chemother. 2202 (2014); Antonio Di Biagio et al.,
*Discontinuation of Initial Antiretroviral Therapy in Clinical Practice: Moving Toward
Individualized Therapy*, 71 J. Acquir. Immune Defic. Syndr. 263 (2016); Judit Penafiel et al.,

occur within the first year of treatment, are diagnosed by periodic laboratory testing, and are usually reversible with change in medication.[4] Because any service member with HIV serving overseas would already be established on a stable, fully-suppressive antiretroviral regimen, the risk of such complications would be slight indeed.

4.   By definition, medical care in a deployed setting is less than ideal and will never be at the same level as medical care available in the United States.[5] The realities of medical care in a deployed setting at times require deviation from "best practices" and a marginal diminishment in the standard of care. While the Department of Defense appropriately strives to maintain the highest of standard of care possible for deployed service members, the standard of care currently delivered in deployed settings should have no more significant detrimental effects on service members living with HIV than on service members who are not living with HIV, including those service members living with other chronic and treatable conditions who are regularly permitted to deploy.

5.   As pointed out in Dr. Hardy's expert report, development of resistance to an ART regimen does not occur randomly; it generally involves non-adherence to medications, because the development of mutations that lead to resistance becomes impossible if the virus is suppressed. Given the low and declining chance of drug side over time (discussed above), the very high rate of suppression for service members living with HIV, and the extremely low possibility of the development of resistance or viral breakthrough for those who are adherent to their medications, the medical monitoring of service members living with HIV

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Tolerability of integrase inhibitors in a real-life setting, 72 J. Antimicrob. Chemother. 1752 (2017).

[4] Id.

[5] Peel Dep. 105:12-18, May 3, 2019.

could be conducted at less frequent intervals and/or scheduled for times when it is most convenient and safe. Current expert panels recommend medical monitoring and laboratory testing for viral load every 6 to 12 months in patents on well tolerated and fully suppressive ART regimens. Providing medical monitoring to deployed HIV-positive service members at approximately 12-month intervals would not be a deviation from the global standard of care,[6] and in the few instances where it could not be accomplished until 14-15 months after the previous medical monitoring appointment, it would not be a significant deviation from the standard of care.

6. The contention that people living with HIV are more susceptible to renal problems as a result of dehydration when compared to persons without HIV infection is not supported by medical literature. Persons with HIV infection, prior to the antiretroviral era, were identified with pre-renal causes of renal dysfunction, but these were causally linked to their HIV infection. Specifically focusing on HIV medications, TDF is most commonly associated with renal dysfunction, usually as a result of renal tubular effects, and the time course is rarely acute as a more chronic pattern of development over many months is most typical. This is usually reversible and the most significant risk factor is pre-existing renal disease, in isolation a likely exclusion for overseas deployment.[7] Dehydration has not been shown to have any particularly detrimental effect on people living with HIV who are taking HIV medications. However, one would expect to observe the same dehydration impact on

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[6] World Health Organization, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* 128 (June 2016); *see also* AIDS Map, *CD4, viral load, and other tests* (Feb. 2017), http://www.aidsmap.com/CD4-viral-load-amp-other-tests/page/1327442/; DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* (Oct. 25, 2018) https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0.

[7] Atefeh Jafari et al., *Tenofovir-induced nephrotoxicity: incidence, mechanism, risk factors, prognosis and proposed agents for prevention*, 70 Eur. J. Clin. Pharmacol. 1029 (2014).

renal function and other organ systems for persons living with HIV as for service members

who are not taking HIV medications. If environmental conditions and water discipline

within the unit result in dehydration, then the dehydration itself and its potentially

devastating effects on unit readiness are a much greater immediate concern than an indolent

development of renal dysfunction from HIV medications over many months.

      7.   As noted in Dr. Hardy's initial expert report, a person who stopped taking their

HIV medications would continue to have a suppressed viral load for 4-12 weeks; there would

be only a rare chance of immediate symptomatic changes (*e.g.*, an acute retroviral syndrome

with cessation of ART) and little impact on long-term disease progression.[8] The typical time

to clinically important disease progression to susceptibility of opportunistic infections and

other AIDS-related conditions takes 8 years. Accounting for the frequency of a few fast-

progressors in an HIV-positive population, the risk of progression to 200 CD4 cells is very

low (around 5% over one year),[9] and they would not experience symptoms of HIV for

several months or years after discontinuing medication. In addition, negative effects of a

treatment interruption of less than a year, *e.g.*, loss of CD4 cells, would very likely be

reversed after the person is placed back on HIV medications, thus avoiding any significant

long-term consequences of such a treatment interruption.

      8.   The concern with antiretroviral resistance, as noted above, is very low with

complete cessation of treatment. By contrast, symptoms and potential impairment of

readiness is more acute with cessation of medical treatment for several other chronic medical

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[8] Amy B. Garlin and Paul E. Sax, *Retroviral Rebound Syndrome with Fatal Outcome after Discontinuation of Antiretroviral Therapy*, 41 Clin. Infect. Dis. e83 (2005).
[9] Thierry Buclin et al., *Development and Validation of Decision Rules to Guide Frequency of Monitoring CD4 Cell Count in HIV-1 Infection before Starting Antiretroviral Therapy*, 6 PLOS One 4 e18578 (2011).

conditions allowed to deploy. For example, within approximately a month, a service member with hypothyroidism who is deprived of their daily medication may become lethargic, suffer joint weakness, and have trouble concentrating or remembering.[10] An asthmatic who is prescribed an inhaler and goes without it for even a short period of time, may suffer acute respiratory distress with trouble breathing and weakness while exercising.[11] Though a person with diabetes is allowed to deploy under certain circumstances,[12] the consequences of not having insulin to control one's blood sugar can be severe and even fatal.[13] Active duty women using oral daily contraceptive medications for dysmenorrhea may experience recurrence of severe abdominal pain in the next menstrual cycle with cessation of dosing,[14] and women using them for pregnancy prevention would be at risk of pregnancy within days of stopping those medications, with the potential for readiness impact within weeks if morning sickness occurs prior to pregnancy diagnosis and the service member is relocated out of a combat zone at time of diagnosis. And though a service member is allowed to join the armed services and deploy with vision that must be corrected with glasses (up to a certain level of deficiency), the loss of those glasses would have an immediate effect on that

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[10] Mayo Clinic, *Hypothyroidism (underactive thyroid): symptoms and causes* (Dec. 4, 2018), https://www.mayoclinic.org/diseases-conditions/hypothyroidism/symptoms-causes/syc-20350284.

[11] Mayo Clinic, *Asthma: symptoms and causes* (Sept. 13, 2018), https://www.mayoclinic.org/diseases-conditions/asthma/symptoms-causes/syc-20369653.

[12] *See* AR 40-501, Ch. 5, § 14(f)(1)-(2) (2017).

[13] Mayo Clinic, *Diabetes: Diagnosis and Treatment* (Aug. 8, 2018), https://www.mayoclinic.org/diseases-conditions/diabetes/diagnosis-treatment/drc-20371451 ("People with type 1 diabetes need insulin therapy to survive. Many people with type 2 or gestational diabetes also need insulin therapy").

[14] Mayo Clinic, *Menstrual cramps: diagnosis and treatment* (Apr. 14, 2018), https://www.mayoclinic.org/diseases-conditions/menstrual-cramps/diagnosis-treatment/drc-20374944.

individual's ability to perform their job. In this regard, a different standard is being applied

to HIV without a legitimate medical reason for doing so.

9.   The concern that deployment will diminish a service member's ability to adhere

to their HIV medications is conjectural, not supported by data, and rests on a flawed analogy

to malaria prophylaxis. The analogy between a soldier's ability to adhere to HIV treatment

and a soldier's ability to adhere to antimalarial prophylaxis in the stress of down range

conditions is not an apt one. First, the service member may have trouble remembering to

take a daily prophylactic medication, e.g., for malaria prophylaxis, because daily medication

adherence is a new behavior that is not well-established prior to deployment and is necessary

due to external infection risk factors as a result of the deployment. In contrast, a service

member living with HIV taking antiretroviral drugs—and having achieved full viral

suppression—must have established a pattern of daily medication adherence through months

and months of taking their medications before they deploy. Second, the symptomatic side

effects of anti-malarial medications are typically worse than the symptomatic side effects of

ART, even upon initiation, and the disparity in terms of side effects profiles is much greater

if the person taking ART is already well-established on their regimen. Third, the incentive

and motivation to take a daily antiretroviral medication that keeps one healthy and prevents

the progression of an already-present, life-threatening disease is much different from the

motivation to take a medication, e.g., malaria prophylaxis that *may protect* one from

acquiring a life-threatening disease to which one *may* be—but has not yet been—exposed.

In fact, the data provided as part of Dr. Murray's disclosures reveals that adherence among

service members is extremely high—significantly higher than in the general population—

with viral suppression reached by 99.8% of those diagnosed between 2012 and 2016 in a

study conducted by the Department of Defense. By comparison, those receiving medical

care through the Ryan White HIV/AIDS Program have only recently reached an 84.9% viral

suppression rate—and were at only 75.0% viral suppression as recently as 2012.[15]

10.   Service members living with HIV do not require special health-related

confidentiality protections in a deployed environment. Though it is true that disclosure of a

person's HIV status may subject that person to some forms of stigma and discrimination

from other service members, the way to address this problem is to make clear that such

conduct will not be permitted—and stigma and discrimination will almost undoubtedly not

be reduced by reinforcing the misconceptions and fear that undergird the current policies of

HIV exceptionalism, including unwillingness to deploy people living with HIV. As long as

personnel in a deployed environment follow the same practices for maintaining patient

confidentiality as are currently employed in the United States, which requires disclosure on a

"need-to-know" basis, the Department of Defense will meet its obligations to maintain the

confidentiality of this health information. Col. Murray's heightened concern for

confidentiality notwithstanding, the military has established several practices related to

identifying and managing HIV that create numerous opportunities to breach the

confidentiality of the service member with HIV. In my own active duty experience leading

the periodic HIV medical evaluation program in the Air Force, I heard countless examples in

which a service member's HIV status was disclosed to non-medical personnel. These were

largely related to informing a non-medical commander of a service member's HIV diagnosis

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[15] Ryan White HIV/AIDS Program, *Annual Client-Level Data Report, Ryan White HIV/AIDS Program Services Report (RSR)* (2016), https://hab.hrsa.gov/sites/default/files/hab/data/datareports/RWHAP-annual-client-level-data-report-2016.pdf.

so that the commander could give the so-called "safe sex order" that every service member

diagnosed with HIV had to sign. On a need-to-know basis, the commander would then

inform a first sergeant and other unit personnel in order to more easily manage periodic

evaluations at other medical facilities and to prepare for OCONUS training or military

deployment that would preclude travel for the service member with HIV. The safe sex order

itself requires HIV-positive service members to disclose their HIV status to all healthcare

providers (which may include medical personnel beyond the primary medical practitioners

providing care) and to all sexual partners, even if a condom is used or when there is no risk

of transmission due to effective virally suppressive HIV treatment.[16]

11.   Colonel Murray's concern that service members with HIV will disregard orders to

donate blood lacks foundation. Upon being diagnosed, a person living with HIV is informed

that they cannot donate blood. Based on my own experience in the military and review of

current policies, I know that a newly-diagnosed service member is repeatedly instructed that

they cannot donate blood. One of those instructions comes from their commanding officer in

the form of an order (colloquially referred to as "safe sex orders," but inclusive of blood

donation), the failure of which to obey is prosecutable under the Uniform Code of Military

Justice. This warning is repeated by both the physician and public health officer at the initial

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[16] *See, e.g.*, AR 600-110, Fig. 4-1, 18 (April 2014) ("Condom use does not remove [the] obligation to inform partners of . . . HIV infection before engaging in intimate sexual contact"); *see also, e.g.*, Virginia Supervie et al., Per Sex-Act Risk Of HIV Transmission Under Antiretroviral Treatment: A Data-Driven Approach, 79 J. Acquir. Immune. Defic. Syndr. 440 (2018); Benjamin R. Bavinton et al., *Viral Suppression and HIV Transmission in Serodiscordant Male Couples: an International, Prospective, Observational, Cohort Study*. 5 Lancet HIV 8 E438 (2018); Alison J. Rodger et al., *Risk Of HIV Transmission through Condomless Sex in Serodifferent Gay Couples with the HIV-Positive Partner Taking Suppressive Antiretroviral Therapy (Partner): Final Results of a Multicentre, Prospective, Observational Study*. Lancet HIV (May 2, 2019) https://dx.doi.org/10.1016/S0140-6736(19)30418-0.

HIV evaluation. This is repeated at each subsequent periodically mandated HIV evaluation quite apart from routine care and with every change of unit commander. Pointing to evidence of a single transfusion transmitted case of hepatitis C as the result of a "walking blood bank" donation by a service member who knew they had tested positive for hepatitis C (HCV) differs importantly from the case of blood donations by persons with HIV. The service member with HCV who donated blood to the walking blood bank did not know that HCV could be transmitted through blood donation.[17] This individual was diagnosed before entering the service and was not screened for HCV, because the military does not require HCV testing upon entry or at regular intervals, as it does with respect to HIV. Additionally, unlike service members with HIV, service members with HCV are not required to receive preventive counseling or an order instructing them not to donate blood. Finally, for years and years, the general population has received public health messages about preventing HIV transmission, whereas HCV is relatively less well known, understood or feared by the general population. Only recently has the drug company that markets HCV treatment medications been advertising the need for HCV screening in order to increase treatment. It is not surprising that a service member may have been given an HCV diagnosis, but did not understand its implications on his ability to donate blood. Because they do not test for it at regular intervals, the risks the military tolerates with respect to the transmission of HCV are much greater than the risks with respect to HIV. Furthermore, even if a service member with HIV were to accidentally donate blood—*and* it was not tested before being transfused—it is

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[17] Shilpa Hakre et al., *Transfusion-transmissible viral infections among U.S. military recipients of whole blood and platelets during Operation Enduring Freedom and Operation Iraqi Freedom*, 51 Transfusion, 473, 480 (2011) ("[the HCV-positive donor] reported that he was never referred for specialty evaluation or care, nor was he ever advised to avoid donating blood").

unclear whether transmission is likely from a person with an undetectable HIV viral load. For example, the reduction in HIV viral load as a result of fully suppressive HIV treatment (regularly achieved in the military) is the same as the difference in the volume and, therefore, viral load associated with an infected unit of blood when compared to the amount of blood associated with transmission of HIV infection through needle sharing or an occupational needlestick injury; this viral load difference accounts for a 150-to-400-fold reduction in HIV transmission risk based on epidemiologic data reviewed by the CDC.[18] If service members with HIV are permitted to deploy, the primary risk to the blood supply in the military will continue to be service members with *undiagnosed* HIV and HCV. In fact, 131 out of 389 (34%) newly diagnosed HIV infections in the US Army between 2001 and 2007 were during deployment to Afghanistan and Iraq; each of these acute infections represents at least a transient viral load 100 times higher as compared to a person with chronic infection without antiretroviral treatment, and 1 million times higher as compared to a person with chronic infection on antiretroviral treatment.[19]
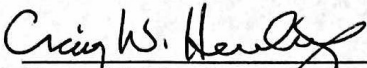
12.   In my opinion, there continues to be no medical justification for preventing or restricting the military service and overseas deployment, including to combat zones, of people living with HIV.

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[18] *See, e.g.*, Pragna Patel et al., *Estimating per-act HIV transmission risk: a systematic review*, 28 AIDS 10, 1509 (2014); Rebecca Baggaley et al., *Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis*. 20 AIDS 6, 805 (2006); Christopher D. Pilcher et al., *Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection*, 21 AIDS 13, 1723 (2007).

[19] Paul T. Scott et al., *Investigation of Incident HIV infections among US Army Soldiers Deployed to Afghanistan and Iraq, 2001-2007*. 28 AIDS Res. Hum. Retrovir. 10, 1308 (2012).

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 6th day of May, 2019

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Craig W. Hendrix, M.D.

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EXHIBIT 46

World Health Organization
Consolidated Guidelines on the Use of Antiretroviral
Drugs for Treating and Preventing HIV Infection

World Health
Organization

GUIDELINES

CONSOLIDATED GUIDELINES ON

THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

SECOND EDITION
2016

CONSOLIDATED GUIDELINES ON

THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

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FOREWORD

With this update of the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO, for the first time, recommends that all people living with HIV be provided with antiretroviral therapy (ART). This will bring us one step closer to achieving universal access to HIV treatment and care and ending AIDS as a public health threat. These guidelines also make service delivery recommendations on how we can expand coverage of HIV treatment to reach the 37 million people living with HIV. Key recommendations aim to improve the quality of HIV treatment and bring us closer to the universal health coverage ideals of integrated services, community-centred and community-led health care approaches, and shared responsibility for effective programme delivery.

With its "treat-all" recommendation, WHO removes all limitations on eligibility for ART among people living with HIV; all populations and age groups are now eligible for treatment, including pregnant women and children. The same once-per-day combination pill is now recommended for all adults living with HIV, including those with tuberculosis, hepatitis, and other co-infections. The guidelines are ambitious in their expected impact, and yet simplified in their approach, and firmly rooted in evidence. They take advantage of recent findings from clinical trials confirming that the early use of ART keeps people living with HIV alive and healthier and reduces the risk of transmitting the virus to their sexual and drug-sharing partners. Earlier treatment has the further advantage of simplifying the operational demands on programmes.

Additional recommendations in the guidelines aim to help programmes deliver services closer to people's homes; expedite reporting of test results; integrate HIV treatment more closely with antenatal, tuberculosis, drug dependence and other services; and use a wider range of health workers to administer treatment and follow-up care.

If we are to achieve universal health coverage, we need to ensure that ART and broader HIV services reach those in greatest need and are sustainable in the long term. Integrating essential HIV services into national health benefit packages, promoting innovative public-private partnerships for increasing access to antiretroviral drugs and strengthening health and community systems to deliver comprehensive and quality services are key elements of an effective response.

Countries have asked WHO to provide timely and practical guidance, guidance that keeps pace with the latest scientific evidence and enables services to be delivered equitably and sustainably to all populations in all countries. I believe these landmark guidelines go a long way towards meeting that request.

The new guidelines support evidence-based interventions that can improve efficiency and effectiveness – so that more can be achieved with the resources at hand. At the same time, implementation of the guidelines will require increased investment from countries and shared responsibility. Implementing these guidelines fully will have an unprecedented impact on preventing people from becoming newly infected and reducing the number of people dying from HIV-related causes over the coming years. The number of people eligible for ART increases from 28 million to all 37 million people currently living with HIV globally.

Expanding access to treatment is at the heart of a new treatment targets for 2020 with the aim of ending the AIDS epidemic as a public health threat by 2030. The 90–90–90 targets include 90% of the people living with HIV know their HIV status, 90% of the people who know their HIV status receiving ART and 90% of the people receiving ART having suppressed viral loads.

I am convinced that the future of the HIV response will follow the pattern of the recent past: that is, a constant willingness to build on past successes and rise to new challenges.

This can fuel the momentum needed to push the HIV epidemic into an irreversible decline. I strongly encourage countries and their development partners to seize this unparalleled opportunity.

Dr Margaret Chan
Director-General
World Health Organization

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SUPPLEMENTARY MATERIAL

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This supplement summarizes the evidence and information that informed the
recommendations and the process by which the recommendations were made.

Web supplement B: Evidence base for benefits and harm
This supplement summarizes all systematic reviews.

Web supplement C: Evidence base for acceptability and feasibility
This supplement summarizes all qualitative evidence synthesis, primary data collection,
feasibility assessments and modelling.

ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
Ab/Ag	antibody/antigen
ACR	albumin–creatinine ratio
ABC	abacavir
ADR	acquired HIV drug resistance
AEM	AIDS Epidemic Model
AIDS	acquired immunodeficiency syndrome
AIM	AIDS Impact Model
AIS	AIDS Indicator Survey
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AUC	area under the curve
AZT	azidothymidine (also known as zidovudine)
BMI	body mass index
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CNS	central nervous system
CrAg	cryptococcal antigen
CVD	cardiovascular disease
CTX	co-trimoxazole
CVD	cardiovascular disease
d4T	stavudine
DAA	direct-acting antiviral (drug)
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs (study)
DBS	dried blood spot (specimen)
DHS	Demographic and Health Survey
DMPA	depot medroxyprogesterone acetate
DST	drug susceptibility testing
DTG	dolutegravir
DRV	darunavir
EFV	efavirenz
EIA	enzyme immunoassay

EID	early infant diagnosis
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETV	etravirine
EWI	early warning indicator
FDC	fixed-dose combination
FTC	emtricitabine
GIPA	greater involvement of people living with HIV/AIDS
GPRS	General Packet Radio Service
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GSM	Global System for Mobile Communications
HA	health accounts
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-DR	HIV drug resistance
HIVST	HIV self-testing
HLA	human leukocyte antigen
HPV	human papillomavirus
HSR	hypersensitivity reaction
HSV	herpes simplex virus
HTS	HIV testing services
IATT	Interagency Task Team
IBBS	integrated biological and behavioural surveillance
INSTI	integrase strand transfer inhibitor (also known as integrase inhibitor)
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
IVD	in vitro diagnostics
NAT	nucleic acid test
LA	latex agglutination
LAM	lipoarabinomannan
LF	urine lateral flow (test for diagnosing TB)
LGBTI	lesbian, gay, bisexual, transgender and intersex
LPV	lopinavir
MDR-TB	multidrug-resistant TB
M&E	monitoring and evaluation
mHealth	mobile health
mhGAP	WHO Mental Health Gap Action Programme

MIPA	meaningful engagement of people living with HIV/AIDS
MICS	Multiple Indicator Cluster Survey
MNCH	maternal, newborn and child health
MQAS	WHO model quality assurance system for procurement
MSF	Médecins Sans Frontières
MSM	men who have sex with men
NASA	national AIDS spending assessment
NAT	nucleic acid amplification testing
NCD	noncommunicable disease
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
OST	opioid substitution therapy
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PDR	pre-treatment HIV drug resistance
PEN	Package of Essential NCD interventions
PI	protease inhibitor
PITC	provider-initiated testing and counselling
PICO	population, intervention, comparator, outcome
PEP	post-exposure prophylaxis
pK/pD	pharmacokinetic/pharmacodynamics
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
QA	quality assurance
QI	quality improvement
RAL	raltegravir
RCT	randomized controlled trial
RDT	rapid diagnostic test
RT	reverse transcriptase
RTV	ritonavir
/r	low-dose ritonavir
SARA	service availability and readiness assessment
SBI	severe bacterial infection
sdNVP	single dose of NVP
SMS	short message service
SPA	service provision assessment
SRH	sexual and reproductive health
STI	sexually transmitted infection

TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TST	tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
US CDC	United States Centers for Disease Control and Prevention
US FDA	United States Food and Drug Administration
Us p24 Ag	ultrasensitive p24 antigen
XDR-TB	extensively drug-resistant tuberculosis
XTC	3TC or FTC
WHO	World Health Organization
VMMC	voluntary medical male circumcision

ARV drugs

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
d4T	stavudine
ddI	didanosine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETV	etravirine
EVG	elvitegravir
FTC	emtricitabine
FPV	fosamprenavir
IDV	indinavir
LPV/r	lopinavir/ritonavir
NVP	nevirapine
RAL	raltegravir
RIL	rilpivirine
RTV	ritonavir
SQV	saquinavir
TAF	tenofovir alafenamide fumarate
TPV	tipranavir

DEFINITION OF KEY TERMS

General

HIV refers to the human immunodeficiency virus. There are two types of HIV: **HIV-1 and HIV-2**.

HIV-1 is responsible for the vast majority of HIV infections globally.

Acute infection is the period between a person being infected with HIV and HIV antibodies being detectable by a serological assay.

Age groups and populations

The following definitions for adults, adolescents, children and infants are used in these guidelines for the purpose of implementing recommendations for specific age groups. It is acknowledged that countries may have other definitions under national laws:

- An **adult** is a person older than 19 years of age.
- An **adolescent** is a person 10–19 years of age inclusive.
- A **child** is a person 1 to younger than 10 years of age.
- An **infant** is a child younger than 1 year of age.

Key populations are groups that have a high risk and disproportionate burden of HIV in all epidemic settings. They frequently face legal and social challenges that increase their vulnerability to HIV, including barriers to accessing HIV prevention, treatment and other health and social services. Key populations include (1) men who have sex with men, (2) people who inject drugs, (3) people in prisons and closed settings, (4) sex workers and (5) transgender people.

Vulnerable populations are groups of people that are vulnerable to HIV in certain situations or contexts, such as adolescents (especially adolescent girls in sub-Saharan Africa), orphans, people with disabilities and migrant and mobile workers. They may also face social and legal barriers to accessing HIV prevention and treatment. These populations are not affected by HIV uniformly in all countries and epidemics and may include key populations. Each country should define the specific populations that are vulnerable and key to their epidemic and response, based on the epidemiological and social context.

Substantial risk of HIV infection is provisionally defined as an incidence of HIV higher than 3 per 100 person-years in the absence of pre-exposure prophylaxis (PrEP). Individual risk varies within groups at substantial risk of HIV infection depending on individual behaviour and the characteristics of sexual partners. People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified with key and vulnerable populations and some people not so identified.

Serodiscordant couples are couples in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these people is referred to as a partner in the relationship. How individuals define their relationships will vary according to their cultural and social context.

Antiretroviral therapy

ARV (antiretroviral) drugs refer to the medicines used to treat HIV.

ART (antiretroviral therapy) refers to the use of a combination of three or more ARV drugs for treating HIV infection. ART involves lifelong treatment. Synonyms are combination ART and highly active ART.

Use of ARV drugs for HIV prevention refers to the HIV prevention benefits of ARV drugs and includes ARV drugs for preventing the mother-to-child transmission (PMTCT) of HIV, ARV drugs to reduce the transmission of HIV to serodiscordant sexual partners and ARV drugs to prevent the acquisition of HIV when a person is exposed (post-exposure prophylaxis (PEP) and PrEP).

Viral suppression refers to a viral load below the detection threshold using viral assays.

Viral failure refers to the inability to achieve or maintain viral suppression below a certain threshold. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of using ART.

Universal access to ART is defined broadly as a high level of treatment coverage (80% or more of the eligible population) that is accessible and affordable. It does not necessarily mean 100% coverage.

Prevention of mother-to-child transmission of HIV refers to the use of ARV drugs to prevent the transmission of HIV from the mother during pregnancy and breastfeeding. Previous WHO guidelines have used the terms "options A, B and B+" to refer to different approaches to the prevention of the mother-to-child transmission of HIV.

HIV testing and prevention

Combination prevention refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

Early infant diagnosis is the testing of infants to determine their HIV status following possible exposure to HIV during pregnancy, delivery and postpartum through breastfeeding.

Point-of-care testing is conducted at or near the site at which care is being provided. The test results are usually returned rapidly so that clinical decisions can be made in a timely and cost-effective manner.

PEP of HIV is the use of ARV drugs by people who are not infected with HIV but who may have been exposed to HIV to block HIV infection.

(PrEP): Oral PrEP of HIV is the use of ARV drugs by people who are not infected with HIV to block the acquisition of HIV.

Rapid diagnostic test: in vitro immunochromatographic or immunofiltration diagnostic test for detecting HIV-1 and -2 antibodies and/or HIV p24 antigen.

Health workforce

Community health workers are health workers who have received standardized and nationally endorsed training outside the nursing, midwifery or medical curricula.

Lay provider is any person who performs functions related to health-care delivery and has been trained to deliver specific services but has not received a formal professional or paraprofessional certificate or tertiary degree.

Midwives are health workers who have successfully completed a midwifery education programme recognized in the country in which the programme is located. This includes registered midwives, community midwives and nurse-midwives.

Non-physician clinicians are professional health workers capable of many of the diagnostic and clinical functions of a physician but who are not trained as physicians. These types of health workers are often known as health officers, clinical officers, physician assistants, nurse practitioners or nurse clinicians and are an important cadre for HIV care and treatment in some countries.

Nurses are people who have been authorized to practise as a nurse or trained in basic nursing skills. This includes registered nurses, clinical nurse specialists, licensed nurses, auxiliary nurses, dental nurses and primary care nurses.

Task shifting and **task sharing** are the rational redistribution of tasks between cadres of health workers with longer training and other cadres with shorter training, such as lay providers.

Service delivery

Adherence is the extent to which a person's behaviour – taking medication, following a diet and/or changing lifestyle – corresponds with agreed recommendations from a health worker.

Continuum of HIV care refers to a comprehensive package of HIV testing, prevention, treatment and care services provided for people at risk of acquiring HIV and people living with HIV and their families. Examples of these services include combination HIV prevention, including PrEP; HIV testing and linkage to care; managing opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care.

Dispensing ART includes dispensing medication to people who are already receiving ART between regular clinic visits and assessing any new signs and symptoms and providing adherence monitoring and support.

Distribution of ART is the process of physically transporting ART from one geographical point to another. The following should be distinguished:

• wholesaler distribution: distributing a large quantity of ARV drugs over long distances;

• clinic distribution or refill: selecting, packing and handing over, to specific users or caregivers, ARV drugs that are known to the users and have proven to be the appropriate choice of treatment regimen with the means available; and

• community distribution: distributing limited quantities of ARV drugs over limited geographical distances destined for specific people who are already receiving ART.

Integrated health services are health services that are managed and delivered in a way that ensures that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, at the different levels and sites of care within the health system, and according to their needs, throughout their whole life.

Linkage is defined as a process of actions and activities that supports people testing for HIV and people diagnosed with HIV in engaging with prevention, treatment and care services as appropriate for their HIV status. For people with HIV, it refers to the period beginning with HIV diagnosis and ending with enrolment in care or treatment.

Retention in HIV care means a person living with HIV who is enrolled in HIV care routinely attends these services in accordance with the need. This excludes people who have died or who were lost to follow-up.

People-centred health services involve an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants as well as beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways. People-centred care requires that people have the education and support they need to make decisions and participate in their own care. It is organized around the health needs and expectations of people rather than diseases.

A public health approach addresses the health needs of a population or the collective health status of the people rather than focusing primarily on managing individual cases. This approach aims to ensure the widest possible access to high-quality services and medicines at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV treatment, key elements of a public health approach include: using simplified drug formularies; using fixed-dose combinations on a large scale for first-line treatment for adults, adolescents and children; providing care and drugs free of user charges at the point of service delivery; decentralizing and integrating services, including task shifting; and using simplified approaches to clinical monitoring.

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EXECUTIVE SUMMARY

These guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the use of antiretroviral (ARV) drugs for treating and preventing HIV infection and the care of people living with HIV. They are structured along the continuum of HIV testing, prevention, treatment and care.

Rationale

WHO first published guidelines on the use of antiretroviral therapy (ART) for HIV infection among adults and adolescents in 2002, and on the use of ARV drugs to prevent mother-to-child HIV transmission in 2004. The 2006 updates of the guidelines introduced the concept of a public health approach, with simplified and harmonized ART regimens. In 2013, for the first time, WHO revised and combined these and other ARV-related guidance documents into consolidated guidelines that address the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the HIV service continuum. This edition updates the 2013 consolidated guidelines on the use of antiretroviral drugs following an extensive review of evidence and consultations in mid-2015, shared at the end of 2015, and now published in full in 2016.

Consolidated simplified guidance was developed in response to expressed needs of country programmes, to include all age groups and populations across both clinical and operational aspects of care. Continuing with this approach allows all guidelines impacting on the continuum of HIV care to be harmonized based on a public health approach.

Several significant developments have occurred in the HIV field since 2013. In treatment, strong evidence has emerged to show that using ART earlier results in better clinical outcomes for people living with HIV compared with delayed treatment. Further, safer and more efficacious ARV drugs are becoming available and a newer class of drugs – integrase inhibitors – is becoming more affordable for low- and middle-income countries. Most countries have moved or are moving to provide lifelong ART regardless of CD4 cell count to all pregnant and breastfeeding women, and many are moving to implement viral load testing as the preferred means of monitoring people who are taking ART. New point-of-care viral load testing technologies offer further potential to expand this approach.

In prevention, clinical trial results have strongly confirmed the efficacy of the ARV drug tenofovir disoproxil fumarate alone or in combination with emtricitabine for use as pre-exposure prophylaxis (PrEP) to prevent HIV acquisition in a wide variety of settings and populations. New innovative approaches to HIV testing are being implemented, including home testing, community-based testing and self-testing. The opportunity to use ARV drugs for treating and preventing HIV more effectively are growing rapidly.

Although countries are at different stages of ART coverage and implementation of the 2013 guidelines, there is a consistent trend towards initiating treatment earlier and

expanding the use of ARV drugs for HIV prevention to achieve greater impact. This is accompanied by strong recognition that expanding access to HIV testing, treatment and prevention in settings with the highest burden of HIV infection and for the most vulnerable populations, along with greater efforts to address stigma and discrimination, are essential to ensure continued focus and to accelerate the response to the epidemic.

These guidelines present several new recommendations, including the recommendation to provide lifelong ART to all children, adolescents and adults, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count. WHO has also expanded earlier recommendations to offer PrEP to selected people at substantial risk of acquiring HIV. Alternative first-line treatment regimens are recommended, including an integrase inhibitor as an option in resource-limited settings and reduced dosage of a key recommended first-line drug, efavirenz, to improve tolerability and reduce costs. Because of their anticipated public health impact, the new recommendations on when to start ART and the use of PrEP contained in these guidelines were released in September 2015.

Implementing all the recommendations in these guidelines at the national and global levels will have important implications for programme priority-setting, funding and service delivery. As in 2013, operational guidance is included to help countries as they work to implement new approaches and strengthen the treatment cascade. These guidelines include 10 new recommendations to improve the quality and efficiency of services to people living with HIV. Implementation of the recommendation on universal eligibility for ART will mean that more people will start ART earlier. Importantly, in this guidance WHO emphasizes the need for differentiated approaches to care for people who are stable on ART, such as reducing the frequency of clinic visits and community ART distribution. Such efficiencies are essential if countries with a high burden of HIV infection are to manage their growing numbers of people receiving ART and reduce the burden on people receiving treatment and health facilities.

The second edition of the consolidated guidelines on the use of antiretroviral drugs is being published in a changing global context for HIV and for health more broadly. The goal of providing HIV treatment to 15 million people by the end of 2015 has been achieved. From 2016, countries need to further accelerate efforts to meet the ambitious Fast-Track target for 2020, including achieving major reductions in the number of people dying from HIV related causes and the 90–90–90 treatment target: ensuring that 90% of the people living with HIV know their HIV status; 90% of the people living with HIV who know their HIV status are accessing treatment; and 90% of people living with HIV who are receiving treatment have suppressed viral load. The clinical and operational recommendations in these guidelines together with two sets of consolidated guidelines on HIV testing services and strategic information published in 2015 should contribute strongly to achieving these goals in the coming years and to other health and development priorities in the Sustainable Development Goals. The forthcoming Global Health Sector Strategy on HIV 2016–2021 describes WHO's contribution to achieving the HIV- and health-related Sustainable Development Goals.

Process of guideline development

This edition of the guidelines was revised in accordance with procedures established by the WHO Guidelines Review Committee. New clinical and operational recommendations in the guidelines are based on the GRADE (Grading of Recommendations, Assessment,

Development and Evaluation) approach to reviewing evidence. Modelling, expert consultations and country case studies have all strongly informed the guidelines. The process has also identified key gaps in knowledge that will help to guide the future HIV research agenda.

Audience

The primary audience for these guidelines is national HIV programme managers in low- and middle-income countries. The guidelines will also be a useful resource for clinicians and should help to shape the priorities of policy-makers in development agencies, international organizations, nongovernmental organizations and other implementing partners during the next few years. The guidelines will also be of value to people living with HIV, communities and civil society organizations that will need to be engaged meaningfully to support their successful implementation.

The 2016 consolidated guidelines on the use of antiretroviral drugs represent an important step towards achieving the goal that the world set itself a decade ago, universal access to ARV drugs for treating and preventing HIV, and the ultimate goal of ending the HIV epidemic as a major public health threat by 2030.

SUMMARY OF RECOMMENDATIONS

The recommendations listed in these guidelines are categorized as follows:

Existing recommendation (not changed in 2016)

The recommendation was published in previous WHO guidelines. The source of the guideline is provided with the recommendation. These recommendations have not been reviewed or changed in 2015. The evidence base for these recommendations is included in the original source document.

Existing recommendation (reviewed and updated in 2016)

The recommendation was published in previous WHO guidelines, and evidence to inform the recommendation was reviewed for this edition. The supplementary web annexes of this guideline include evidence to support the recommendation. Where changes have been made to the strength of the recommendation, this is noted in the relevant chapter.

New recommendation (2016)

NEW

The recommendation is new and published for the first time in these guidelines. These recommendations address new topic areas or replace previous recommendations. The supplementary web annexes of these guidelines provide evidence to support the recommendation.

The following table presents all recommendations included in these guidelines, including the strength of the recommendation and quality of the evidence.

Chapter	Recommendation
2. HIV DIAGNOSIS	
2.2 Retesting prior to enrollment in care	
WHO reminds national programmes to retest all newly diagnosed people with HIV. WHO information note – 22 October 2014. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/vct/retest-newly-diagnosed-plhiv-full/en/)	
	Retest all clients diagnosed HIV-positive with a second specimen and a second operator using the same testing strategy and algorithm before enrolling the client in care and/or initiating ART, regardless of whether or not ART initiation depends on CD4 count.
	Retesting people on ART is not recommended, as there are potential risks of incorrect diagnosis, particularly for in vitro diagnostics (IVDs) that use oral fluid specimens.
2.3 Pre- and post-test services	
Guideline on HIV disclosure counselling for children up to 12 years of age. Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/hiv_disclosure/en/)	
	Initiatives should be put in place to enforce privacy protection and institute policy, laws and norms that prevent discrimination and promote the rights of people living with HIV. This can help create environments where disclosure of HIV status is easier (strong recommendation, low-quality evidence).
2.4 Principles and approaches for service delivery	
Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/)	
Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva: World Health Organization; 2007 (http://www.who.int/hiv/pub/vct/pitc2007/en).	
2.4.1 Improving quality and efficiency	Lay providers who are trained and supervised can independently conduct safe and effective HIV testing using rapid diagnostic tests (RDTs) (strong recommendation, moderate-quality evidence).
2.4.2 HIV testing approaches Facility-based HIV testing services and provider-initiated testing and counselling (PITC)	*Generalized HIV epidemic* PITC should be offered for all clients and in all services (including services for sexually transmitted infections (STI), viral hepatitis, tuberculosis (TB), children under the age of 5 years, immunization, malnutrition, antenatal care and all services for key populations) as an efficient and effective way to identify people with HIV. *Concentrated HIV epidemic* PITC should be offered for clients (adults, adolescents and children) in clinical settings who present with symptoms or medical conditions that could indicate HIV infection, including presumed and confirmed TB cases. *Regardless of epidemic type* PITC should be considered for malnutrition clinics, STI, hepatitis and TB services, ANC settings and health services for key populations. For TB settings, routine HIV testing should be offered to all clients with presumptive and diagnosed TB; partners of known HIV-positive TB patients should be offered voluntary HTS with support for mutual disclosure (strong recommendation, low-quality evidence in accordance with the recommendation for the partners of all people living with HIV), and TB control programmes should mainstream provision of HTS in their operations and routine services.

Chapter	Recommendation
Community-based HIV testing services	*Generalized HIV epidemic* WHO recommends community-based HIV testing services with linkage to prevention, treatment and care services in addition to routinely offering PITC for all populations, particularly key populations (strong recommendation, low-quality evidence). *Concentrated HIV epidemic* WHO recommends community-based HIV testing services, with linkage to prevention, treatment and care, in addition to PITC for key populations (strong recommendation, low-quality evidence).

2.5 HIV diagnosis in infants and children

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en).

WHO recommendations on the diagnosis of HIV infection in infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/hiv/pub/paediatric/diagnosis/en).

2.5.1 Overview	It is strongly recommended that HIV serological assays used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality assured laboratory conditions (strong recommendation, moderate-quality evidence). It is strongly recommended that HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally greater than 98%, and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions (strong recommendation, moderate-quality evidence). It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children below 18 months of age (strong recommendation, high-quality evidence). In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use: HIV DNA on whole blood specimen or DBS; HIV RNA on plasma or DBS; Us p24 Ag on plasma or DBS (strong recommendation, high-quality evidence). It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter (strong recommendation, high-quality evidence). In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen is collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test (strong recommendation, high-quality evidence). It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/caregiver as soon as possible, but at the very latest within four weeks of specimen collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART (strong recommendation, high-quality evidence). It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4–6 weeks) or other child health visit have their HIV exposure status ascertained (strong recommendation, high-quality evidence). It is strongly recommended that HIV-exposed infants who are well undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Infants who have reactive serological assays at 9 months should have a virological test to identify HIV infection and the need for ART (strong recommendation, low-quality evidence).

Chapter	Recommendation
	It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing (strong recommendation, low-quality evidence). It is strongly recommended that children (18 months or older) with suspected HIV infection or HIV exposure have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults (strong recommendation, high-quality evidence).
NEW 2.5.2 Timing of virological testing	Addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis (EID) testing approaches can be considered to identify HIV infection in HIV-exposed infants (conditional recommendation, low-quality evidence).
NEW 2.5.3 Point-of-care technologies for the diagnosis of HIV infection in infants and children	Nucleic acid testing (NAT) technologies that are developed and validated for use at or near to the point of care can be used for early infant HIV testing (conditional recommendation, low-quality evidence).
	Rapid diagnostic tests (RDTs) for HIV serology can be used to assess HIV exposure only in infants less than 4 months of age. HIV-exposure status in infants and children 4–18 months of age should be ascertained by undertaking HIV serological testing in the mother (conditional recommendation, low-quality evidence). Rapid diagnostic tests for HIV serology can be used at 9 months to rule out HIV infection in asymptomatic HIV-exposed infants (conditional recommendation, low-quality evidence). Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection in children older than 18 months following the national testing strategy (strong recommendation, moderate-quality evidence).
NEW 2.5.4 Provider-initiated HIV testing and counselling for infants and children	In generalized epidemic settings, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV (strong recommendation, low-quality evidence). In generalized epidemic settings, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics (conditional recommendation, low-quality evidence).

2.6 Other priority populations

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples. Geneva: World Health Organization; 2012 (http://www.who.int/hiv/pub/guidelines/9789241501972/en/index.html).

Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en).

2.6.1 Adolescents	HIV testing services, with linkages to prevention, treatment and care, should be offered for adolescents from key populations in all settings (strong recommendation, very low-quality evidence). Adolescents with HIV should be counselled about the potential benefits and risks of disclosure of their HIV status and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very low-quality evidence).

Chapter	Recommendation
	Generalized HIV epidemic HIV testing services with linkage to prevention, treatment and care should be offered to all adolescents in generalized epidemics (strong recommendation, very low-quality evidence). *Concentrated HIV epidemic* HIV testing services with linkage to prevention, treatment and care should be *accessible* to adolescents in low-level and concentrated epidemics (conditional recommendation, very low-quality evidence).
2.6.2 Pregnant women	*High-prevalence settings* PITC for women should be considered a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings. In such settings, where breastfeeding is the norm, lactating mothers who are HIV negative should be retested periodically throughout the period of breastfeeding. All HIV-negative pregnant women should be retested in the third trimester, postpartum and/or during labour, because of the high risk of acquiring HIV during pregnancy. *Low-prevalence settings* PITC can be considered for pregnant women in antenatal care as a key component of the effort: • to eliminate mother-to-child transmission of HIV • to integrate HIV testing with other key testing (for viral hepatitis, syphilis, etc.) as relevant to the setting • to retest HIV negative pregnant women who are in a serodiscordant couple, from a key population group or have known ongoing HIV risk.
2.6.3 Couples and partners	Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure. This applies also to couples and partners from key populations (strong recommendation, low-quality evidence). In antenatal care settings, couples and partners should be offered voluntary HIV testing services with support for mutual disclosure (strong recommendation, low-quality evidence). HIV testing services for couples and partners, with support for mutual disclosure, should be offered to individuals with known HIV status and their partners (strong recommendation, low-quality evidence for all people with HIV in all epidemic settings; conditional recommendation, low-quality evidence for HIV-negative people depending on country-specific HIV prevalence).
2.6.5 Key populations	HIV testing services should be routinely offered to all key populations in the community, in closed settings such as prisons and in facility-based settings. Community-based HIV testing services for key populations linked to prevention, treatment and care services are recommended, in addition to routine facility-based HIV testing services, in all settings (strong recommendation, low-quality evidence).

Chapter	Recommendation
2.7 Diagnostics	

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Technical guidance update on quality assurance for HIV rapid diagnostic tests. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/181244/1/WHO_HIV_2015.28_eng.pdf?ua=1&ua=1).

High-prevalence settings

In settings with greater than 5% HIV prevalence in the population tested, a diagnosis of HIV positive should be provided to people with two sequential reactive tests.

For individuals with discrepant test results where Assay 1 is reactive, Assay 2 is non-reactive and Assay 3 is reactive, the results should be considered inconclusive and the client should be asked to return in 14 days for retesting.

For individuals with discrepant test results where Assay 1 is reactive, Assay 2 is non-reactive and Assay 3 is non-reactive, the final result should be considered HIV negative.

Low-prevalence settings

In settings with less than 5% HIV prevalence in the population tested, a diagnosis of HIV positive should be provided to people with three sequential reactive tests.

For individuals where Assay 1 result is reactive and Assay 2 result is non-reactive, the final result should be considered HIV negative. However, in the case of such results and where Assay 1 is a fourth-generation assay (antibody/antigen [Ab/Ag]) and Assay 2 is an Ab-only assay, the result should be considered inconclusive and the person should be retested after 14 days.

For individuals with results in which Assay 1 is reactive, Assay 2 is reactive and Assay 3 is non-reactive, the result should be considered inconclusive and the client should be asked to return in 14 days for retesting.

All settings

HIV testing services may use combinations of RDTs or combinations of RDTs/enzyme immunoassays (EIAs)/supplemental assays rather than EIA/Western blot combinations.

Chapter	Recommendation
3. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION	
3.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV	
NEW	Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk[1] of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).
3.2 Post-exposure prophylaxis Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).	
	A regimen for post-exposure prophylaxis for HIV with two drugs is effective, but three drugs are preferred (conditional recommendation, very low-quality evidence). Post-exposure prophylaxis ARV regimens for adults and adolescents: TDF + 3TC (or FTC) is recommended as the preferred backbone[2] regimen for HIV post-exposure prophylaxis in adults and adolescents (strong recommendation, low-quality evidence). LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for adults and adolescents (conditional recommendation, very low-quality evidence). Where available, RAL, DRV/r or EFV can be considered as alternative options. Post-exposure prophylaxis ARV regimens for children ≤10 years: AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children aged 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens (strong recommendation, low-quality evidence). LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for children younger than 10 years (conditional recommendation, very low-quality evidence). An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.[3] *Prescribing practices* A full 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment (strong recommendation, low-quality evidence). Enhanced adherence counselling[4] is suggested for all individuals initiating HIV post-exposure prophylaxis (conditional recommendation, moderate-quality evidence).

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[1] Provisional definition of substantial risk is defined as HIV incidence higher than 3 per 100 person-years in the absence of PrEP.

[2] Backbone regimen refers to the two-NRTI component of an ART regimen (normally comprising 3 ARV drugs).

[3] NVP should not be used in children above the age of two years.

[4] Enhanced adherence counselling includes baseline individual needs assessment, adherence counselling and education sessions and follow-up telephone calls.

Chapter	Recommendation
4. CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY	
4.3 When to start ART	
NEW 4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
NEW 4.3.2 When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).
NEW 4.3.3 When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence).
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
4.3.4 When to start ART in children younger than 10 years of age	**NEW** ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:
	• Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence).
	NEW • Children living with HIV 1 year old to less than 10 years old (conditional recommendation, low-quality evidence).
	As a priority, ART should be initiated in all children <2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤750 cells/mm^3 or CD4 percentage <25% and children 5 years of age and older with WHO clinical stage 3 or 4 or CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).
4.3.5 Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count (strong recommendation, high-quality evidence).[1]
	TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high-quality evidence).[2]
	HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment.
	ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment regardless of the CD4 cell count and clinical stage (strong recommendation, low-quality evidence).
	Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

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[1] The quality of evidence for this recommendation was upgraded to high in 2015.
[2] The quality of evidence for this recommendation was upgraded to high in 2015.

Chapter	Recommendation
4.4 What to start: first-line ART	

4.4.1 First-line ART for adults	First-line ART for adults[1] should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI):
	
	 • TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
	 • If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended:
	  ° AZT + 3TC + EFV
	  ° AZT + 3TC + NVP
	  ° TDF + 3TC (or FTC) + NVP
	  (strong recommendation, moderate-quality evidence).

	NEW TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional recommendation, moderate-quality evidence).
	Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).
	Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
NEW 4.4.2 Fixed-dose combinations	Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (strong recommendation, moderate-quality evidence).
NEW 4.4.3 First-line ART for adolescents	First-line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI: TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, low-quality evidence). TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV_{400}[2] may be used as alternative options to initiate ART (conditional recommendation, low-quality evidence). If preferred regimens are contraindicated or not available, one of the following alternative options is recommended (strong recommendation, moderate-quality evidence): ABC + 3TC + EFV ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
4.4.4 First-line ART for children aged 3 to 10 years of age	For children 3 to less than 10 years of age, the NRTI backbone[3] should be one of the following, in preferential order (conditional recommendation, moderate-quality evidence[4]): • ABC + 3TC • AZT or TDF + 3TC (or FTC)
	For children 3 years and older, EFV is the preferred NNRTI for first-line treatment and NVP is the preferred alternative (strong recommendation, low-quality evidence).

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[1] Includes pregnant and breastfeeding women (further guidance in Box 4.3).

[2] EFV at a lower dose (400 mg/day).

[3] Backbone regimen refers to the two-NRTI component of an ART regimen (normally comprising 3 ARV drugs).

[4] Strength of evidence reviewed in 2015.

Chapter	Recommendation
4.4.5 First-line ART for children younger than 3 years of age	For infants and children younger than 3 years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC (strong recommendation, moderate-quality evidence[1]).
	A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than 3 years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (strong recommendation, moderate-quality evidence).
	Where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained (conditional recommendation, moderate-quality evidence).
	For infants and children infected with HIV younger than 3 years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (strong recommendation, moderate-quality evidence).
4.4.7 Infant prophylaxis	**NEW** Infants born to mothers with HIV who are at high risk of acquiring HIV[2] should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate-quality evidence).
	NEW Breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality evidence).
	Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding).
	Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
4.4.8 Infant feeding in the context of HIV	National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be HIV infected to either breastfeed and receive ARV[3] interventions or avoid all breastfeeding.
	In settings where national authorities have decided that maternal and child health services will principally promote and support breastfeeding and antiretroviral interventions as the strategy that will most likely give infants born to mothers known to be HIV infected the greatest chance of HIV-free survival, mothers known to be infected with HIV should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life.[4] Breastfeeding should then stop only once a nutritionally adequate and safe diet without breast-milk can be provided (strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months).
	Guidelines on HIV and infant feeding 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241599535/en).

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[1] Strength of evidence reviewed in 2015.

[2] High-risk infants are defined as those:
- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding; or
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

[3] All women living with HIV are eligible for initiation of ART regardless of CD4 count.

[4] Infants who are HIV infected will benefit from extended breastfeeding and should continue breastfeeding for as long as feasible and desired.

Chapter	Recommendation
4.5 Monitoring the response to ART and diagnosing treatment failure	
4.5.1 Laboratory monitoring before and after initiating ART	**NEW** Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting[1] (conditional recommendation, very low-quality evidence).
	NEW In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed[2] (conditional recommendation, low-quality evidence).
	Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failurea (strong recommendation, low-quality evidence). Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a 3-month interval, with adherence support between measurements) after at least 6 months of starting a new ART regimen. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
	NEW Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV viral load. A threshold of 1000 copies/mL can be used to determine virological failure when using dried blood spot samples, as defined for testing in plasmac (conditional recommendation, low-quality evidence).
4.8 What ART regimen to switch to (second and third line)	
4.8.1 Second-line ART for adults and adolescents	Second-line ART in adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a ritonavir-boosted protease inhibitor (PI). The following sequence of second-line NRTI options is recommended: • After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens. • After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens. Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (strong recommendation, moderate-quality evidence). Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (strong recommendation, moderate-quality evidence).
	NEW A heat-stable fixed-dose combination of DRV/r can be used as an alternative boosted PI option for second-line ART (conditional recommendation, low-quality evidence).
	NEW A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen (conditional recommendation, low-quality evidence).

[1] Viral load testing should be performed early after initiating ART (within 6 months), at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible.

[2] WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL). For service delivery recommendations in these guidelines (see Chapter 6 "Service delivery"), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.

Chapter	Recommendation
4.8.2 Second-line ART for children	**NEW** After failure of a first-line LPV/r-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen (conditional recommendation, very low-quality evidence).
	NEW After failure of a first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL (conditional recommendation, very low-quality evidence).
	After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred (conditional recommendation, very low-quality evidence).
	After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC (strong recommendation, low-quality evidence).
	After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) (strong recommendation, low-quality evidence)
4.8.3 Third-line ART	National programmes should develop policies for third-line ART (conditional recommendation, low-quality evidence). Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs (conditional recommendation, low-quality evidence). Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (conditional recommendation, very low-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Chapter	Recommendation
5. CLINICAL GUIDELINES: PREVENTION, SCREENING AND MANAGEMENT OF COMMON COINFECTIONS AND COMORBIDITIES	
5.2 Prevention, screening and management of common coinfections	
5.2.1 Co-trimoxazole prophylaxis	Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence). • In settings where malaria and/or severe bacterial infections (SBIs) are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (conditional recommendation, moderate-quality evidence). • Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression (conditional recommendation, low-quality evidence). • In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage (conditional recommendation, moderate-quality evidence). Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count (strong recommendation, high-quality evidence). Co-trimoxazole prophylaxis is recommended for infants, children, and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children less than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 ≤350 cells/mm^3 (strong recommendation, high-quality evidence). • In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood, irrespective of whether ART is provided (conditional recommendation, moderate-quality evidence). • In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 count >350 cells/mm^3 (strong recommendation, very low-quality evidence). Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding (strong recommendation, very low-quality evidence). Guidelines on post-exposure prophylaxis and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).
5.2.2 Tuberculosis	Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having HIV-associated TB or multidrug resistant TB (strong recommendation, adults: high-quality evidence; children: very low-quality evidence). Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients suspected of having TB meningitis (strong recommendation, very low-quality evidence). Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence). Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: WHO policy update. Geneva: World Health Organization; 2013 (http://www.who.int/tb/laboratory/xpert_policyupdate/en).

Chapter	Recommendation
	Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill,[1] urine lateral flow (LF)-LAM should not be used for the diagnosis of TB (strong recommendation, low-quality evidence). LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 cell count less than or equal to 100 cells/mm^{3} or people living with HIV who are seriously ill regardless of CD4 count or with unknown CD4 count (conditional recommendation, low-quality evidence).[2] LF-LAM should not be used as a screening test for active TB (strong recommendation, low-quality evidence). The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis.in people living with HIV: Policy guidance. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf).
	TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of a rifampicin-containing treatment regimen. The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high-quality evidence). WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en).
Isoniazid preventive therapy (IPT)	Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (strong recommendation, moderate-quality evidence). Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least 6 months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals regardless of the degree of immunosuppression and also to those on ART, those who have previously been treated for TB and pregnant women (strong recommendation, high-quality evidence). Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test status and among whom active TB disease has been safely ruled out should receive at least 36 months of IPT. IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment, and pregnancy (conditional recommendation, moderate-quality evidence). Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT preventive therapy regardless of their age (strong recommendation, low-quality evidence). Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive 6 months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care (strong recommendation, moderate-quality evidence).

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[1] Seriously ill is defined as four danger signs: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.

[2] This recommendation also applies to adults living with HIV who are outpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/mm^{3}, or who are seriously ill regardless of CD4 count or with unknown CD4 count, based on the generalization of data from inpatients. This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults, while acknowledging that data are very limited and that there are concerns regarding low specificity of the LF-LAM assay in children.

Chapter	Recommendation
	In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of IPT if the evaluation shows no TB disease (strong recommendation, low-quality evidence).
	All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional 6 months (conditional recommendation, low-quality evidence).
	Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).
Infection control	Administrative (facility-level infection control committee and protocols) • A triage system should be in place to identify people suspected of having TB and minimize diagnostic delays with rapid diagnostics e.g. Xpert MTB/RIF. • Separate people with suspected or confirmed TB • Ensure cough etiquette and respiratory hygiene • Minimize the time spent in health-care facilities (e.g. through community-based approaches) (all administrative recommendations: strong recommendation, low-quality evidence). Health workers and carergivers • Inform and encourage health workers with TB symptoms to undergo TB diagnostic investigation as well as HIV testing and counselling. • Provide a package of care for HIV positive-workers (ART and isoniazid preventive therapy). • Relocation for health workers living with HIV to a lower-risk area. (all health worker recommendations: strong recommendation in settings with a high prevalence of HIV and conditional with a low prevalence, high-quality evidence). Use of particulate respirators • Protective equipment (particulate respirator masks that meet or exceed N95 standards set by the CDC/NIOSH or the FFP2 standards that are CE certified) should be provided for health workers caring for patients with infectious TB (suspected or confirmed) (strong recommendation, low-quality evidence). Environmental • Ventilation (i.e. natural and/or mechanical) (strong recommendation, low-quality evidence) • Upper-room ultraviolet germicidal irradiation (conditional recommendation, low-quality evidence). WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (http://www.who.int/tb/publications/2009/9789241598323/en).
Multidrug-resistant TB and HIV	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line antituberculosis drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment (strong recommendation, very low-quality evidence). Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf).
5.3.2 Cryptococcal disease Diagnosis of cryptococcal disease	Prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach. (strong recommendation, moderate-quality evidence).

Chapter	Recommendation
Prevention of cryptococcal disease	The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm³, and who are CrAg-negative or where CrAg status is unknown, is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely (strong recommendation, high-quality evidence). The use of routine serum or plasma CrAg screening in ART-naive adults, followed by pre-emptive antifungal therapy if CrAg-positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in: a) patients with a CD4 count less than 100 cells/mm³; and b) where this population also has a high prevalence (>3%)[1] of cryptococcal antigenaemia (conditional recommendation, low-quality evidence). The use of routine CrAg screening in ART-naive adolescents and children with pre-emptive antifungal therapy if CrAG positive, prior to ART initiation is not recommended (conditional recommendation, low-quality evidence).
Induction, consolidation, and maintenance antifungal treatment regimens	For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week antifungal regimens are recommended in order of preference: a. Amphotericin B + flucytosine (strong recommendation, high-quality evidence). b. Amphotericin B + fluconazole (strong recommendation, moderate-quality evidence). c. Amphotericin B short course (5–7 days) + high dose fluconazole (to complete 2 weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full 2-week induction period (conditional recommendation, low-quality evidence). d. Fluconazole high dose + flucytosine, when amphotericin B is not available (conditional recommendation, low-quality evidence). e. Fluconazole high dose alone, when amphotericin B is not available (conditional recommendation, low-quality evidence). For the consolidation phase treatment of HIV infected adults, adolescents and children with cryptococcal meningitis or disseminated non-meningeal disease, the following 8-week antifungal regimen is recommended: Fluconazole 400–800mg/day after a two-week induction with amphotericin B regimen (6–12 mg/kg/day up to 400–800 mg/day if below 19 years). Fluconazole 800 mg/day after induction treatment with short-course amphotericin B or fluconazole-based induction regimen (fluconazole 12 mg/kg/day up to 800 mg/day if below 19 years) (strong recommendation, low-quality evidence). For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents and children, oral fluconazole 200 mg daily (6 mg/kg/day up to 200 mg/day if below 19 years) is recommended (strong recommendation, high-quality evidence). For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded). Fluconazole 800 mg/day (or 12 mg/kg/day if below 19 years) for two weeks, then 400 mg/day (or 6 mg/kg/day up to 400–800 mg/day if below 19 years) for 8 weeks, and continued maintenance with fluconazole 200 mg/day is recommended. The optimal antifungal regimen in this population remains to be determined (conditional recommendation, low-quality evidence).

[1] The prevalence threshold above which screening is cost–effective was 1% using LFA (Meya D, Rajasingham R, Rolfes M, Birkenkamp K, Boulware D. Cost benefit of integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. In: International AIDS Conference, Washington, DC, 22–27 July 2012 [Abstract MOAB0102]). The prevalence cost–effectiveness threshold is likely to vary depending on the cost of the antigen assay used (latex agglutination [LA] vs. LFA) and cost of drug treatment.

Chapter	Recommendation
Prevention, monitoring and management of amphotericin B toxicity	In HIV-infected adults receiving amphotericin B–containing regimens for treatment of cryptococcal disease, a minimum package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B–related toxicities of hypokalaemia and nephrotoxicity (strong recommendation, moderate-quality evidence).
Timing of ART initiation	Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening (conditional recommendation, low-quality evidence) In HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and after 4 weeks of induction and consolidation treatment with amphotericin B–containing regimens combined with flucytosine or fluconazole, or after 4–6 weeks of treatment with a high-dose oral fluconazole induction and consolidation regimen (conditional recommendation, low-quality evidence)
Discontinuation of azole maintenance treatment (secondary prophylaxis)	In HIV-infected adults and adolescents with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal maintenance treatment is recommended based on the following criteria: a. If HIV viral load monitoring is available: when patients are stable and adherent to ART and antifungal maintenance therapy for at least 1 year and have a CD4 cell count of greater than or equal to 200 cells/mm^3 (two measurements 6 months apart) (strong recommendation, low-quality evidence). b. If HIV viral load monitoring is available: when patients are stable and adherent to ART and antifungal maintenance treatment for at least one year and with CD4 cell count of greater than or equal to 100 cells/mm^3 (two measurements 6 months apart) and a suppressed viral load (conditional recommendation, low-quality evidence). In children aged less than two years with successfully treated cryptococcal disease, antifungal maintenance treatment should NOT be discontinued (strong recommendation, low-quality evidence). In HIV-infected children aged between 2 and 5 years with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal treatment maintenance is recommended if the child is stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count percentage greater than 25% or absolute count greater than 750 cells/mm^3 (two measurements 6 months apart) (strong recommendation, low-quality evidence). Maintenance therapy for cryptococcal disease should not be discontinued in children less than two years (strong recommendation, low-quality evidence). Maintenance treatment for cryptococcal disease should be restarted if CD4 count drops to 100 cells/mm^3, or below in HIV-infected adults and adolescents (or CD4 cell count less than or equal to 25% or 750 cells/mm^3 in children aged between 2 and 5 years), or if a WHO stage 4 clinical event occurs, irrespective of patient age (strong recommendation, low-quality evidence). Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/cryptococcal_disease2011/en).

Chapter	Recommendation
5.3 Prevention, screening and management of other comorbidities and chronic care for people living with HIV	
NEW 5.3.1 Assessment and management of noncommunicable diseases	Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population[1] (conditional recommendation, very low-quality evidence).
NEW 5.3.2 Assessment and management of depression in people living with HIV	Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV (conditional recommendation, very low-quality evidence).

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[1] The WHO PEN protocol targets the following populations for CVD screening: age >40 years, smokers, people with known hypertension or diabetes mellitus, waist circumference >90 cm in women and >110 cm in men, and family history of diabetes mellitus or premature CVD (www.who.int/cardiovascular_diseases/ publications/ pen2010/en).

Chapter	Recommendation
6. SERVICE DELIVERY	
6.4 Linkage from HIV testing to enrolment in care	
NEW 6.4.1 Interventions to ensure timely linkage	Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV (strong recommendation, moderate-quality evidence). The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis: • streamlined interventions to reduce time between diagnosis and engagement in care including (i) enhanced linkage with case management; (ii) support for HIV disclosure; (iii) patient tracing; (iv) training staff to provide multiple services, and (v) streamlined services (moderate-quality evidence); • peer support[1] and navigation approaches for linkage (moderate-quality evidence); and • quality improvement approaches using data to improve linkage (low-quality evidence).
NEW 6.4.2 CD4 cell count testing at the point of care	CD4 cell count testing at the point of care can be used to prioritize patients for urgent linkage to care and ART initiation (conditional recommendation, low-quality evidence).
NEW 6.4.3 Laboratory connectivity	Electronic communication can be considered to transfer test results and reduce delays in acting on the results of early infant diagnosis and other essential laboratory tests (conditional recommendation, low-quality evidence).
NEW 6.5 Retention in care	Programmes should provide community support for people living with HIV to improve retention in HIV care (strong recommendation, low-quality evidence). The following community-level interventions have demonstrated benefit in improving retention in care: • package of community based interventions[2] (children low-quality and adults very low-quality evidence) • adherence clubs[3] (moderate-quality evidence) • extra care for high-risk people (very low-quality evidence).
NEW 6.6 Adherence	Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence). The following interventions have demonstrated benefit in improving adherence and viral suppression: • peer counsellors (moderate-quality evidence) • mobile phone text messages (moderate-quality evidence) • reminder devices (moderate-quality evidence) • cognitive-behavioural therapy (moderate-quality evidence) • behavioural skills training/medication adherence training (moderate-quality evidence) • fixed-dose combinations and once-daily regimens (moderate-quality evidence)
NEW 6.7 Frequency of visits	Less frequent clinical visits (3–6 months) are recommended for people stable on ART (strong recommendation, moderate-quality evidence).[4] Less frequent medication pickups (3-6 months) are recommended for people stable on ART (strong recommendation, low-quality evidence).[5]

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[1] Peer support includes peer counselling.

[2] Patient advocates, treatment and peer support interventions providing adherence and psychosocial support in the community.

[3] Peer support, distribution of ARV drugs and assessment by non-clinical or lay providers.

[4] When routine clinical consultations are due, they should be coordinated with planned medication pick-up to reduce visit frequency.

[5] ARV supply management should be strengthened to ensure the availability of ARV medicines and prevent stock-outs in the context of less frequent medication pickup.

Chapter	Recommendation
6.8 Task shifting and sharing	**NEW** Trained and supervised lay providers can distribute ART to adults, adolescents and children living with HIV (strong recommendation, low-quality evidence).
	Trained non-physician clinicians, midwives and nurses can initiate first-line ART (strong recommendation, moderate-quality evidence). Trained non-physician clinicians, midwives and nurses can maintain ART (strong recommendation, moderate-quality evidence). Trained and supervised community health workers can dispense ART between regular clinical visits (strong recommendation, moderate-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
6.9 Decentralization	Decentralization of HIV treatment and care should be considered as a way to increase access to and improve retention in care: • initiation of ART in hospitals with maintenance of ART in peripheral health facilities (strong recommendation, low-quality evidence); • initiation and maintenance of ART in peripheral health facilities (strong recommendation, low-quality evidence); • initiation of ART at peripheral health facilities with maintenance at the community level (strong recommendation, moderate-quality evidence).[1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

6.10 Integrating and linking services

Chapter	Recommendation
6.10.1 Delivering ART in maternal and child health-care settings	In generalized epidemic settings, ART should be initiated and maintained in eligible[2] pregnant and postpartum women and in infants at maternal and child health-care settings, with linkage and referral to ongoing HIV care and ART, where appropriate (strong recommendation, very low-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
6.10.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings	In settings with a high burden of HIV and TB, ART should be initiated for people living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART (strong recommendation, very low-quality evidence). In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made (strong recommendation, very low-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
6.10.3 ART in settings providing opioid substitution therapy	ART should be initiated and maintained in eligible[3] people living with HIV at care settings where opioid substitution therapy (OST) is provided (strong recommendation, very low-quality evidence). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

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[1] Community level includes external outreach sites, health posts, home-based services or community-based organizations. The frequency of clinical visits will depend on health status.

[2] All people living with HIV are now eligible for initiating ART at any CD4 cell count.

[3] All people living with HIV are now eligible for initiating ART at any CD4 cell count.

Chapter	Recommendation
NEW 6.10.4 STI and family planning in HIV care settings	Sexually transmitted infection (STI) and family planning services can be integrated within HIV care settings (conditional recommendation, very low-quality evidence).
6.11 Adolescent-friendly health services	**NEW** Adolescent-friendly health services should be implemented in HIV services to ensure engagement and improved outcomes (strong recommendation, low-quality evidence).
	Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV (conditional recommendation, very low-quality evidence). Training of health-care workers can contribute to treatment adherence and improvement in retention in care of adolescents living with HIV (conditional recommendation, very low-quality evidence). Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV status to others and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very low-quality evidence). HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

Good practice statements

The table includes good practice statements made by the 2015 Guideline Development Groups.

Chapter	Good practice statement
NEW 2.5.4 Provider-initiated HIV testing and counselling	In all settings, children with a parent living with HIV should be routinely offered HIV testing and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention.
NEW 4.3.6 Accelerated ART initiation	Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.
NEW 4.4.6 Infant prophylaxis	In settings with a high risk of mother-to-child transmission, in addition to providing enhanced infant prophylaxis, ART should be initiated urgently in all pregnant and breastfeeding women, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.[1]
NEW 5.3.1 Assessment and management of cardiovascular diseases	Strategies for the prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as blood pressure, smoking, status obesity, unhealthy diet and lack of physical activity should be applied to all people living with HIV.
NEW 6.8 Task shifting and task sharing	Trained and supervised non-laboratory staff including lay people can undertake blood finger-prick for sample collection.
NEW 6.12 Improving the quality of HIV care services	HIV programmes should: • provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families to play an active role in their own care by informed decision-making; • offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general; • promote efficient and effective use of resources.

[1] Whenever possible, all efforts should be made to identify pregnant women living with HIV early enough to avoid the need for high-risk prophylaxis.

INTRODUCTION

1

1 INTRODUCTION

1.1 Context

These guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. They are structured along the continuum of HIV testing, prevention, treatment and care. This edition updates the 2013 WHO consolidated guidelines on the use of antiretroviral drugs *(1)*, based on an extensive review of new evidence conducted in 2015.

Although countries are at different stages of ART coverage and implementation of the 2013 edition of the guidelines, in 2016 there is a consistent trend towards further expanding access to ART, initiating treatment earlier and expanding the use of ARV drugs for HIV prevention. These guidelines present several new recommendations, including the recommendations to provide lifelong ART to all children, adolescents and adults living with HIV, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count. WHO has also expanded earlier recommendations to offer pre-exposure prophylaxis (PrEP) to selected key populations, to all populations with an incidence of HIV above 3 per 100 person-years.[1] A newer class of ARV drugs is now recommended as an option for first-line treatment option in resource-limited settings, as well as a reduced dosage of a previously recommended drug, efavirenz, to improve tolerability.

Implementing the new recommendations and approaches in these guidelines at the national and global levels will have important implications for programme priority setting, funding and service delivery. Similar to the 2013 edition, the guidelines provide operational and service delivery guidance to help countries as they work to implement new approaches, including guidance on effective integration of HIV and other services and strategies to optimize the quality of services along the continuum of care, including linkage, retention, adherence to treatment and adolescent-friendly health services. Importantly, the service delivery guidance in 2016 (Chapter 6) emphasizes the need for countries to provide differentiated care through reduced frequency of clinic visits and community ART distribution to help countries manage the growing cohort of people who are stable on ART and reduce the burden on people receiving treatment and health facilities as more people become eligible for treatment in accordance with these guidelines.

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1 Due to the anticipated public health impact, the new recommendations in these guidelines on when to start ART and pre-exposure prophylaxis (PrEP) were published in September 2015 (Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en, accessed 6 October 2015).

1.2   Objectives

The objectives of these guidelines are:

- to provide updated, evidence-based clinical recommendations outlining a public health approach to providing ARV drugs for HIV prevention and treatment in all age groups and populations in the context of the continuum of HIV care, focusing on settings with limited health system capacity and resources;

- to provide guidance on key operational and service delivery issues that need to be addressed to increase access to HIV services, strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems; and

- to provide programmatic guidance for decision-makers and planners at the national level on adapting, setting priorities for and implementing the clinical and operational recommendations and monitoring their implementation and impact.

1.3   Target audience

The guidelines are primarily intended for use by national HIV programme managers. They will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;

- national TB programme managers;

- national hepatitis programme managers;

- managers of sexually transmitted infection services;

- managers of maternal, newborn and child health and sexual and reproductive health programmes;

- clinicians and other health workers;

- managers of national laboratory services;

- people living with HIV and community-based organizations; and

- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in low- and middle-income countries.

1.4   Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations:

- The guidelines should contribute to and expedite the achievement of key global and national HIV goals for 2016–2021 *(2)* and to realizing the Sustainable Development Goals *(3)*.

- The guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment and care.

- Developing and implementing the guidelines should realize the rights and responsibilities of people living with HIV and promote the greater involvement of people

living with HIV (GIPA) and meaningful involvement of people living with HIV (MIPA) principles.

- In addition to strengthening the continuum of HIV services, the recommendations in the guidelines should be implemented with a view to strengthening broader health systems and provision of universal health care.

- Implementation of the guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.

- Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources and comorbidities, the organization and capacity of the health system and anticipated cost–effectiveness.

1.5   Methods for developing the guidelines

1.5.1   Guideline contributors

WHO convened five groups to perform specific guideline development functions:

- An internal WHO Guideline Steering Group coordinated the overall guideline development process.

- A Core Group of external experts provided strategic guidance to the guideline development process. Members of the Core Group also performed external review of the guidelines.

- A Clinical Guideline Development Group reviewed the evidence and developed clinical recommendations related to HIV testing and the use of ARV drugs for prevention and treatment.

- An Operational Guideline Development Group reviewed the evidence and developed recommendations related to package of care and service delivery components in these guidelines.

- An External Review Group provided peer review of the full guideline document.

The composition of both Guideline Development Groups was in accordance with WHO procedures for developing guidelines *(4)* and included HIV experts, researchers, programme managers, epidemiologists, human rights experts, representatives of United Nations agencies and representatives of civil society organizations and networks of people living with HIV. Appropriate representation by region and sex was considered. Representatives from civil society were selected from a call for nominations; eight participants were selected from more than 90 applications. The WHO HIV Civil Society Reference Group contributed to the selection process of civil society participants. The Chairs of both Guideline Development Groups also participated in the Core Group to ensure consistency. The members of the External Review Group were selected to provide further geographical representation.

1.5.2 Competing interests

Conflicts of interests were managed as follows:

1. All external contributors to the development of these guidelines, including members of the Core Group, the Clinical and Operational Guideline Development Groups and the External Review Group, were required to complete a WHO Declaration of Interests (DOI) form before engaging in the guideline development process and before participating in the Guideline Development Group meetings. All contributors were requested to promptly notify WHO if any change in the disclosed information occurred during the course of this work.

2. In accordance with the WHO DOI policy for experts, a brief biography of all members of the Guideline Development Groups was published on the WHO HIV website for a period of 14 days with a description of the objective of the Groups' meetings. No public comments or objections were received concerning the Groups' membership.

3. The completed DOI forms were reviewed by the WHO Guideline Steering Group with a view to managing disclosed interests in the use of antiretroviral drugs for treating and preventing HIV infection. Where any conflict of interest was declared, the WHO Guideline Steering Group determined whether such conflicts were serious enough to affect the expert's objective judgement on the guideline development process and recommendations. To ensure consistency, the WHO Guideline Steering Group applied the criteria for assessing the severity of conflict of interests in the *WHO handbook for guideline development (4)*.

4. The procedures for the management of declared conflicts of interests were undertaken in accordance with the *WHO guidelines for declaration of interests (experts)*. Conflicts of interest that warranted actions by the WHO Guideline Steering Group arose where experts had obtained funding from a body or an institution to perform primary research directly related to any of the guideline recommendations. At the Guideline Development Group meetings, the concerned experts were restricted from participating in discussions and/or formulating recommendations pertaining to their academic conflicts of interest.

5. All relevant declared interests (x out of x for Clinical Guideline Development Group and x out of x for Operational Guideline Group) are summarized with the agreed management plan (Annexes 1 and 2). The majority of the participants of the Guideline Development Groups did not declare significant conflicts of interest for either meeting.

6. Declared interests were shared with all participants at the meeting of the Guideline Development Groups so that the Groups were aware of any existing interests among the members.

7. Comments on the guidelines received from the External Review Group were reviewed in relation to the interests declared by the individual members.

8. All Declaration of Interests forms are on electronic file at the WHO Department of HIV/AIDS and will be maintained for 10 years.

1.5.3 Evidence synthesis

Systematic reviews of the evidence

The WHO Guideline Steering Group formulated PICO questions to guide the systematic reviews. The following technical advisory meetings held in 2014 and 2015 contributed to this process:

• a consultation on the treatment of HIV among adolescents *(5)*;

• a consultation on new strategies to optimize care in the postnatal period: infant prophylaxis, feeding and diagnosis;

• Paediatric ARV Drug Optimization 2 *(6)*;

• The future with PrEP in combination HIV prevention, WHO and UNAIDS; Scoping for the development of further recommendations on the use of PrEP for the prevention of sexual transmission of HIV and the Technical Advisory Group for Pre-Exposure Prophylaxis;

• a scoping consultation on care packages for people living with HIV *(7)*;

• a scoping consultation on chronic comorbidities in people living with HIV *(8)*;

• a scoping consultation on priority areas and required work on ARV toxicity *(9)*;

• a scoping meeting on the use of viral load and CD4 testing in the management of HIV; and

• a consultation on strengthening the quality of HIV clinical services in resource-limited settings.

Systematic review teams (Web Supplement B) developed protocols and conducted reviews. PRISMA guidelines for systematic reviews and meta-analyses were used for reporting of reviews *(10)*. Web Supplement B includes search strategies, quality assessment and synthesis of findings for all systematic reviews conducted in 2015. Data from the systematic reviews were summarized and presented as evidence profiles using the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach *(11)*.

Several reviews were conducted using a network meta-analysis to evaluate the inference of the comparative effectiveness of interventions that may or may not have been evaluated against each other. The WHO GRADE working group was consulted on the interpretation of findings and use of GRADE in evaluating the overall quality of evidence from these reviews.

Diagnostic test accuracy reviews were conducted following Cochrane methods. Summary-of-evidence profiles were developed using an adapted GRADE approach in consultation with the WHO Guidelines Review Committee and the methodologist in the Clinical Guideline Development Group.

Values of outcomes

A list of potential outcomes of interest was circulated to members of both Guideline Development Groups. The members were asked to score the importance on a scale of 1 (not important) to 9 (critical) from the perspective of individuals living with HIV, to consider the importance of the values to service users. The average of the scores and variability for each outcome were used to determine the outcomes critical to decision-making.

Overall quality of the evidence

The GRADE method was used to rate the overall quality of the evidence (Table 1.1).

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to inform a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low. Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose–response relationship or if all plausible residual confounding would reduce the demonstrated effected or increase the effect if no effect were observed.

The strength of a recommendation reflects the degree of confidence of the Guideline Development Group that the desirable effects of the recommendation outweigh the undesirable effects *(12)*. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced incidence of HIV and reduced morbidity and mortality); reduction of the burden on the individual and/or health services; and potential cost savings for the individual, communities, programme and/or health system. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Harm may include the resource use and cost implications

Table 1.1. GRADE quality of evidence

Quality of evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Middle	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

of implementing the recommendations; adverse clinical outcomes (such as drug resistance or drug toxicity); and legal ramifications, in which certain practices are criminalized.

Strength of the recommendations

The strength of a recommendation can be either strong or conditional.

A strong recommendation is one for which there is confidence that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation is one for which the Guideline Development Group concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects or are closely balanced, but the Groups are not confident about these trade-offs in all situations. At implementation, monitoring and rigorous evaluation is needed to address these uncertainties, which are likely to provide new evidence that may change the calculation of the balance of trade-offs and to suggest how to overcome any implementation challenges.

Key information sources

Modelling of potential impact

Modelling data on the impact of interventions were used to support decision-making. A causal modelling analysis comparing the effect of various treatment initiation criteria on death and growth response for children and adolescents aged 5–16 years old was used to support the recommendation on when to start ART for children and adolescents. Models developed to simulate how immediate ART initiation regardless of CD4 cell count could affect HIV mortality and transmission in sub-Saharan Africa contributed to decision-making on the recommendation on when adults should start ART.

The benefits of alternative approaches to monitoring people receiving ART were also modelled, including prediction of one-year mortality using the current CD4 percentage and count among children receiving ART. The results of this work informed the CD4 criteria for switching therapy in children without access to viral load monitoring. The costs and consequences of viral load monitoring with dried blood spot versus plasma specimens in low- and middle-income countries were also used to support decision-making.

Resource use

The prices for drugs in ART regimens were collected from the WHO Global Price Reporting Mechanism: http://apps.who.int/hiv/amds/price/hdd/.

Equity and acceptability

Evidence on the acceptability and views of service users was collected using a mixed-methods approach. The WHO Guideline Steering Group reviewed all PICO questions to identify those for which collecting service user data would best inform decision-making. The service users considered were people living with HIV, caregivers of children living with HIV and health workers.

Table 1.2. Components of CERQual used to assess confidence in findings

Component	Description
Methodological limitations	The extent to which there are problems in the design or conduct of primary studies that contributed to the evidence review.
Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context in the review question.
Adequacy of data	Overall determination of the degree of richness and quantity of data supporting a review finding.
Coherence	The coherence of the review finding addresses the question of whether the finding is well grounded in data from the primary studies

Four qualitative evidence syntheses were conducted on the following topics: 1) the role of ARV drug toxicity in influencing adherence among people living with HIV; 2) barriers to and facilitators of interventions to improve linkage to care; 3) barriers to and facilitators of interventions to improve ARV adherence; and 4) barriers to and facilitators of interventions to improve retention in care for people receiving ART. The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) *(13)* approach was used to assess the confidence in the findings from the qualitative evidence syntheses, using four factors (Table 1.2).

Qualitative literature reviews (published and grey literature) were conducted on the following topics: 1) the timing of ART initiation for all populations (including pregnant and breastfeeding women); 2) the duration of infant prophylaxis; 3) PrEP; 4) the frequency of clinic visits and medication pickups; 5) initiating ART on the same day as HIV testing; 6) task shifting for sample collection and diagnostic tests, and 7) delivering sexual transmitted infection and family planning services in HIV clinic settings.

A community consultation was conducted on when to start ART and the use of viral load testing for monitoring of people living with HIV. Seven networks of people living with HIV, supported by a global research organization, conducted 24 workshops to assess the acceptability of initiating ART earlier for people living with HIV, caregivers and service providers in eight countries (India, Indonesia, Kenya, Peru, Portugal, Ukraine, Zambia and Zimbabwe). An additional global consultation on adolescent treatment and care and a facility-based situational analysis also contributed to the evidence base on the acceptability of initiating ART earlier among adolescents.

Community networks conducted focus group discussions to explore the views on early infant diagnosis of women living with HIV and the mothers of infants exposed to HIV on in Kenya, Namibia and Nigeria. An online survey on the quality of HIV care experienced by people living with HIV collated responses from 534 individuals and was used to support the guidance on quality of care in Chapter 6.

Feasibility

Programmatic data from country implementation experience were used to support decision-making. Programme data from Brazil, Rwanda, Thailand, Uganda and VietNam were presented to the Guideline Development Groups *(14)*. Qualitative interviews and an

online survey were used to ascertain the views of HIV programme managers in three WHO regions and the conclusions from these assisted discussions on the feasibility of interventions.

WHO also conducted a survey in low- and middle-income countries on the availability and use of HIV diagnostics *(15)* and ARV drugs. The outcomes from a meeting with diagnostic manufacturers informed the decision-making *(16)*.

Meetings of the Guideline Development Groups

The Clinical and Operational Guideline Development Groups met in Geneva, Switzerland in June 2015 to review evidence and formulate recommendations. The Operational Guideline Development Group met following the Clinical Guideline Development Group so that participants could consider the implementation considerations of decisions made in the clinical meeting.

The Clinical Guideline Development Group considered evidence for PICO questions A1.1 to E1.1. The Operational Guideline Development Group considered evidence for PICO questions F1.1 to F6.2. The Clinical Guideline Development Group held an additional virtual meeting in September 2015 to review two PICO questions that were not fully reviewed in June. A quorum of the Clinical Guideline Development Group attended this meeting and a 'round-robin' approach was used to gain consensus on the recommendations. Email communication followed to ensure that all members of the Clinical Guideline Development Group agreed with the recommendations made by virtual discussion.

The systematic reviews and evidence-to-decision-making tables prepared in accordance with the GRADE process (Table 1.3) were presented at the meetings, and the respective methodologist facilitated discussions. Web Supplement A provides all evidence-to-decision-making tables, including GRADE evidence profile tables for all PICO questions that led to a recommendation.

The Guideline Development Groups made decisions by consensus. The Clinical Guideline Development Group voted as a decision-making aid for the question of when adults should initiate ART in relation to the strength of the recommendation (with a majority vote of 70%). No other votes were held to decide strength or directionality of recommendations.

Good practice statements

Good practice statements were made when the Guideline Development Groups considered the benefits to substantially outweigh any undesirable consequences, in many cases considering a large body of indirect evidence with indirect comparisons to strongly support the decision. Principles for developing good practice statements were applied *(17)*. Formal GRADE methods have not been applied to these statements. Where statements have been referenced from other guidelines (often referred to as good practice principles or practices), the source is noted.

Table 1.3. Criterion for consideration in evidence-to-decision-making tables

Domain	Rationale
Quality of the evidence	This is an assessment of the degree of confidence in the estimate of the effect: that is, the likelihood that the effect will differ substantially from what the research found. "Differ substantially" means a large enough difference that it might affect a decision.
Benefits and risks	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Values of outcomes	This is a judgement of how much the people affected by an intervention or option value each of the outcomes. How much people value outcomes in relation to each other needs to be considered when weighing up the desirable effects of a treatment against the undesirable effects.
Costs and resource implications	How large the requirements are in resource use of the intervention and the alternative. Costs: the value of the resources that are consumed (such as staff time, drugs and use of equipment) as the consequences of an intervention or option. Cost–effectiveness: the cost of a treatment in relation to its effects. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness is more likely to support a strong recommendation.
Equity	The absence of avoidable or remediable health differences among groups of people that may be defined socially, economically, demographically or geographically.
Acceptability	How much a treatment or recommendation is accepted by the people who are affected by it or who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. A great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted make a conditional recommendation more likely.
Feasibility	Is it feasible to implement an intervention and to sustain it? If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

1.5.4 External review

Members of the External Review Group were invited and selected to ensure geographical and gender balance, ensuring that members with a broad expertise in public health, programme management and community representation reviewed a draft of the guidelines for comments on validity, reliability and feasibility. An online format was used to compile comments and suggested revisions. This format enabled all external reviewers to see other comments from reviewers and agree or disagree to form consensus. All comments were then reviewed by by a relevant member of the WHO Guideline Steering Group. All comments received were recorded with subsequent action; indicating whether specific changes had been made to the guideline in response to the comments. The draft guideline was reviewed by members of the Guideline Development Groups and the Core Group.

1.6   Organization of the guidelines

1.6.1   Chapter contents

The structure of the guidelines is based on the continuum of HIV testing, prevention, treatment and care (Fig.1.1).

Fig. 1.1. Continuum of care and relevant sections of the guideline
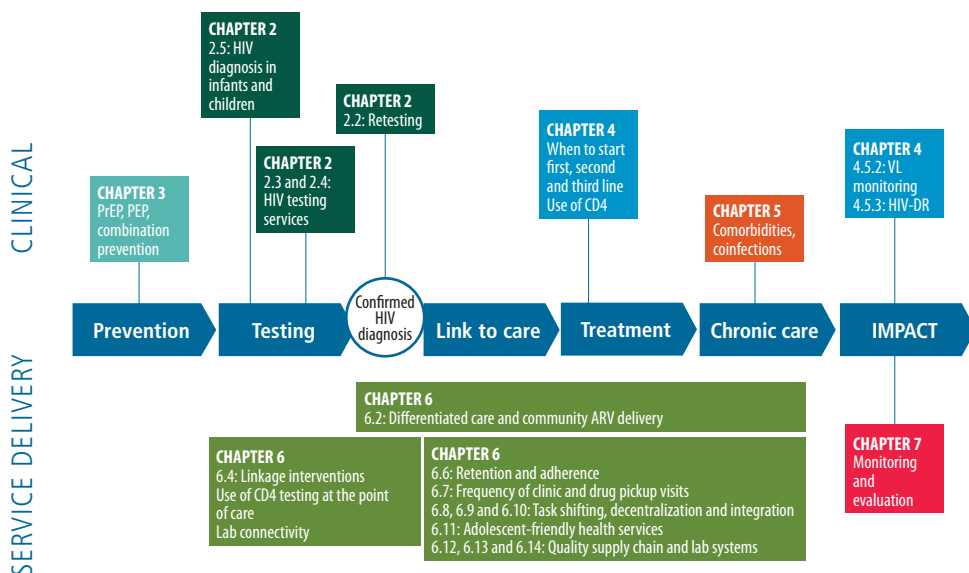
The chapters of the guidelines include the following information:

Chapter 2 discusses and summarizes existing WHO guidance on HIV testing services, including information to be provided during pre- and post-test counselling, approaches to service delivery and considerations for priority populations. Detailed analysis is provided of new evidence on HIV diagnosis in infants and children, together with new recommendations on the timing of and approaches to virological testing among infants and the use of new testing technologies.

Chapter 3 addresses the use of ARV drugs for HIV prevention. A new recommendation for 2015 is presented on the use of oral PrEP to prevent the acquisition of HIV. Existing recommendations on post-exposure prophylaxis are summarized and the importance of combination HIV prevention approaches is discussed.

Chapter 4 addresses ART for people living with HIV, including when to start treatment (first-line regimens for adults, adolescents and children) and what regimens to switch to (second- and third-line treatment). The chapter contains the new recommendations that all adults, adolescents and children should initiate ART regardless of CD4 cell count or

disease stage, including lifelong treatment for pregnant and breastfeeding women. Preferred first-line regimens for adults and adolescents include newly recommended options for a reduced dosage of efavirenz and, for the first time, use of the integrase inhibitor class of drugs. The evidence for the recommended approaches to first-line regimens for children up to three years of age and 3–10 years of age have also been reviewed. Revised recommendations are presented on options for second- and third-line ART for adults and children and infant ARV drug prophylaxis. Existing recommendations on timing of ART for people with TB and infant feeding by women living with HIV are summarized. The chapter includes new recommendations on stopping CD4 count testing where viral load testing is available and the use of new technologies for viral load testing and a detailed summary of guidance on managing toxicities related to ARV drugs and key ARV drug interactions.

Chapter 5 summarizes existing WHO guidance on the management of common coinfections and comorbidities associated with HIV, including the use of co-trimoxazole preventive therapy, TB case finding, treatment of active TB, and managing cryptococcal infection and viral hepatitis. The importance of assessing and managing the risk of noncommunicable diseases among people living with HIV is highlighted in two new recommendations on cardiovascular disease and depression.

Chapter 6 discusses key service delivery issues related to providing ART and supports the concept of differentiated care for people with advanced HIV disease and people who are stable on ART. Reducing the frequency of clinic visits and medication pickups for people who are stable on ART and more convenient and accessible approaches to distributing ARV drugs are newly recommended to reduce the growing burden on people receiving ART and health facilities. New recommendations are also provided to help to strengthen linkage to care following HIV diagnosis and long-term retention in care, including community-based approaches and measures to support adherence. Existing guidance on task shifting and integrating and decentralizing services is summarized. New guidance in this chapter emphasizes the importance of providing adolescent-friendly health services to meet the particular needs of adolescents.

Chapter 7 summarizes a range of recommended approaches to monitoring and evaluating programmes along the continuum of testing, prevention and care, including using recommended programme indicators and strategies to monitor ARV drug toxicity and ARV drug resistance.

Chapter 8 outlines how the guideline will be published and disseminated to stakeholders. Guidance on adoption and adaptation is given and reference made to tools to support implementation.

The **annexes** include algorithms, reference tables to support key recommendations and checklists and case studies to support country adaptation.

The **web supplements** present evidence-to-decision frameworks, summaries of evidence reviews, consultations and other relevant information collected in developing these guidelines.

1.6.2 Presentation of the recommendations

New recommendations developed in 2015 are highlighted and are typically presented in the following format to reflect the review of the evidence and other considerations by the Guideline Development Groups.

- **Recommendation.** The recommendation and the strength and quality of evidence assessed are stated.

- **Background.** Previous WHO guidance in this area and developments since the recommendations were last reviewed are described. When the recommendation relates to a specific population, key issues for that population may be briefly summarized.

- **Rationale and supporting evidence.** New evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation are summarized.

- **Implementation considerations.** Key implementation issues specific to the recommendation are discussed.

- **Research gaps.** Issues requiring further research are briefly described.

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CLINICAL GUIDELINES: HIV DIAGNOSIS

2

2 CLINICAL GUIDELINES: HIV DIAGNOSIS

2.1 Introduction

HIV testing is the gateway to HIV prevention, treatment, care and other support services. HIV testing services (HTS) refer to the full range of services that should be provided with HIV testing, including counselling (pre-test information and post-test counselling); linkage to appropriate HIV prevention, treatment and care, and other clinical services; and coordination with laboratory services to support quality assurance (QA) and the delivery of accurate results.

The overarching goals of HTS are as follows:

- to identify people with HIV through the provision of quality testing services for individuals, couples and families;
- to effectively link individuals and their families to HIV treatment, care and support, as well as HIV prevention services, based upon their status; and
- to support the scaling up of high-impact interventions to reduce HIV transmission and HIV-related morbidity and mortality.

The diagnosis of HIV includes testing services in health-care facilities, free-standing sites and a wide range of community-based approaches, as well as HIV self-testing (HIVST). These approaches are described in detail in the 2015 WHO *Consolidated guidelines on HIV testing services (1)*.

The use of HIV rapid diagnostic tests (RDTs) at the point of care has become an important strategy to expand access, increase the return of same-day results and enable immediate linkage and follow-up. Countries should choose a strategic mix of service delivery models to achieve equitable access to HIV testing services, based on the local context, nature of the epidemic, cost–effectiveness and available resources. The mix should facilitate diagnosis of as many people living with HIV as early as possible to enable timely enrolment in care and access to antiretroviral therapy (ART).

The WHO Five C's – consent, confidentiality, counselling, correct test results and connection to care and treatment – are principles that apply to all models of HTS and in all circumstances. The Five C's are as follows:

- **Consent**: People receiving HTS must give informed consent to be tested and counselled. Verbal consent is sufficient; written consent is not required. They should be informed of the process for HIV testing and counselling and of their right to decline testing.
- **Confidentiality**: HTS must be confidential, meaning that what the HTS provider and the client discuss will not be disclosed to anyone else without the expressed consent of

the person being tested. Confidentiality should be respected, but it should not be allowed to reinforce secrecy, stigma or shame. Shared confidentiality with a partner, family members, trusted other and a health-care provider is often highly beneficial.

- **Counselling**: Pre-test information can be provided in a group setting, but all people should have the opportunity to ask questions in a private setting if they request it. All HIV testing must be accompanied by appropriate and high-quality post-test counselling, based on the HIV test result and HIV status reported. QA mechanisms as well as supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.

- **Correct**: Providers of HIV testing should strive to provide high-quality testing services. Quality management systems (including QA) should be in place for all HTS, regardless of where testing takes place, to ensure that people receive a correct diagnosis. QA should include both internal and external measures, and should receive support from the national reference laboratory. All people who receive a positive HIV diagnosis should be retested to verify their diagnosis before initiation of HIV care or treatment.

- **Connection**: Linkage to prevention, treatment and care services should include effective and appropriate follow-up, including long-term prevention and treatment support.

All HTS should be provided using a validated national testing algorithm. Based on the HIV prevalence of the population being tested, the WHO-recommended testing strategy for either low prevalence or high prevalence should be utilized (*see* Annexes 6 and 7).

2.2   Retesting prior to enrolment in care

Recommendations

- National programmes should retest all people newly and previously diagnosed with HIV before they enrol in care and initiate ART.

- Retesting people on ART is not recommended, as there are potential risks of incorrect diagnosis, particularly for in vitro diagnostics (IVDs) that use oral fluid specimens.

Source: WHO reminds national programmes to retest all newly diagnosed people with HIV. WHO information note – 22 October 2014. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/vct/retest-newly-diagnosed-plhiv-full/en).

It is a priority to retest all people who are diagnosed to be HIV positive prior to enrolment in HIV care and/or treatment in order to verify their serostatus *(2)*. Failure to do this may lead, in rare cases, to people being diagnosed incorrectly, with potentially serious adverse long-term consequences.

Retesting a person diagnosed to be HIV positive to verify the diagnosis should include:

- retesting of a new specimen for each newly diagnosed individual, preferably conducted by a different provider using the same testing algorithm, prior to initiation of ART;

- retesting that is preferably conducted at a different site, ideally the site where the decision about ART initiation will be made.

Retesting aims to rule out possible technical or clerical errors, including specimen mix-up through mislabelling and transcription errors, as well as random error either by the provider or the test device. While retesting will not exclude misdiagnosis related to poor choice of a testing algorithm, this risk should be minimal with adequate validation of the testing algorithm.

Certain testing services, such as prevention of mother-to-child transmission (PMTCT) services providing ART for all pregnant and postpartum women living with HIV, are programmatically organized to conduct HIV testing, provide a diagnosis and offer immediate initiation of ART. In these programmes, it may not always be feasible to retest at a different site, although it should usually be feasible for a different provider to conduct retesting on a new specimen. If the HIV status is the same upon retesting, the person's HIV-positive status should be considered verified. If the status is not the same upon retesting, the person or their specimen should be referred for additional testing at a higher-level facility. Specific guidance on retesting in such settings can be found in the annex of the WHO *Consolidated guidelines on HIV testing services and technical guidance update on quality assurance for HIV rapid diagnostic tests* (http://apps.who. int/iris/bitstream/10665/181244/1/WHO_HIV_2015.28_eng.pdf?ua=1&ua=1).

Retesting people on ART is not recommended, as there are potential risks of incorrect diagnosis. The effect of ART in suppressing viral replication may extend to suppression of the immune response and therefore of antibody production. Once a person is started on ART, low antibody titres – particularly if oral fluid-based rapid diagnostic tests are used – make it challenging to discern whether an individual is indeed HIV positive *(3–5)*.

People undergoing HIV testing must be made aware of the risk of incorrect diagnosis if they do not disclose that they are on ART. All people receiving HIV testing should be asked if they have been tested previously and told that they are HIV infected and/or if they are now on ART or have ever received ART. WHO has published a meeting report on misdiagnosis (http://www.who.int/hiv/pub/meetingreports/hiv-misdiagnosis-report/en).

2.3   Pre- and post-test services

2.3.1 Overview

Receipt of a diagnosis of HIV should offer an opportunity to empower a person to make informed decisions about HIV prevention, treatment and care, which will affect both HIV transmission and his or her health. Linkage to appropriate services following diagnosis should be regarded as a key component of effective and comprehensive HTS (Fig. 2.1).

All HTS providers must remain committed to preserving confidentiality, one of the Five C's of HTS. Confidentiality applies not only to the test results and reports of HIV status but also to any other personal information, such as information concerning sexual behaviour and the use of illegal drugs. HTS should avoid practices that can inadvertently reveal a client's test results or HIV status to others in the waiting room or in the health facility.

Fig. 2.1. Continuum of linkage to care and prevention

Create **demand** for HIV testing and treatment → **Link** to HIV testing → **Deliver** pre-test information → HIV **diagnosis** → **Deliver** post-test counselling → Refer and **link** to other health services

ADDITIONAL TESTING NEEDED
- Test for triage
- Verify HIV-positive diagnosis

ELIGIBILITY ASSESSMENT

HIV-positive → Link to care / Link to prevention services → Link to ART → Adherence and viral suppression

HIV-negative → Link to prevention services

Recommendation

Initiatives should be put in place to enforce privacy protection and institute policy, laws and norms that prevent discrimination and promote the rights of people living with HIV. This can help create environments where disclosure of HIV status is easier (strong recommendation, low-quality evidence).

Source: Guideline on HIV disclosure counselling for children up to 12 years of age. Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/hiv_disclosure/en).

2.3.2 Pre-test services

Lengthy and intensive pre-test counselling and individual risk assessment are not advised, as they may create barriers to service delivery and require significant health-care worker time and resources, often with minimal benefit to clients. Depending on local conditions and resources, programmes may provide pre-test information through individual or group information sessions and through media such as posters, brochures, websites and short video clips shown in waiting rooms. When children and adolescents are receiving HTS, information should be presented in an age-appropriate manner to them and – as appropriate – their guardians, to ensure that it is understood *(6,7)*. Activities that may increase the demand for and utilization of HTS are described in the 2015 WHO *Consolidated guidelines for HIV testing services (1)*.

Pre-test information sessions for people receiving HIV testing should include clear information about:

- the benefits of HIV testing;
- the meaning of an HIV-positive and an HIV-negative test;

- the services available in the case of an HIV-positive diagnosis, including where ART is provided;

- a brief description of prevention options and encouragement of partner testing;

- the fact that the test result and any information shared by the client are confidential;

- the fact that the client has the right to refuse to be tested;

- potential risks to the client, especially for those whose sexual or other behaviour is stigmatized;

- an opportunity to ask the provider additional questions; and

- provision of informed consent for testing.

2.3.3 Post-test services

Post-test information and counselling for **people who test HIV negative** should include the following:

- an explanation of the test result;

- information on methods to prevent HIV acquisition and provision of male and/or female condoms, lubricant and guidance on their use;

- emphasis on the importance of knowing the status of sexual partners and information about the availability of partner and couples testing services;

- referral and linkage to relevant HIV prevention services, such as needle and syringe programmes, opioid substitution therapy for people who inject drugs, post-exposure prophylaxis, pre-exposure prophylaxis and, in priority countries, voluntary medical male circumcision (VMMC);

- advice to people who test negative but report recent risky behaviour to return in 4 weeks for repeat testing; if they again test HIV negative after 4 weeks, people with ongoing risk should be advised to return for testing every 6–12 months;

- encouragement of partner testing when pregnant women test HIV negative in high-prevalence settings, as incident HIV in pregnancy and during the postpartum period is associated with a high risk of mother-to-child transmission; and

- no requirement for repeat testing (window period) for people who report no recent risk.

Post-test information and counselling for **people who test HIV positive** should include the following:

- an explanation of the test result and diagnosis, giving the client time to consider the result and helping the client to cope with emotions arising from the diagnosis;

- discussion of immediate concerns and help for the client to decide who in his or her social network may be available to provide immediate support;

- assessment of the risk of intimate partner violence and discussion of possible steps to ensure the client's physical safety;

- assessment of the risk of suicide, depression and other mental health consequences of an HIV-positive diagnosis and referral to relevant services;

- clear information on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to access ART;

- arranging a specific date and time for active referral and follow-up of clients who are unable to enrol in HIV care on the day of diagnosis;

- information on how to prevent transmission of HIV, including information on the reduced transmission risks when virally suppressed on ART;

- provision of male or female condoms and lubricants and guidance on their use;

- discussion of the risks and benefits of disclosure, particularly among couples and to partners, and couples counselling should be offered to support mutual disclosure;

- encouragement and offer of HIV testing for sexual partners, children and other family members, which can be done individually, through couples testing, index case testing, family testing or partner notification;

- provision of or referral to prevention, counselling, support and other services as appropriate, including screening and treatment for tuberculosis (TB) and sexually transmitted infections (STIs), prophylaxis for opportunistic infections, contraception, antenatal care, opioid substitution therapy, and access to sterile needles and syringes; and

- offering time for the client to ask additional questions.

Absorbing all of this information in one session may be very challenging, and a follow-up session may be required. This may be necessary if the client wishes to bring a partner, family member or friend for counselling.

In addition to the information described above, counselling for **pregnant women whose test result is HIV positive** should include the following:

- discussion of childbirth plans and encouragement to deliver in a health facility for personal well-being and to ensure access to services for PMTCT;

- use of ARV drugs both for the client's health and to prevent transmission to the infant;

- the importance of partner testing and information on the availability of couples testing services;

- ensuring screening for TB and testing for other infections, such as syphilis and hepatitis B;

- counselling on maternal nutrition, including iron and folic acid, advice on infant-feeding options and support to carry out the mother's infant-feeding choice; and

- HIV testing for the infant and necessary follow up for HIV-exposed infants.

An **inconclusive test result** means that the first reactive test result was not confirmed after additional testing or that the first two test results are reactive but the third assay is non-reactive. All people with an inconclusive status should be encouraged to return in 14 days for additional testing *(1,8)*. Inconclusive results may be confusing and stressful for the individual or couple and may be difficult for the provider to explain. Most inconclusive results can be resolved by retesting after 14 days.

Intensified post-test counselling combined with follow-up counselling by community health workers may be needed for **key populations who test HIV positive**. People who inject drugs should be linked and referred to harm reduction, including opioid substitution therapy and needle and syringe programmes, where appropriate. Some people from key populations may lack social networks and/or a supportive family to help them deal with their diagnosis, and additional counselling and peer support may be needed.

In addition to standard messages for all people diagnosed with HIV, post-test counselling for **adolescents whose test result is HIV positive** should include the following:

• tailored advice with linkage to HIV care and treatment;

• counselling, referral and linkage to specific psychosocial and mental health services tailored to both the situation in which infection happened and the developmental age of the individual;

• information on adolescent rights and responsibilities, especially the right to confidentiality;

• counselling, referral and linkage to specific sexual and reproductive health services, including contraception, and an opportunity to ask questions and discuss issues related to sexuality;

• individualized planning on how, when and to whom to disclose the HIV status; and

• referral for group counselling and peer support groups.

2.4   Principles of and approaches to service delivery

2.4.1 Improving quality and efficiency

Several WHO-recommended health programming practices can improve the quality and efficiency of HTS in clinical and community settings. These practices include:

• integration of HTS with other health services;

• decentralization of HTS to primary health-care facilities and outside the health system; and

• task-sharing of HTS responsibilities to increase the role of trained lay providers.

Integration

WHO recommends the integration of HIV services, including HTS, with a range of other relevant clinical services, such as those for TB, maternal and child health, sexual and reproductive health, harm reduction programmes for people who inject drugs and, in priority countries, VMMC programmes. The primary purpose of such integration is to make HTS more convenient for people coming to health facilities for other reasons, and to increase the uptake of HIV testing. Integration is appropriate in all epidemic settings and is particularly important where HIV prevalence is high.

Decentralization

Decentralization of HTS may be appropriate in both high-prevalence and low-prevalence settings. For example, providing HIV testing in places closer to people's homes may reduce transportation costs and waiting times experienced in central hospitals and thereby increase uptake. Community-based testing has been endorsed by WHO and is widely practised *(9)*. Close collaboration between community programmes conducting HIV testing and nearby health facilities and health-care providers is likely to improve rates of early enrolment in care. Linkage for ART and care services should be provided as quickly as possible in all decentralized sites and programmes.

Decentralization of HTS may not always be appropriate or acceptable to potential users. In some settings, centralized HIV services may provide greater anonymity than neighbourhood services for key populations or others who fear stigma and discrimination. In some low-prevalence settings, decentralizing HTS may be inefficient and costly. Context, needs, service gaps and overall costs and benefits should be weighed to determine the extent and manner of decentralizing HTS.

Task-sharing

Many countries continue to face shortages of trained health workers. Task-sharing – the rational redistribution of tasks from cadres of health-care providers with longer training to cadres with shorter training – is a pragmatic response to health workforce shortages. It seeks to increase the effectiveness and efficiency of available personnel and thus enable the existing workforce to provide HTS to more people. WHO has recommended task-shifting in the health sector and now specifically recommends that trained and supervised lay providers provide HIV testing services, both in the community and in health facilities.

Recommendation

Lay providers who are trained and supervised can independently conduct safe and effective HIV testing using rapid diagnostic tests (RDTs) (strong recommendation, moderate-quality evidence).

Source: Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/).

2.4.2 HIV testing service approaches

WHO recommends a variety of facility-based and community-based approaches to delivering HTS. The 2015 WHO *Consolidated guidelines on HIV testing services* provide guidance on how to plan and decide which approaches to use.

Facility-based HIV testing services

Facility-based HIV testing services – often referred to as provider-initiated testing and counselling (PITC) – are those that are routinely offered in a health facility or by private medical practitioners. They may be offered in a range of clinical settings, depending on the type of epidemic, the population served and the capacity of the facility.

Recommendations

Generalized HIV epidemic

- PITC should be offered for all clients and in all services (including services for sexually transmitted infections (STI), viral hepatitis, tuberculosis (TB), children under the age of 5 years, immunization, malnutrition, antenatal care and all services for key populations) as an efficient and effective way to identify people with HIV.

Concentrated HIV epidemic

- PITC should be offered for clients (adults, adolescents and children) in clinical settings who present with symptoms or medical conditions that could indicate HIV infection, including presumed and confirmed TB cases.

Regardless of epidemic type

- PITC should be considered for malnutrition clinics, STI, hepatitis and TB services, ANC settings and health services for key populations.

- For TB settings, routine HIV testing should be offered to all clients with presumptive and diagnosed TB; partners of known HIV-positive TB patients should be offered voluntary HTS with support for mutual disclosure (strong recommendation, low-quality evidence in accordance with the recommendation for the partners of all people living with HIV, and TB control programmes should mainstream provision of HTS in their operations and routine services.

Sources:

Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva: World Health Organization; 2007 (http://www.who.int/hiv/pub/vct/pitc2007/en/).

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/).

Community-based HIV testing services

Community-based HTS have been widely implemented in some countries. This is an important approach to reach first-time testers and people who seldom use clinical services, including people from key populations in all settings. It also facilitates early diagnosis, especially in generalized epidemic settings *(10)*. Services may be offered in community sites such as community-based organizations, schools, workplaces and religious institutions. Mobile services can be provided through mobile vans or tents and in places of entertainment such as bars and clubs. In some settings, people with reactive results may need to be referred for confirmatory testing, sometimes known as "test for triage". More details on community-based services as well as test for triage may be found in the 2015 WHO *Consolidated guidelines on HIV testing services.*

Close collaboration is needed between community-based testing programmes and clinical facilities to ensure that all people who test reactive in community settings receive confirmed results from an appropriate clinical facility and to ensure that all people with confirmed HIV-positive results benefit from rapid and effective linkages to care and treatment.

Recommendations

Generalized HIV epidemic

- WHO recommends community-based HIV testing services with linkage to prevention, treatment and care services, in addition to routinely offering PITC for all populations, particularly key populations (strong recommendation, low-quality evidence).

Concentrated HIV epidemic

- WHO recommends community-based HIV testing services, with linkage to prevention, treatment and care, in addition to PITC for key populations (strong recommendation, low-quality evidence).

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en/).

HIV self-testing

HIVST is a process in which a person who wants to know his or her HIV status collects a specimen, performs a test and interprets the result by himself or herself, often in private. This emerging approach can extend HTS to people who may be unable or reluctant to attend existing HTS as well as to people who frequently retest *(1)*.

HIVST does not provide a definitive diagnosis. A reactive self-test result always requires additional testing according to a validated national diagnostic testing algorithm. A person who self-refers for ARV drugs after self-testing should be retested following the national algorithm, beginning with the first test. Following further testing, as with all other HIV testing, linkage and referral to onward prevention, treatment and care services are advised.

A provider distributing test kits for HIVST should advise anyone who has a non-reactive self-test result to retest if he or she has recent or ongoing HIV risk. Individuals with HIV who are on ART should be advised that self-testing may result in a false-negative test result, particularly when oral fluid-based rapid diagnostic testing is used. Facility- or community-based HTS are preferable for anyone who feels uncertain about or unable to correctly conduct a self-test procedure and read the test result. Mandatory or coercive HIV testing is never warranted *(11)*.

Countries considering the implementation of HIVST should conduct demonstration projects and weigh its potential risks and benefits. More detailed information on HIVST may be found in the 2015 WHO *Consolidated guidelines on HIV testing services*. WHO will provide updated guidance on this in late 2016.

2.5   HIV diagnosis in infants and children

2.5.1   Overview

Because mortality in the first year of life is very high among untreated HIV-infected infants, early HIV testing, prompt return of results and rapid initiation of treatment are essential *(12,13)*. In this population, HIV infection can be definitively confirmed only with virological testing using nucleic acid testing (NAT) technologies. This is because transplacentally transmitted maternal HIV antibody may persist in the child up to 18 months of age, preventing the use of serological testing to diagnose HIV infection *(14,15)*. Access to early infant diagnosis (EID) has improved significantly in recent years, but only 50% of all HIV-exposed infants were tested by the second month of age in 2014 *(16)*. For infants who are tested, delays in obtaining results and further losses in the testing-to-treatment cascade still occur, so that only 30% *(17)* of perinatally infected infants are effectively linked to services and started on ART in a timely manner. Innovative approaches such as the use of assays at point of care and adding a NAT at or around birth (0–2 days) can improve rapid identification and treatment initiation in infants *(18–20)*.

While EID is critical for minimizing early mortality, other opportunities for testing are also essential to capture HIV-infected infants and children who are infected postnatally or who were missed by EID services. In children older than 18 months of age, serological testing is used in the same manner as in adults following the nationally validated testing algorithm. As voluntary counselling and testing services are poorly utilized in paediatric populations, provider-initiated testing is essential to improve identification of children with HIV, especially those who are born to mothers who have not received interventions for PMTCT *(1)*.

Recommendations

- It is strongly recommended that HIV serological assays used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality-assured laboratory conditions (strong recommendation, moderate-quality evidence).

- It is strongly recommended that HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally more than 98%, and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions (strong recommendation, moderate-quality evidence).

- It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children below 18 months of age (strong recommendation, high-quality evidence).

- In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use: HIV DNA on whole blood specimen or DBS; HIV RNA on plasma or DBS; Us p24Ag on plasma or DBS (strong recommendation, high-quality evidence).

- It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter (strong recommendation, high-quality evidence).

- In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test (strong recommendation, high-quality evidence).

- It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/caregiver as soon as possible, but at the very latest within 4 weeks of specimen collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART (strong recommendation, high-quality evidence).

- It is strongly recommended that all infants with unknown or uncertain[a] HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4–6 weeks) or other child health visit have their HIV exposure status ascertained (strong recommendation, high-quality evidence).

- It is strongly recommended that HIV-exposed infants who are well undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Infants who have reactive serological assays at 9 months should have a virological test to identify HIV infection and the need for ART (strong recommendation, low-quality evidence).

[a] Unknown exposure: mother available but never tested for HIV. Uncertain exposure: mother dead, unable to test mother for HIV.

- It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing (strong recommendation, low-quality evidence).

- It is strongly recommended that children (18 months or older) with suspected HIV infection or HIV exposure have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults (strong recommendation, high-quality evidence).

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en).

WHO recommendations on the diagnosis of HIV infection in infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/hiv/pub/paediatric/diagnosis/en).

2.5.2 Timing of virological testing

Recommendation

NEW

Addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis (EID) testing approaches can be considered to identify HIV infection in HIV-exposed infants (conditional recommendation, low-quality evidence).

Background

Infants who have HIV detectable by NAT at birth are likely infected in utero, will progress to disease rapidly and, in the absence of treatment, experience high mortality in the first few months of life *(12,13,21,22)*. Infants infected at or around delivery may not have virus detectable by NAT for several days to weeks. The ability of NAT to detect virus in the blood may be affected by ARV drugs taken by the mother or infant for postnatal prophylaxis, resulting in false-negative results. This includes drug that is present in the breast-milk as a result of maternal ART during breastfeeding *(23,24)*. In addition, as HIV prevalence in the population decreases as a result of effective PMTCT interventions, the proportion of false-positive NAT results increases, underscoring the need to effectively confirm those identified as positive *(20)*. Finally, the ongoing risk of acquiring HIV during breastfeeding can delay final determination of HIV status beyond 18 months. For all of these reasons, identifying the optimal timing and frequency of infant testing is very challenging. Existing testing approaches have attempted to enhance programmatic simplicity and maximize uptake of testing by aligning timing of testing with the childhood immunization schedule. However, given the recent cost reduction of assays and the expansion of EID programmes, consideration can now be given to alternative testing approaches that maximize uptake, retention and timely treatment initiation while responding to changing epidemic and transmission dynamics *(20)*.

Rationale and supporting evidence

The optimal timing of virological testing to diagnose HIV infection in infants is determined by four factors: (1) when infection occurs (in utero, intrapartum or postpartum during breastfeeding); (2) the sensitivity and specificity, and predictive values of the assay being used; (3) mortality risk by age; and (4) retention in the testing-to-treatment cascade (20). Relevant evidence that informed this recommendation includes survival curves, available data on the testing-to-treatment cascade and a recent diagnostic accuracy review on the performance of NAT at birth (0–2 days) and at 4–6 weeks of age in the context of exposure to ARV drugs (25).

While concerns have been raised about the potential delay of HIV detection as a result of ARV exposure (23,24), there is currently no direct evidence to confirm that the performance of NAT on dried blood spots (DBS) at 4–6 weeks is lower in the context of ARV exposure (pooled sensitivity and specificity were 100% and 99.0% (95% CI, 98.2–99.9%). However, the quality of available evidence is low and more data on the performance of virological testing is urgently needed, particularly in the context of maternal ARV exposure and enhanced (prolonged and multidrug) infant postnatal prophylaxis. In light of the available evidence, the ability to detect both in utero and intrapartum infections and to remain aligned with the provision of routine maternal and child health services such as scheduled immunization visits and co-trimoxazole prophylaxis, the period of 4–6 weeks remains the critical point at which to provide virological testing, as recommended in existing testing strategies (Annex 8).

A diagnostic test accuracy review (25) was conducted to consider the addition of NAT at birth to detect perinatal HIV infection. Two studies were identified with overall sensitivity and specificity of 67.8% (95% CI, 60.9–74.8%) and 99.7% (95% CI, 99.4–100.0%) respectively, reflecting the difficulty of detecting intrapartum infections. Due to relatively poor sensitivity emerging from the currently available evidence, a single test of one NAT assay at birth is likely to miss a significant number of infections and should only be considered as an additional opportunity for testing rather than as a substitution for the existing approach of testing at 4–6 weeks.

Overall, there is insufficient empirical evidence to recommend universal inclusion of NAT at or around birth (0–2 days) as a way to improve patient and programme outcomes. Nevertheless, there are potential benefits of this approach, as it provides an additional opportunity for testing and enables earlier identification of infected infants in the context of poor scale-up of EID. Linkage of birth testing to prompt ART initiation and care has the potential to reduce early mortality and morbidity observed in infants who are infected in utero and for whom disease progression is faster. From a programmatic perspective, there are potential advantages – but a lack of experience – with adding NAT at birth (0–2 days) and uncertainty around the clinical benefits and potential difficulties of treatment from birth, as well as the potential complexity and cost of adding an additional test in a new service delivery point. There are also challenges associated with starting treatment in newborns and pre-term infants, given currently available ARV drugs for this age group (*see* section 4.3.4 and Annex 11c, Table 4).

Focus group discussions (26) with a total of 105 women living with HIV from Kenya, Namibia and Nigeria suggest that earlier infant testing could be acceptable, given that mothers are motivated to diagnose HIV infection earlier and avoid disease progression in the infant. However, there are also concerns about the potential lack of understanding

regarding the need to retest infants with negative NAT and the associated loss to follow-up. There is also the potential emotional overload for women immediately after giving birth and the challenge of preserving confidentiality in the presence of family, partners and others in labour wards. Overall, women in the focus groups showed some reluctance to accept routine virological testing at birth and were more in favour of having a range of options from which to choose.

Model-based analysis *(27)* supports optimizing 6-week testing prior to adding NAT at birth. In addition, it suggests that under the ideal scenario of full uptake and retention (100% of HIV-exposed infants being tested and retained in the testing-to-treatment cascade), a two-NAT strategy, with the first test at birth and the second test after 6 weeks of age, improves survival compared to a single test at 6 weeks. Any testing programme, whether at birth or 6 weeks, must have a mechanism to return test results promptly and link HIV-infected infants to care and ART. Using programmatic, clinical and cost data from South Africa over the lifetime of HIV-exposed infants, the modelling found that a programme of birth and 6-week testing could be very cost–effective in settings similar to South Africa. The model confirmed that false-positive results may be common (about 30 positive results out of 100 may be falsely positive), even with relatively high assay specificity (98.0–99.0%), especially where the risks of mother-to-child transmission are low (i.e. less than 2% at 6 weeks). To minimize toxicity, stigma and costs for uninfected infants with false-positive results, confirmatory testing is critical.

In light of the risks, benefits, possible acceptability and potential cost–effectiveness, the addition of NAT at or around birth (0–2 days) can be considered where feasible, but only in parallel with efforts to strengthen and expand existing EID testing approaches. Existing recommendations that infants with an initial positive virological test result should start ART without delay remain important. At the same time, a second specimen should be collected to confirm the initial positive virological test result. Immediate initiation of ART saves lives and should not be delayed pending the results of the confirmatory test.

Implementation considerations

As EID programmes are further scaled up, every effort should be made to improve uptake of NAT at 4–6 weeks, strengthen retention along the testing-to-treatment cascade, ensure confirmation of NAT-positive results with a second sample and ensure that infants who test negative by NAT are retained in care until a final diagnosis is made. Where consideration is being given to adding NAT at birth, effective linkage to maternal HIV screening at the time of delivery should be ensured and the following steps should be taken:

• collection of data on performance and feasibility of birth testing during implementation;

• improvement of uptake and retention in the testing-to-treatment cascade;

• active tracking of infants with negative NAT at birth to ensure that they return at 6 weeks for retesting and co-trimoxazole initiation; and

• retesting of infants who test positive at birth with a second specimen as soon as possible. ART should be started immediately after the first positive test, and if the second specimen tests negative, a third NAT should be performed before interrupting ART.

In settings where transmission risk is low (<5% at 6 weeks) as a result of good coverage of interventions to prevent mother-to-child transmission, adding birth testing may be considered, as up to 70% of the small number of residual perinatal transmissions (intrauterine and intrapartum) are expected to occur in utero *(28)*. However, as the positive predictive value of any test is lower in settings where the prevalence of HIV in the population being tested is low, the proportion of false-positive results will be relatively high. It will therefore be critical to ensure retesting of any positive result, as recommended for all positive results, by polymerase chain reaction (PCR). ART should be initiated without waiting for receipt of the second test result because of the high risk of mortality with in utero infection; if the second specimen tests negative, a third NAT should be performed before interrupting ART. In settings with low transmission risk, a large number of infants will need to be tested to identify one infected infant (about 27:1). Available resources and funding priorities will therefore need to be taken into account *(29)*.

In settings where transmission risk is high (>5% at 6 weeks) as a result of poor coverage of interventions to prevent mother-to-child transmission, the proportion of children with *in utero* infection is lower, but the overall number of infants with HIV infection will be substantially higher. Birth testing can therefore have a high yield at the first test (low number of tests per infant identified, approximately 4:1). However, the negative predictive value of the test for perinatal (intrauterine and intrapartum) infection in a setting with high transmission risk is low. It is therefore particularly critical to ensure retention in the testing cascade and actively track infants who test NAT negative at birth *(29)* (Table 2.1).

Table 2.1. Implications of adding NAT at birth: expected number of tests to be undertaken per infant identified and expected number of false-positive results based on NAT performance and transmission rates *(29)*

	NAT at 6 weeks	NAT at birth AND 6 weeks
No PMTCT (expected 30% transmission by 6 weeks – 1/3 IU, 2/3 IP)[a]	HIV-positive women: 5 000 HIV-infected infants: 1 500 Total NAT to undertake: 6 535 tests **Tests per positive infant identified: 4.36** **Per 100 infants testing positive on first NAT: 2 false positives**	HIV-positive women: 5 000 HIV-infected infants: 1 500 Total NAT to undertake: 11 035 tests **Tests per positive infant identified: 7.36** **Per 100 infants testing positive on first NAT: 4 false positives**
PMTCT (expected 5% transmission by 6 weeks – 2/3 IU, 1/3 IP)[a]	HIV-positive women: 5 000 HIV-infected infants: 250 Total NAT to undertake: 5 297 tests **Tests per positive infant identified: 21.2** **Per 100 infants testing positive on first NAT: 16 false positives**	HIV-positive women: 5 000 HIV-infected infants: 250 Total NAT to undertake: 10 130 tests **Tests per positive infant identified: 40.5** **Per 100 infants testing positive on first NAT: 27 false positives**

[a]   When highly effective PMTCT interventions are used, up to 75% (2/3) of the small number of residual perinatal transmissions (intrauterine=IU and intrapartum=IP) are expected to occur in utero *(28)*. This is in contrast to the natural history of mother-to-child HIV transmission, as without any PMTCT intervention, the majority of infections are known to occur intrapartum.

2.5.3 Point-of-care technologies for the diagnosis of HIV infection in infants and children

Point-of-care early infant diagnosis

NEW

Recommendation

Nucleic acid testing (NAT) technologies that are developed and validated for use at or near to the point of care can be used for early infant HIV testing (conditional recommendation, low-quality evidence).

Background

Virology assays are designed to detect either viral nucleic acid (HIV DNA, RNA or total nucleic acid) or ultrasensitive p24 antigen (Us p24 Ag). Currently, qualitative detection of HIV DNA or RNA by NAT is most commonly performed on venous and/or capillary blood prepared as DBS specimens on filter paper, with specimens collected and prepared at local health facilities and transported for testing at centralized laboratories. Innovations such as NAT technologies that can be used at or near the point of care offer potential solutions to address gaps in laboratory-based testing services, including same-day results that may contribute to testing uptake and enable better linkage to care. The clinical value of point-of-care EID may be greatest where long turnaround times for laboratory results are associated with loss to follow up of mother–infant pairs and increased infant mortality *(19)*.

Rationale and supporting evidence

A diagnostic test accuracy review *(30)* was conducted to assess the performance of point-of-care EID technologies compared to gold standard laboratory-based NAT. Three studies evaluated virological testing with two point-of-care reverse-transcriptase (RT)-PCR platforms *(31–33)*. All studies were conducted in sub-Saharan Africa: one in a local field setting and two in which samples were sent for testing to a laboratory. The overall sensitivity and specificity were 97.8% (95% CI 96.0–98.8%) and 99.9% (95% CI 99.5–100.0%), respectively. The studies were limited by the fact that none used commercially available assays or versions of the assay that had received stringent regulatory approval. Only two of the studies were conducted independently of the testing platform's manufacturer *(31,32)* and, while point-of-care EID platforms have been shown to be highly accurate, the index test in all studies was often performed in laboratory conditions and not under typical field settings where performance may be poorer. There are also no data available on the performance of these assays at birth.

The anticipated benefits of point-of-care EID are substantial, including fast turnaround time, fewer losses in the testing cascade, relative portability and the potential for task-shifting from reference laboratories to clinics and less sophisticated laboratories. Equity of access in remote and rural areas could be enhanced. This approach also offers versatility of use through the potential inclusion of tests such as HIV viral load and TB diagnostics, which could facilitate programme integration. However, there are potential risks associated with the slight loss of sensitivity compared to laboratory-based testing,

error rates that may require the collection of additional heel prick samples and the low throughput for most devices. Some platforms are not suitable for use at primary health-care facilities and would be more appropriate for district laboratory settings due to the level of skill required to operate the equipment and the need for electrical power.

Experience with point-of-care CD4 testing suggests that the introduction of point-of-care EID could be widely implementable and well accepted by patients and health-care providers compared to laboratory-based testing *(33–35)*. Point-of-care CD4 testing has also demonstrated the feasibility of task-shifting from laboratories to clinicians and laypeople.

Even with slightly lower sensitivity, point-of-care assays for EID offer the potential for quick turnaround of results and clinical benefits for HIV-infected infants compared to laboratory-based NAT assays and are expected to be cost–effective in many settings *(27)*. Similar results have been obtained regardless of whether the first assay conducted at the point of care is confirmed with a laboratory-based NAT or a second NAT at the point of care, provided that rates of returning results are high when either assay is used.

Despite limited experience with this technology to date, the potential operational advantages and anticipated positive impact of scaling up EID at the point of care favour the use of point-of-care EID for diagnosis of HIV in infants, together with a second test to confirm a positive result, as for any NAT. The advantages include reduced turnaround time, faster treatment initiation and improved retention in the testing-to-treatment cascade.

Implementation considerations

There is very little programme experience to date with implementing point-of-care EID testing. Practical considerations, such as how to ensure quality control, how to confirm an initial HIV NAT-detectable test result, when to start ART after a positive point-of-care test and how to ensure that point-of-care tests are captured in the national EID database, will all have to be addressed through targeted implementation research and lessons from programmatic experience. Point-of-care EID is expected to complement and enhance conventional testing approaches by offering a flexible and faster testing approach that could be implemented by non-laboratory staff *(36)*. Decentralization of ART or strengthening of referral systems for ART initiation will be of critical importance to ensure that the reduction in the turnaround time for results translates into impact on infant outcomes.

Rapid diagnostic tests for HIV serology

Recommendations

Rapid diagnostic tests (RDTs) for HIV serology can be used to assess HIV exposure only in infants less than 4 months of age. HIV-exposure status in infants and children 4–18 months of age should be ascertained by undertaking HIV serological testing in the mother (conditional recommendation, low-quality evidence).

Rapid diagnostic tests for HIV serology can be used at 9 months to rule out HIV infection in asymptomatic HIV-exposed infants (conditional recommendation, low-quality evidence).

Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection in children older than 18 months following the national testing strategy (strong recommendation, moderate-quality evidence).

Background

WHO recommends the use of serological assays to diagnose HIV in children older than 18 months and to ascertain exposure in young infants and children below 18 months of age. Use of serological assays has also been recommended at 9 months of age to rule out established infection in HIV-exposed infants who are well *(37)*.

Children who are started on ART as early as 3–6 months of age are unlikely to develop antibody response to the virus and may falsely test HIV negative using a serological assay. Antibody testing should therefore not be used to confirm or rule out infection in children who are already receiving ART *(38–40)*.

HIV antibody assays reliably detect HIV antibodies in children but cannot distinguish persisting maternal HIV antibody from antibodies produced by the child. A positive HIV antibody test in infants and children less than 18 months of age therefore confirms exposure to HIV but cannot definitively diagnose infection. In contrast, the presence of HIV antibodies is a quick and reliable means of definitively diagnosing HIV infection in children older than 18 months because maternal HIV antibodies are usually no longer detectable. Current WHO guidelines recommend the use of HIV antibody testing with a minimum sensitivity of 99% and minimum specificity of 98% *(41)*.

RDTs with performance comparable to that of traditional laboratory-based serological assays are commercially available. These assays may be particularly appropriate for use in resource-limited settings, as they can be performed in clinic or community settings with minimal infrastructure. However, some concerns exist about the performance of RDTs, particularly with regard to their ability to determine exposure and effectively exclude HIV infection at different ages *(41)*.

Rationale and supporting evidence

Assessing HIV exposure in infants and children younger than 18 months

A diagnostic test accuracy review was conducted to explore the performance of RDTs as serological assays to assess HIV exposure and HIV diagnosis at different points in time *(42)*. The four studies identified showed that the diagnostic accuracy of current commercially available RDTs corresponded closely with the reference standard (enzyme-linked immunosorbent assay [ELISA]) in infants aged 0–3 months, when maternal antibody is detectable, with an average sensitivity of 95.4% (95% CI: 89.3–98.1%) and an average specificity of 99.7% (95% CI: 92.2–100.0%). RDT assay performance after 4 months was lower, with average sensitivity for identifying HIV exposure dropping to 51.9% (95% CI: 40.9–62.8%); this is likely to be the result of waning maternal antibodies.

Although RDTs have significant potential for increasing access to and uptake of HIV testing, including in rural and remote areas, the available evidence suggests that there is a potentially high risk that these tests will not capture HIV-exposed infants older than 4 months of age. Testing of mothers is the best way to ascertain exposure and should be prioritized whenever possible. When testing mothers is not possible, RDT can be used reliably to ascertain HIV exposure in infants younger than 4 months of age. By contrast, when RDT is used in infants and children 4–18 months of age, a negative result should not be considered as a definitive exclusion of HIV exposure, and retesting should be undertaken at 18 months. If a child younger than 18 months is sick and the mother is not available for exposure to be assessed, a NAT should be performed regardless of the RDT result (Table 2.2).

Ruling out HIV infection at nine months in HIV-exposed infants

Provision of serological testing at 9 months has been recommended as a way to rule out HIV infection and to more rapidly obtain a final diagnosis for those HIV-exposed infants who are not breastfed, as opposed to waiting until the child reaches 18 months of age. However, concerns exist about the performance of RDTs as serological tests to rule out HIV infection in infants with known HIV exposure. Evidence for the diagnostic accuracy of RDTs to assess HIV infection in infants and children was gathered from 11 studies, all of which provide results for commercially available assays *(42)*. Diagnostic accuracy was found to be poor in infants aged 0–9 months when the presence of maternal antibodies in infants leads to a high rate of false-positive results. Averaged across all assays at 7–9 months of age, the sensitivity was 94.2% (95% CI: 83.2–98.2%), with an average specificity of 81.2% (95% CI: 61.1–92.2%). When the analysis was restricted to known HIV-exposed infants, the sensitivity further improved (99.8%; 95% CI: 99.5–100.0%), indicating a very low risk for false-negative results. In light of the very low risk for false-negative results, particularly when considering known HIV-exposed infants, RDTs can be used at 9 months as a serological test to exclude established HIV infection. However, infants who are still breastfeeding and therefore remain at risk for HIV acquisition will require an age-appropriate testing strategy at the end of the breastfeeding period to definitively exclude HIV infection and determine final HIV status. HIV-exposed infants with a positive RDT at or after 9 months should receive NAT to confirm the diagnosis of HIV. If NAT is positive, ART should be initiated promptly until the result of a second NAT confirms the diagnosis. If the second NAT is negative, HIV infection is ruled out unless the child is still being still breastfed, in which case retesting at the end of breastfeeding is required for final determination of HIV status.

Table 2.2. Use of RDT for HIV serology based on age, exposure status and breastfeeding practice

Age group	Known HIV exposed	Unknown HIV exposure status and breastfeeding	Unknown HIV exposure status and not breastfeeding[a]
0–4 months	Not useful, as exposure is known and RDT cannot determine infection status	**Test mother** If mother is not available, RDT in the child can reliably assess exposure.	**Test mother** If mother is not available, RDT in the child reliably determines exposure.
5–8 months	Not useful, as exposure is known and RDT cannot determine infection status at this age	**Test mother** If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. Infants with positive RDT will still need NAT to confirm infection. Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding. If sick and mother is not available, perform NAT directly to assess HIV infection status.	**Test mother** If mother is not available, RDT for the child does not fully rule out exposure. If sick and mother is not available, perform NAT directly to assess HIV infection status.
9–18 months	RDT useful to rule out established HIV infection Infants with *positive* RDT will still need NAT to confirm infection. Infants with *negative* RDT who are still breastfeeding will need NAT at the end of breastfeeding.	**Test mother** If mother is not available, a positive RDT establishes exposure, but a negative RDT does not fully rule it out. Infants with positive RDT will still need NAT to confirm infection. RDT useful to rule out established HIV infection. Infants with positive RDT will still need NAT to confirm infection. Infants with negative RDT who are still breastfeeding will need NAT at the end of breastfeeding. If sick and mother is not available, perform NAT directly to assess HIV infection status.[b]	**Test mother** If mother is not available, RDT in the child does not fully rule out exposure. RDT is useful to rule out established HIV infection. • Infants with positive RDT will still need NAT to confirm infection. • Infants with negative RDT who are not breastfeeding can be considered uninfected. If sick and mother is not available, perform NAT directly to assess HIV infection status.
>18 months	Serological testing (including RDT) is recommended to assess HIV infection status unless still breastfed. If still breastfed, serological testing (including RDT) should be provided 3 months after cessation of breastfeeding.		

[a] Not breastfed for at least 12 weeks before testing.

[b] Consider initiating ART for presumed HIV infection if there is high degree of suspicion while waiting for NAT results, especially if RDT positive.

HIV diagnosis in children older than 18 months

Five relevant studies showed that diagnostic accuracy in children older than 18 months using currently available commercial assays met existing WHO predefined standards for serology with an average sensitivity of 97.6% (95% CI: 89.7–99.5%) and average specificity of 99.1% (95% CI: 97.7–99.7%) *(33)*. The risk of a false-negative or false-positive result is likely to be limited and outweighed by the potential increase in uptake of testing, particularly when following the national validated testing algorithms used for adults.

Implementation considerations for the use of RDTs in infants and children

Overall, the use of RDTs for infants and children will make HIV testing available in rural and remote areas. While formal assessment of the cost implications is not available, RDTs are less expensive than serological laboratory-based assays (taking into account the total cost of testing, rather than the cost of tests alone) and likely to be cost–effective, as suggested by similar analyses conducted in the adult population *(43)* and on the use of RDTs to screen for syphilis and malaria *(44–46)*.

2.5.4 Provider-initiated HIV testing and counselling for infants and children

NEW

Recommendations

In generalized epidemic settings, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV (strong recommendation, low-quality evidence).

In generalized epidemic settings, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics (conditional recommendation, low-quality evidence).

NEW

Good practice statement

In all settings, children with a parent living with HIV should be routinely offered HIV testing and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention.

Background

Access to EID is for the most part limited to infants who are born to mothers enrolled and retained in PMTCT programmes. In these women, vertical transmission rates are generally very low, so the majority of infants who receive EID will test negative. By contrast, mothers who receive inadequate or no PMTCT interventions will have much higher transmission rates, and yet their infants are unlikely to be tested and identified as

HIV infected. This contributes to the large gap between coverage of and need for ART among children and persistently high paediatric HIV-related mortality. Previous WHO guidelines have emphasized the importance of case finding and testing outside of PMTCT programmes in order to identify children who did not benefit from PMTCT interventions, but for a variety of reasons, PITC for children has not been optimally implemented *(20)*.

Rationale and supporting evidence

A systematic review was undertaken to compare the standard approach of testing infants and children in PMTCT programmes with testing in a range of clinical settings outside PMTCT programmes *(47)*. The primary outcomes examined were yield of testing in terms of the HIV seropositivity rate and acceptability by caregivers. The objective was to provide additional evidence to reinforce and contextualize guidance on testing children for HIV.

No studies directly compared the yield of testing within PMTCT programmes with testing outside of those programmes. However, 24 studies were identified that reported on the yield of PITC for children under 5 years of age in a variety of settings, including inpatient, outpatient, nutritional rehabilitation centres and immunization clinics. Twenty-two of the 24 studies were conducted in sub-Saharan Africa and 18 of 22 were in high HIV-prevalence (>5%) settings. One study provided data for both outpatient and immunization clinics *(41)*, but the remainder assessed yield in only one setting (inpatient 16, outpatient 2, nutrition centres 3 and immunization clinics 2).

A third of the studies were conducted during or after 2013 when WHO issued guidance for the use of triple-drug ART for all pregnant and breastfeeding women (option B or B+). The yield of positive test results was very high in paediatric inpatient settings (22.5%, 95% CI 16.0–29.0%) and high in nutrition centres (14.2%, 95% CI 2.3–26.1%). Rates were lower in immunization clinics and outpatient settings, at 3.3% (95% CI 0–6.9%) and 2.7% (95% CI 0.3–5.2%), respectively. Positivity rates varied significantly by geographical region. Across 18 studies in eastern and southern Africa, the prevalence was 22.6% (95% CI 17.2–28.0%), whereas in four studies conducted in western and central Africa (where population HIV prevalence is lower), prevalence was less than half, at 9.7% (95% CI 2.2–17.2%). There were too few studies from Asia and Oceania to perform a subanalysis.

A total of eight studies were identified that utilized a universal testing approach in paediatric inpatient settings; these were compared with eight studies that used an assessment of symptoms approach to determine which children to test. Although symptom-based testing approaches showed a slightly higher yield of positive results, (23.1%, 95% CI 14.9–31.3% versus 21.9%, 95% CI 12.4–31.4%), this difference was not statistically significant.

Data from countries with a lower prevalence were limited, but one study from western Africa reported a positivity rate of 25% in nutritional centres *(49)*, suggesting that if coverage with maternal ARV drugs used to prevent mother-to-child transmission is poor, the yield of paediatric PITC in selected settings may be high, even when overall HIV prevalence in the country is low. Unpublished data from Ethiopia suggest that prevalence rates among children – even in inpatient settings – have declined significantly over the past 10 years, but remained consistently high at more than 5% among children of index clients (Tsague T, UNICEF, personal communication, June 2015).

There are no reports on the cost–effectiveness of testing children for HIV in specific paediatric health-care settings. Integrating HIV services (including HIV testing) into other health programmes has been found to be generally cost-effective, but the cost–effectiveness of PITC for children (especially in immunization programmes and outpatient clinics where the yield of positive results is likely to be lower) will depend on factors such as maternal prevalence and the coverage of PMTCT *(50)*. In settings where maternal prevalence is high and the level of PMTCT coverage is low, it is likely that testing infants and children will be a highly cost–effective strategy to prevent HIV-associated mortality. Moreover, PITC during infancy may identify infants who are exposed to HIV with detectable antibodies but are not yet infected, providing an opportunity to prevent transmission during breastfeeding.

Of the 24 studies assessed in the systematic review, 13 reported on caregiver acceptance rates of paediatric HIV testing. Acceptance rates varied by location of testing as well as by region, but the overall mean acceptance rate was high, at 92.2% (range 73–100%). The majority of caregivers surveyed were motivated to accept testing by a desire to know the child's HIV status (78.1%). A small minority (4.9%) reported being influenced by other parents whose children had been tested. In a study in South Africa to inform the acceptability and feasibility of routine HIV testing in immunization clinics, just over half of all eligible children and caregivers accepted HIV testing *(51)*. The Guideline Development Group made a strong recommendation to provide routine HIV testing for infants and children admitted for inpatient care or attending malnutrition clinics, citing existing vast programme experience and testing yield, along with high levels of feasibility and acceptability, despite the low-quality evidence.

Implementation considerations

Despite the fact that the guidance for active case-finding and PITC in children has been in place since 2007, uptake of this recommendation has been poor. Issues around the legal age of consent and provider discomfort with disclosure have contributed to this lack of uptake, especially for adolescents and older children. A recent study in six primary clinics in Zimbabwe identified a number of other factors, including a perceived lack of importance attached to testing older children and a sense that testing was not warranted if children were asymptomatic *(52)*. Lack of time and reagents, and discomfort with approaching male caregivers, were also noted as reasons for not testing. At the same time, a WHO survey of health workers, policy-makers and programme managers from 17 countries found that almost half of all respondents felt that testing children in immunization clinics would either be easy or very easy to do, suggesting that this policy is highly feasible to implement. Experience from countries that have been trying to roll out paediatric PITC highlights the importance of thorough linkage to care and services for children who are exposed or infected. Linkage to care may be easier for children in inpatient settings than for those in busy outpatient clinics. The negative impact of HIV testing on uptake of other essential childhood interventions, such as immunization, has been cited as an argument against integration of testing in immunization clinics *(53)*. A study in the United Republic of Tanzania showed that, while integration of HIV testing resulted in an increase in immunization rates in urban centres, there was a decrease in rural facilities, possibly reflecting higher levels of stigma in rural communities *(54)*.

Research gaps

A number of critical research gaps need to be addressed to fully inform implementation of infant testing strategies. The optimal timing for the first virological test to diagnose HIV in HIV-exposed infants requires further investigation in the context of broader exposure to maternal ART and multidrug postnatal prophylaxis. Similarly, more experience and data are needed to assess the impact of adding virological testing at birth on the successful initiation of newborn ART, infant outcomes and uptake of virological testing at 6 weeks. The feasibility and acceptability of virological testing at birth also need to be further explored in the context of national programmes at different prevalence settings and in different epidemic contexts.

Field evaluations of commercially available point-of-care technologies are also needed to confirm the accuracy of results and the strategic placement of this technology within national programmes. In addition, further investigations are required to assess the impact of using point-of-care EID on patient management, treatment and infant outcomes. The frequency of testing during breastfeeding and weaning should be explored to enhance early diagnosis in this period.

2.6   Other priority populations

2.6.1   Adolescents

In high-prevalence settings there are two groups of adolescents (aged 10–19 years of age) who need access to HIV testing: (1) perinatally HIV-infected adolescents who were not diagnosed in infancy or earlier in childhood; and (2) adolescents who acquire HIV through sex or injecting drug use, particularly people from key populations. WHO has issued specific guidance on delivering HIV testing services to adolescents *(7)*.

Recommendations

- HIV testing services, with linkages to prevention, treatment and care, should be offered for adolescents from key populations in all settings (strong recommendation, very low-quality evidence).

- Adolescents with HIV should be counselled about the potential benefits and risks of disclosure of their HIV status, and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very low-quality evidence).

Generalized HIV epidemic

- HIV testing services with linkage to prevention, treatment and care should be offered to all adolescents in generalized epidemics (strong recommendation, very low-quality evidence).

Concentrated HIV epidemic

• HIV testing services with linkage to prevention, treatment and care should be *accessible* to adolescents in low-level and concentrated epidemics (conditional recommendation, very low-quality evidence).

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

2.6.2 Pregnant women

WHO has published detailed guidance on HIV testing for pregnant women in both high- and low-prevalence settings *(1)*. Identifying HIV-positive pregnant women and promptly enrolling them in treatment has benefits for the woman, the infant and the woman's sexual partner. Testing of pregnant women is one of the most successful examples of population-based provider-initiated testing, with many high-burden countries now reporting uptake rates above 90% *(55)*. Routine offer of HIV testing at the first ANC visit has been critical to the roll-out of universal ART for all pregnant women living with HIV (option B+) and the resultant significant reduction in new infections in children.

Recommendations

High-prevalence settings

• PITC for women should be considered a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings. In such settings, where breastfeeding is the norm, lactating mothers who are HIV negative should be retested periodically throughout the period of breastfeeding.

• All HIV-negative pregnant women should be retested in the third trimester, postpartum and/or during labour, because of the high risk of acquiring HIV during pregnancy.

Low-prevalence settings

• PITC can be considered for pregnant women in antenatal care as a key component of the effort:
  – to eliminate mother-to-child transmission of HIV
  – to integrate HIV testing with other key testing (for viral hepatitis, syphilis etc.) as relevant to the setting
  – to retest HIV negative pregnant women who are in a serodiscordant couple, from a key population group or have known ongoing HIV risk.

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Delivering HIV test results and messages for re-testing and counselling in adults. Geneva: World Health Organization; 2010 (http://www.who.int/hiv/pub/vct/hiv_re_testing/en/index.htm).

2.6.3 Couples and partners

The partners and family members (including children) of all people enrolled in HIV care and treatment should be offered HIV testing. There is considerable evidence that many people living with HIV) For TB settings, routine HIV testing should be offered to all clients with presumptive and diagnosed TB; partners of known HIV-positive TB patients should be offered voluntary HTS with support for mutual disclosure (strong recommendation, low-quality evidence in accordance with the recommendation for the partners of all people living with HIV), and TB control programmes should mainstream provision of HTS in their operations and routine services., including those on ART, have an uninfected partner; these couples are called serodiscordant couples. WHO has published detailed guidance on serving serodiscordant couples and couples where both are infected and in need of treatment *(56)*.

Recommendations

- Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure. This applies also to couples and partners from key populations (strong recommendation, low-quality evidence).

- In antenatal care settings, couples and partners should be offered voluntary HIV testing services with support for mutual disclosure (strong recommendation, low-quality evidence).

- HIV testing services for couples and partners, with support for mutual disclosure, should be offered to individuals with known HIV status and their partners (strong recommendation, low-quality evidence for all people with HIV in all epidemic settings; conditional recommendation, low-quality evidence for HIV-negative people depending on the country-specific HIV prevalence).

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/).

Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples. Geneva: World Health Organization; 2012 (http://www.who.int/hiv/pub/guidelines/9789241501972/en/index.html).

2.6.4 Men

In high-prevalence settings, fewer men than women report ever testing for HIV. As a result, men are more likely to start ART at later stages of HIV disease. Barriers to men accessing HIV testing include fear, stigma, the perception that health facilities are spaces for women and both the direct costs and opportunity costs of accessing services. Greater emphasis is needed on reaching men with both HIV testing services and linkages to care and treatment.

2.6.5 Key populations

Recommendations

- HIV testing services should be routinely offered to all key populations in the community, in closed settings such as prisons and in facility-based settings.

- Community-based HIV testing services for key populations linked to prevention, treatment and care services are recommended, in addition to routine facility-based HIV testing services, in all settings (strong recommendation, low-quality evidence).

Source: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en/).

In most settings, the incidence of HIV is high in key populations, and they frequently have limited access to HIV services, including testing and ART. They need tailored approaches to and messages for HIV testing.

Health-care workers should receive appropriate and recurrent training and sensitization to ensure that they have the skills and understanding to provide services for adults and adolescents from key populations. Health-care workers should respect the rights of all people to health, confidentiality and non-discrimination. Links with key population networks and community-based organizations to support or provide HTS – including services delivered by peers – may increase reach, uptake and acceptability of HTS in these populations.

2.7 Diagnostics

Detailed guidance on appropriate HIV testing strategies for different epidemic types and settings is available in the 2015 WHO *Consolidated guidelines on HIV testing services.* All sites and facilities providing HIV testing services should participate in QA programmes. QA implemented through quality management systems is essential for any testing service, ranging from HIV testing conducted in laboratories and health facilities to community-based settings, including RDTs performed by lay providers. Detailed guidance on quality systems is provided in the 2015 WHO *Consolidated guidelines on HIV testing services* and other relevant publications *(57,58)*.

Recommendations

High-prevalence settings

- In settings with greater than 5% HIV prevalence in the population tested, a diagnosis of HIV positive should be provided to people with two sequential reactive tests.
  - For individuals with discrepant test results where Assay 1 is reactive, Assay 2 is non-reactive and Assay 3 is reactive, the results should be considered inconclusive and the client should be asked to return in 14 days for retesting.
  - For individuals with discrepant test results where Assay 1 is reactive, Assay 2 is non-reactive and Assay 3 is non-reactive, the final result should be considered HIV negative.

Low-prevalence settings

- In settings with less than 5% HIV prevalence in the population tested, a diagnosis of HIV positive should be provided to people with three sequential reactive tests.
  - For individuals where the Assay 1 result is reactive and Assay 2 result is non-reactive, the final result should be considered HIV negative. However, in the case of such results and where Assay 1 is a fourth-generation assay (antibody/antigen [Ab/Ag]) and Assay 2 is an Ab-only assay, the result should be considered inconclusive and the person should be retested after 14 days.
  - For individuals with results in which Assay 1 is reactive, Assay 2 is reactive and Assay 3 is non-reactive, the result should be considered inconclusive and the client should be asked to return in 14 days for retesting.

All settings

- HIV testing services may use combinations of RDTs or combinations of RDTs/enzyme immunoassays (EIAs)/supplemental assays rather than EIA/Western blot combinations.

Sources:

Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Technical guidance update on quality assurance for HIV rapid diagnostic tests. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/181244/1/WHO_HIV_2015.28_eng.pdf?ua=1&ua=1).

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CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

3

3 CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

3.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV

NEW

Recommendation

Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).

Source: Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).

Background

Oral PrEP is the use of antiretroviral (ARV) drugs before HIV exposure by people who are not infected with HIV in order to block the acquisition of HIV.

Twelve trials on the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women *(1–12)*. Where adherence has been high, significant levels of efficacy have been achieved, showing the value of this intervention as part of combination prevention approaches.

In 2012, WHO recommended PrEP for use among serodiscordant couples, men who have sex with men and transgender people on the basis that demonstration projects were needed to ascertain optimal delivery approaches *(13)*. The 2013 *WHO Consolidated guidelines on the use of antiretroviral drugs in treating and preventing HIV infection* recommended PrEP in the context of demonstration projects. In 2014, WHO developed consolidated HIV guidelines for key populations, including men who have sex with men, people who inject drugs, sex workers, transgender people, and people in prisons and other closed settings *(14)*. In those guidelines, PrEP was strongly recommended for men who have sex with men.

This recommendation replaces previous WHO recommendations on PrEP and enables the offer of PrEP to be considered for people at substantial risk of acquiring HIV rather than limiting the recommendation to specific populations. Box 3.1 discusses the definition of "substantial risk". The new recommendation will enable a wider range of populations to benefit from this additional prevention option. It also allows the offer of PrEP to be

Box 3.1 Defining "substantial risk"

Substantial risk of HIV infection is provisionally defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP. HIV incidence higher than 3 per 100 person-years has been identified among some groups of men who have sex with men, transgender women in many settings, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. Individual risk varies within groups at substantial risk, depending on individual behaviour and the characteristics of sexual partners. Most of the PrEP trials reviewed for this recommendation identified and recruited groups at substantial risk of acquiring HIV, as demonstrated by the HIV incidence rate among participants in control arms that ranged between 3 and 9 per 100 person-years in most studies. Indeed, the HIV incidence in control arms of PrEP trials was often higher than anticipated, suggesting that PrEP attracts people at particularly high risk *(11)*. In locations where the overall incidence of HIV infection is low, there may be individuals at substantial risk who would be attracted to and benefit from PrEP services.

HIV incidence higher than 2 per 100 person-years was considered sufficient to warrant offering oral PrEP in the recommendations issued by the International Antiviral Society – USA expert panel in 2014 *(15)*. Thresholds for offering PrEP may vary depending on a variety of considerations, including epidemiological context or trends, available resources and the relative costs, feasibility and demand for PrEP.

Risk assessment tools for better defining substantial risk are being developed as part of WHO PrEP implementation guidance to be published in 2016.

based on local epidemiology and individual assessment, rather than risk group, and is intended to foster implementation that is informed by local information regarding the settings and circumstances of HIV transmission.

Rationale and supporting evidence

A systematic review and meta-analysis of PrEP trials containing TDF demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection. The level of protection did not differ by age, sex, regimen (TDF versus FTC + TDF) and mode of acquiring HIV (rectal, penile or vaginal exposure) *(16)*. The level of protection was strongly correlated with adherence.

HIV infection

HIV infection was measured in 11 randomized controlled trials comparing PrEP to placebo; three randomized controlled trials comparing PrEP to no PrEP (such as delayed PrEP or "no pill") and three observational studies. A meta-analysis of data from 10 trials comparing PrEP with placebo demonstrated a 51% reduction in risk of HIV infection for PrEP versus placebo *(16–18)*.

Mode of acquisition

When studies were stratified by mode of acquisition (rectal, vaginal or penile exposure), PrEP showed similar effectiveness across groups. The relative risk of HIV infection for PrEP versus placebo for rectal exposure is 0.34 (95% CI: 0.15–0.80, $P = 0.01$). For penile or vaginal exposure, the relative risk of HIV infection for PrEP versus placebo is 0.54 (95% CI: 0.32–0.90, $P = 0.02$) *(16)*. Parenteral exposure to HIV was not analysed separately because only one study explicitly included people who inject drugs, and their exposure to HIV arose from sexual practices and incomplete access to sterile injection equipment.

Sex and gender

Of 10 randomized PrEP trials reporting HIV outcomes, women were included in six studies and men in seven studies. PrEP was effective for both men and women. The relative risk of HIV infection for PrEP versus placebo was 0.57 (95% CI 0.34–0.94; $P = 0.03$) among women and 0.38 (95% CI 0.20–0.60; $P = 0.0001$) among men. Two placebo-controlled trials that targeted women exclusively showed very low uptake of PrEP (less than one third) in the active arm and no effectiveness on an intent-to-treat basis *(7,10)*. The effectiveness of PrEP among women in four trials that included both women and men was higher. For example, among women younger than 30 years in a trial that included both men and women, the effectiveness was 72% (95% CI: 29–92%, $P = 0.01$) for TDF and 77% (95% CI: 25–90%, $P = 0.01$) for FTC + TDF PrEP *(4)*. The results from a recent study (HPTN 067) among young, predominantly single South African women receiving open-label FTC + TDF as PrEP showed that young women can maintain adherence, with 80% having substantial concentrations of detectable drug at week 4 and 65% at week 24 in the daily PrEP arm *(19)*. More information is needed about PrEP in transgender populations.

Adherence

When all studies were analysed together, the results showed significant heterogeneity. The results from meta-regression conducted to evaluate whether certain variables moderated the effect of PrEP on reducing the risk of acquiring HIV infection demonstrated that adherence is a significant moderator.

When studies were stratified according to adherence levels (high, moderate and low based on the proportion in the active arms with detectable drug in blood), heterogeneity in effectiveness was greatly reduced within adherence subgroups, demonstrating that most heterogeneity between studies can be explained by differing adherence levels. Within adherence subgroups, PrEP is the most effective among the high-adherence group (defined as higher than 70% drug detection, but all studies in this group had adherence at or above 80%) and significantly reduces the risk of acquiring HIV in studies that had moderate levels of adherence (41–70% drug detection). Among studies with low adherence (40% or lower drug detection), PrEP shows no effect in reducing HIV infection *(16)*.

Safety

Ten randomized controlled trials comparing PrEP with placebo presented data on any adverse event. Across studies, the rates of any adverse event did not differ for PrEP versus placebo. Similarly, there was no statistical difference in rates of any adverse event

across subgroups, including mode of acquisition, adherence, sex, drug regimen, drug dosing or age *(16)*.

Eleven randomized controlled trials comparing PrEP with placebo presented the results for any grade 3 or 4 adverse event. Across studies, there was no statistical difference in the rates of any grade 3 or 4 adverse event for PrEP versus placebo, and there were no statistical differences across subgroup analyses, including adherence, sex, drug regimen, drug dosing or age *(16)*.

Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users *(20–22)*. These subclinical changes did not result in clinical events and were not progressive over time.

Drug resistance

The risk of drug resistance to FTC was low overall (11 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users, or 0.1%), and this occurred mainly among people who were acutely infected with HIV when initiating PrEP: 7 people of the 11 with FTC- or TDF-resistant HIV infection among 9222 PrEP users. The proportion of people with drug-resistant HIV did not differ in the PrEP and placebo groups among everyone at risk, although the number of events was low (*n* = 6 people infected). Multiple HIV infections (8–50) were averted for every case of FTC resistance associated with starting PrEP in the presence of acute HIV infection *(16)*. Modelling the HIV drug resistance resulting from ART is predicted to far exceed that resulting from PrEP *(23)*. Although mathematical models inform the risk of resistance, their results rely on data from clinical trials and make assumptions about the risk of selection of drug-resistant virus during PrEP. How implementation of PrEP on a large scale affects resistance overall is unknown. Active surveillance during PrEP scale up may therefore be warranted.

Sexual and reproductive health outcomes

No evidence indicated that PrEP led to risk compensation in sexual practices, such as decreased condom use or more sexual partners *(24,25)*.

PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends towards higher rates of pregnancy among oral contraceptive users who also took PrEP. When multivariate analysis accounted for confounders, this relationship was not significant. Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy *(4,10)*. More information is needed about interactions between PrEP and hormone therapy used by transgender people.

The systematic review sought to evaluate the effectiveness of PrEP in preventing HIV infection in the context of access to a combination of standard approaches to HIV prevention *(16)*. Across all trials, PrEP was provided in the context of a package of HIV prevention interventions, including regular HIV testing and counselling, provision of condoms, screening and treatment for sexually transmitted infections (STIs), adherence counselling and other options relevant to the study population, such as access to contraception for women and methadone maintenance therapy for people who inject opioids.

Cost and cost–effectiveness

The HIV incidence threshold for cost-saving implementation of PrEP will vary, depending on the relative costs of PrEP versus treatment for HIV infection and the anticipated effectiveness of PrEP. In some situations, PrEP may be cost saving, but other interventions may be more cost saving and scalable. Monetary costs should not be the only consideration, as staying free of HIV and having control over HIV risk is of intangible value to people and communities.

Offering PrEP in situations where the incidence of HIV is higher than 3 per 100 person-years is expected to be cost saving in many situations. Offering PrEP at lower incidence thresholds may still be cost-effective.

A review of cost–effectiveness studies for PrEP found that, in generalized epidemics, giving priority for the use of PrEP to people at substantial risk of acquiring HIV infection increases impact *(26)*. Some of these studies found PrEP to be cost–effective within the context of ART expansion; others found no benefit. In concentrated epidemics (such as among men who have sex with men in the United States), PrEP could have a significant impact. Studies have found PrEP to be cost–effective, depending on the cost of the drug and delivery systems when PrEP uptake is higher among people at substantial risk. Higher PrEP uptake and adherence have been observed among men who have sex with men in demonstration projects *(2,27)*. The results vary widely depending on epidemic type, location and model parameters, including efficacy, cost, HIV incidence and target population *(28)*.

Equity and acceptability

Preventing HIV among PrEP users will contribute to equitable health outcomes by sustaining their health and the health of their sexual partners. Access to PrEP also provides opportunities for accessing sexual health services, and people at substantial HIV risk are often currently medically underserved and have few other effective HIV prevention options. Broadening PrEP recommendations beyond narrowly defined groups (such as men who have sex with men and serodiscordant couples) allows for more equitable access, is likely to be less stigmatizing than targeting specific risk groups and will reduce future treatment costs overall by preventing HIV infection in populations with a high incidence.

PrEP acceptability has been reported in multiple populations, including women, serodiscordant couples, female sex workers, young women, people who inject drugs, transgender people and men who have sex with men. A qualitative literature review (131 peer-reviewed articles and 46 abstracts *(29)*) showed that individuals have substantial interest in accessing PrEP as an additional choice for HIV prevention. Population support for provision of PrEP was based on the knowledge of safety and effectiveness and the compatibility of PrEP with other prevention strategies.

Feasibility

Provision of oral PrEP to diverse populations has proven feasible in multiple trial settings and demonstration projects. Two placebo-controlled trials among women *(7,10)* found significant barriers to uptake and adherence, including the social stigma of being identified as living with HIV because of taking the medication, cultural barriers and lack of family or social support. However, programme settings differ from trials. PrEP adherence among women has been high when open-label PrEP is provided *(19,30)*.

The iPrEx OLE project and the Partners Demonstration Project both show that PrEP implementation is feasible for different populations, including men and women *(1,2)*. The PROUD study, conducted in the United Kingdom among men who have sex with men and designed to mimic real-life settings, demonstrated that PrEP is feasible and effective and is not associated with significant changes in behavioural risk *(11)*. Other PrEP demonstration projects in Botswana, South Africa, Thailand and the United States confirm that protective levels of adherence are feasible for most PrEP users *(19,30–34)*, although challenges remain to achieving high levels of adherence among young people *(34)*.

Implementation considerations

There are significant concerns about implementing PrEP, especially in legal environments in which the rights of people at substantial risk for HIV are violated. PrEP should not displace or threaten the implementation of effective and well-established HIV prevention interventions, such as condom programming and harm reduction. Stigma is a driver of HIV and could be decreased or increased depending on how PrEP is implemented. PrEP should be promoted as a positive choice among people for whom it is suitable and their communities, in conjunction with other appropriate prevention interventions and services, including sexual and reproductive health services.

WHO will publish comprehensive implementation guidance for PrEP in 2016. The guidance will include practical suggestions for human resource utilization, laboratory monitoring, pharmacy services, drug procurement, counselling, communication, community engagement, coordination of services (including testing, treatment, PrEP, post-exposure prophylaxis (PEP) and other sexual and reproductive health services) and programme management. A number of implementation issues are addressed below.

Provider training

Health-care providers should be trained and supported so that they can explore sexual and injecting risk behaviour with people and help them consider their risk of acquiring HIV and the range of prevention options, including PrEP. This involves providing respectful and inclusive services, a familiarity with techniques for discussing sensitive behaviour and a strong patient–provider relationship that enables discussions of facilitators and barriers to engagement in health-care services, adherence and self-care. Service providers should be aware of the emotional and physical trauma that people at substantial risk of acquiring HIV infection may have experienced *(35)*. The capacity for respectful work with people who have experienced trauma involves communication and skills development. Services that are appropriate for young people – especially young women and key populations – are essential for the success of all HIV treatment and prevention programmes, including PrEP.

Involving communities

Meeting the needs of populations at substantial risk of HIV infection requires the full participation of communities in developing and implementing programmes. The following are good participatory practices.

• Recognize the leadership and resilience of key populations in addressing the HIV epidemic at both the local and global levels and sustain their participation through adequate funding and support for community-based organizations.

- Ensure access to accurate knowledge and information about PrEP and early treatment by strengthening the capacity of community-based organizations in educating and training their communities about the use of PrEP.

- Promote and expand community-based services, especially services led by key populations.

- Ensure that PrEP is offered as a choice, free of coercion, and with access to other prevention strategies that may be preferred by individuals at substantial risk.

- Increase political commitment to rights, including the rights of key populations, by decriminalizing consensual sexual activity and gender expression.

Linking PrEP with other health and community services

People at substantial risk of acquiring HIV are often medically underserved, have few other effective HIV prevention options and frequently face social and legal challenges. Providing PrEP may give opportunities for increased access to a range of other health services and social support, including vaccinations for hepatitis B, reproductive and sexual health services (including managing STIs), mental health services, primary health care and legal services.

Community-based organizations – especially those working with key populations – should play a significant role in the roll-out of PrEP by engaging people at substantial risk, providing information about the availability and use of PrEP and promoting linkages between PrEP providers and other health, social and community support services.

PrEP as part of combination prevention

PrEP should always be provided together with other HIV prevention options. Harm-reduction interventions – including access to sterile or new injection materials – are the mainstay of preventing HIV transmission through unsafe injecting practices, and such supplies should be made available to anyone using injected substances or medications. Condoms and lubricants should be made available, including for sex workers, who should be empowered to insist on their use *(36)*.

New recommendations for early initiation of treatment and PrEP in these guidelines are expected to facilitate the identification of people recently infected with HIV. Whenever possible, people in their social and sexual networks should be offered HIV testing, treatment and prevention services. PEP and PrEP should be considered, in combination with other prevention services, for HIV-uninfected partners of recently diagnosed people.

HIV testing

HIV testing is required before PrEP is offered and regularly while PrEP is taken. People who test HIV negative but report high risk can be linked to prevention services where the potential for PrEP use can be assessed. HIV testing is required before PrEP is offered and should be conducted regularly (e.g. every three months) while PrEP is taken. The frequent HIV testing during PrEP use should also ideally become an opportunity for STI screening and management. Using quality-assured HIV testing is important, and using more sensitive tests has multiple advantages, including earlier HIV diagnosis and treatment, better counselling for people with acute HIV infection and minimizing the risk of drug resistance during PrEP and PEP. Rapid point-of-care third-generation HIV

antibody tests that use whole blood obtained by finger-prick or phlebotomy are available and are preferred to the use of oral fluids or second-generation tests when starting PrEP. Referral of people who test HIV positive to treatment services is essential.

Monitoring renal function

All PrEP trials tested renal function using serum creatinine before starting PrEP and at least quarterly during PrEP use, and these test results were used to exclude participants from trials and to stop study medication if they had abnormal results that were confirmed by repeat testing. Renal function returned to normal after stopping PrEP except for a few people who had underlying comorbidities such as systemic hypertension and diabetes mellitus. Unless more data become available, creatinine testing is preferred before starting PrEP and quarterly during PrEP use for the first 12 months, then annually thereafter. Point-of-care and laboratory-based assays for creatinine and HIV are available.

Hepatitis B

Hepatitis B virus (HBV) is endemic in many parts of the world where HIV is transmitted. The medications used for PrEP are active against HBV. Withdrawal of active therapy against HBV can lead to virological and clinical relapse. Clinical relapse did not occur during or after PrEP use in trials that included people with chronic HBV *(6,8)*. These trials excluded people with clinical liver cirrhosis and people with significant elevations in liver function tests. Testing PrEP users for hepatitis B surface antigen (HBsAg) is preferred. People with detectable HBsAg and alanine transaminase (ALT) elevated more than twice the upper limit of normal or clinical signs of cirrhosis could benefit from long-term therapy for HBV. Rapid point-of-care tests are available for HBsAg.

Adherence

Support for adherence should include information that PrEP is highly effective when used. Brief client-centred counselling that links daily medication use with a daily habit (such as waking up, going to sleep or a regular meal) may be helpful. Special programmes to facilitate adherence among particular groups – such as young people and women – may be needed. Support groups for PrEP users, including social media groups (for example, https://www.facebook.com/groups/PrEPFacts) may be helpful for peer-to-peer sharing of experience and challenges.

People who start PrEP may report side-effects in the first few weeks of use. These side-effects include nausea, abdominal cramping or headache, are typically mild and self-limited and do not require discontinuation of PrEP. People starting PrEP who are advised of this start-up syndrome may be more adherent.

PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained. Engaging with community support groups is important to facilitate the recognition of circumstances that involve substantial risk of acquiring HIV. PrEP is only likely to be needed during periods of risk rather than for life. Such periods of risk may begin and end with changes in relationship status, alcohol and drug use, leaving school, leaving home, trauma, migration or other events *(37,38)*.

PrEP users should be advised that PrEP reaches protection after 7 doses *(39)*. Pharmacological studies suggest that full protection may require 4 doses for anal sex and 7 doses for vaginal sex *(39,40)*.

People who report exposure to HIV before full protection from PrEP has been achieved should be considered for PEP *(41)*. As with PEP, PrEP may be discontinued 28 days after the last potential exposure to HIV if people do not have continuing substantial risk for acquiring HIV.

Pregnancy

Pregnancy is associated with a higher risk of acquiring HIV, and HIV acquired during pregnancy or breastfeeding is associated with an increased risk of HIV transmission to the infant. In PrEP trials, exposure to TDF-containing PrEP during the first trimester of pregnancy was not associated with adverse pregnancy or infant outcomes. There is growing evidence of the safety of TDF and FTC + TDF during pregnancy and breastfeeding when used for treating maternal HIV or HBV *(42)*. Contraception services, safer conception management and links to antenatal care should be available when providing PrEP services for women. The risks and benefits of and alternatives to continuing to use PrEP during pregnancy and breastfeeding should be discussed with each person. Further research is needed to fully evaluate PrEP use during pregnancy and breastfeeding.

Research gaps

Implementation research is needed in diverse settings to generate demand for prevention services (including PEP and PrEP) and to identify and engage people at substantial risk for HIV. Additional research is needed on how to support adherence, especially for adolescents, young women and transgender people. Such research should generate practical knowledge and skills through implementation.

Severe long-term toxicity of TDF use for HIV treatment is rare. Surveillance of large-scale use of PrEP could identify rare but important clinical adverse events. For outcomes with few events (drug resistance and reproductive health outcomes), active surveillance during PrEP scale-up is warranted. Issues related to toxicity of TDF are addressed in section 4.6.3.

The impact of PrEP on sexual practices may vary according to social and cultural contexts. The implementation of PrEP in diverse situations will provide opportunities for understanding how PrEP influences sexual practices, which may include improved sexual health and emotional well-being, reduced stigma and discrimination against people living with HIV or increased use of other HIV prevention methods. Adverse behavioural and social outcomes are also possible, although they have not been observed so far. The role of gender norms may also influence the uptake of prevention and treatment services, including PrEP, and could be a useful focus for qualitative implementation research.

The IPERGAY trial showed high efficacy of PrEP dosing before and after sex among men who have sex with men who reported frequent sexual activity *(31)*. The HPTN 067 trial randomly compared recommendations for daily and non-daily PrEP regimens and found that the daily recommendation was associated with the highest concentrations of drug, the highest adherence and high coverage of sex events with pre- and post-exposure dosing among men who have sex with men in Bangkok and New York and women in Cape Town *(19,31,32)*. Medication requirements and use were also higher for those randomized to daily use. Daily dosing was the preferred choice for the majority of users. How best to adapt PrEP recommendations to diverse and changing sexual practices is an important focus for further implementation research.

PrEP costs are not limited to the cost of drugs and include costs for clinic staff, laboratory testing, pharmacy services, community education, provider education and monitoring and evaluation. Implementation research for minimizing costs should include evaluation of strategies that do not compromise the safety, effectiveness or quality of the information provided to prospective PrEP users. Lower prices for medications and laboratory tests could be achieved by purchasing at volume. PrEP is amendable to algorithmic care, which would enable task-sharing with less costly and more diverse personnel.

Research is needed to determine whether HIV status and renal function can be monitored less frequently without increasing the risk of adverse clinical outcomes. Optimal recommendations for starting and stopping PrEP to maximize use during periods of substantial risk would decrease medication requirements and increase the impact on HIV transmission.

Additional research is needed on how best to integrate PrEP with other services. PrEP is compatible with HIV testing, HIV treatment services, sexual health services, condom provision, behavioural counselling, harm reduction, empowerment programmes, contraceptive services, reproductive health services and primary health care. PEP started after recent exposure to HIV can be transitioned to PrEP after 28 days if there is continuing substantial risk. How best to integrate PrEP into existing services is not known and may vary in different settings.

3.2   Post-exposure prophylaxis

Background

The most recent WHO guideline on HIV PEP was published in December 2014 *(43)*. Recognizing the need to improve uptake and completion rates for PEP, the guideline does not differentiate between exposure sources but rather provides recommendations across all exposures. This section summarizes its main recommendations and clinical considerations. The full guideline includes more detailed information, including management of possible exposure to other conditions such as viral hepatitis, STIs, tetanus and pregnancy.

Assessing eligibility

HIV PEP should be offered and initiated as early as possible in all individuals with an exposure that has the potential for HIV transmission, preferably within 72 hours. For individuals who may not be able to access services within this time, providers should consider the range of essential interventions and referrals that should be offered to clients presenting after 72 hours.

Eligibility assessment should be based on the HIV status of the source whenever possible, and may include consideration of background prevalence and local epidemiological patterns.

Exposures that may warrant HIV PEP include the following:

- body fluids: blood, bloodstained saliva, breast milk, genital secretions and cerebrospinal, amniotic, peritoneal, synovial, pericardial or pleural fluid. While these

Recommendations

- A regimen for post-exposure prophylaxis for HIV with two ARV drugs is effective, but three drugs are preferred (conditional recommendation, very low-quality evidence).

Post-exposure prophylaxis ARV regimens for adults and adolescents:

- TDF + 3TC (or FTC) is recommended as the preferred backbone regimen[a] for HIV post-exposure prophylaxis for adults and adolescents (strong recommendation, low-quality evidence).

- LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for adults and adolescents (conditional recommendation, very low-quality evidence). Where available, RAL, DRV/r, or EFV can be considered as alternative options.

Post-exposure prophylaxis ARV regimens for children ≤10 years:

- AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children aged 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens (strong recommendation, low-quality evidence).

- LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for children younger than 10 years (conditional recommendation, very low-quality evidence). An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.

Clinical considerations

NVP should not be used in children above the age of 2 years.

Prescribing practices

- A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment (strong recommendation, low-quality evidence).

- Enhanced adherence counselling[b] is suggested for individuals initiating HIV post-exposure prophylaxis (conditional recommendation, moderate-quality evidence).

[a] Backbone regimen refers to the two-NRTI component of an ART regimen (normally comprising of 3 ARV drugs).
[b] Enhanced adherence counselling includes baseline individual needs assessment, adherence counselling and education sessions and follow-up telephone calls.

Source: Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

fluids carry a high risk of HIV infection, this list is not exhaustive. All cases should be assessed clinically, and health workers should make decisions as to whether the actual exposure constitutes a significant risk.

• types of exposure: 1) mucous membrane, i.e. sexual exposure; splashes to eye, nose, or oral cavity; and 2) parenteral.

Exposures that do not require HIV PEP include the following:

• when the exposed individual is already HIV positive;

• when the source is established to be HIV negative; and

• exposures to bodily fluids that do not pose a significant risk, i.e. tears, non-bloodstained saliva, urine and sweat.

In cases that do not require PEP, the exposed person should be counselled about limiting future exposure risk. Although HIV testing is not required, it may be provided if desired by the exposed person.

Clinical considerations

As with PrEP, there is concern about the potential risk of hepatic flares among people with chronic HBV once TDF-, 3TC- or FTC-based PEP is stopped. Assessment of HBV infection status should not be a precondition for offering TDF-, 3TC- or FTC-based PEP, but people with established chronic HBV infection should be monitored for hepatic flare after PEP discontinuation. Among people with unknown HBV status and where HBV testing is readily available, people started on TDF-, 3TC- or FTC-based PEP should be tested for HBV to detect active HBV infection and the need for ongoing HBV therapy after discontinuing PEP.

NVP should not be used for PEP for adults, adolescents and older children because of the risk of life-threatening serious adverse events associated with HIV-negative adults using this drug.

EFV is widely available as a third agent, as this drug is used as part of the preferred first-line ART regimen. EFV is well tolerated for treatment but has limited acceptability for use as PEP, as there are concerns about giving a drug associated with early neuropsychiatric adverse events to HIV-negative people who may have anxiety related to HIV exposure.

NVP has been widely used to prevent the transmission of HIV from mothers to HIV-uninfected infants and should be used for preterm babies or infants younger than two weeks of age where LPV/r oral liquid cannot be used. However, because the NVP toxicity profile beyond infancy remains unclear, its use should be avoided in children beyond the age of 2 years.

Full guidance on the management of other conditions associated with possible exposure to HIV is provided in the 2014 *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children* (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

3.3 Combination HIV prevention

Combination prevention programmes use a mix of biomedical, behavioural and structural interventions to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest possible impact on reducing new infections. Well-designed combination prevention programmes are carefully tailored to national and local needs and conditions. They focus resources on the mix of programmatic and policy actions required to address both immediate risks and underlying vulnerability. They should be thoughtfully planned and managed to operate synergistically and consistently on multiple levels (e.g. individual, relationship, community and society) and over an adequate period of time. Combination prevention mobilizes communities, the private sector, governments and global resources in a collective undertaking. It requires and benefits from enhanced partnership and coordination and should incorporate mechanisms for learning, capacity building and flexibility to permit continual improvement and adaptation to the changing environment.

ARV drugs play a key role in HIV prevention. People taking ART who achieve optimal viral suppression are extremely unlikely to pass HIV to sexual partners. ARV drugs taken by people without HIV as PrEP or PEP are highly effective in preventing HIV acquisition.

Other **biomedical interventions** that reduce HIV risk practices and/or the probability of HIV transmission per contact event include the following:

- **Male and female condoms and condom compatible lubricant:** male condoms are estimated to reduce heterosexual transmission by at least 80% and to offer 64% protection in anal sex among men who have sex with men, if used consistently and correctly *(44,45)*. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect *(46)*.

- **Needle and syringe programmes** are highly associated with a reduction in HIV transmission through injecting drug use *(47)*.

- **Opioid substitution therapy** with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviour and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART *(48,49)*.

- **Voluntary medical male circumcision (VMMC):** three randomized clinical trials in Africa demonstrated an approximately 60% reduction in the risk of female-to-male sexual transmission *(50–52)*. For high-burden settings, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended the inclusion of VMMC as an additional important strategy for presentation of heterosexually acquired HIV infection in men. Male circumcision should be offered as part of a comprehensive HIV prevention package, including safer sex education, providing and promoting condom use, providing HIV testing services (HTS) and linkage to care for those in need, and management of STIs. This intervention has reached over 10 million males in eastern and southern Africa *(53)*.

Behavioural interventions can reduce the frequency of potential transmission events, including the following:

- **Targeted information and education:** these are programmes that use various communication approaches, for example, school-based sex education, peer counselling and community-level and interpersonal counselling, including brief interventions to disseminate behavioural messages. These messages encourage people to reduce risk behaviour and increase behaviour that is protective (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, using male and female condoms correctly and consistently and knowing your HIV status and that of your partner). There is growing recognition that social media and mobile technology are important tools that can be integrated in HIV prevention programmes, and can be particularly critical in informing about and providing prevention services to populations such as men who have sex with men.

- **Structural and supportive interventions** may increase access to, uptake of and adherence to behavioural and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reforms, measures to reduce stigma and discrimination (including in the health sector). In addition, they involve the promotion of gender and lesbian, gay, bisexual, transgender and intersex (LGBTI) equality and prevention of gender-based and LGBTI violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

Combination prevention for key populations

WHO recommends a comprehensive package of evidence-based HIV-related recommendations for all key populations. The package comprises clinical interventions and a set of critical enablers required for successful implementation of programmes for the five key populations (Box 3.2).

Box 3.2 Comprehensive package of HIV prevention for key populations

a) Essential health sector interventions

1. Comprehensive condom and lubricant programming

2. Harm-reduction interventions for substance use (in particular, needle and syringe programmes, opioid substitution therapy and naloxone)

3. Behavioural interventions

4. HTS

5. HIV treatment and care

6. Prevention and management of coinfections and other comorbidities, including viral hepatitis, tuberculosis and mental health conditions

7. Sexual and reproductive health interventions

b) Essential strategies for an enabling environment

1. Supportive legislation, policy and financial commitment, including decriminalization of certain types of behaviour of key populations

2. Addressing stigma and discrimination, including by making health services available, accessible and acceptable

3. Community empowerment

4. Addressing violence against people from key populations

Source: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en).

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CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

4

4 CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

4.1 Preparing people living with HIV for ART

Before people start antiretroviral therapy (ART), health-care providers should initiate a detailed discussion about the willingness and readiness of patients to initiate ART, the antiretroviral (ARV) drug regimen, dosage, scheduling, likely benefits, possible adverse effects and the required follow-up and monitoring visits. In the case of children with HIV, this conversation should directly involve the caregiver and include discussion about disclosing their HIV status. Retesting all people living with HIV before initiating ART is recommended to ensure a correct diagnosis of HIV infection. Initiation of ART should always consider nutritional status, any comorbidities and other medications being taken to assess for possible interactions, contraindications and dose adjustment.

The choice to accept or decline ART ultimately lies with the person or his or her caregiver, and if they choose to defer initiation, ART can be offered again at subsequent visits. If the person faces mental health or substance use issues or other potential barriers to ART initiation or adherence, appropriate support should be provided and readiness to initiate ART should be reassessed at regular intervals. Community and peer support can help a person to prepare and make the decision to start therapy.

People starting treatment and carergivers should be informed that the first ART regimen offers the best opportunity for effective viral suppression, immune recovery and consequently clinical benefit and that successful ART requires all medications to be taken as prescribed. It is important to acknowledge that there are situations where delays in starting ART can have negative consequences, particularly for people with tuberculosis (TB) or advanced immunosuppression, who are at high risk of death. People should be advised that many adverse effects are temporary or may be treated, and that substitutions can often be made for the ARV drugs associated with adverse effects. In preparation for treatment initiation, it is important to assess the need for psychosocial support to optimize adherence. People receiving ART and caregivers should also be asked regularly about any other medications that are being taken, including herbal remedies and nutritional supplements.

People commencing ART should be given advice on safer sex, including condom use and avoidance of other high-risk activities such as sharing of injecting equipment, to prevent transmitting HIV to other people.

4.1.1 Accelerated ART initiation

NEW

Good practice statement

Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.

ART initiation is often seen as a non-emergency intervention, and various approaches are used to help prepare people to begin treatment. However, there is increasing recognition of the benefits of accelerated ART initiation, for example, in pregnant women, in order to avoid unacceptably high rates of loss to follow-up after HIV diagnosis. However, concerns remain that accelerated initiation of ART may lead people to start before they are ready, with adverse consequences for adherence and treatment outcomes.

Current implementation experience of rapid ART initiation is largely derived from experience with option B+ (lifelong ART for all pregnant and breastfeeding women). Although ART initiation in these programmes is not necessarily on the same day as testing, the majority of women initiate treatment within a short space of time. Of nearly 22 000 women who started ART under option B+ in Malawi, 17% were lost to follow-up six months after ART initiation. Loss to follow-up was highest among women who began ART at large clinics on the day they were diagnosed with HIV *(1)*.

A systematic review *(2)* identified two ongoing studies that evaluated accelerated ART initiation, including treatment initiation on the same day as HIV diagnosis to reduce loss to follow up. The Rapid Initiation of Antiretroviral Therapy to Promote Early HIV/AIDS Treatment in South Africa (RapIT) study randomized individuals to rapid initiation versus standard care *(3)*. Preliminary data showed a relative risk of 1.33 of initiation of ART in 90 days, with a risk difference of 24% (73% in the standard-of-care arm compared to 97% in the rapid initiation arm). The START-Streamlined Initiation trial is examining accelerated ART initiation in Uganda *(4)*. START components include (i) real-time point-of-care CD4 testing, (ii) targeted knowledge transfer to health-care workers and (iii) feedback and reporting to the clinic and providers.

Findings from community consultations show that early ART initiation is acceptable, but universal same-day ART initiation following HIV diagnosis is considered to be challenging because of the wide variation in individuals' understanding of the implications of test results and preparedness to commence lifelong treatment *(5)*. There is a perceived difference in motivation to start ART when sick compared to when healthy.

While these guidelines recommend initiation of ART in all people with HIV regardless of CD4 cell count or disease stage, and preliminary data suggest that accelerated ART initiation is possible, the available data are currently inadequate to support a recommendation in these guidelines in favour of same-day or otherwise accelerated ART initiation.

The following principles may inform future guidance.

- Treatment should be started based on a person's informed decision to initiate ART.

- Interventions to remove barriers to ART initiation once an individual is diagnosed HIV positive should be implemented.

- HIV programmes should promote treatment literacy among all people with HIV, including information on the benefits of early treatment, the lifelong commitment required, the risks of delaying treatment and available adherence support.

- Care providers should be trained to support shared decision-making.

- Although ART initiation is rarely urgent, it may need to be expedited in certain circumstances, such as serious ill health and for pregnant women in labour whose HIV test result is positive.

4.2   What to expect in the first months of ART

Although ART is a lifelong commitment, the first months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections (OIs) and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of treatment. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are most common when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 cell counts or are severely malnourished *(6,7)*. Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

4.3   When to start ART

4.3.1   When to start ART in adults (>19 years old)

Recommendation

- **ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).**

- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

Sources:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Since they were first published in 2002, WHO guidelines on ART have evolved as the body of evidence to support earlier initiation of ART has grown *(8)*. The 2013 WHO ARV guidelines recommended initiating ART for all adults with HIV and a CD4 count at or below 500 cells/mm³, regardless of WHO clinical stage, giving priority to those with severe or advanced HIV disease (WHO clinical stage 3 or 4) or a CD4 cell count at or below 350 cells/mm³ *(9)*. This strong recommendation was based on moderate-quality evidence from three randomized controlled trials *(10–12)* and 21 observational studies *(13–34)*, showing that initiating ART at or below a CD4 threshold of 500 cells/mm³ compared with later initiation reduced the risk of progression to AIDS and/or death, TB and a non-AIDS-defining illness and increased the likelihood of immune recovery. In addition, high-quality evidence from one randomized controlled trial indicated that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners in heterosexual couples *(11)*.

Mathematical models and ecological studies also suggested that initiating ART earlier could affect HIV incidence at the population level if there is high uptake and sustained HIV testing, ART coverage and retention *(35–39)*. For people with certain clinical conditions – TB, hepatitis B virus (HBV) coinfection requiring HBV treatment and during pregnancy and breastfeeding – and for HIV-serodiscordant couples, the 2013 guidelines recommended initiating ART regardless of WHO clinical stage or at any CD4 cell count.

Global ART coverage for all people living with HIV had reached approximately 41% – or 15 million people – by March 2015 *(40)*. According to the WHO Country Intelligence Database, by June 2014, 60% of the 58 WHO HIV focus countries had adopted the CD4 threshold of 500 cells/mm³ or less for initiating ART and 7% had already moved the CD4 threshold to above 500 cells/mm³ *(41)*. Although the median CD4 count at the time of ART initiation is increasing, it remains significantly lower than 350 cells/mm³ in almost all settings, including high-income countries *(42,43)*. Late presentation for treatment is associated with high early mortality rates, higher direct health-care costs and poor retention in care *(44–46)*. Increasing knowledge of HIV status, strengthening links between testing and care, modifying health systems to manage patient volumes and ensuring optimal long-term retention and adherence remain significant challenges in many settings *(47)*.

Rationale and supporting evidence

Initiating ART among all adults living with HIV regardless of WHO clinical stage or at any CD4 cell count

Since 2013, evidence and programmatic experience have continued to favour earlier initiation of ART because it results in reduced mortality, morbidity and HIV transmission outcomes. Increasing evidence from systematic reviews and cohort analyses also indicates that untreated HIV infection may be associated with the development of several non-AIDS-defining conditions, including cardiovascular, kidney and liver disease, several types of cancer and neurocognitive disorders *(48–51)*, and that initiating ART earlier reduces such events and improves survival. Recent evidence from a large randomized controlled trial also shows that, as demonstrated for heterosexual serodiscordant couples, ART substantially reduces sexual transmission to HIV-negative sexual partners among homosexual couples *(52)*.

The recommendation to initiate ART at any CD4 cell count was based on a systematic review with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence profiles that assessed the quality and strength of the evidence from one randomized controlled trial *(53)* and 17 observational studies *(18,19,22–26,28,30,34,37,54–59)* reporting clinical, immunological) reporting clinical, immunological and virological outcomes and HIV transmission.

In the analysis of data from the single randomized controlled trial (TEMPRANO), moderate-quality evidence (downgraded from high quality because of imprecision) showed that initiating ART at a CD4 cell count above 500 cells/mm^3, in the absence of other treatment indications, leads to less severe HIV morbidity (combined outcome of death, AIDS and severe non-AIDS diseases such as malignancies and bacterial diseases) compared with treatment initiation at a CD4 cell count at or below 500 cells/mm^3 *(53)*.

Data from another randomized controlled trial (START study), although supportive of the new recommendations, were unpublished at the time of the Clinical Guideline Development Group meeting for these guidelines *(60)*. The START study was planned for completion in 2018, but after an interim analysis in mid-2015, the trials Data Safety Monitoring Board advised immediate dissemination of the findings because of predefined stopping rules. Data from this study could not be incorporated into the systematic review or GRADE table because the comparison groups did not match the review population, intervention, comparator and outcome question (PICO) and therefore could not be considered in relation to the quality of the evidence. Box 4.1 summarizes the study's key findings.

Box 4.1. Strategic Timing of Antiretroviral Treatment (START) study

The study enrolled 4685 people with CD4 counts higher than 500 cells/mm^3 at 215 sites in 35 countries. Twenty-seven per cent of the participants were women and approximately half were men who have sex with men. The study examined the rates of serious AIDS-defining illness or death among people who were randomized to receive immediate ART versus deferred ART (until their CD4 count dropped below 350 cells/mm^3). The median baseline CD4 count was 651 cells/mm^3 in the intervention group that initiated ART at enrolment. In the deferred group, the median CD4 count at ART initiation was 408 cells/mm^3. Follow-up lasted for a mean of 3 years. A total of 86 events (death, serious AIDS events and serious non-AIDS events) occurred among those with later treatment initiation, whereas 41 events occurred among those who started ART immediately, representing a 57% reduction in negative outcomes among those treated early. In both groups, most events occurred when CD4 counts were higher than 500 cells/mm^3. The study also showed that immediate ART reduced both serious AIDS-related and serious non-AIDS-related events, but the benefit was greater for AIDS events. TB, Kaposi sarcoma and lymphoma – the most common AIDS-related events – all occurred less frequently in the immediate ART group. Cancer rates (combined AIDS and non-AIDS malignancies) were lower in the immediate ART group, but cardiovascular disease rates were similar between the groups. The occurrence of drug-related adverse events was not significantly different between the two groups. These effects were consistent in countries at different income levels and across geographical regions.

Analysis of the observational studies found a significantly lower risk of HIV disease progression *(57)*, and modelling from the TEMPRANO randomized controlled trial data demonstrated the potential lower rates of HIV transmission to uninfected partners *(53)*, but the evidence was rated as very low quality in both cases. However, interim data from the HPTN 052 clinical trial indicated that early ART is highly effective in preventing the sexual transmission of HIV *(61)*. Similar to the START trial, relevant data from the HPTN 052 were unpublished at the time of the guidelines review meeting and were not incorporated into the systematic review due to a different comparator from that of the review. Box 4.2 summarizes these data.

Box 4.2. The HIV Prevention Trials Network (HPTN) 052 study

HPTN enrolled 1763 HIV serodiscordant couples from 13 sites in nine countries and followed them for approximately four years. Ninety-seven per cent of the couples were heterosexual. The HIV-positive partners in the participating couples were randomly assigned to immediate ART initiation or ART initiation was delayed until their CD4 counts fell below 250 cells/mm^3 or they were diagnosed with an AIDS-related illness. All participants in both groups received counselling on safe sex practices, free condoms, treatment for sexually transmitted infections (STIs), frequent HIV testing and evaluation and treatment for any complications related to HIV. The median CD4 count at study entry was 436 cells/mm^3. Seventy-eight initially HIV-negative partners became infected with HIV and 46 of 70 (66%) had their linkage status confirmed, i.e. their HIV infection could be linked to the HIV-positive partner using phylogenetic analysis.

Three of the 46 linked infections occurred in the early ART arm and 43 in the delayed ART arm, leading to a 93% risk reduction for linked transmissions. In the final analysis, all linked partner infections that were diagnosed after ART initiation occurred when the virus was not suppressed by the treatment regimen (four from a total of eight cases). There were no linked partner infections when the HIV-positive partner's virus was stably suppressed by ART. The results show that ART is highly effective at preventing the heterosexual transmission of HIV if viral suppression is achieved and maintained.

Moderate-quality evidence from the TEMPRANO trial showed that initiating ART at a CD4 count above 500 cells/mm^3 was not associated with an increased risk of grade 3 or 4 adverse events *(53)*. Low-quality evidence from observational data showed an increased risk of any severe laboratory adverse event and hepatic adverse events in individuals initiating ART at a CD4 count above 500 cells/mm^3, although this was not associated with treatment discontinuation *(55)*.

Programmatic data from several countries that are offering earlier ART either to all people living with HIV or to specific populations have shown significant increases in ART uptake and linkage to care, reduction in the time between HIV diagnosis and ART initiation regardless of baseline CD4 cell count and an increase in the median CD4 value at ART initiation. Retention in care has not differed between individuals who start at CD4 counts above 500 cells/mm^3 compared with those whose initiation to ART was based on the standard of care *(62–64)*.

Initiating ART among adults with severe or advanced HIV disease or with a CD4 count at or below 350 cells/mm³ as a priority

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 cell counts. The strength and quality of evidence for this recommendation established in the 2010 WHO guidelines on *Antiretroviral therapy for HIV infection in adults and adolescents (65)* remains unchanged. Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4 counts at or below 350 cells/mm³ significantly reduces mortality, disease progression and the incidence of OIs, especially TB and non-AIDS-defining conditions *(66)*. Furthermore, several studies and programmatic data suggest that late diagnosis (often defined as a CD4 count at or below 350 cells/mm³) and late treatment initiation are very common, even in high-income settings *(67,68)*.

Comparing benefits and harm

The benefits of earlier ART initiation include fewer events caused by severe HIV morbidity and disease progression, improved uptake and initial linkage to care, better immune recovery and decreased HIV transmission. Despite being statistically significant, the comparative outcome differences among study arms with higher baseline CD4 cell counts (e.g. CD4 counts between 350 and 500 cells/mm³, compared to those with CD4 counts over 500 cells/mm³) were modest. Furthermore, not all observational studies have consistently demonstrated the beneficial effect of initiating ART at a CD4 cell count at or above 500 cells/mm³ on mortality, the incidence of inflammation-related non-AIDS events and ongoing viral replication, compared with initiation at CD4 count at or below 500 cells/mm³. Concerns have also been expressed that, given limited resources, very early treatment could result in some people who urgently need treatment being displaced by those for whom treatment would be beneficial but is less urgently needed. The long-term safety profile of ART and the implications of earlier treatment initiation on drug resistance, toxicity, adherence and retention need to be closely monitored. Follow-up will be needed to evaluate the potential harm and benefits of ART over a lifetime.

It is increasingly recognized that, in settings with a high burden of HIV and TB infections, increasing ART coverage is associated with decreasing TB case notifications, and this is likely to improve when ART is started earlier.

A modelling study based on national cohort data from four countries in sub-Saharan Africa concluded that programmatic gains and mortality reduction were accrued by eliminating the pre-ART period, suggesting that making treatment available to everyone will strengthen the continuum of care *(69)*.

Cost and cost–effectiveness

The same modelling study indicates that expanding the ART eligibility criterion to above 500 cells/mm³ or regardless of CD4 cell count and linking to HIV care could result in 6–14% fewer people dying from HIV-related causes during the next decade *(69)*. In this study, the majority of the impact is caused by programmatic simplification, leading to more people initiating ART in a timely manner and therefore avoiding adverse outcomes during the pre-ART period rather than direct therapeutic benefits. The increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing people from acquiring HIV

infection. The modelling suggests that such a change is likely to be cost–effective in many settings if individuals initiating ART are adherent to treatment and retained in care. Costs will increase significantly but will be far less than if the additional outreach interventions required for maintaining people in pre-ART care are also included.

According to estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS), expanding ART to all people living with HIV is projected to avert 21 million AIDS-related deaths and 28 million new infections by 2030 *(70)*. However, these benefits require high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The cost implications at the regional and country levels can also vary and should be further explored, as countries have different levels of current treatment coverage and local cost considerations, depending on their context and resources.

Equity and acceptability

Disclosure of HIV status is essential for accessing adherence support and may be particularly difficult for people who have never been ill. For this reason, initiating ART among adults with severe or advanced HIV disease or with a CD4 count at or below 350 cells/mm³ is recommended as a priority in these guidelines. Additional concerns that mandatory or coercive approaches will be used among at-risk marginalized populations highlight the importance of adequate patient information, informed consent, appropriate health worker training and rights-based legal frameworks to facilitate access.

A community-led global consultation examined the acceptability of earlier initiation of ART at a higher CD4 count for people living with HIV, caregivers and service providers and found that earlier initiation was considered acceptable *(5)*. Participants in the consultation emphasized the need for collaborative decision-making with service providers to ensure that the ultimate decision to initiate ART rests with the person living with HIV. Motivation to start and adhere to treatment may be more difficult for people who feel well and have higher CD4 counts than for people who are or have been ill. Stigma and discrimination continue to act as barriers to treatment access and adherence. Critical factors in promoting ongoing engagement in care and adherence include ensuring a stable supply of free or affordable ARV drugs, facilities that are easily accessible and that ensure confidentiality, sympathetic providers and appropriate adherence support.

A qualitative literature review showed that acceptability of earlier treatment is greater when people know that treatment reduces mortality risk. Service providers recognize the clinical and preventive benefits of earlier ART and the need for earlier ART initiation for asymptomatic people. Among people living with HIV, acceptance increases when they also have comorbidities or conditions associated with a higher risk of HIV transmission. Issues cited in the literature supported those identified in community consultations *(71)*.

Feasibility

According to cohort and national programme data, the number of people needing treatment could increase by up to 35% if ART is initiated at any CD4 count rather than at or below 500 cells/mm³ *(70)*. Modelling estimates predict that this increase would be lower, in the range of 7–21% over five years, because not all people living with HIV are diagnosed and therefore, unlikely to initiate care and treatment immediately. Country experience has also shown that moving to a higher CD4 threshold for ART initiation may not necessarily lead to a significant immediate increase in the number of people who

actually access treatment unless there is also increased uptake of HIV testing, stronger linkage to care, adequate treatment monitoring and sustained adherence support. Late presentation for treatment is still common, with the median CD4 count at ART initiation being below 350 cells/mm³ in the majority of settings, including in high-income countries *(66,67)*.

Implementation considerations

Regardless of the epidemic profile and disease burden, priority should be given to people with symptomatic HIV disease or with a CD4 count at or below 350 cells/mm³ who are at high risk of mortality and most likely to benefit from ART in the short term.

Initiating ART at CD4 counts above 500 cells/mm³ may involve the need for additional human, infrastructure and financial resources. Countries have different health system capacity and are at different levels of ART coverage and programme quality. A phased approach to implementation may be needed, especially in settings with a high burden of HIV, low ART coverage, low rates of testing, modest pre-ART care, scarce human resources, limited laboratory capacity, budget constraints and/or competing health priorities. In such settings, equity considerations and giving priority to those who most need treatment should guide implementation (*see* section 8.2 "Dissemination and implementation").

The increased need for ART associated with early initiation may place demands on the health system in some settings, which could increase the risk of drug resistance, such as drug stock-outs, insufficient patient preparation and suboptimal adherence. To maximize the long-term effectiveness of first-line ART regimens and ensure that people are taking the most effective regimen, the scaling up of ART should be accompanied by measures to monitor and improve service quality at the site and programme levels (*see* sections 6.12 "Improving the quality of HIV care services" and 6.13 "Procurement and supply chain management").

In all settings, continued monitoring will be needed of the long-term safety profile of ARV drugs, and the implications of earlier initiation for drug resistance, toxicity and adherence. It also remains essential to address the structural and social barriers to accessing treatment faced by key populations, such as criminalization, stigma and discrimination *(72–74)*.

Research gaps

Several ongoing implementation trials are evaluating the feasibility, acceptability, cost–effectiveness and impact of immediate treatment for all people living with HIV regardless of CD4 cell count at the population level (SEARCH and MaxART studies) *(75,76)*. Primary outcome results are not expected before 2017 or 2018. Three large randomized trials are examining the population effect of early ART initiation on HIV incidence and mortality (Botswana Combination Prevention Trial, HPTN-071 [PopART] study and 12249 ANRS TasP trial), with results expected after 2016 *(77–79)*.

Other research priorities include assessing the incidence of short- and long-term severe adverse events as a result of increased exposure to ART, barriers to and enablers of adherence and long-term retention in care, the impact of early initiation of ART on the cascade of care and the magnitude of the prevention benefit, especially among key populations and adolescents.

4.3.2 When to start ART in pregnant and breastfeeding women

Recommendation

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

Source: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

Background

Programmes for the prevention of mother-to-child transmission (PMTCT) were some of the earliest public health interventions that used ARV drugs to reduce the risk of acquisition of HIV. Initially, the regimens recommended by WHO were short courses or single doses of ARV drugs given to the mother and to the infant in the first few days of life. With the scaling up of national HIV programmes from 2003, WHO guidelines made an important shift, recommending that pregnant women living with HIV should be assessed for treatment eligibility and those considered eligible for treatment should be offered lifelong combination ART for their own health, while those who were not eligible should receive short courses of ARV prophylaxis for PMTCT. Although eligibility criteria have changed and the preferred regimens for ART and for PMTCT prophylaxis have evolved, this distinction between treatment and prophylaxis became a fixture of PMTCT programmes.

In 2013, the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* recommended that all pregnant and breastfeeding women should be initiated on ART regardless of clinical eligibility. This recommendation was supported by programmatic experience (including from Malawi, which has pioneered universal ART access for all pregnant women), demonstrating that prophylaxis for PMTCT (using different drugs at different times in the course of pregnancy, labour and delivery, as well as long duration of infant prophylaxis while breastfeeding) was more challenging to implement in the field than giving ART to all pregnant women (especially if the ART regimen was a once-daily fixed-dose combination tablet). However, the 2013 WHO guidelines *(9)* still offered programmes the option to either continue ART lifelong in all women (option B+) or to stop ART after the period of mother-to-child transmission risk in women who did not otherwise meet eligibility criteria (option B). Option B+ was considered to be of the greatest benefit in settings with a high HIV prevalence, high fertility and long duration of breastfeeding, in which initiating ART in all pregnant and breastfeeding women would reduce HIV incidence and prevent HIV transmission in both current and future pregnancies.

Following the release of the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)*, many countries adopted option B+ as the preferred approach for PMTCT programmes in both high- and low-prevalence settings. The 2014–2015 Global AIDS Response Progress Report showed that the majority of countries, including almost all the 22 high-priority countries included in

the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive *(80)* are now either piloting or implementing lifelong ART for all pregnant and breastfeeding women living with HIV at a national scale. A readiness assessment checklist includes guidance for countries planning this transition (Annex 9).

Increasing evidence to support earlier ART initiation among all adults, together with widespread uptake of option B+ and emerging programme data on its success in practice, all support a revised recommendation in 2015 that moves away from "options" for PMTCT and instead advocates that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment, regardless of clinical or CD4 cell count or stage of disease.

Providing ART to all pregnant and breastfeeding women living with HIV serves three synergistic purposes: (i) improving the mother's health; (ii) preventing mother-to-child transmission of HIV; and (iii) preventing the transmission of HIV from the mother to a sexual partner. It is important to note that these recommendations are relevant for all epidemic settings, although implementation will be context specific. Because ART has individual health benefits for all individuals living with HIV, the recommendation applies to both breastfeeding and non-breastfeeding populations.

Rationale and supporting evidence

The evidence on options B and B+ and the clinical and immunological impact of stopping ART among postpartum women was reviewed by the Clinical Guideline Development Group in the context of increasing data showing the benefit of ART at all stages of HIV disease and the recommendation to initiate ART among all adults with HIV at any CD4 cell count.

A systematic review *(81)* compared option B and option B+ in terms of maternal health outcomes. The review did not identify any randomized controlled trials or observational studies that directly compared the outcomes of options B and B+. However, 18 studies reported on option B outcomes – comprising four randomized controlled trials *(82–85)*, three single-arm trials *(86–88)* and 11 cohort studies *(89–99)* – and 10 cohort studies reported on outcomes associated with option B+ *(100,101–108)*. All the studies evaluating option B+ suggested that women experienced health benefits in terms of immunological and clinical parameters. None of the studies included in the review reported on how option B+ affected HIV transmission rates to partners, although this is an important likely benefit for women who remain on lifelong ART.

As the key difference between option B and option B+ is not when ART is started but whether it is stopped, literature on the clinical and immunological impact of stopping ART among women during the postpartum period was also evaluated in a separate review. Five cohort studies and one randomized controlled trial were identified, which examined changes in clinical and immunological parameters following discontinuation of ARV drugs. The majority of these studies used the historical threshold (2010 recommendations) for ART eligibility of CD4 count below 350 cells/mm^3, and in several cases, mothers were receiving ARV prophylaxis rather than ART, but all showed a gradual decline in immune function after ARV drugs were stopped. Using the time frame of six months after discontinuation, 6–20% of women with a baseline CD4 count below 500 cells/mm^3 had reached the eligibility threshold of 350 cells/mm^3. A lower baseline CD4 count was also associated with a 2.5-fold higher risk of WHO stage 2 or 3 clinical events *(109)*.

Apart from the impact on clinical and immunological outcomes, there are programmatic consequences of stopping ARV drugs among postpartum women. In one cohort study from Malawi, loss to follow-up post delivery was much higher in women with a baseline CD4 above 350 cells/mm³ (who were not eligible for treatment) than those with a CD4 below 350 cells/mm³ (who were eligible and started on ART) *(110)*. The findings were similar in a South African cohort where the women who were considered ineligible for ART were twice as likely to be lost to follow up at six months postpartum as the women who had started treatment *(111)*. A key challenge to implementation of option B is the difficulty of distinguishing between those who were eligible for lifelong treatment and those who were not, prior to initiation of ART.

An increasing body of evidence demonstrates the advantages of lifelong ART for pregnant and breastfeeding women and adds to the compelling data from randomized controlled trials *(53,60)* suggesting that all adults with HIV benefit from ART at any CD4 cell count, regardless of their clinical stage of disease.

Comparing benefits and harm

The majority of countries are moving to adopt universal ART for all pregnant and breastfeeding women. The benefits include improved health outcomes, lower rates of mother-to-child transmission and the potential for reduction of horizontal transmission of HIV. Although there is no documented evidence for this reduction in horizontal transmission, rates of partner serodiscordance are high. In one study among couples in five African countries, between 30% and 40% of women living with HIV were in serodiscordant relationships *(112)*. In a recent demographic health survey in Kenya, rates of discordance were reported to be above 50% *(113)*. Another important potential benefit of universal ART for pregnant and breastfeeding is that women may be less likely to drop out of care after the end of the transmission risk period and may avoid some of the clinical and operational complexities of repeated cycles of stopping and starting ART in subsequent pregnancies.

The possible harm of offering lifelong ART to all pregnant and breastfeeding women living with HIV (as opposed to only those who are "eligible") includes the potential for cumulative drug toxicity and the possibility of poor adherence with long-term use, leading to the development of drug resistance. In general, these risks for pregnant and breastfeeding women are similar to those for non-pregnant adults. Pre-conception ART may be associated with added risks related to both the outcomes of pregnancy and newborn morbidity. To date, no evidence suggests a significantly increased risk of congenital anomalies associated with the currently recommended first-line ARV drug regimens *(114)*. Special considerations for toxicity monitoring for pregnant and breastfeeding women are discussed in section 4.6.6 "Monitoring of and substitutions for ARV drug toxicities".

Overall, the health benefits of universal ART for pregnant and breastfeeding women outweigh potential harm, but the decision to initiate treatment remains a personal one that must be made on the basis of informed consent.

Feasibility and resource use

As with all populations, the costs associated with implementing universal ART for pregnant and breastfeeding women will require increased resources, especially in the

short term. In a cost-modelling exercise, the total cost (including drugs, diagnostics and service delivery) of keeping a woman on option B+ was estimated at US$ 2069 over five years *(115)*. However, as maintaining a woman off ART also incurs costs for monitoring and follow-up, the incremental cost of moving from option B to option B+ was relatively low and varied between US$ 92 and US$ 605, depending on the baseline CD4 cell count and breastfeeding status. Several model-based analyses have assessed the cost–effectiveness of strategies for PMTCT of HIV, with many finding options B and B+ to be cost saving or highly cost-effective compared with option A (AZT for the mother during pregnancy, single-dose NVP plus AZT and 3TC for the mother at delivery and continued for a week postpartum and 6 weeks of infant NVP prophylaxis). When outcomes beyond the mother-to-child transmission of HIV are considered, such as maternal health, preventing the mother-to-child transmission of HIV in future pregnancies and preventing horizontal transmission, option B+ has been found to be highly cost-effective compared with option B *(116,117)*.

Equity and acceptability

A qualitative literature review on the acceptability of option B+ indicated high acceptability of lifelong ART among pregnant and breastfeeding women as well as service providers *(71)*. Women have raised concerns of ARV drug toxicity for themselves and their infants but generally value the health benefits and the ability to protect their children and their partners from HIV *(118,119)*. The review also highlighted some of the challenges of lifelong treatment, including disclosure to partners and employers, stigma, lack of support, and costs and time off work associated with clinic visits and drug pickups.

Early programme experience from South Africa suggests that pregnant women find same-day initiation of ART (starting ART on the day of HIV diagnosis) acceptable, especially because in this setting, many women may already be aware of their status, have high levels of treatment literacy and can access support services *(120)*. By contrast, same-day ART initiation in Malawi during the early years of the roll-out of option B+ was associated with a high rate of early loss to follow-up, with many women failing to return for a second visit *(1)*. For national programmes, it is important to strike a balance between starting pregnant women without delay and ensuring that women are adequately prepared, have accepted lifelong ART and have access to support systems, including peer support, to promote treatment adherence.

Although universal ART for all people living with HIV is generally acceptable, there are legitimate concerns about access to lifelong treatment, the limited range of treatment options and the long-term sustainability of ART. As countries implement these recommendations, the right of women to informed consent for all medical services – including the initiation of ART – remains paramount. An approach to ART that is rights based and that offers women the opportunity to make an informed decision will probably result in better acceptability and improved health outcomes.

Implementation considerations

Many concerns raised about the recommendation to provide lifelong ART to all pregnant and breastfeeding women relate to implementation. Although routine testing in antenatal care settings is well established and continues to be recommended by WHO, the goal should be to test pregnant woman at the first antenatal care visit in order to maximize the benefit of early ART. When implementing this recommendation, programme managers

must ensure the quality and accuracy of HIV testing, including retesting all women who test positive prior to initiating ART. Newly diagnosed women should be counselled about the benefits of lifelong treatment as well as the importance of adherence and regular follow-up. Although ART should be initiated without delay, it is important to allow women to make an informed choice. Experience from Malawi and other national programmes that were early adopters of option B+ shows that ART services can be effectively decentralized and provided within maternal, newborn and child health clinics (*see* section 6.10.1 "Delivering ART in maternal and child healt-care settings").

Integration of services benefits mothers and their infants, and is feasible in settings with a high burden of HIV. However, achieving integration will depend on the context and the resources available in terms of staff time and physical space. In one retrospective cohort study from Malawi, 45% of the women interviewed reported that, although they started ART in an antenatal care clinic, they were referred to separate ART services soon after delivery *(106)*. There is no consistent model for when to transition mothers on ART out of maternal, newborn and child health services, but a cohort study *(121)* from South Africa highlighted the importance of this potential additional loss point in the care cascade. In a retrospective review of women referred to ART clinics in the postpartum period, up to 25% did not remain in care five months after referral *(121)*. Roll-out of universal ART for pregnant women should be accompanied by messaging and outreach to the community to underscore the benefits of ART even for asymptomatic people and the importance of remaining in follow-up even after the period of risk for mother-to-child transmission has passed. Such messaging should be harmonized with messages for early treatment initiation for all individuals living with HIV.

Although treatment monitoring using viral load is important for all people on ART, it may be especially valuable for pregnant and breastfeeding women for whom there is added benefit in terms of PMTCT. In these guidelines, enhanced ARV prophylaxis is recommended for HIV-exposed infants at higher risk of acquiring HIV. A maternal viral load above 1000 copies/mL during the last few weeks before delivery is a reliable determinant of increased transmission risk. Viral load testing during pregnancy would be a useful tool for clinical decision-making, and as viral load testing is introduced on a national scale, pregnant and breastfeeding women should be prioritized for access.

In addition to issues related to service delivery, key considerations for national programmes include the need for strengthened data systems to track women on ART across multiple delivery sites, better laboratory support including access to viral load testing and targeted interventions to improve adherence and retention (*see* sections 6.4 "Linkage from HIV testing to enrolment in care", 6.5 "Retention in care" and 6.6 "Adherence"). Women who commence lifelong ART, especially those with young children, may face considerable challenges in seeking regular HIV care and maintaining adherence to treatment regimens. Efforts to scale up treatment require a holistic approach to women's lives and parallel investments in community-based support to improve women's treatment literacy, preparedness and ability to remain in follow-up and adhere to treatment.

Research gaps

Significant knowledge gaps remain about how best to implement universal ART and how to address the challenges of retention and follow-up of the mother and infant pair. The

integration of ARV drug delivery in antenatal care and maternal, neonatal and childcare services (as opposed to referral to ART clinics) requires further implementation experience and assessment. Over time, an increasing proportion of women living with HIV will already be on ART prior to conception. This provides an opportunity to understand the impact of this shift in the epidemic on rates of mother-to-child transmission as well as other pregnancy outcomes, including preterm delivery and low birth weight.

Adolescents and young women living with HIV face unique challenges in preventing the transmission of HIV to their children and attending to their own health needs, including poor access to reproductive health services, poor uptake of testing and poor retention in care *(122)*. Implementation research is urgently needed to identify the drivers of poor outcomes among adolescents, to define how adolescent-friendly maternal and newborn health services should be provided and to develop specific strategies to improve retention in care.

Although ART during pregnancy and breastfeeding provides clear public health benefits in terms of maternal health and preventing transmission to the child, the possible effects of ART (especially preconception ART) on pregnancy outcome require future research. In addition, the potential long-term harm of fetal and infant exposure to maternal drugs is not fully understood. The risk of congenital birth defects is likely to be low for the currently recommended first-line ARV drugs, but little is known about newer drugs and the possible effects on growth, development and organ maturation resulting from exposure to ART absorbed across the placenta and through breast milk.

4.3.3 When to start ART in adolescents (10–19 years of age)

NEW

Recommendations

- ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence).

- As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

Source:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

An estimated 2.1 million adolescents (10–19 years old) were living with HIV globally in 2013. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second-leading cause of death among adolescents worldwide *(123)*.

Adolescence is marked by rapid physical, neurodevelopmental, emotional and social changes *(124)*. Although accurate global data are lacking on mortality due to HIV in this

age group, adolescents appear to be underserved by current HIV services. They have significantly worse access to and coverage of ART than adults, high risk of loss to follow-up *(125–127)*, suboptimal adherence, and special requirements for comprehensive care, including psychosocial support, and sexual and reproductive health care *(128–130)*. Adolescents also face significant barriers to accessing essential health and support services, especially because of policy and legal barriers related to the age of consent *(131)*.

Perinatally infected adolescents are more likely to experience chronic diseases and neurodevelopmental growth and pubertal delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* aligned the clinical and immunological criteria for ART eligibility among adolescents with those for adults (treatment initiation for WHO clinical stage 3 or 4 disease or at a CD4 count at or below 500 cells/mm^3) with the aim of enhancing programmatic simplicity and avoiding delays in treatment initiation while assessing eligibility.

Rationale and supporting evidence

The review of evidence, programmatic data, operational considerations and values and preferences expressed by young people living with HIV led to the development of a separate recommendation for adolescents in 2015. This highlights the important considerations of initiating ART and providing treatment and care for adolescents living with HIV.

The recommendation is based on the strong operational and programmatic advantages of alignment with the criteria for initiating ART among adults and children and the clinical benefits demonstrated by evidence from adult studies *(53)*. There are some limitations in extrapolating from the evidence for adults or children and some uncertainty around the potential benefits that immediate initiation of ART may have on adolescent health outcomes, given the unique challenges that may arise in achieving long-term adherence and retention among adolescents.

A systematic review of the evidence did not identify any studies investigating ART initiation strategies specific to adolescents. This subgroup was also not captured by adult studies that assessed the clinical outcomes of immediate versus delayed ART initiation *(132,133)*. For this reason, the overall quality of the evidence for treating all adolescents living with HIV was rated as low, as indirect evidence from adults was used.

To assess the potential benefits of starting ART earlier, a causal modelling of data from southern and western Africa and Europe was conducted. This examined 4553 ART-naive perinatally infected adolescents 10–15 years of age (median age 12.4 years), of whom 14% presented with CD4 counts above the existing eligibility thresholds of 500 cells/mm^3. In the analysis, median follow-up time was 656 days. Mortality appeared higher when ART was started very late. However, after four years of follow-up, the difference between immediate ART versus initiating ART at or below 500 cells/mm^3 was not significant. These differences were similar for the adolescents who presented with a

CD4 count above 500 cells/mm^3. Overall, the study did not show any clear survival or growth benefit from early initiation of treatment in this population *(134)*.

Indirect evidence shows that perinatally infected adolescents for whom treatment initiation is delayed to 10 years of age are unlikely to normalize CD4 cell count *(135)* and, after onset of chronic lung disease, do not fully recover lung functioning *(136)*, suggesting that perinatally infected adolescents who have survived through childhood untreated may have limited gains from initiating ART earlier compared with initiating treatment in younger children.

The high risk of loss to follow-up in this age group, particularly among adolescents aged 15–19 years *(137–141)*, is an important factor in assessing the trade-off between the risks and benefits of earlier ART initiation. Adolescents are also known to have lower rates of adherence than adults and younger children *(142)*. Two systematic reviews on adherence and viral suppression showed varying rates for adolescents *(143,144)*, and treatment failure was observed among 10% of 1007 perinatally infected children in a multicohort analysis, with the risk being higher with a longer time on ART and when treatment was started in adolescence *(145)*.

While indirect evidence was extracted from paediatric cohort studies for perinatally infected adolescents, no data were found that specifically addressed the key clinical features of behaviourally infected adolescents with regard to timing of ART initiation.

Clinical evidence in support of earlier treatment initiation for both perinatally and behaviourally infected adolescents is limited. Although there is a potential for ARV drugs to have adverse effects on bones, brain and other organs still in development and concerns about the risk of drug resistance due to poor adherence, experience to date suggests that aligning with the initiation criteria for adults will contribute to simplifying programming and further expanding ART coverage *(146)*. It would also present crucial opportunities to engage adolescents living with HIV in care.

Equity and acceptability

In community consultations, adolescents, service providers, parents and caregivers emphasized the importance of ensuring that priority be given to adolescents most in need of treatment as well as the challenge of adherence *(5,147–149)*. The key challenges identified included forgetting to take medicines, having unstable lives that are not conducive to taking daily medication, fear of disclosure and relative lack of power in treatment decision-making. This further highlights the importance of better and more tolerable formulations to support successful treatment.

Feasibility and resource use

Earlier initiation of ART among adolescents is likely to be feasible within existing health systems. Because of late diagnosis *(150)*, many adolescents are already likely to be eligible based on the WHO 2013 initiation criteria, and the increase in the overall number of adolescents starting treatment would therefore be relatively small *(147)*. Increased patient enrolment would nevertheless increase demands on supply chains and provider workload. The experience of some national programmes has shown that, although all adolescents aged 10–15 years can be treated, challenges include ensuring that commodities are available, strengthening laboratory systems and conducting provider training *(148)*.

Increased demand for commodities, human resources and infrastructure is expected to require additional funding. A costing analysis shows that ARV drugs are likely to be the most significant cost driver *(151)*. Laboratory commodities are likely to be the second largest contributor to total cost, followed by human resources and co-trimoxazole.

Implementation considerations

Ensuring that adolescents are diagnosed and receive ART in a timely manner will require developing adolescent-friendly health services (*see* section 6.11 "Delivering HIV services to adolescents"), appropriate provider training and programmes that strongly emphasize support for adherence and retention in care, including through peer support. Specific challenges faced by adolescent girls, such as stigma and gender inequality, will also need to be addressed.

Research gaps

How earlier ART initiation affects retention, adherence and selection of HIV drug resistance among adolescents with less advanced disease requires further investigation. Better-quality age disaggregation of existing cohort and surveillance data is also needed to improve understanding of adolescent-specific issues and needs.

4.3.4 When to start ART in infants and children younger than 10 years of age

Recommendations

ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:

- Infants diagnosed in the first year of life (strong recommendation, moderate-quality evidence);

- **Children living with HIV 1 year old to less than 10 years old** **NEW** **(conditional recommendation, low-quality evidence).**

As a priority, ART should be initiated in all children ≤2 years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count ≤750 cells/mm³ or CD4 percentage <25%, and children 5 years of age and older with WHO HIV clinical stage 3 or 4 disease or CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

Sources:

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Infants and young children living with HIV have an exceptionally high risk of poor outcomes, with up to 52% of children born with HIV dying before the age of 2 years in

the absence of any intervention *(152).* By 5 years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults *(153,154)*. Improved access to early infant diagnosis (EID) has increased the identification of infants living with HIV, but rates of ART initiation among infants living with HIV – all of whom should be initiated on treatment – remain suboptimal. Overall, most children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults: 32% versus 40% globally in 2014 *(155)*.

Diagnosing and retaining children exposed to and living with HIV in care present unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high *(156)*, with retention especially challenging for children who are in HIV care but not receiving ART*(157)*.

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* aligned clinical and immunological criteria for ART eligibility for children older than 5 years with those for adults: that is, treatment was recommended for WHO clinical stage 3 or 4 disease or CD4 cell counts at or below 500 cells/mm^3. ART was also recommended for all children living with HIV younger than 5 years of age, regardless of clinical or immunological status, based largely on operational advantages. For children between 1 and 5 years of age, it was recommended that those younger than 2 years of age with WHO stage 3 or 4 clinical disease or CD4 percentage below 25% or CD4 cell count below 750 cells/mm^3 be given priority. For infants younger than 1 year of age, a strong recommendation to treat regardless of clinical and immunological conditions was maintained, while recognizing the challenges of treating infants in their first 2 weeks of life because of lack of treatment options for which safe and effective dosing has been established and the lack of experience globally. Treatment is further complicated by the high rates of prematurity and low birth weight in low- and middle-income countries.

Countries with a high burden of HIV among children have rapidly adopted the WHO 2013 treatment initiation criteria *(155)*, and some countries have decided to expand ART to all children and adolescents younger than 15 years to simplify ART delivery *(158)*.

Rationale and supporting evidence

A review of the evidence, together with programmatic data and operational considerations, has led to revised recommendations in 2015 to initiate ART in all children with HIV, aligning the recommendation for children with the recommendations for adults and adolescents.

A systematic review *(132)* conducted in 2013 and updated in 2015 identified only one randomized controlled trial, PREDICT, which assessed the clinical benefit of early ART initiation among children *(159)*. The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 percentage above 15% and without United States Centers for Disease Control and Prevention (US CDC) stage C disease, randomizing them to either early treatment or deferred treatment until the CD4 percentage fell below 15%. There was no difference in AIDS-free survival or neurodevelopmental outcomes between the two arms, but height gain was better among those initiating ART earlier *(160)*.

Causal modelling *(161)*, also updated in 2015 using a broader set of prospective data, assessed outcomes for 7358 ART-naive children 5–10 years old (median age 7.2 years), of

whom 26% (1903) presented with CD4 counts exceeding the existing eligibility threshold of 500 cells/mm^3. In this analysis, after five years of follow-up, early ART showed a slight but significant mortality benefit compared to waiting for the CD4 count to fall below 500 cells/mm^3. The causal modelling analysis also showed significantly better growth response among those starting ART immediately *(134)*.

Other evidence suggests that initiating ART earlier could mitigate the negative effects of HIV infection on growth and pubertal and nervous system development *(135,162–167)*.

Earlier initiation of ART may also promote immune recovery. In a retrospective cohort study of the long-term effects of ART on CD4 cell evolution in children receiving ART based on the 2010 WHO initiation criterion, children with a greater degree of immunosuppression at baseline did not recover enough to reach normal values (CD4% >25%) even after five years of ART, whereas the CD4 percentage among children starting ART at higher CD4 levels normalized within a year of receiving ART *(168)*. As shown by the normalization of inflammatory markers, earlier ART initiation is also likely to reduce HIV-induced chronic immune activation, thus potentially limiting the onset of chronic lung disease and increased risk of cardiovascular disease, for which clinical correlates are still missing among children *(169)*.

The recommendation to start ART immediately is conditional for children living with HIV from 1 to less than 10 years of age because of the paucity of evidence supporting ART initiation regardless of the clinical and immunological conditions in this population *(134)*. However, this approach is expected to provide significant programmatic advantages, especially in settings with limited access to immunological testing, a high burden of HIV disease and low ART coverage among children.

Comparing benefits and harm

In addition to clinical considerations, earlier initiation of ART is likely to expand coverage in this age group. A rapid assessment to assess the implementation of a policy to treat all children younger than 15 years in Uganda identified a 74% increase in the number of children newly initiating ART and an increase in ART coverage among children from 22% to 32% between 2013 and 2014 *(146)*. No drop in the testing and ART coverage for infants was noticed, and the proportion of children receiving ART at lower-level health facilities increased from 29% to 35%, suggesting that simplifying the criteria for initiating treatment could also be instrumental in effectively decentralizing ART services. In addition, the time from eligibility to ART initiation significantly decreased, suggesting that simpler initiation criteria allowed more rapid treatment initiation. Programmatic experience suggests that children receiving ART have better retention than those in care but not receiving ART *(146)*. The retention rates in Uganda appeared to be comparable among children starting ART when eligible or with CD4 counts above 500 cells/mm^3, but there was a reduction in retention at six months, highlighting the need to ensure that children and caregivers receive appropriate counselling and support to stay in care *(145)*.

The potential harm of earlier ART initiation includes short-term side-effects that may predispose children to suboptimal ART adherence and subsequently treatment failure *(170,171)*, along with the emergence of drug resistance and the need for second- and third-line regimens, for which options suitable for children are still limited. Treatment failure was observed in 10% of cases in the multicohort analysis, with the risk being higher the longer children are on ART and the older they are when initiating ART *(145)*.

Increasing demands on the health system, drug stock-outs and consequent treatment discontinuation may also contribute to treatment failure and HIV drug resistance. Long-term side-effects and chronic disease may result in increased morbidity and affect the quality of life in adulthood. On balance, the likely clinical and programmatic benefits of earlier ART are likely to outweigh these potential types of harm.

Equity and acceptability

Expanding ART to every child living with HIV is expected to increase equity and be well accepted. In community consultations, the acceptability of earlier treatment for children living with HIV from the perspectives of parents, caregivers and health-care providers was based on the perceived health benefits for the child. However, psychosocial support for parents and caregivers, especially for disclosure, was highlighted as critical to facilitating initiation and improving adherence *(172)*.

Feasibility and resource use

Implementing this recommendation is likely to be feasible, as it represents a relatively small increased burden on current health systems *(146)*. Late diagnosis is still common *(150)*, and an estimated 80% or more of children identified as being HIV positive would already be eligible for ART based on the WHO 2013 recommendations. However, larger numbers of children receiving ART may also lead to higher demand on supply chain systems and increased provider workload. Laboratory monitoring will need to be strengthened to monitor treatment efficacy and identify treatment failure among children. The experience of some national programmes has demonstrated that treating all children with HIV is feasible but highlights the importance of secure commodity supplies, adequate health worker training and the need to ensure sustainability of resources *(146)*.

Increased demand for HIV commodities, human resources and infrastructure may require increased funding. A costing analysis in Zambia has shown that ARV drugs are likely to be the most significant cost driver, accounting for 81% of total costs among children 0–14 years old. Laboratory commodities were the second largest contributor to total cost, followed by human resources and co-trimoxazole *(151)*.

Implementation considerations

As ART is expanded to all children regardless of clinical and immune status, priority for treatment should be given to certain groups of children. These include children younger than 2 years or children with WHO stage 3 or 4 disease or CD4 percentage below 25% or CD4 count at or below 750 cells/mm³ (if younger than 5 years) and CD4 counts at or below 350 cells/mm³ (if older than 5 years). This is because of their higher risk of death and rapid disease progression.

Implementation approaches should include using opportunities to deliver ART for children in maternal, newborn and child health settings *(173)*.

Expanding ART services for children will require strategies to improve retention in care and support adherence. Careful clinical monitoring remains essential to assess the risk of treatment failure, but lack of laboratory monitoring should not be a barrier to initiating ART *(174)*.

Research gaps

How earlier ART affects retention, adherence and potential HIV drug resistance among children with less advanced disease requires further investigation. Optimal service delivery models are also needed to ensure rapid identification of and ART initiation among HIV-infected infants and children as well as strategies to provide an integrated package of care to reduce overall child mortality.

4.3.5 Timing of ART for adults and children with TB

> #### Recommendations
>
> - **ART should be started in all TB patients living with HIV, regardless of CD4 cell count (strong recommendation, high-quality evidence).**[a]
>
> - TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high-quality evidence).[a]
>
> - HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment.
>
> - ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of antituberculosis treatment, regardless of the CD4 cell count and clinical stage (strong recommendation, low-quality evidence).
>
> [a] The quality of evidence for this recommendation was upgraded to high in 2015.
>
> *Source (children)*: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Early initiation of ART for patients with HIV-associated TB is critical in reducing morbidity and mortality. Since 2010, WHO has recommended that ART be started in all TB patients living with HIV, regardless of CD4 cell count, as soon as possible within the first 8 weeks of TB treatment. Since then, several additional results from randomized controlled trials have been published. In 2015, a systematic review was conducted to reassess the optimal timing of ART initiation among people living with HIV and active TB to minimize death, AIDS-defining events, severe treatment-related adverse events and incidence of IRIS.

Rationale and supporting evidence

The review of evidence focused on the relative benefits of early ART started within 2 weeks (defined as "earlier initiation") or 8 weeks (defined as "early initiation") of TB treatment initiation, compared to ART initiated after 8 weeks (defined as "delayed initiation"). Early and earlier initiation was also compared to delayed ART, initiated after 8 weeks but before completion of TB treatment. Particular consideration was given to people with profound immunosuppression (CD4 cell count less than 50 cells/mm^3).

High-quality evidence from eight trials *(175–182)* showed that, across the CD4 strata, early ART (within 8 weeks of TB treatment) is associated with a reduction in overall mortality, compared with ART initiated after 8 weeks of TB treatment or after TB treatment is completed. In a subanalysis of patients with a CD4 count of less than 50 cells/mm^3, the reduction in mortality was statistically significant *(175,178,183,184)*. High-quality evidence from four trials also demonstrated a reduction in mortality when ART was started within 2 weeks of starting TB treatment, compared with delayed initiation but during TB treatment, across all CD4 counts *(175–177,181)*. Similarly, earlier ART for patients with a CD4 count of less than 50 cells/mm^3 was associated with a reduction in mortality *(175,184)*. Furthermore, one trial found a significant reduction in the combined outcome of AIDS-defining illness or death among this group *(185)*.

Overall, the systematic review found similar levels of grade 3 or 4 non-IRIS adverse events among patients starting ART early or earlier with all CD4 cell counts compared to delayed ART *(186)*. Subanalysis of patients with a CD4 cell count of less than 50 cells/mm^3 showed similar findings when comparing early ART with delayed ART within 24 weeks of starting TB treatment.

The evidence showed a tendency towards reduction in AIDS-defining illnesses across all CD4 strata when early and earlier ART were compared with delayed initiation during TB treatment. Subanalysis of patients with a CD4 count of less than 50 cells/mm^3 showed similar findings with early ART *(175)* and earlier ART compared with delayed ART within 24 weeks of starting TB treatment.

However, overall there was a statistically significant, higher incidence of IRIS in patients who initiated ART within 8 weeks when compared with delayed ART initiation across the CD4 strata and in the subanalysis of CD4 count less than 50 cells/mm^3. A separate subanalysis was conducted of high-quality evidence from five randomized controlled trials to assess IRIS-related mortality. While there was a statistically significant increase in IRIS-related mortality associated with early ART, the number of deaths was small (9/335) in comparison with overall deaths *(177,178,180,182,187,188)*.

Based on this evidence, ART should be started in all TB patients living with HIV, regardless of CD4 count because of the overall benefit of early ART. A direct comparison of the effect of starting ART within 2 weeks compared with after 2 weeks but within 8 weeks of TB treatment was not feasible. However, ART initiation within 2 weeks is important in people with CD4 cell counts less than 50 cells/mm^3 because mortality in this group is particularly high. Inability to measure CD4 cell count should not be a barrier to starting ART earlier.

Data from the reviewed studies primarily included adults and adolescents and were not disaggregated according to age, so it was not possible to measure the effect of early ART among children with HIV-associated TB. However, data from one observational study in South Africa showed increased mortality and poorer virological response in children with HIV-associated TB when ART was initiated more than 8 weeks after starting TB treatment, particularly in children with severe immunosuppression *(189)*. The existing strong recommendation developed in 2010 that was based on low-quality evidence is therefore maintained in these guidelines.

Caution is needed in people living with HIV with TB meningitis, as immediate ART is significantly associated with more severe adverse events when compared with initiation of ART 2 months after the start of TB treatment *(190)*.

Feasibility and resource use

Among HIV-positive TB patients detected globally in 2013, 70% were given ART during TB treatment, showing the overall feasibility of the intervention *(191)*. Routine data on the timing of ART is not reported globally. However, data are collected in special surveys in some countries. For example, survey findings undertaken in 22 randomly selected ART centres across India suggested the feasibility of early ART in TB patients, with 70% of patients receiving ART within 30 days and 88% within 2 months (Rewari, WHO India, unpublished data, June 2015). No important differences in resource use are expected when comparing early and late timing of ART among TB patients, as it is anticipated that all patients will start ART within a few months. However, the increased incidence of IRIS associated with early ART initiation may require additional resources to diagnose and manage this condition.

Implementation considerations

Patients should be closely followed up to assess the occurrence of side-effects related to co-treatment and of TB-associated IRIS, which is common in patients with TB started on ART but usually self-limited. Stakeholders and service providers should establish mechanisms to ensure that people living with HIV receive TB treatment along with ART, emphasizing integrated and patient-centred care, preferably at the same location (*see* section 6.10.2 "Delivering ART in TB treatment settings and TB treatment in HIV care settings").

Research gaps

Research gaps include questions addressing the optimal timing of initiation of ART in children living with HIV being treated for TB and patients with drug-resistant TB. There is also a need for studies that compare the effect of starting ART within 2 weeks and from 2 weeks but within 8 weeks of TB treatment. More research is also needed into the optimal timing of initiation of ART in adults and children with TB meningitis.

4.3.6 Diagnosis and treatment of recent HIV infection

Recent HIV infection is defined as the period up to 6 months following HIV acquisition, during which specific anti-HIV antibodies become detectable by serological tests (seroconversion) and when the viral load steady state (set point) and viral reservoirs are usually established *(192–194)*. During the first weeks of this phase, people recently infected with HIV can (but will not always) develop an acute clinical syndrome associated with the initial and rapid burst of viraemia characterized by the presence of some self-limited clinical signs and symptoms – such as fever, myalgia, pharyngitis and rash – that usually subside after 2–4 weeks *(195)*. During this early stage of HIV infection, the immune system also starts to get damaged and the frequently unsuspecting infected person may be most infectious to others *(196–198)*.

With the increasing availability of more accurate diagnostic testing, more effective drug regimens and better knowledge of the dynamics of HIV transmission and viral reservoirs, early diagnosis during recent HIV infection has been viewed as an opportunity for treatment and prevention interventions, with a potentially important public health impact *(11)*.

Clinical studies have indicated that initiation of ART during recent HIV infection can reduce the size of the latent viral reservoir and delay viral rebound after ART discontinuation *(199–203)*. Diagnosis and treatment of people with very early HIV infection are therefore potentially critical for research on a cure for HIV, because such people are likely have smaller reservoirs, decreased viral replication and genetic diversity, sustained T-cell and B-cell function and better immune restoration potential. In addition, they have a lack of extended inflammatory responses and comorbidities associated with chronic infections and no or limited previous exposure to ARVs *(11)*. There are several clinical trials addressing this subject *(204–208)*.

HIV transmission can be greatly amplified during recent infection *(209,210)* because the HIV founder viruses causing early infection are particularly infectious *(211)* and the viral loads of people with recent infection are exceptionally high *(212)*. The diagnosis and treatment of people with recent HIV infection may therefore represent a potentially significant public health intervention. However, the proportion of transmission events attributable to recent infection is challenging to study and estimate, because of the difficulty of diagnosis. The impact of HIV transmission during the early stages of infection has been modelled in different settings and population groups, with studies showing quite divergent results, suggesting that anywhere from 2% to 89% of HIV transmission can occur during this stage of infection *(209,213–222)*. This large variation between studies can be explained by the variability of several key factors, such as duration of infection, behaviour, use of barrier methods, clustering and epidemic phase, which influence the proportion of transmissions that can take place during early HIV infection in different settings but need to be better understood.

Identifying people with recent HIV infection is complicated by the brevity of the phase, the non-specific symptoms associated with the acute infection and the initial absence of anti-HIV antibodies. Because traditional and point-of-care HIV diagnostic tests cannot accurately detect the earliest phase of infection, the diagnosis of recent infection relies on direct detection of the virus, which is complex, costly and not widely available. Finding people with recent infection either in longitudinal cohorts of subjects at high risk for acquiring the virus or through cross-sectional screening has proven very difficult, and the opportunity for diagnosis is generally missed during this phase *(223)*. There are also substantial financial, technical and logistical barriers involved in diagnosis, linkage and treatment *(224,225)*.

In light of the opportunities and challenges, WHO has not yet established a diagnostic strategy or any specific recommendation to identify or treat people during this phase of infection. However, important areas of research have been identified that will help to guide surveillance, diagnosis and management of recent HIV infection, particularly in low- and middle-income countries. Further technical advances and more knowledge on the pathogenesis of the early stages of HIV infection are essential to enable more effective detection of people with recent infection in order to improve HIV treatment outcomes and prevent HIV transmission.

4.4   What to start: first-line ART

Table 4.1. First-line ART regimens for adults, pregnant or breastfeeding women, adolescents and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[c] TDF + 3TC (or FTC) + EFV$_{400}$[c,e] TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG[c,d] TDF (or ABC) + 3TC (or FTC) + EFV$_{400}$[c,d,e] TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

[a]   For adults and adolescents, d4T should be discontinued as an option in first-line treatment.

[b]   ABC or boosted protease inhibitors (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

[c]   Safety and efficacy data on the use of DTG and EFV$_{400}$ in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.

[d]   Conditional recommendation, moderate-quality evidence.

[e]   EFV at lower dose (400 mg/day).

3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.

4.4.1 First-line ART for adults

Recommendations

- First-line ART for adults[a] should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI).

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).

- If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended:

  – AZT + 3TC + EFV

  – AZT + 3TC + NVP

  – TDF + 3TC (or FTC) + NVP
    (strong recommendation, moderate-quality evidence).

- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional recommendation, moderate-quality evidence).** **NEW**

- Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

[a] Adults include pregnant and breastfeeding women, for whom additional guidance is found in Box 4.3.

3TC lamivudine, AZT zidovudine, d4T stavudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Table 4.2. First-line ART regimens for adults (see Annex 11 for doses)

Preferred regimen	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP)
	TDF + 3TC (or FTC) + DTG[a]
	TDF + 3TC (or FTC) + EFV$_{400}$[b]
	TDF + 3TC (or FTC) +NVP
Special circumstances[c,d]	Regimens containing ABC and boosted PIs

[a] Safety and efficacy data on DTG for pregnant and breastfeeding women and TB coinfection are still pending.

[b] Efficacy data for EFV at a lower dose of 400 mg/day in the case of pregnant and breastfeeding women and TB coinfection are still pending.

[c] Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug–drug interactions, drug procurement and supply management issues, or for other reasons.

[d] Using stavudine (d4T) as an option in first-line treatment should be discontinued.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Background

WHO promotes a public health approach to ART involving less toxic, more convenient and simplified ARV regimens, with a limited number of preferred first-line options that may be used across a range of populations. Other requirements are that they should be pharmacologically compatible with recommended therapies for coinfections and comorbidities that commonly affect people living with HIV *(226–232)*.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* recommend tenofovir (TDF) + lamivudine (3TC) (or emtricitabine [FTC]) + efavirenz (EFV) as the preferred first-line regimen for treatment initiation in ART-naive adults, preferably as a fixed-dose combination (FDC). This approach has clinical, operational and programmatic benefits when compared with other NNRTI- and PI-based options *(9,233)*. The 2013 guidelines also emphasized the importance of discontinuing the use of stavudine (d4T) in first-line regimens because of its well-known long-term mitochondrial toxicity *(234–238)*.

Almost 70% of all people taking first-line ART were using this preferred combination at the end of 2014, but only 60% were using it as an FDC. The global phasing out of d4T as a preferred option in first-line ART has been substantial, with less than 5% of individuals living with HIV on ART using this drug *(239)*.

A large body of clinical and programmatic evidence representing an estimated 15 million person-years of experience supports the use of EFV 600 mg in a range of settings when combined with TDF and 3TC (or FTC) *(240–242)*. This provides a level of confidence that does not exist with the currently available alternatives, including the effectiveness of this dose in patients receiving concomitant rifampicin-based treatment for TB, and the efficacy of this regimen during pregnancy. However, observational studies suggest that up to half of people using EFV may present with central nervous system (CNS) side-effects such as dizziness, sleep disturbance, abnormal dreams and depression. These side-effects may overlap significantly with other neuropsychiatric manifestations of HIV, complicating the

establishment of the real cause and frequency of these events in patients taking EFV *(243)*. A recent analysis of trial data found a twofold increased hazard of suicide with initial treatment using an EFV-containing regimen compared with regimens without EFV *(244)*. However, no evident association was found in other studies *(245–247)*.

New developments in ARV drugs and formulations include the introduction of new drug classes and dose reduction studies for some key first-line ARV drugs that show lower toxicity risk and similar or higher therapeutic efficacy when compared with current standard treatment options. This could potentially extend the benefits and durability of anti-HIV regimens *(248–254)*.

Rationale and supporting evidence

TDF + 3TC (or FTC) + EFV as the preferred first-line ART regimen

Systematic reviews conducted to establish the preferred first-line ART regimen for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* found moderate-quality evidence indicating that the once-daily combination of TDF + 3TC (or FTC) + EFV is less frequently associated with severe adverse events and has a better virological and treatment response when compared with other once- or twice-daily NNRTI- or protease inhibitor (PI)-containing regimens *(255)*. Furthermore, TDF + 3TC (or FTC) + EFV offers the opportunity to harmonize regimens across different populations: TDF + FTC or TDF + 3TC is the preferred NRTI backbone for people coinfected with HIV and HBV and can be used for people coinfected with TB and pregnant women. EFV is also the preferred NNRTI for people with HIV and TB due to pharmacological compatibility with TB drugs and for people with HIV and HBV coinfection due to lower risk of hepatic toxicity. A published meta-analysis and a further updated analysis comparing the use of EFV and other ARV drugs during the first trimester of pregnancy showed no increased risk of birth defects, confirming the suitability of EFV for use in pregnant women *(114,256,257)*.

In 2015, a systematic review was conducted of the comparative safety of EFV-containing regimens and their impact of CNS adverse events. The review showed that that 90% of patients remained on EFV-containing regimens (with a median of 78 weeks of follow-up). Although the relative risk of discontinuation due to adverse events was higher when compared with other first-line options the absolute difference was low (<5%). No difference in terms of severe adverse events was found in this comparative analysis *(247)*.

Recent data on the safety of TDF and EFV during pregnancy are also reassuring, confirming studies reviewed for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (257,258)*. There was no evidence of an increased risk of congenital anomalies with TDF or EFV compared to other ARV drugs *(259,260)*. The risk of neural tube defect associated with EFV remains low and is comparable to the general population in the United States *(259,261)*. (More information on TDF and EFV toxicity may be found in section 4.6 "Monitoring of and substitutions for ARV drug toxicities".)

The availability of this regimen as a generic FDC and the significant price reductions in the past few years also support maintaining TDF + 3TC (or FTC) + EFV as the preferred option for ART initiation.

DTG and EFV 400 mg/day as new alternative options in first-line regimens

In 2015, a systematic review and network meta-analysis was conducted to assess the direct and indirect comparative evidence of the efficacy and safety of the integrase inhibitors (INSTIs) dolutegravir (DTG), raltegravir (RAL) and elvitegravir/cobicistat (EVGC/COBI) as well as EFV at the lower dose of 400 mg/day in adults with HIV *(262)*. Seventy one trials, involving 34 032 patients randomized to 161 treatment arms were included in the review. Direct comparative evidence was obtained from seven randomized controlled trials *(263–269)*. The analysis showed moderate-quality evidence that two NRTIs + INSTI was a generally more effective regimen (with higher viral suppression and CD4 cell recovery rates and lower risk of treatment discontinuation) than two NRTIs + EFV at the standard dose of 600 mg/day in ART-naive adults and that DTG has a comparable effect to that of RAL but better than that of EVG + cobicistat in terms of viral suppression and treatment discontinuation. There was a non-statistically significant tendency towards increased viral suppression with DTG when compared with EFV at a lower dose of 400 mg/day.

In the same systematic review, there was moderate-quality evidence showing that EFV 400 mg/day was comparable to EFV 600 mg/day in terms of viral suppression but better in terms of CD4 cell count recovery and protective in terms of treatment discontinuation due to adverse events. Furthermore, all treatment regimens were comparable with respect to mortality or AIDS-defining illnesses (low-quality evidence) and emergent serious adverse events, with the exception of nevirapine (NVP) (moderate-quality evidence).

DTG also has other clinical and programmatic advantages when compared with EFV 600 mg, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier when compared with EFV and other ARV drugs. Its long half-life, low cost and low dose mean that it is feasible to include this drug in a small once-daily FDC *(270)*. DTG has documented in vitro and clinical activity against HIV-2 infection, which is naturally resistant to EFV *(271,272)*. When compared with the standard dose of EFV, EFV 400 mg/day is also associated with lower toxicity, lower cost and smaller pill size.

The safety and efficacy of DTG and EFV 400 mg/day during pregnancy and among TB/HIV-coinfected patients using rifampicin has not been established. Pharmacokinetic studies show that rifampicin-based treatment leads to short-term reductions in drug levels of EFV at the standard dose of 600 mg/day during the first 2 weeks of treatment, but increases in EFV drug levels have been consistently observed across several pharmacokinetic studies after longer-term treatment together with rifampicin-based combinations *(273)*. However, it is not clear whether the same consistent efficacy will be seen for the lower 400-mg dose of EFV. Similarly, rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary, but there are very few studies and limited clinical experience with this combination, particularly in TB-coinfected patients *(274)*.

While two recent studies suggest that pregnancy may lower EFV plasma concentrations *(275,276)*, a recent review of six studies concluded that there was a limited effect on the pharmacokinetics of EFV at the standard 600-mg once-daily dose during the third trimester of pregnancy *(277)*. Rates of vertical transmission of HIV in these studies were low. There are currently no published safety or efficacy data available on the outcomes of treatment with DTG during pregnancy and breastfeeding. Furthermore, calcium or iron

supplements frequently used during pregnancy could significantly reduce DTG drug levels *(278)*. Pharmacokinetic studies of EFV 400 mg/day and DTG in pregnancy and when co-administered with TB drugs are either planned or in progress *(279,280)*.

Single formulations and FDCs containing these two new options are expected to be available in 2017 and 2018, respectively, with forecasting projections suggesting a good potential for price reduction as a result of generic competition in the future *(281,282)*.

The clinical and potential programmatic benefits of DTG and EFV 400 mg/day for the majority of patients warrant their inclusion as new alternative options in first-line ART. However, further research is needed to establish their suitability for use during pregnancy and concurrent rifampicin-based TB treatment.

Other alternative first-line ARV regimens

As stand-alone formulations and FDCs containing DTG and EFV 400 mg/day are not likely to be available in the next few years, the alternative regimens containing zidovudine (AZT) and NVP recommended in 2013 are maintained. If TDF + 3TC (or FTC) + EFV cannot be used, other once- or twice-daily NNRTI-containing regimens (AZT + 3TC + EFV, AZT + 3TC + NVP and TDF + 3TC [or FTC] + NVP) can be used as alternative first-line regimens in ART-naive people but have potential clinical and programmatic disadvantages when compared with the preferred option and the new alternative regimens containing DTG and EFV 400 mg/day. In special circumstances, ABC and boosted PIs are acceptable as potential back-up options but are not recommended as preferred alternatives; they should be used only when other options are not available.

There are persistent concerns about the higher risk of severe adverse events with NVP compared with EFV and other ARV drugs, particularly in ART-naive patients with high baseline CD4 cell counts *(283–286)*. A systematic review conducted for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* showed that people receiving NVP are twice as likely as those receiving EFV to discontinue treatment due to adverse events *(256)*. The review of new first-line ART options conducted in 2015 confirmed this finding, with moderate-quality evidence showing that all treatment regimens investigated were comparable with respect to the occurrence of serious adverse events, with the exception of NVP *(262)*. Some studies showed an increased risk for severe hepatic and skin reactions when using NVP, particularly among pregnant women *(287–290)*. However, other studies, including a systematic review on the risk of NVP-associated toxicity in pregnant women, suggest that the frequency of adverse events is higher but no greater than that observed in the general adult population with HIV *(291–294)*. The current body of evidence therefore confirms the increased risk of adverse events associated with NVP use. NVP should be used with caution as an alternative in individuals with a high baseline CD4 cell count, including pregnant women and women who might be pregnant. However, other alternative drugs with better overall toxicity profiles should be considered. More studies on this topic are still needed. (More information on NVP toxicity can be found in section 4.6.5 "Toxicity monitoring for other ARV drugs in adults, adolescents and children".)

WHO recommends that the use of d4T-containing regimens be discontinued *(295)*. In settings where d4T regimens are still used for initiating ART, plans for phasing out d4T should be implemented or accelerated with a view to replacing d4T with TDF-based first-line regimens *(296)*.

Research gaps

Further research is required to determine the safety of DTG and the efficacy of EFV 400 mg/day in people with HIV/TB coinfection and in pregnant and breastfeeding women. EFV exhibits significant genetic-based interindividual pharmacokinetic variability, which can make it challenging to undertake accurate pharmacokinetic/pharmacodynamic (pK/pD) analysis. There is a need to conduct this modelling in African and non-African populations and in people without the CYP2B6 genotype.

Box 4.3. ART in pregnant and breastfeeding women and strategies for PMTCT

These guidelines provide recommendations for universal treatment at any CD4 cell count and any stage of disease, harmonized across all populations, including pregnant and breastfeeding women. The preferred first-line regimen is also harmonized for all adults and adolescents, whether pregnant or not, but there are a few key differences in terms of the alternative regimens for first-line ART. Although there are no data to suggest that any of the INSTIs including DTG have any fetal toxicity, DTG has not been sufficiently studied in pregnant women for it to be recommended as an alternative in this population, unless the perceived benefits outweigh the potential risks. In addition, the efficacy of low-dose EFV in pregnancy has not been studied. As a result, alternative first-line ART for pregnant and breastfeeding women includes only NVP in place of EFV and AZT in place of TDF. For pregnant women on second-line ART, the options are the same as for non-pregnant adults and include boosted PIs such as lopinavir/ritonavir (LPV/r) and atazanavir (ATV)/r, but it is noteworthy that a subanalysis of women given LPV/r in the PROMISE trial *(297)* suggests an association between the use of boosted PIs and prematurity. (*See* section 4.6.6 "Special considerations for toxicity monitoring during pregnancy and breastfeeding".)

Universal ART is an important element of PMTCT, but in order to achieve elimination of new infections among children, PMTCT programmes must incorporate a spectrum of activities, including HIV prevention for HIV-negative women, access to family planning to prevent unintended pregnancy, widespread testing of pregnant women early in antenatal care and support to women living with HIV to remain adherent to ART and retained in care throughout pregnancy and breastfeeding and for life. In the case of women testing negative for HIV who live in high-burden settings, testing should be repeated later in pregnancy and during breastfeeding to identify newly acquired HIV infection.

In addition to receiving ART, pregnant women living with HIV should be offered the recommended package of pregnancy care, and additional interventions such as screening for STIs (such as hepatitis B and syphilis), nutritional support, infant feeding counselling and family planning guidance. Careful monitoring for the development of pregnancy-induced hypertension and pre-eclampsia – especially for women on ART prior to conception – is advised.

Throughout pregnancy, key principles and practices of safe motherhood should be followed, including reinforcement of recommended antenatal clinic visits and facility-based delivery by skilled birth attendants. Instrumentation should be avoided unless essential, and newborns should be washed of any blood and cared for using non-invasive techniques as much as possible. Health workers should follow universal precautions for all deliveries, including deliveries by women living with HIV. Special efforts should be made to ensure that delivery care for women living with HIV is provided in a non-stigmatizing and supportive manner.

Although elective caesarean section has been shown to protect against HIV acquisition, especially in the absence of ARV drugs or in the case of a high viral load, WHO does not recommend it in resource-limited settings specifically for HIV infection; rather, it is recommended for obstetric and other medical indications.

Newborn prophylaxis remains an important aspect of PMTCT and, for mothers who start ART later in pregnancy, these guidelines propose enhanced prophylaxis recommendations that call for longer duration of prophylaxis and multiple drugs. (*See* section 4.4.7 "Infant prophylaxis".)

Sources:

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WHO recommendations on postnatal care of the mother and newborn. Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/postnatal-care-recommendations/en).

4.4.2 Fixed-dose combinations and once-daily regimens

NEW

Recommendation

Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (strong recommendation, moderate-quality evidence).

Background

WHO has recognized the potential benefits of FDCs and once-daily regimens for ART since 2003. FDCs are recommended by WHO in other disease areas such as TB and malaria as a way to improve adherence, simplify prescribing and procurement, and reduce prescribing errors *(298,299)*. New ARV drugs and formulations are available that support an expanded evidence base, allowing for a rigorous assessment of the clinical and programme impact of FDC once-daily regimens.

Rationale and supporting evidence

Two systematic reviews assessed the benefits of FDCs *(233)* and once-daily regimens *(300)*.

The first review identified 21 studies and found that, compared to separate tablets, patients receiving FDCs tended to have higher levels of adherence, both in randomized trials and observational cohorts *(233)*. There was also a tendency towards greater viral suppression among patients receiving FDCs in randomized trials and observational cohort studies. In all studies reporting patient preference, FDCs were preferred. The overall quality of the evidence was rated as moderate for randomized trials and low for observational studies. The second review of 19 randomized trials found that average adherence was higher for once-daily regimens than twice-daily regimens *(300)*. The overall quality of the evidence was rated as moderate due to the risk of bias.

The Operational Guideline Development Group concluded that the recommendation favouring FDCs and once-daily regimens should be strong in view of the clear patient preference, as measured by improved quality of life *(301–304)*, patient satisfaction *(302,304–306)*, patient preference *(302,303,307,308)* and ease of regimen use *(309)*. Programme managers and procurers have also recognized the benefits *(310)*.

Implementation considerations

Some of the preferred regimens recommended by WHO are currently not available as FDCs, particularly for younger children, and manufacturers are encouraged to explore the potential for co-formulation. Patients may need to switch to separate tablets in case of drug substitutions due to intolerance, contraindications or development of resistance; in such cases, additional adherence counselling and monitoring may be required to manage this change. Finally, in some countries, FDC regimens are more expensive than corresponding separate-tablet regimens, and donors and procurers will need to balance cost and benefits.

4.4.3 First-line ART for adolescents

Recommendations

First-line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI:

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, low-quality evidence).

- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV$_{400}$[a] may be used as alternative options to initiate ART (conditional recommendation, low-quality evidence).**

If preferred regimens are contraindicated or not available, one of the following alternative options is recommended (strong recommendation, moderate-quality evidence):

ABC + 3TC + EFV
ABC + 3TC + NVP
AZT + 3TC + EFV
AZT + 3TC + NVP
TDF + 3TC (or FTC) + NVP

[a] EFV at a lower dose (400 mg/day).

Table 4.3. Summary of first-line ART regimens for adolescents

Preferred regimens[a]	TDF + 3TC (or FTC) + EFV
Alternative regimens	TDF (or ABC) + 3TC (or FTC) + DTG
	TDF (or ABC) + 3TC (or FTC) + EFV$_{400}$
	ABC + 3TC + EFV
	ABC + 3TC + NVP
	AZT + 3TC + EFV
	AZT + 3TC + NVP
	TDF + 3TC (or FTC) + NVP
Special circumstances[b,c]	Regimens containing boosted PIs

[a] To date, there is limited experience with the use of low-dose EFV and DTG in adolescents. While no age or weight restrictions apply to the use of EFV 400 mg/day, which can be used starting from a weight of 20 kg (Annex 11c), the use of DTG is approved only for adolescents who are older than 12 years and weigh more than 40 kg *(311)*. In addition, safety and pharmacokinetic data on TB coinfection and pregnancy are still pending.

[b] Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug–drug interactions, drug procurement and supply management issues or for other reasons.

[c] Using d4T as an option in first-line treatment should be discontinued.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Background

Identifying the most suitable regimen for adolescents is of critical importance in light of the documented risk of poor adherence relative to adults in some settings *(143,144),* which places them at high risk for treatment failure and the development of drug resistance *(145)*.

The toxicity profile of the currently recommended first-line adult regimen – particularly the CNS effects of EFV at standard dosing – is of potential concern due to the impact that the CNS effects may have on the quality of life and level of adherence. In this context, more acceptable and forgiving regimens have been proposed for this specific age group, but introducing them while also preserving regimen harmonization remains challenging.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that adolescents be started on an EFV-containing regimen combined with TDF + FTC or 3TC to reduce pill burden and promote harmonization with adult regimens and formulations. New recommendations in 2015 are based on careful consideration of risks and benefits, the values and preferences of adolescents living with HIV and the programmatic advantage of full harmonization with first-line adult recommendations.

Rationale and supporting evidence

Two systematic reviews *(312,313)* were conducted to evaluate alternative first-line options for adolescents, but only one randomized controlled trial of first-line NNRTI-based versus PI-based regimens was identified. The PENPACT 1 randomized controlled trial *(314)* was conducted in high- and middle-income countries (Europe, USA, Brazil, Argentina, Bahamas and Puerto Rico) and included adolescents. At 4 years after ART initiation, no significant difference was detected between the two arms in terms of efficacy or toxicity, and findings did not differ based on age. However, the overall quality of the evidence is low due to the serious indirectness of the data, as adolescents were underrepresented in the trial population (the median age was 6.5 years) and many initiated regimens containing NVP or nelfinavir instead of the currently recommended first-line regimen. Overall, the potential use of PI-based regimens in first-line therapy is feasible but is likely to add complexity to treatment programmes by further diversifying the use of drugs across age groups.

In light of this and the paucity of data, it is possible to extrapolate from the evidence gathered in adults and recommend full harmonization of first-line regimens for adolescents. DTG-based and low-dose EFV-based regimens are therefore recommended as alternative preferred regimens where available and when age appropriate. These options are considered particularly suitable for adolescents in light of the potential for reduced side-effects and reduced risk of selecting drug resistance *(269)*. DTG, which is currently licensed for adolescents 12 years of age and older and above 40 kg *(315)*, has a very favourable genetic barrier to resistance, which would reduce the risk for selection of resistance mutations even in cases of poor adherence *(316)*. However, due to the lack of specific comparative evidence from trials, some uncertainty remains with regard to the use of these regimens in adolescents.

Clinical considerations

In general, the choice of regimens for adolescents should be guided by:

- the need to use potent and forgiving first-line regimens that minimize toxicity;
- the convenience of once-daily dosing and the use of FDCs whenever possible;
- the use of non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and
- the desirability of aligning recommended regimens for adolescents with those for adults.

A specific consideration for clinicians and other health-care providers relates to whether and how regimen changes can be introduced among clinically stable adolescents who started ART during childhood. As children get older, more options become available with advantages over current first-line regimens, such as FDCs, improved toxicity profile and dosing advantages. Modifying ART regimens of clinically stable adolescents may simplify treatment management and harmonize the regimens in use. The choice between a full

Table 4.4. Considerations for simplifying and harmonizing ART for adolescents with no history of treatment failure on any regimen[a]

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	Reduced risk of d4T-related toxicity May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen)	Aligned with adult regimens
LPV/r	No need to change, but consider substituting LPV/r with EFV600[b], EFV400[c] or DTG	May improve adherence as a result of once-daily dosing Reduced risk of metabolic alterations	Aligned with adult regimens Preserve PI for second-line ART
AZT	No need to change but may consider changing to TDF	May improve adherence as a result of once-daily dosing (if on EFV or DTG) May reduce the risk of exacerbating anaemia	Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	Fixed-dose combinations can be used (if also on EFV)	Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV600[b], EFV400[c] or DTG	May improve adherence as a result of once-daily dosing (if combined TDF)	Aligned with adult regimens

[a] Defined according to the criteria for treatment failure adopted nationally, preferably using viral load testing, where feasible and available.

[b] EFV at standard dose (600 mg/day).

[c] EFV at lower dose (400 mg/day).

ABC abacavir, AZT zidovudine, DTG daltegravir, EFV efavirenz, LPV lopinavir, NVP nevirapine, r ritonavir, PI protease inhibitor, TDF tenofovir

regimen change and single drug substitutions should be made in the context of adult regimen harmonization and the convenience of once-daily medications in the best formulations available. Table 4.4 summarizes relevant considerations for simplifying and harmonizing ART in adolescents with no history of treatment failure.

Research gaps

The long-term efficacy and safety of TDF and EFV or DTG in adolescents and the recommended regimens need further investigation. More data are needed on the bone, growth and renal toxicity profiles of TDF in adolescents, especially in the context of malnutrition and delays in growth and development (i.e. puberty). Similarly, adverse events associated with EFV during adolescence, such as CNS effects, require investigation to ensure safe harmonization with adult regimens. Toxicity surveillance systems implemented alongside ART, particularly for new approaches such as DTG or low-dose EFV, can provide data to better understand the frequency and clinical relevance of toxicities. In addition, studies to inform the development of long-acting formulations of existing and newer compounds, which would be particularly beneficial for this population, should be prioritized.

4.4.4 First-line ART for children 3–10 years of age

Recommendations

For children 3 to less than 10 years of age, the NRTI backbone should be one of the following, in preferential order (conditional recommendation, moderate-quality evidence[a]):

- ABC + 3TC

- AZT or TDF + 3TC (or FTC).

For children 3 years and older, EFV is the preferred NNRTI for first-line treatment and NVP is the preferred alternative (strong recommendation, low-quality evidence).

[a] Strength of evidence reviewed in 2015.

Table 4.5. Summary of recommended first-line ART regimens for children 3–10 years of age

Preferred	ABC + 3TC + EFV
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir

Background

Despite increased access to EID and the widespread availability of several child-friendly FDCs, ART coverage among children lags significantly behind that of adults *(317)*. Treatment recommendations for children should be implemented at all levels of the health system, including the primary care level, and by all ART service providers, rather than paediatric specialists alone.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommended starting with an EFV-containing regimen combined with an NRTI backbone in children 3 years and older. Despite the lack of direct comparison, the recommended NRTI backbones, in preferential order, were ABC + 3TC followed by AZT or TDF + 3TC (or FTC). Although more effective and better-tolerated drugs – such as DTG – have become available for adults and adolescents since 2013, EFV remains the only widely accessible option to ensure harmonization of regimens across age groups. At the same time, new evidence has become available to inform the choice of NRTI backbone *(318)*, leading to a revised recommendation in 2015.

Rationale and supporting evidence

A systematic review was conducted to assess the efficacy and safety of ABC-containing regimens compared to AZT and TDF-containing regimens. Only one randomized controlled trial was identified, involving the comparison of different NRTI backbones in combination with NNRTI in a large cohort of African children. This study *(318)* demonstrated that ABC and AZT were comparable in their clinical, immunological and virological response, as well as safety and tolerability. However, the choice of first-line NRTIs affects second-line ART, and failure of AZT results in the accumulation of thymidine analogue mutations, reducing susceptibility to ABC or TDF in a subsequent regimen (if two or more thymidine analogue mutations are present). For these reasons, ABC + 3TC should remain the preferred option for the first-line NRTI backbone in children in this age group.

The systematic review did not identify any study that directly compared TDF with AZT or ABC. The United States Food and Drug Administration (US FDA) and European Medicines Agency approved the use of TDF in children older than 2 years of age in 2011 *(319,320)*, providing an opportunity to offer the same regimen to both adults and children. Harmonizing treatment recommendations with adult regimens could improve children's access to ART. Other benefits of TDF include the ability to combine it with 3TC and EFV to

create a potent once-daily regimen for children *(321,322)*. In addition, the fact that HIV resistance to TDF – specifically the K65R mutation – can enhance the antiviral effect of AZT in subsequent regimens may make TDF a good choice for first-line therapy *(323–325)*. However, experience with TDF in young children is limited, and although TDF has been associated with reduced bone mineral density *(326)*, the dynamics, persistence and long-term impact (future patterns of growth and fracture risk) of these changes are not well defined.

A systematic review on TDF toxicity *(327)* showed a decline in renal function parameters over time (creatinine clearance, hypophosphataemia, estimated glomerular filtration rate [eGFR]) and a reduction in bone mineral density at 24 weeks, suggesting that TDF toxicity among children and adolescents could be similar to that seen in adults *(328,329)*. However, data are still lacking, and renal and bone toxicities in growing children and adolescents remain a concern. In addition, TDF formulations for younger children are not widely available and, to date, there are no TDF-containing paediatric FDCs. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been better studied in children and is generally well tolerated, without the risks of bone and renal toxicity. ABC is also available in paediatric FDC formulations but is significantly more costly than other NRTIs. Furthermore, among people with the HLA-B*5701 allele, it can cause a potentially fatal hypersensitivity. While hypersensitivity can affect 3–4% of Caucasian and Asian children, it is very rare among African children *(330)*. A systematic review demonstrated that ABC does not lead to higher rates of toxicity or discontinuation and can be safely used for first-line or second-line ART in children and adolescents *(331)*.

The review of evidence conducted in 2013 indicated that EFV has a better short-term toxicity profile and is associated with better virological response than NVP *(332,333)*. Nevertheless, most children are currently treated with regimens that contain NVP due to the availability of FDCs, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. Children who are well controlled and stable on NVP-containing regimens do not need to substitute EFV for NVP, but EFV would be a better choice for those initiating ART with other once-daily drugs.

Clinical considerations for scaling up ART for children

In general, the choice of regimens in this age group should be guided by:

• the importance of using potent first-line regimens;

• the convenience of once-daily dosing and the use of FDCs whenever possible;

• the use of non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and

• the provision of treatment recommendations for older children that are aligned with those for adolescents and adults.

An important specific consideration for clinicians and other health-care providers relates to whether and how regimen changes can be introduced among children who are clinically stable. As children get older, new FDCs with advantages over current first-line regimens – such as improved toxicity profile or dosing advantages – may become available. Modifying the ART regimens in clinically stable people may be considered to

simplify treatment management and harmonize the ART regimens in use. Relevant considerations are shown in Table 4.6.

Table 4.6. Considerations for simplifying and harmonizing ART for children with no history of treatment failure on any regimen[a]

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	Reduced risk of d4T-related toxicity May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen)	Aligned with adult regimens
LPV/r	No need to change, but consider substituting LPV/r with NVP or EFV if there is sustained virological response on LPV/r	May improve adherence as a result of better palatability and use of fixed-dose combinations in more manageable formulations (once-daily scored tablets) Reduced risk of metabolic alterations	Aligned with adult regimens Preserve PI for second-line ART No cold-chain requirement Reduced drug cost
AZT	No need to change but may consider changing to ABC or TDF	May improve adherence as a result of once-daily dosing (if on EFV) May reduce the risk of exacerbating anaemia	Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	Fixed-dose combinations can be used (if also on EFV)	Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV, particularly from age 3 years onwards	May improve adherence as a result of once-daily dosing (if combined with ABC or TDF)	Aligned with adult regimens

[a] Defined according to the criteria for treatment failure adopted nationally, preferably using viral load testing, where feasible and available.

ABC abacavir, AZT zidovudine, ART antiretroviral therapy, d4T stavudine, EFV efavirenz, LPV/r lopinavir/ritonavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

Research gaps

The long-term efficacy and safety of TDF, ABC and EFV and the recommended combinations need further investigation. More data are needed on bone, growth and renal toxicity profiles for TDF in children, especially in the context of malnutrition and stunting. Similarly, adverse events associated with EFV particularly during adolescence, such as CNS effects, require investigation to ensure safe harmonization with adult treatment regimens. Toxicity surveillance systems implemented alongside ART at sentinel sites can provide data to better understand the frequency and clinical relevance of these toxicities. In addition, pharmacokinetic studies to inform the development of better FDCs and the introduction of newer, more potent and less toxic components, such as INSTIs and tenofovir alafenamide fumarate (TAF), remain of critical importance for this population.

4.4.5 First-line ART for children younger than 3 years of age

Recommendations

For infants and children younger than 3 years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC (strong recommendation, moderate-quality evidence).[a]

An LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than 3 years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (strong recommendation, moderate-quality evidence).

Where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained (conditional recommendation, moderate-quality evidence).[a]

For infants and children infected with HIV younger than 3 years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted (strong recommendation, moderate-quality evidence).

[a] Revised in 2015.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Optimizing first-line ART in children younger than 3 years is critical to achieving effective and rapid control of viral replication in the context of high viral load and rapid infant growth. Considerations that may lead to alternative therapeutic approaches compared to those used in adults include the limited availability of drugs in appropriate formulations, the long-term toxicities of ARV drugs, difficulty with adherence and the possibility of pre-existing viral resistance because of exposure to ARV drugs for PMTCT *(337)*.

Based on evidence from randomized controlled trials showing the superiority of LPV/r-based over NVP-based regimens for treating young children *(338–340)*, the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (9)* recommended the use of LPV/r-based treatment in children younger than 36 months of age where feasible, regardless of NNRTI exposure. Due to the lack of robust evidence comparing different NRTI backbones, ABC and AZT in combination with 3TC were equally recommended as the preferred NRTI backbone to be used in children younger than 3 years.

Alternative strategies were also recommended to overcome the challenges of using LPV/r-based regimens or to provide potent alternatives in settings in which using LPV/r is not feasible or is problematic because of the high prevalence of TB. These strategies included

Table 4.7. Summary of first-line ART regimens for children younger than 3 years

Preferred regimens	ABCᵃ or AZT + 3TC + LPV/rᵇ
Alternative regimensᶜ	ABCᵃ or AZT + 3TC + NVP
Special circumstancesᵈ	ABCᵃ or AZT + 3TC + RALᵉ

a   Based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens, ABC should be considered as the preferred NRTI whenever possible. Availability and cost should be carefully considered.

b   As recommended by the US FDA, using LPV/r oral liquid should be avoided in premature babies (born 1 month or more before the expected date of delivery) until 14 days after their due date or in full-term babies younger than 14 days of age *(335)*. Dosing for children younger than 6 weeks should be calculated based on body surface area (Annex 11c). Restrictions also apply to LPV/r pellets, where administration challenges extend to infants up to 3 months of age. Additional information regarding optimal administration of this formulation will be provided as more data become available *(335)*.

c   Challenges may arise when treatment is started in the first two weeks of life following early diagnosis at or around birth, particularly in case of prematurity or low birth weight. In these situations, an NVP-based regimen containing AZT and 3TC should be started, and NVP should be substituted with LPV/r at the earliest opportunity, preferably at two weeks when LPV/r syrup can be administered (Annex 11c). In settings where LPV/r syrup is not available and LPV/r pellets are the only formulation available, administration of NVP should continue until 3 months with close clinical monitoring for those children considered at high risk for carrying NNRTI resistance (i.e. prolonged NVP-based postnatal prophylaxis or documented NNRTI failure in the mother).

d   Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug–drug interactions, drug procurement and supply management issues or for other reasons.

e   RAL is approved for use in infants and children from the age of 4 weeks, but there is very limited evidence to inform the use of raltegravir (RAL) as a first-line drug in infants and young children *(336)*. The use of this INSTI could be considered where available in instances of poor tolerability or administration challenges with LPV/r, particularly in settings where as a result of rapid expansion of maternal treatment, infants and children are at very high risk of carrying an NNRTI resistance virus. Use of RAL should however consider the challenges of existing granule formulation, despite being suitable for use in infants 4 weeks and older, as reconstitution in water is required before administration. While dispersion of RAL chewable tablets is considered to be a potential alternative, additional information regarding the appropriateness of this approach will be provided as more data become available.

3TC lamivudine, ABC abacavir, AZT zidovudine, LPV lopinavir, r ritonavir, RAL raltegravir.

substituting LPV/r with an NNRTI (EFV if 3 years and older) once viral suppression is achieved or using a triple NRTI regimen for children who develop TB while on an ART regimen containing NVP or LPV/r.

Since 2013, new evidence has become available to inform the choice of NRTI backbone *(318)*, and the safety and efficacy of strategies to substitute LPV/r with an NNRTI when viral suppression is achieved *(341,342)*. This has led to revised recommendations in these guidelines.

Rationale and supporting evidence

LPV/r-based treatment as a preferred regimen for infants and young children

A systematic review of two randomized controlled trials *(338–340)* shows that children younger than 36 months have a reduced risk of discontinuing treatment and viral failure or death if they start an LPV/r-based regimen instead of an NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT *(338)*. In addition, surveillance of drug resistance among children younger than 18 months *(343,344)* provides further evidence of detectable NNRTI resistance even among HIV-infected infants and young children without any history of exposure to ARV drugs for

PMTCT or whose exposure status is unknown, suggesting that a history of NNRTI exposure for PMTCT may not be an accurate marker for identifying children at higher risk of HIV resistance to NNRTIs. LPV/r is known to have a better resistance profile, which protects against the selection of NRTI resistance without compromising the use of other PIs in second-line regimens *(314,323,345,346)*. In addition, a potential advantage is offered by the considerable reduction in the incidence of malaria among children receiving LPV/r-based ART, as demonstrated in a randomized controlled trial comparing the use of LPV/r versus NVP or EFV-based ART among children in Uganda receiving an artemether + lumefantrine combination for treating malaria episodes *(347)*.

Providing an LPV/r-based regimen to infants and children younger than 3 years in some resource-limited settings may be challenging. The current LPV/r syrup formulation requires a cold chain until the point of dispensing. The syrup is unpalatable, with the potential for suboptimal adherence, as highlighted by caregivers and health workers. In addition, the risk of metabolic complications among children who initiate LPV/r early in life is unknown. LPV/r pellets, a heat-stable formulation that recently obtained tentative US FDA approval *(348,349)*, were shown to be more acceptable to parents and caregivers than the syrup *(350)* and are expected to increase the feasibility of this recommendation. However, palatability remains suboptimal, and there is still some uncertainty regarding the most appropriate way to administer this formulation to breastfed infants less than 3 months of age *(335)*. Both formulations of LPV/r are more expensive than NVP, and administering LPV/r with TB treatment is complex because drug levels are reduced by rifampicin.

Alternative approaches are proposed to overcome these challenges. Randomized controlled trials *(312)* have evaluated a strategy in which LPV/r is started and later substituted with an NNRTI (NVP or EFV) after confirmed viral suppression. Such PI-sparing strategies aim to reduce exposure to LPV/r, offer an easier approach to maintaining treatment and preserve PI-based therapy for second-line ART. A systematic review *(341,342,351,352)* has shown this approach to be safe and effective in the clinical trial setting for children with sustained viral suppression achieved after receiving LPV/r-based first-line therapy, especially in the absence of HIV resistance to NNRTI before initiating ART *(352)*. This strategy demonstrated better outcomes when substituting LPV/r with EFV compared to NVP in children aged 3 years or older with viral suppression on LPV/r-based ART *(341)*, leading to a revised recommendation in 2015. However, uncertainty remains with regard to the appropriateness of this strategy in children exposed to maternal ART as well as standard or enhanced postnatal prophylaxis while breastfeeding. The randomized controlled trials supporting the use of this approach defined viral suppression as a viral load of or below 400 copies/mL *(342,351)* or below 50 copies/mL *(341)*, with the goal of identifying the children who are more likely to be able to safely substitute LPV/r with an NNRTI. It is important to note that the use of a higher viral load cut-off for determining viral suppression has not been studied in the context of this strategy. In addition, this approach may also add complexity to treatment programmes and, because it requires access to virological monitoring, may therefore be relevant only in settings where viral load and/or genotype testing are available.

In settings where none of these approaches is affordable or feasible, and for treating infants identified at birth or soon afterwards, an NVP-based regimen provides an effective alternative to LPV/r, especially given the availability of two- and three-drug FDCs. As

observed in a large randomized controlled trial, good virological outcomes can be achieved by starting children on ABC, 3TC and an NNRTI *(174)*.

RAL is approved for use in infants and children (from the age of 4 weeks), and while there is very limited evidence to inform the use of RAL as a first-line drug in infants and young children *(336)*, it could be considered where available in cases of poor tolerability to or administration challenges with LPV/r, particularly in settings where, as a result of rapid expansion of maternal treatment, infants and children are at very high risk of having NNRTI resistance. However, despite being particularly suitable for use in infants 4 weeks of age and older, the existing RAL granule formulation requires reconstitution in water and may be challenging to administer *(353)*. Dispersed chewable tablets may be more suitable for this age group, but data on their use are not yet available.

Choice of NRTIs for infants and young children

The choice of NRTIs should aim to construct a robust and durable backbone that minimizes toxicity and cost and is most feasible. A systematic review identified one randomized trial that compared the effectiveness and safety of different NRTI backbones *(312)*. ABC and AZT combined with 3TC were demonstrated to be comparable in terms of clinical, immunological and virological response as well as safety and tolerability profile *(318)*. However, the choice of first-line NRTIs affects second-line ART, and failure on AZT may result in the accumulation of thymidine analogue mutations that reduce susceptibility to ABC or TDF in a subsequent regimen (if two or more thymidine analogue mutations are present). The risk of this occurring is greater with an NNRTI-based regimen; using it in the context of an LPV/r-based regimen may therefore be less problematic. By contrast, HIV resistance to ABC preserves or even increases the susceptibility of HIV to AZT for second-line use *(354)*.

Although ABC may be preferable in terms of ART sequencing *(354)* and harmonization with regimens for older children, availability is limited in resource-limited settings. In addition, the cost of ABC may be a significant barrier to adoption in many countries, especially when combined with LPV/r. These factors, together with outcomes from a technical consultation on paediatric ARV optimization *(355)*, led to the recommendations developed in 2013 being maintained.

Since 2010, WHO has recommended that d4T be phased out because of its known long-term toxicity. Since 2013, d4T use has reduced significantly in both adults and children. Accordingly, in settings where AZT may not be advisable because of the high risk of anaemia (such as malaria-endemic settings), access to ABC is essential.

Clinical considerations

In general, the selection of regimens for this age group should be guided by the following considerations:

- the importance of potent, first-line regimens for which there is evidence of good virological response as indicated by randomized controlled trials in this age group;

- the need to address the increasing evidence of HIV resistance to NNRTIs among children younger than 18 months, especially in the context of the recommendation to treat all pregnant and breastfeeding women with EFV-based regimens to prevent mother-to-child transmission;

- the desirability of having one preferred regimen for children younger than 3 years while providing alternative strategies that remain less costly, preserve second-line options and address feasibility concerns;

- the use of non-thymidine analogues in first-line regimens to preserve the response to AZT in second-line regimens and to harmonize the regimens for older children and adults, while also recognizing the additional expense; and

- the identification of a subset of children who can benefit from alternative strategies to preserve PIs for use in second-line ART, as indicated by a randomized controlled trial.

An important specific consideration for health-care providers relates to the challenges of providing LPV/r to young children. When clinicians anticipate significant difficulties in storing or administering LPV/r either in liquid or pellet form, NVP (especially an NVP-based FDC) can be considered.

Dosages of LPV/r for children younger than 6 weeks should be calculated based on body surface area (Annex 11c). In addition, LPV/r oral liquid should be avoided in premature or in full-term babies younger than 14 days *(335)*. While LPV/r pellets do not require a cold chain and overcome the procurement challenges of the syrup formulations, there is very limited experience administering these to very young infants less than 3 months of age. Additional information regarding optimal administration of this formulation will be provided as more data become available.

Challenges may also arise when treatment is started in the first 2 weeks of life following early diagnosis at or around the time of birth, particularly in case of prematurity or low birth weight. If initiating ART in an infant less than 2 weeks of age, a regimen of AZT + 3TC + NVP should be started and NVP substituted with LPV/r at the earliest opportunity, preferably at 2 weeks of age, when LPV/r syrup can be used (Annex 11c). In settings where LPV/r syrup is not available and LPV/r pellets are the only formulation available, NVP should be continued until the age of 3 months, with close clinical monitoring for children considered to be at high risk for carrying NNRTI resistance as a result of prolonged NVP-based postnatal prophylaxis or documented NNRTI failure in the mother. Where it is available, RAL could also be considered as an option in special circumstances, such as lack of LPV/r in any of the above formulations.

Table 4.8. Sequencing of ARV formulations for newborns starting treatment at around birth

	0–2 weeks ➜	2 weeks–3 months ➜	3–36 months
Preferred	AZT + 3TC + NVP	ABC or AZT + 3TC + LPV/r syrup	ABC or AZT + 3TC + LPV/r pellets
Alternative	AZT + 3TC + NVP		ABC or AZT + 3TC + LPV/r pellets
Special circumstances	AZT + 3TC + NVP	ABC or AZT + 3TC + RAL	

3TC lamivudine, ABC abacavir, AZT zidovudine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir.

Research gaps

The extent to which new approaches to PMTCT influence the resistance pattern of children becoming infected with HIV despite exposure to ARV drugs needs to be explored outside trial settings. In this context, more evidence is needed to confirm the appropriate dosing and safety of EFV-containing regimens as a first-line option for children less than 3 years or as part of PI-sparing strategies in the absence of facilities for viral load measurement or genotyping. Studies are also needed to specifically address the long-term metabolic implications of using LPV/r-based regimens for infants and young children. In addition, it is of critical importance to conduct studies to explore improved and safer formulations of LPV/r for neonates and alternative options (such as INSTI) that provide highly effective and well-tolerated drugs in formulations that are palatable and suitable, particularly for administration to newborns, as well as infants and young infants.

4.4.6 TB co-treatment for children with HIV

TB is one of the most common OIs affecting children with HIV. While isoniazid preventive therapy is strongly recommended as part of the comprehensive package of HIV care for all children living with HIV, it remains poorly implemented and TB continues to be a common cause of morbidity and mortality *(356)*. Vigilant contact tracing and routine case finding are also recommended to ensure early detection and survival. If diagnosed, ART should be started as soon as possible within 8 weeks of TB treatment initiation (*see* section 4.3.5 "Timing of ART for adults and children with TB"). However, selecting regimens that are compatible with TB therapy continues to be challenging, for example, due to interactions between rifampicin and LPV/r or NVP.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommended using triple-nucleoside therapy based on a randomized controlled trial in children *(174)*. This study showed preliminary evidence on the efficacy of triple-nucleoside therapy as a suitable option for children who require TB treatment while already receiving ART, with substitution of a standard first-line regimen once TB treatment is completed (Table 4.9). Since 2010, WHO has recommended the approach of "super-boosting" LPV/r with additional ritonavir (RTV) (1:1 instead of 4:1 LPV/r ratio, i.e. equal doses of LPV and RTV) to manage rifampicin-based TB co-treatment in children on an LPV/r-based regimen. An interim analysis of an ongoing open-label non-randomized pharmacokinetic study further supports this approach *(357)*, but a final analysis is needed to confirm these results.

Recommended regimens for children diagnosed with TB and starting ART are summarized in Table 4.9, together with broader guidance on choosing regimens for co-treatment of HIV and TB.

Table 4.9. Summary of recommended ART regimens for children who need TB treatment

Recommended regimens for children and adolescents initiating ART while on TB treatment[a,b]	
Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[c]
3 years and older	Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[c]

Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP, ensuring that the dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[c]
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)[c]

Recommended regimen for children and infants initiating TB treatment while receiving ART[a]		
Child on standard PI-based regimen (two NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d]
	3 years and older	If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV[e] or Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d] If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC)[c] or Continue LPV/r, adding RTV to achieve the full therapeutic dose[d] Consider consultation with experts for constructing a second- line regimen

[a] Ensure optimal dosing of rifampicin based on dosing guidelines (Annex 11c).

[b] Substitute ARV drugs based on an age-appropriate ART regimen in line with nationally recommended first-line ART.

[c] Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted when rifampicin-based therapy ends. Based on the findings from the ARROW trial *(174)*, this regimen should be considered as the preferred option for children younger than 3 years who are receiving an LPV/r-based regimen when starting TB treatment. The US FDA approval for the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg offers a potential alternative to the triple-NRTI approach *(358)*. An EFV-based regimen in children under 3 years is still not recommended because pharmacokinetic data are needed to ensure that the co-administration of rifampicin does not decrease drug levels below the therapeutic level. Triple NRTI should also be considered as the preferred regimen for children older than 3 years with a history of failure on an NNRTI-based regimen.

[d] Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.

[e] Substitution with EFV should be considered as the preferred option *(359)*, and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir.

4.4.7 Infant prophylaxis

NEW

Good practice statement

ART should be initiated urgently in all pregnant and breastfeeding women, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent mother-to-child HIV transmission is to reduce maternal viral load.[a]

[a] Whenever possible, all efforts should be made to identify HIV-infected pregnant women early enough to avoid the need for high-risk prophylaxis.

Recommendations

- **Infants born to mothers with HIV who are at high risk of acquiring HIV[a] should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate-quality evidence).** **NEW**

- **Breastfed infants who are at high risk of acquiring HIV,[a] including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality evidence).** **NEW**

- Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding).

[a] High-risk infants are defined as those:
   – born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
   – born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load measurement available; OR
   – born to women with incident HIV infection during pregnancy or breastfeeding; OR
   – identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Although rates of mother-to-child HIV transmission have fallen in recent years, there were still an estimated 220 000 infants born with HIV in 2014. Several factors have been proposed to explain this, including women not receiving antenatal testing or treatment, women presenting late for antenatal care and women acquiring HIV during pregnancy or breastfeeding. In some countries, incident HIV infection in mothers is thought to be a significant source of new infections in children, as transmission rates are especially high in this situation *(360,361)*. Incident HIV infection is often not diagnosed until delivery or in the postpartum period. One cohort study from Zimbabwe has reported that up to 20% of all breastfeeding-associated transmission takes place in women who acquire HIV in the postnatal period *(362)*.

Addressing these gaps requires continued emphasis on promoting universal testing and treatment in the antenatal period, as well as retesting of HIV-negative women during pregnancy, at delivery and during breastfeeding to identify incident HIV infection, especially in high-burden settings. At the same time, it is important to revisit the approach to infant prophylaxis for the infants born to mothers who have not received early, effective ART.

WHO guidance on infant prophylaxis in the setting of maternal ART has not been modified since 2010. It is recommended that breastfeeding infants be given 6 weeks of daily NVP and that non-breastfeeding infants be given either daily AZT or twice daily NVP for 4–6 weeks.

Previous WHO guidelines have acknowledged that when maternal ART is started late in pregnancy, during labour or in the postpartum period, infants who are breastfeeding may not be adequately protected from HIV because it takes several weeks for maternal viral load to be suppressed. In such situations, programmes were advised to consider increasing the duration of infant prophylaxis to 12 weeks rather than 6 weeks of NVP. Since that time, new data have become available, showing that combination infant prophylaxis is more effective than single-drug prophylaxis for the prevention of intrapartum mother-to-child transmission in infants born to mothers who have not received antepartum ARV drugs.

The goal of the new recommendations is to optimize infant prophylaxis and further reduce rates of peripartum and breast milk transmission, especially for infants whose mothers have not benefited from optimal care.

Rationale and supporting evidence

A systematic review was undertaken to examine the evidence for increasing the number of ARV drugs provided for infant prophylaxis and/or for extending the duration of prophylaxis beyond the current recommendations for infants at high risk of HIV infection due to limited or no maternal ART and/or high maternal viral load. WHO also convened an expert consultation to review the evidence and other considerations.

The systematic review *(363)* focused on studies that report on outcomes following the use of combined and/or prolonged infant prophylaxis regimens compared with the current standard of care. Although some of the studies reviewed were conducted in settings where formula feeding is the norm, the findings can still be applied to breastfeeding populations, as peripartum HIV transmission is an important driver of mother-to-child HIV

transmission in both settings. Four studies met the criteria for inclusion, of which two were randomized controlled trials and two were observational studies.

HPTN 040 randomized high-risk non-breastfeeding infants whose mothers had received no ARV drugs during pregnancy to one of three infant prophylaxis regimens: single drug (6 weeks of AZT), two drugs (6 weeks of AZT plus three doses of NVP in the first week of life) or three drugs (6 weeks of AZT plus an initial 2 weeks of nelfinavir and 3TC). The intrapartum transmission rate was significantly lower with the two-drug and the three-drug regimens compared to AZT alone *(364)*. Of the total infants, 8.4% experienced serious adverse events possibly related to study drugs and 3.4% experienced serious adverse events probably related to study drugs. Higher rates were observed in the three-drug group (12.2% and 4.9%) than in the AZT-alone group (6.9% and 3.7%) or the two-drug group (6.2% and 1.8%). Grade 2 or higher neutropaenia and anaemia accounted for the majority of serious adverse events. Only two skin-related serious adverse events were reported (one each in the two- and three-drug groups), but neither was related to the study drugs and there was no difference in mortality between study arms.

HPTN 046 was a randomized controlled trial conducted in sub-Saharan Africa. Breastfeeding HIV-exposed infants received 6 weeks of NVP and were then randomized to either receive an additional 4.5 months of NVP or placebo. In this breastfed population, infants who received 6 months of NVP experienced a 54% lower transmission rate at six months compared to those who received only 6 weeks of NVP. Most mothers in this study were not receiving ART antepartum or postpartum. However, it is important to note that, among the infants born to mothers receiving ART at the time of randomization, the postnatal transmission rate was extremely low and did not differ between those who received longer-duration NVP prophylaxis and those who received placebo. Serious adverse events in the infants did not differ between infants receiving extended NVP (16%) and those receiving placebo (15%), and the frequency of adverse events overall and mortality did not differ significantly between the treatment groups *(365)*.

One of the observational studies identified by the review involved an analysis of 5285 "high-risk" mother–infant pairs (either no or only intrapartum maternal ARV drugs or detectable maternal viral load at delivery) from eight European cohorts. Neonatal prophylaxis was administered to 88% of infants, with 24% receiving combination neonatal prophylaxis. While infant prophylaxis significantly reduced mother-to-child transmission, there was no observed difference in transmission risk between one drug and combination infant prophylaxis: the transmission rate was 18% with no infant prophylaxis, 3.4% with a single drug and 6.3% with combination prophylaxis. However, this finding likely represented residual confounding, as combination prophylaxis was associated with known risk factors for transmission, including a fourfold increased probability that infants who were given combination prophylaxis were born to mothers with a viral load above 1000 copies/mL at delivery. The authors provided toxicity data on a subset (32%) of the cohort. Overall, there was no difference in serious adverse events between infants who received one, two or three drugs. When neutropaenia was compared between the two-drug and three-drug arms, there was a trend towards more events in the three-drug arm, but this was not significant *(366)*.

The second observational study was a single-arm study with a historical observational control in non-breastfeeding infants in Thailand. In this study, if mothers received less

than 8 weeks of antepartum ART, the infant received AZT + 3TC + NVP for 2 weeks, followed by AZT + 3TC for an additional 2 weeks (the standard-of-care infant prophylaxis regimen is 4–6 weeks of AZT). In this study, there were no intrapartum infections in 88 mother–infant pairs compared to a predicted intrapartum transmission rate of 2.0% based on historical data when only infant AZT was received. The rate of serious adverse events in infants receiving intensified prophylaxis was 13.6%, compared to 21.7% in the historical observational cohort *(367)*.

None of the studies reviewed addressed infants identified in the postpartum period or infants exposed to an incident HIV infection either during pregnancy or while breastfeeding. However, it is likely that the findings of the systematic review could be applicable to these settings as well.

It is important to note that the recommendations for extended prophylaxis in breastfeeding infants are predicated upon maternal ART being initiated at or before the time when infant prophylaxis is begun (whether at birth or when maternal HIV is first detected postpartum), as infant prophylaxis is intended only to provide a bridge of protection to the infant during the period in which maternal viral load is decreasing on ART.

Defining high-risk infants

Although not addressed in the systematic review, a range of factors may be considered when assessing ris.

Factors such as prolonged rupture of membranes, preterm delivery and low birth weight are no longer associated with increased risk of transmission when mothers are receiving ART. The critical determinants of transmission risk in the ART era are maternal viral load and duration of maternal ART. The following scenarios may be considered as working definitions of "high-risk":

- incident HIV infection in a pregnant or breastfeeding woman (defined as new HIV diagnosis in a pregnant or breastfeeding woman with a prior negative HIV test during pregnancy);

- HIV exposure first identified at delivery or in the postpartum period in a breastfed infant;

- if viral load testing is available, pregnant women whose viral load exceeds 1000 copies/mL within four weeks prior to delivery; and

- if viral load testing is not available, pregnant women on ART for less than four weeks.

Modifying the testing approach

Consistent with the recommendations on EID, no specific approach to the testing of high-risk newborns is recommended. However, because infants who are first identified as HIV-exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated, an HIV polymerase chain reaction (PCR) test should be performed around the time of initiating prophylaxis. This will help to minimize the risk of development of resistance due to extended prophylaxis in infected infants and help to promote linkage to timely initiation of ART.

Equity and acceptability

A qualitative literature review explored acceptability relating to the duration and number of ARV drugs used for infant prophylaxis *(368)*. Nine published studies and one report from a global survey included the values and preferences of caregivers of HIV-exposed infants and health workers with regard to infant prophylaxis in general. Overall, the studies revealed that mothers place very high value on protecting their children from acquiring HIV and that short-term interventions in the infant to protect against transmission are generally acceptable. Some studies noted the difficulties of actually administering medication to infants, underscoring the need for better formulations and simplified dosing. Mothers expressed concern about the long-term risks of ARV drugs given to babies and noted that there was a lack of information provided on dosing and potential toxicities. In a survey of health workers, the majority noted that it would be challenging to give multiple drugs for prophylaxis and that, if a baby-friendly "infant prophylaxis tablet" were available, it would significantly increase acceptability and reduce the likelihood of prescribing errors.

Implementation considerations

The feasibility of enhanced prophylaxis is related to operational issues. These include the identification of infants at high risk and the administration of prophylaxis regimens. While maternal viral load around the time of delivery is perhaps the most reliable indicator of transmission risk, access to viral load testing and timely availability of results are limited in many settings. Point-of-care platforms may simplify virological testing at delivery, but in the absence of such advances, clinical parameters need to be simple and clear. Options for the management of incident infection and maternal refusal of ART should also be considered.

Providing multiple drugs to newborns is challenging from an operational perspective, and while AZT and NVP are proposed based on the available data, one is administered once daily and the other twice daily. Provider training will be critical to the successful uptake of these recommendations, and innovative approaches to dosing (such as using twice-daily dosing of NVP) may help to simplify administration. The availability of a dispersible FDC tablet containing doses suitable for infant prophylaxis would greatly facilitate uptake of these recommendations and should be considered a priority for drug development. When the recommended regimen is not available or feasible, use of a triple-drug FDC containing AZT, NVP and 3TC may be considered to simplify administration. It is recognized that, while there is no proven benefit to using three drugs in place of two and there is some risk of increased toxicity, in practice this toxicity is minor and short lived. As the doses contained in the commercially available triple-drug FDC are higher than the doses recommended for prophylaxis, expert consultation is advised in order to establish how the FDC tablet should be divided and administered for high-risk prophylaxis.

Research gaps

Potential areas for research include clinical and pharmacological studies to inform the development of improved ARV formulations, including FDCs in appropriate doses for newborns and infants. In addition, implementation science research to evaluate the optimal definition of high risk in the context of universal maternal ART would be valuable. Research into the use of alternative drugs for prophylaxis that are better tolerated and that may have greater efficacy for infant prophylaxis such as INSTIs could also be considered.

4.4.8 Infant feeding in the context of HIV

Recommendations

National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be HIV infected to either breastfeed and receive ARV[a] interventions or avoid all breastfeeding.

In settings where national authorities have decided that maternal and child health services will principally promote and support breastfeeding and antiretroviral interventions as the strategy that will most likely give infants born to mothers known to be HIV infected the greatest chance of HIV-free survival, mothers known to be infected with HIV should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life.[b] Breastfeeding should then stop only once a nutritionally adequate and safe diet without breast milk can be provided (strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months).

[a] All women living with HIV are eligible for initiation of ART regardless of CD4 count.

[b] Infants who are HIV infected will benefit from extended breastfeeding and should continue breastfeeding for as long as feasible and desired.

Source: Guidelines on HIV and infant feeding 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010 (http://www.who.int/maternal_child_adolescent/documents/9789241599535/en).

WHO recommendations on HIV and infant feeding highlight increasing levels of HIV-free survival of HIV-exposed infants. These guidelines have been unchanged since 2010, but updated WHO recommendations on HIV and infant feeding will be released in 2016 and will specifically address the duration and timing of breastfeeding in the context of lifelong maternal ART.

In countries where diarrhoea, pneumonia and malnutrition remain significant causes of child mortality, recommendations aim to reduce the risk of HIV transmission through breast milk. This is done primarily by providing ART to mothers living with HIV and ARV prophylaxis to their infants, while avoiding malnutrition and the increased risk of serious infections in infants and children through the promotion of breastfeeding. In other settings, avoidance of all breastfeeding is currently recommended.

WHO guidance has been based on evidence that the maximum benefit of breastfeeding in preventing mortality from diarrhoea, pneumonia and malnutrition is in the first 12 months of life and that the risk of transmitting HIV to infants through breastfeeding is low when the mother is receiving ART *(369,370)*. In 2010, breastfeeding beyond 12 months was not recommended because of uncertainty about the ability of health systems to retain mothers in care and to support maternal adherence to ARV drugs over long periods of time. There were also only limited data available on potential adverse events among infants exposed to low doses of ARV drugs through breast milk *(371–373)*.

National-level adaptation of the WHO recommendation has been very consistent, although a few countries have standardized the recommended duration of breastfeeding for mothers living with HIV at 24 months, similar to that for HIV-negative mothers. Contrary to WHO recommendations, some countries continue to recommend less than 12 months of breastfeeding.

Implementation considerations

The 2010 WHO recommendations placed major emphasis on promoting and supporting mothers living with HIV to breastfeed their infants until 12 months of age. These guidelines acknowledged that some mothers might not be able to provide a safe and adequate diet to children beyond 12 months of age without breastfeeding. In these situations, it is suggested that breastfeeding should continue while mothers are receiving ART. WHO is currently considering whether to recommend unrestricted breastfeeding among mothers living with HIV who are on ART.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for breastfeeding by mothers living with HIV while receiving ART include:

- communicating clearly and effectively to health workers, mothers and the community the effectiveness of ART to reduce the postnatal transmission risks through breastfeeding;

- highlighting the value of breastfeeding for the health, development and survival of mothers living with HIV and their children when the mother is receiving ART;

- implementing and sustaining specific interventions (such as integrated follow up with immunization and other well-child services) to improve postpartum follow up of mother–infant pairs, and supporting breastfeeding practices and ART adherence;

- emphasizing postnatal prophylaxis for infants: infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP, or if they are considered at high risk, enhanced infant prophylaxis using AZT and NVP for 6 weeks followed by either AZT and NVP or NVP alone for an additional 6 weeks (*see* section 4.4.7 "Infant prophylaxis"); and

- linking EID results with appropriate infant-feeding practices: infants who are HIV infected should continue breastfeeding until 24 months or longer.

In addition, there is a need for enhanced monitoring for potential toxicities from prolonged infant exposure to ARV drugs through breast milk and to continue toxicity surveillance, as new drugs are included in maternal ART regimens. In particular, the effects of ARV drugs on neurodevelopmental outcomes, growth and renal and bone health need to be better understood. This could be achieved through sentinel site monitoring of infant cohorts during the first two years of life. For infants who become infected despite interventions to prevent mother-to-child transmission, exposure to drugs through breastfeeding has implications for resistance as well as toxicity, and this may have an impact on the success of ART regimens for the child.

Research gaps

Programmatic data are needed on postnatal ART adherence and patterns of retention in care, in addition to the duration of breastfeeding among women living with HIV to more accurately estimate the number of infants being infected postnatally. The incident HIV infection rate among breastfeeding mothers in areas with a high prevalence of HIV infection is also required to determine the magnitude of this population and their particular risks.

Further studies are needed of short- and long-term infant health outcomes related to prolonged, low-dose exposure to ARV drugs (especially EFV and TDF) through breast milk, including neurodevelopmental outcomes, nutritional status (including micronutrients), bone metabolism and growth. The penetration of ARVs into breast milk is incompletely understood, and pharmacological studies to determine the ratio of breast milk and maternal plasma – as well as infant plasma drug levels – are needed to better understand drug levels in breast milk and the "dose delivered" to the infant for many of the ARV drugs currently in use. Such data are required for each ARV drug, as these characteristics are likely to differ between different drugs.

Greater understanding is needed regarding the relationship between viral load and postnatal transmission risk according to whether the mother is on ART or not. Research is also needed on interventions to improve retention in care and adherence to postnatal ARV drugs and breastfeeding.

4.5   Monitoring the response to ART and diagnosing treatment failure

4.5.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals following a positive HIV diagnosis to assess for coinfections, noncommunicable diseases (NCDs) and other comorbidities that may have an impact on treatment response. Limited laboratory testing is also recommended for monitoring the response to treatment and possible toxicity of ARV drugs. Table 4.10 summarizes the recommended laboratory tests for HIV screening and monitoring as well as approaches to screening for coinfections and NCDs.

Table 4.10. Recommended tests for HIV screening and monitoring and approaches to screening for coinfections and noncommunicable diseases

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months) CD4 cell count TB symptom screening	HBV (HBsAg) serology[a] HCV serology Cryptococcus antigen if CD4 cell count ≤100 cells/mm^3 [b] Screening for STIs Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child Assessment for major noncommunicable chronic diseases and comorbidities[c]
Follow-up before ART	CD4 cell count (every 6–12 months in circumstances where ART initiation is delayed)	
ART initiation		Haemoglobin test for starting AZT[d] Pregnancy test Blood pressure measurement Serum creatinine and estimated glomerular filtration rate (eGFR) or starting TDF[e] Alanine aminotransferase for NVP[f] Baseline CD4 cell count
Receiving ART	HIV viral load (at 6 months and 12 months after initiating ART and every 12 months thereafter) CD4 cell count every 6 months until patients are stable on ART	Serum creatinine and eGFR for TDF[c] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV
Suspected treatment failure	Serum creatinine and eGFR for TDF[c] Pregnancy test, especially for women of childbearing age not receiving family planning and on treatment with DTG or low-dose EFV	HBV (HBsAg) serology[a,g] (before switching ART regimen if this testing was not done or if the result was negative at baseline and the patient was not vaccinated thereafter)

[a] If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

[b] Can be considered in settings with a high prevalence of cryptococcal antigenaemia (>3%).

[c] Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols (see section 5.3 "Prevention, screening and management of other comorbidities and chronic care for people living with HIV"). Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria. See formula for eGFR in the footnote to section 4.6.3.

[d] Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

[e] Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

[f] Among people with a high risk of adverse events associated with NVP, such as being ART-naive, women with HIV with a CD4 count >250 cells/mm^3 and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

[g] For HIV/HBV coinfected individuals who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen.

ART antiretroviral therapy, AZT zidovudine, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, EID early infant diagnosis, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, HCV hepatitis C virus, STI sexually transmitted infection, TDF tenofovir.

4.5.2   Monitoring the response to ART and diagnosis of treatment failure

NEW

Recommendations for routine monitoring

Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting[a] (conditional recommendation, very low-quality evidence).

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed[b] (conditional recommendation, low-quality evidence).

[a] Viral load testing should be performed early after initiating ART (within 6 months), at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible.

[b] WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL). For service delivery recommendations in these guidelines (*see* Chapter 6 "Service delivery"), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.

Recommendations for diagnosis of treatment failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure[a] (strong recommendation, low-quality evidence).

If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate-quality evidence).

Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (that is, two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.

Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV viral load. A threshold of 1000 copies/mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma[a] (conditional recommendation, low-quality evidence).

NEW

[a] Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Monitoring people on ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure. In 2013, WHO recommended viral load testing as the preferred monitoring approach to diagnose and confirm ARV treatment failure. Compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes *(374)*. Measuring viral load can also help to distinguish between treatment failure and non-adherence. Studies suggest that around 70% of patients on first-line ART who have a first high viral load will resuppress following an adherence intervention *(375)*, indicating non-adherence as the reason for the high viral load in the majority of cases. Viral load can also serve as a proxy measure for the risk of transmission and effectiveness of prevention interventions at both the individual level, especially for pregnant women *(376)*, and at the population level *(377)*.

Many national guidelines now recommend either targeted or routine viral load monitoring, and countries are in the process of scaling up access to these approaches. However, regular access to routine viral load testing remains limited, and this has been identified as a key reason for lower-than-expected rates of identified treatment failure in resource-limited settings *(378)*.

Routine versus targeted viral load monitoring to detect viral failure

Viral load should be monitored routinely at 6 months, at 12 months, and then every 12 months thereafter if the patient is stable on ART to detect treatment failure earlier and more accurately. A systematic review was conducted to assess the optimal timing for initial viral load testing and thereafter *(380)*. Despite very low-quality evidence from the review findings, the Clinical Guideline Development Group recognized the importance of clear guidance around the timing of routine viral load testing and made a conditional recommendation to synchronize routine viral load monitoring with routine monitoring systems, citing better alignment of outcomes, feasibility and acceptability *(380)*.

In settings with limited access to viral load testing, a targeted viral load strategy to confirm suspected treatment failure based on immunological or clinical criteria should be used to avoid unnecessary switching to second-line ART regimens. Targeted viral load monitoring is less costly than routine viral load testing, but as with clinical and immunological monitoring, it has the potential to delay switching to second-line ART and may subsequently increase the risk of disease progression, selection of ARV drug resistance and HIV transmission.

Threshold for defining viral failure

The optimal threshold for defining viral failure and for switching ART regimens has not been established. WHO recommends a threshold of 1000 copies/mL based on the fact that the risk of HIV transmission and disease progression is very low when viral load is lower than 1000 copies/mL *(381–383)*, and that below this threshold, viral blips or intermittent low-level viraemia (50–1000 copies/mL) can occur during effective treatment but have not been associated with an increased risk of treatment failure *(384)*. Most standard viral load platforms using plasma specimens have good diagnostic accuracy at

Table 4.11. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)[a] after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count at or below 250 cells/mm^3 following clinical failure[b] or Persistent CD4 levels below 100 cells/mm^3 **Children** *Younger than 5 years* Persistent CD4 levels below 200 cells/mm^3 *Older than 5 years* Persistent CD4 levels below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed

a   See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 10.

b   Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm^3 following clinical failure is based on an analysis of data from Uganda and Zimbabwe *(379)*.

this lower threshold. Prior concerns regarding the sensitivity of dried blood spot specimens have been clarified through a systematic review conducted for these guidelines.

Determining treatment failure in the absence of viral load monitoring

Where viral load monitoring is not available, clinical monitoring and CD4 monitoring are recommended. However, immunological and clinical criteria have poor sensitivity and specificity to detect treatment failure, particularly at higher CD4 cell counts, and more accurate immunological criteria are yet to be identified *(385)*. In the absence of better criteria to predict treatment failure, it is important to use CD4 cell count and clinical assessment to identify those at the highest risk of disease progression and mortality. Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. Recognizing the limitations of the current criteria, several studies have proposed alternative

approaches, including a single CD4 count at or below 250 cells/mm^3 following clinical failure *(379)* and CD4-based risk charts with optimal cut-offs for guiding targeted viral load testing *(386)*. Such approaches merit validation in other settings.

A cohort analysis, updated for the revision of these guidelines *(387)*, explored the risk of mortality associated with CD4 cell counts in children and confirmed the appropriateness of existing CD4 thresholds in identifying infants and children for whom ART is failing and at the highest risk of mortality (more than 5% 1-year mortality risk). Since the publication of the 2013 guidelines, a large randomized controlled trial in children *(174)* has shown that CD4 monitoring provides clinical benefit over clinical monitoring after the first year on ART and that failure to thrive is a sensitive indicator of treatment failure. The association between poor weight gain and increased risk of death was described in a large observational dataset *(388)* emphasizing the importance of growth monitoring in the routine clinical assessment of children living with HIV (*see* section 4.3.4 "When to start ART in children younger than 10 years of age") and suggesting that loss of weight or poor weight gain are potential signs of treatment failure.

Stopping CD4 count monitoring where viral load testing is available

Recent studies suggest that in situations where viral load testing is routinely available and individuals are virally suppressed, long-term CD4 cell count monitoring adds little value, and stopping the estimation of CD4 for monitoring purposes will have major cost savings. A number of countries have either reduced the frequency of or stopped routine CD4 cell count monitoring altogether in people who are stable on ART, and rely on viral load alone to monitor the response to ART and detect potential virological failure.

A systematic review identified 13 studies carried out in Asia, Africa, Europe, the United States and Australia and found that CD4 count declines among adults and children who are virally suppressed on ART are rare and mainly transient events that are mostly explained by non-HIV factors, such as concomitant immunosuppressive therapy. Overall, the evidence suggests that for individuals stable on ART who are monitored virologically, routine monitoring of CD4 could be stopped *(383)*. This recommendation is further supported by the substantial cost savings that could be gained from stopping routine CD4 count monitoring *(389–391)* and modelling. The latter suggests that viral load testing is cost-effective for stable individuals if provided as part of a package of care that includes less frequent clinic visits and stopping CD4 count monitoring (*see* Chapter 6 "Service delivery").

It is important to note that the evidence for children was limited to one study, in which the probability of CD4 decline was lowest (2.8%) in children older than 2 years with no or mild immunosuppression *(392)*. CD4 count monitoring may still be warranted in children below this age.

Viral load for assessing transmission risk

In some clinical settings, viral load testing may have additional value for assessing the risk of transmission. This is especially true in the case of pregnant women where, in the absence of ART, viral load is proportionate to the risk of mother-to-child transmission *(393)*. Although ART markedly reduces transmission risk, the same association between transmission and viral load persists. These guidelines propose enhanced infant

prophylaxis using AZT *and* NVP together, instead of AZT *or* NVP, as a means to reduce transmission in high-risk infants *(394)*. Although risk can be defined using clinical criteria, viral load is the best determinant of risk. The opportunity to offer an intervention and potentially prevent infection in an infant is a strong rationale to prioritize rollout of viral load testing to women during pregnancy and around the time of delivery.

Dried blood spot specimens for viral load monitoring

Dried blood spot (DBS) specimens provide a way to improve the coverage and reach of viral load testing, particularly in remote and rural areas where preparation and transport of plasma specimens is limited by cold-chain requirements and lack of staff trained to perform venepuncture and plasma separation. Several countries have begun implementation of the use of DBS specimens for viral load testing using protocols recommended by manufacturers despite its off-label use, and DBS specimens have been widely used for EID with qualitative nucleic acid testing and high acceptability.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that a higher threshold for detection of treatment failure may need to be applied if DBS specimens are used due to uncertainty about the accuracy of DBS specimens for viral load testing below 1000 copies/mL.

A systematic review identified 43 studies that compared DBS specimens to plasma specimens for viral load testing. Overall, performance of DBS specimens was found to have acceptable sensitivity and specificity for identifying virological failure when compared to a reference standard of the same assay using a matched plasma specimen at 1000 copies/mL for most commonly used technologies (*see* Table 4.12) *(395)*. However, it should be noted that some of the assay types were found to have low sensitivity at the time this evaluation was performed (up to June 2015) and should be avoided. While this reduced sensitivity means that plasma specimens are preferred for viral load testing, modelling suggests that if viral load testing with DBS specimens can be performed with reasonable sensitivity and specificity (>85%) then costs and outcomes are similar. Other modelling work done to support the development of these guidelines suggests that viral load testing using DBS specimens is cost–effective for determining virological failure at a threshold of 1000 copies/mL and at the level of accuracy reported by the meta-analysis

Table 4.12. Performance of assay type using DBS compared to plasma using a viral load threshold of 1000 copies/mL

Failure	Abbott RealTime	Biocentric Charge Virale	bioMerieux Nucleisens	Roche TaqMan FVE	Roche TaqMan SPEX	Siemens kPCR
Sensitivity[a] (95% confidence interval [CI])	95% (82–99%)	95% (71–99%)	84% (79–89%)	85% (77–91%)	99% (97–100%)	91% (69–98%)
Specificity[a] (95% CI)	92% (79–97%)	55% (35–74%)	95% (86–98%)	94% (85–98%)	44% (18–74%)	88% (75–94%)

[a] Pooled estimates of sensitivity and specificity based on published data up to June 2015 *(395)*.

when used to support differentiated care (i.e. less frequent clinic visits for stable individuals, as discussed in Chapter 6 "Service delivery") *(396)*.

An important limitation of the evidence supporting DBS specimens for viral load testing is that the majority of studies included in the review used venous whole blood specimens prepared in the laboratory using precision pipettes to dispense the blood onto the filter paper rather than based on specimens obtained in clinical settings. In addition, when plasma specimens are used for viral load monitoring, lack of integrity of the cold chain may influence accuracy. Research is needed to validate the performance of DBS specimens in routine programme settings, with an emphasis on specimen preparation done by less skilled health staff and using different types of filter paper.

Implementation considerations

Access to ART should be the first priority for all age groups, and lack of testing for monitoring treatment response should not be a barrier to initiating ART. If viral load testing capacity is limited, it should be introduced in a phased approach. Examples of phased approaches include:

• using viral load initially as a targeted test to confirm treatment failure;

• leveraging existing systems of DBS collection and transport for infant diagnosis in order to roll out viral load testing in maternal and child health settings;

• prioritizing viral load testing for pregnant and breastfeeding women, especially around the time of delivery, as sustained viral suppression is critical to prevention of transmission to the child, and documented high viral load at delivery is an indication for enhanced infant prophylaxis;

• preferentially offering viral load testing to HIV-infected infants and children for whom CD4-based criteria are particularly poor and in light of the limited drug options available for lifelong treatment; in addition, infants exposed to maternal ART and/or postnatal prophylaxis have been reported to have high risk of acquiring and selecting HIV drug resistance *(343)* and, as a result, are at higher risk of treatment failure early, especially if treated with NNRTI-based regimens;

• giving consideration to more frequent viral load testing in adolescents who are at the highest risk for HIV drug resistance and for whom monitoring of adherence might be particularly challenging in settings where viral load monitoring is widely available; and

• ensuring that health-care providers are adequately trained to conduct timely viral load testing and take appropriate clinical actions when the viral load is high, such as intensified adherence support and possible regimen switches.

Views expressed during a community consultation undertaken for these guidelines underscored the importance of improving literacy about viral load testing *(5)*. It is generally understood that access to viral load testing gives clients a measure of understanding, control and motivation to adhere to and manage their HIV infection. Adherence counselling needs to address the implications of a detectable or undetectable viral load, particularly in settings where treatment success was previously described only in terms of a rising CD4 cell count.

CD4 cell count for ART monitoring should be stopped only in settings where viral load

monitoring can be assured. CD4 measurement still has an important role to play in assessing baseline risk of disease progression, particularly for individuals presenting with advanced disease, decisions regarding starting and stopping prophylaxis for OIs, and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART.

Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children are found in Annex 12.

Research gaps

While efforts continue to increase access to viral load testing, it is recognized that in some settings, viral load testing may remain difficult to access for some time. In such situations, there is a need to further validate the accuracy of alternative clinical and immunological strategies for predicting virological failure.

4.5.3 Monitoring ARV drug resistance

Current approaches to resistance testing remain too costly and complex for routine use as part of a public health approach, and WHO does not currently recommend routine resistance testing to guide ART regimen selection.

Some countries use resistance testing to inform treatment decisions. WHO recognizes the value of resistance testing for individual patients in such situations, provided that adequate treatment options are available and in-country expertise exists to properly interpret results.

To inform population-level decision-making, WHO recommends routine surveillance for HIV drug resistance (HIV-DR) in populations initiating ART and in populations on ART for 12 months and more than 48 months. The results of these surveys support the choice of recommended first- and second-line ART, and pre- and post-exposure prophylaxis *(397)*.

Emergence of HIV-DR in treated populations is associated with factors related to patient care (and viral suppression at 12 months), patient behaviour (adherence) and clinic-level and programme management (retention on first-line ART, and procurement and supply management of ARV drugs).

Many factors are associated with the emergence of HIV-DR. Broadly, these factors may be divided into three categories: (i) viral factors (such as HIV subtype, replication capacity and pre-existing polymorphisms); (ii) drug-related factors (such as drug potency, pharmacokinetics, drug–drug interactions, tolerance and genetic barrier to resistance); and (iii) programme factors (such as adherence to prescribed ART, drug supply continuity and retention of patients on treatment). Although viral and drug-related factors are often beyond the control of public health authorities or programme managers, the monitoring of ART programme factors can alert ART clinics and national programme planners to situations that may favour population-level virological failure and/or the emergence of resistance. Once such situations have been identified, clinic- or programme-level action

may be implemented to optimize patient care, thus minimizing the emergence of preventable HIV-DR.

WHO recommends that prevention of HIV-DR be integrated into national HIV programmes, through the annual monitoring of early warning indicators (EWIs) and through the implementation of HIVDR surveillance (*see* section 7.6.2 "Drug resistance surveillance").

Prescription- or pill-based methods for estimating adherence to ART are objective estimates calculated from routinely captured pharmacy data and have been demonstrated to predict virological and drug-resistance outcomes *(398)*.

Randomized controlled trials report selection of HIV-DR in at least 70% of patients with virological failure *(399)*, with some studies documenting no resistance at ART initiation *(400)*. Numerous studies have documented HIV-DR in substantial proportions of patients with confirmed virological failure *(401–404)*.

It should be possible to evaluate the recommended EWIs through routine programme data. Global targets support the indicators. Indicator analysis and action plans based on their results support optimization of HIV treatment and minimize the emergence of HIV-DR. Further information on monitoring for HIV-DR is provided in section 7.6.2 "Drug resistance surveillance".

4.6   Monitoring of and substitutions for ARV drug toxicities

4.6.1 Guiding principles

• The availability of laboratory monitoring is not required for initiating ART.

• Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

4.6.2 Major types of ARV toxicities

As in 2013, these guidelines recommend a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs. Table 4.13 lists the key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring of drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment outcomes. More data are also needed on whether routine laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all people or only those at risk. In general, in the event of severe and life-threatening toxicity or hypersensitivity, ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated.

Information on systems approaches to monitoring ARV drug toxicity is provided in section

Table 4.13. Types of toxicities associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Do not use ABC in the presence of HLA-B*5701 allele. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease; Concomitant use of other drugs that may prolong the PR or QRS intervals; Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤200 cells/mm³	Substitute with TDF or ABC. Consider use of low-dose zidovudine *(405)*.
	Lactic acidosis or severe hepatomegaly with steatosis; Lipoatrophy; Lipodystrophy; Myopathy	BMI >25 (or body weight >75 kg); Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity; Hypersensitivity reactions	Hepatitis B or C coinfection; Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
DRV/r	Hepatotoxicity	Underlying hepatic disease; HBV and HCV coinfection; Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease; HBV and HCV coinfection; Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	

Table 4.13. (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
EFV	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).
ETV	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol misuse	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men)	If hepatotoxicity is mild, consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	

Table 4.13. (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC. Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

ABC abacavir, ATV atazanavir, AZT zidovudine, CNS central nervous system, DRV darunavir, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, HBV hepatitis B virus, HCV hepatitis C virus, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir, TDF tenofovir.

4.6.3 Monitoring TDF toxicity

Monitoring TDF toxicity in adults

The renal toxicity of TDF is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease, and also with bone mineral density loss *(406,407)*. However, the incidence of clinically significant renal toxicity with TDF is very low in randomized controlled trials, with grade 3 and 4 elevations in serum creatinine reported in less than 1% of patients *(408–410)*. In 2015, a systematic review on TDF toxicity *(411)* indicated that TDF was associated with fewer discontinuations overall, and fewer discontinuations due to adverse reactions compared to AZT and d4T. Nevertheless, concerns about TDF toxicity remain. The review showed that TDF is associated with modest reductions in eGFR[1] and creatinine clearance and reductions in bone mineral density in both hip and spine as well as increases in serum creatinine. The systematic review found that, compared to TDF, there was lower mortality, fewer treatment discontinuations overall, fewer discontinuations due to adverse reactions and significantly higher eGFR at 48 weeks with TAF *(412)*.

In April 2016, the United States FDA approved TAF, an investigational pro-drug of TDF with a lower dose of active ingredient, but its availability is still very limited. The

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[1] Using the Cockcroft–Gault (CG) or Modification of Diet in Renal Disease (MDRD) study formulas for estimation. CG formula: eGFR = 140 − age (years) × body weight (kg) × 0.85 (if female)/(72 × serum Cr in mg/dL): http://nephron.com/cgi-bin/CGSI.cgi. MDRD formula: eGFR = 175 × (Serum Cr)$^{-1.154}$ × (age)$^{-0.203}$ × (1.212 if black) × (0.742 if female): http://touchcalc.com/e_gfr.

systematic review highlighted the need for further monitoring to determine whether eGFR reduction with TDF stabilizes after 48 weeks of treatment. One trial suggested that an early change in eGFR following treatment initiation was followed by stabilization *(413)*. However, when combining the values reported in cohorts over a longer period of time, the trend suggested continued decrease in eGFR over an extended period. Further research is needed to explore whether renal impairment is reversible after stopping TDF *(414–416)*. Overall, the incidence of chronic kidney disease remained low in patients exposed to TDF, and the incidence of acute kidney injury was very low *(417–420)*. The evidence suggests that the overall improvement in renal function resulting from ART can offset the risk of TDF toxicity among people with HIV who do not have secondary renal disease or risk factors.

Serum creatinine and glomerular tests may not adequately measure tubular injury. The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory for initiating treatment with TDF. However, it is advisable to detect and limit further progression of renal impairment in high-risk people. The major risks for TDF-related kidney damage are underlying kidney disease; age more than 50 years; low body weight (<50 kg), notably in females; untreated hypertension; and diabetes. Use of TDF with other nephrotoxic drugs, including those sold over the counter, nonsteroidal anti-inflammatory drugs, boosted PIs and ledipasvir, a direct-acting antiviral (DAA) drug to treat hepatitis C infection, leads to a greater initial decline in renal function. This decline may be worse when TDF is given in combination with ATV/r compared to when combined with LPV/r *(420)*. People with impaired eGFR at baseline (<50 mL/min) should not initiate TDF.

Many countries are recommending creatinine clearance monitoring, but lack of availability should not be a barrier to TDF initiation. A systematic review *(421)* examined whether in settings without a standard laboratory, a urine dipstick is an effective intervention to detect loss of renal function or proximal tubular dysfunction. Evidence was also reviewed comparing urine glucose or albumin proteins on a dipstick. No evidence was found to guide practice on estimating the accuracy of urine glucose dipstick testing to detect renal toxicity in patients with HIV on TDF in the absence of laboratory capacity. In addition, indirect evidence showed poor sensitivity of urine proteinuria dipstick testing to detect renal damage in routine monitoring *(422)*. The use of eGFR, albumin–creatinine ratio (ACR) or albumin–protein ratios or tests of low-molecular-weight proteins using urinary samples have been documented, but it is still not clear how and whether these are related to the clinically relevant target conditions for TDF toxicity *(423)*. No recommendation could be made on a point-of-care strategy for monitoring TDF renal toxicity using urinary dipsticks *(424)*.

Monitoring TDF toxicity in adolescents and children

The systematic review indicated that TDF toxicity among children and adolescents could be similar to that seen in adults *(411)*. However, data are still lacking, and renal and bone toxicities in growing children and adolescents remain a concern. In the context of lack of paediatric formulations, increasing monitoring for TDF toxicity should be considered, including in young children or adolescents with low body weight who are using split adult tablets *(321)*.

Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while adolescents and children are receiving TDF *(328)*. When serum phosphate testing is available, by extrapolation, low serum phosphate

should give rise to concern about bone mineral density loss. Increasing dosing accuracy in children and adolescents is extremely important for reducing toxicity *(329)* (*see* Annex 11: Dosages of recommended antiretroviral drugs).

Clinical considerations

• Laboratory screening is not mandatory to initiate treatment with TDF.

• Routine blood pressure monitoring should be used to assess for hypertension.

• If the creatinine test is routinely available, the eGFR at baseline should be used before initiating a TDF-containing regimen.

• TDF should not be initiated when the eGFR is <50 mL/min or in uncontrolled hypertension or diabetes and renal failure.

• Patients should be screened and treated for associated risk factors such as hypertension or diabetes and their treatment monitored.

• Growth should be carefully monitored in children using TDF.

4.6.4 Monitoring the toxicity of integrase inhibitors

New INSTIs have demonstrated a favourable safety profile and low potential for drug interaction in clinical trials *(425–427)*. In 2015, a systematic review on the toxicity of the INSTIs RAL and DTG *(411)* found fewer discontinuations overall compared to EFV and NVP and a trend towards fewer discontinuations due to adverse reactions (2–3%).

DTG may cause generally mild or moderate nausea, headache and diarrhoea that do not limit treatment. Serious adverse effects include abnormal liver function, particularly in patients with HBV or HCV coinfection, and potentially serious hypersensitivity reactions *(428)*. DTG does not need a boosting agent (such as RTV or COBI), which minimizes drug interaction potential *(429)*. DTG is reported to affect renal function, with a 10% serum creatinine increase due to inhibition of renal transport protein and consequently an estimated reduction in creatinine clearance, but without any eGFR modification. No tubulopathy or discontinuation of DTG due to renal toxicity has been reported *(429)*.

RAL has a favourable profile, with the most commonly reported adverse reactions – diarrhoea, nausea and headache – reported as being mild to moderate and not limiting treatment *(430)*. Severe adverse reactions – rash, hypersensitivity reactions, severe acute renal failure associated with rhabdomyolysis and depression – have been reported only rarely. RAL has also been linked to instances of Stevens-Johnson syndrome, which can be accompanied by hepatic involvement. Preliminary data show that RAL could be used concurrently with TB treatment (rifampicin) with no drug interaction and few side-effects. However, because of the small size of the study, these results need further assessment *(431)*. Evidence from the systematic review *(411)* showed that RAL is less likely to lead to dyslipidaemia than LPV/r and has less impact on bone mineral density than is observed with therapy containing EFV, DRV/r and ATV/r.

The toxicity profile of RAL in children and adolescents 2–18 years of age is comparable to that observed in adults *(411)*. The profile of DTG has not been established in children younger than 12 years of age or weighing less than 40 kg, or in INSTI-experienced paediatric patients with documented or clinically suspected INSTI resistance.

There are limited data on the use of INSTIs (DTG and RAL) in pregnant or breastfeeding women. *See* section 4.6.6 "Special considerations for toxicity monitoring during pregnancy and breastfeeding".

4.6.5 Monitoring the toxicity of other ARV drugs in adults, adolescents and children

Monitoring the toxicity of abacavir

The use of ABC has been limited due to its toxicity profile, including an increased risk of hypersensitivity reaction (HSR) and myocardial infarction in adults *(432)*. HSR, which is associated with the presence of the HLA-B*-5701 allele, represents a main concern in children *(433–435)*. An updated systematic review and meta-analysis conducted for these guidelines *(331)* reported adverse outcomes for 1769 children (age between 0 and 18 years) exposed to an ABC-containing regimen among 2546 patients treated. Despite heterogeneity between studies with regard to the incidence of adverse outcomes, the review found no increase in HSRs, treatment discontinuations due to toxicity, grade 3 and 4 reactions or death associated with ABC exposure compared to exposure to other ARV drugs. The estimated incidence of HSR from the systematic review among children exposed to ABC was low (2.2%), as was the number of reported deaths (3.3%), with none of the deaths reported as being associated with ABC toxicity.

Among adults, a strong relationship was reported between HSR related to ABC and HLA-B*-5701 allele genotype *(436)*, but this association has not been studied in children. The review included comparative data from two randomized controlled trials *(437,438)* conducted in one setting of high prevalence of the HLA-B*-5701 allele before the introduction of any pre-treatment screening of this allele and one low-prevalence setting *(318)*. The prevalence of the HLA-B*-5701 allele genotype seems to differ significantly according to ethnicity, with a prevalence higher than 5% in people of Caucasian origin, intermediate in people of Asian origin (4.0% among Thais, 3.4% among Cambodians) but lower than 2% in people of African origin and 0.6% in people of Chinese origin. Screening for the HLA-B*-5701 allele before initiating ABC therapy has been recommended in the drug label by the US FDA and United States paediatric ARV guidelines since 2008, as well as in the drug label by the European Medicines Agency. More evidence is needed to assess the prevalence of the HLA-B*-5701 allele in Asian populations. In the meantime, because HSR remains rare, where screening is not feasible, appropriately trained clinical staff should manage patients clinically, with education provided to caregivers and older children.

Overall, the review found a high frequency of treatment discontinuation due to toxicities, including both severe adverse reactions and other milder reactions (grade 1 or 2, such as vomiting, nausea, fever, diarrhoea and rash) with paediatric drugs (ABC, AZT or d4T). Qualitative evidence synthesis highlighted caregivers' concerns about adverse reactions, often resulting in children's refusal to take ART (moderate confidence) *(439)*. Clinical vigilance is required to be alert to adverse reactions in children and adolescents on ART.

Monitoring the toxicity of efavirenz

The main type of toxicity of EFV is CNS side-effects, which typically resolve after a few weeks. In some cases, they can persist for months or not resolve at all *(440)*.

A recent systematic review comparing the risk of discontinuation due to adverse drug reactions associated with EFV compared to other ARV drugs in first-line therapy found that EFV was well tolerated, with over 90% of patients remaining on an EFV-based first-line regimen after an average follow-up time of 78 weeks. While the relative risk of discontinuation was higher for EFV compared to most other first-line options, absolute differences were less than 5%, and there was no difference in the risk of severe clinical adverse reactions. The rate of suicidal ideation was low (0.6%), and no suicides were reported *(247)*. In children, CNS toxicity will need to be monitored more closely, as younger children may have more difficulty in characterizing symptoms.

A randomized trial comparing standard-dose EFV at 600 mg/day with the reduced dose of 400 mg/day in non-pregnant adults found that fewer EFV-related adverse reactions were reported with the lower dose, including fewer CNS symptoms, a finding that informs the new recommendation to use the lower dose as part of first-line ART *(269)* (*see* section 4.4.1 "First-line ART for adults").

Despite concerns about the potential risk of teratogenicity associated with the use of EFV during pregnancy, an update of a systematic review in 2015 found no overall increase in the incidence of birth defects with first-trimester EFV exposure compared with other ARV drugs *(259)*. The safety of EFV among pregnant women is discussed further in section 4.6.6 "Special considerations for toxicity monitoring during pregnancy and breastfeeding".

Monitoring the toxicity of nevirapine

The laboratory measurement of liver enzymes has very low predictive value for adverse reactions to NVP-containing regimens. However, monitoring hepatic enzymes is recommended where feasible, especially for women with HIV who have CD4 counts above 250 cells/mm^3 and people with HIV who also have HBV or HCV.

Monitoring the toxicity of zidovudine

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin should be considered before initiating ART, mainly among adults and children with low body weight, low CD4 cell counts and advanced HIV disease. Monitoring severe anaemia at baseline (haemoglobin <6.5 g/dL) and during treatment in adults and children is recommended, notably in those receiving AZT as part of first-line therapy (*see* section 4.6.2 "Major types of ARV toxicities").

4.6.6 Special considerations for toxicity monitoring during pregnancy and breastfeeding

Safety of efavirenz and tenofovir during pregnancy

In 2015, updated systematic reviews and meta-analysis showed that data on the safety of EFV and TDF during pregnancy were reassuring, confirming prior reviews conducted for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (259,260,441)*.

Review of the evidence showed no increased risk in overall congenital anomalies with EFV compared to other ARVs. The risk of neural tube defects associated with EFV remained low (0.05%) and is comparable to the general population in the United States

of 0.02–0.2%, confirming studies reviewed for the WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (259,441,442)*.

Review of the evidence showed no increased risk of abnormal pregnancy outcomes such as congenital anomalies, growth, bone health, low or mean birth weight, prematurity, pregnancy loss or miscarriage or other serious maternal adverse reactions with TDF-based ART compared with pregnant women receiving other triple-drug regimens without TDF. The evidence review is consistent with data from the Antiretroviral Pregnancy Registry *(442)*, which now includes a sufficient number of first-trimester TDF exposures to be able to rule out at least a 1.5-fold increased risk of overall birth defects, with a prevalence of overall birth defects with first-trimester TDF exposure of 2.3%, comparable to the 2.7% prevalence in the general population of the United States. Current human data available suggest that TDF does not increase the risk of major congenital anomalies.

Data on maternal toxicity or infant growth and adverse bone effects associated with TDF exposure remain limited. Only one study directly measured bone mineral density in newborns and found a significant loss of bone mineral density in TDF-exposed newborns compared to those who were not exposed to the drug. However, longitudinal data were not available, and the clinical significance of this finding remains unclear *(443)*. Although significant differences in anthropometric parameters have not been found in TDF-exposed compared to TDF-unexposed newborns at birth, one study reported slightly lower mean length-for-age-scores in TDF-exposed compared to TDF-unexposed infants at 1 year of age. However, in another study with a follow-up of two years, this difference did not persist *(370,444)*.

Safety of dolutegravir and raltegravir during pregnancy

There is a lack of data on the safety of INSTIs during pregnancy and breastfeeding *(411,442)*. The safety of DTG in pregnancy in particular is not well established, as there are no published safety or efficacy data on the outcomes of treating women with DTG during pregnancy. Furthermore, calcium or iron supplements frequently used during pregnancy could significantly reduce DTG drug levels *(445)*. Although there are no animal data to suggest that any of the INSTIs have any fetal toxicity, the current update of the Antiretroviral Pregnancy Registry reports only 391 documented INSTI exposures during pregnancy *(442)*. In the absence of well-controlled studies in pregnant women, DTG and RAL should be used only if the perceived benefits outweigh the risk. For practical purposes, in most settings, first-line therapy for pregnant women should continue to be based on drugs for which adequate safety data are available. For these reasons, EFV-based regimens are preferred over DTG-based regimens until more data become available.

Safety of nevirapine during pregnancy

Concerns about a higher risk of severe hepatic and skin reactions with NVP compared with EFV were addressed for the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. The systematic review conducted at the time suggested that the frequency was increased but no higher than in the general adult population and concluded that NVP needs to be used with caution in pregnant women or women who might become pregnant *(294)*. The higher risk of hepatic and skin reactions with NVP in pregnancy and at higher CD4 counts led to the 2013 recommendation favouring EFV as a first-line NNRTI.

Specific considerations on the safety of ART prior to conception

Use of ART during pregnancy, particularly when it begins before conception, has been associated in some studies from both high-income and resource-limited countries with increased risk of adverse birth outcomes, such as preterm delivery and low birth weight *(446–449)*. In 2015, a systematic review conducted for these guidelines to assess the safety of ART use in terms of pregnancy outcomes compared ART use prior to conception to starting ART during pregnancy *(450)*. Evidence showed an increased risk associated with preconception ART for adverse pregnancy outcomes of preterm delivery (12 studies, low-quality evidence), low birth weight (three studies, moderate-quality evidence), stillbirth (one study, very low-quality evidence), miscarriage (one study, very low-quality evidence), and possible increased risk of pregnancy-induced hypertension and pre-eclampsia (two studies, very low-quality evidence). However, the severity of prematurity and low birth weight were not well delineated in the published literature, with no papers discussing the association of preconception ART with very preterm delivery (<34 weeks gestation) or very low birth weight (<1500 g), which would be expected to have more severe neonatal consequences compared to preterm delivery (34–37 weeks) and low birth weight (1500–2500 g). Although better data on magnitude and impact are needed, the clear benefits of ART use during pregnancy for both child and mother outweigh the risk of adverse reactions. In addition, because pregnancy-induced hypertension and pre-eclampsia have been identified as predictors of pregnancy adverse outcomes, active screening and management of pregnancy-induced hypertension should be prioritized for all high-risk women, including those receiving ART and particularly those receiving ART prior to conception.

Safety of recommended first-line regimens (TDF + FTC or 3TC + EFV)

The PROMISE randomized controlled trial *(297)* compared the prevention efficacy and safety of ART regimens given to women with healthy immune systems (CD4 cell count above 350 cells/mm^3). It compared a prophylaxis regimen of AZT from 14 weeks followed by a single dose of NVP (sdNVP) during labour and two weeks of TDF + TFC after delivery with one of two triple-drug regimens (AZT + 3TC + LPV/r and TDF + FTC + LPV/r). The study reported a significantly lower risk of mother-to-child transmission with the triple-drug regimens (0.6%, compared to 1.8% with the AZT + sdNVP regimen). However, there was also a significantly higher risk of low birth weight (<2500 g) and preterm delivery (<37 weeks) with the triple-drug regimens compared to the prophylaxis regimen of AZT + sdNVP. Additionally, in a subanalysis comparing the two triple-drug regimens, the TDF + FTC + LPV/r regimen had a higher risk of severe preterm delivery (<34 weeks) and early infant death compared with the AZT + 3TC + LPV/r regimen. The most common reported cause of these deaths was prematurity. This subanalysis included only about a third of the patients enrolled in the study, and further analyses are in progress.

The WHO-recommended first-line regimen for pregnant women is distinct from the LPV/r-based regimens used in the PROMISE study. The results from other studies have not suggested that TDF or TDF + FTC is associated with excess adverse pregnancy outcomes. By contrast, PIs, including LPV/r, have been reported to be associated with prematurity and low birth weight. Additionally, there may be pharmacokinetic interactions between TDF and LPV/r, which could result in raised TDF levels. As LPV/r-based regimens are recommended in second-line treatment, toxicities associated with these regimens need further research. Although analysis is ongoing, the PROMISE study results to date support

the recommendation in these guidelines of lifelong ART for all pregnant women, as well as the preferred first-line regimen of TDF + 3TC or FTC + EFV *(451)*.

Clinical considerations

Active screening and management of hypertension in pregnancy should be prioritized for all high-risk women, including those receiving ART and particularly those receiving ART prior to conception.

Research gaps

Better research evidence is needed on the association between clinically relevant renal disorders and exposure to TDF. The trends in renal function parameters among people exposed to TDF over time and the potential reversibility of renal impairments when stopping TDF need further surveillance. Studies are also needed to establish which laboratory test(s) reliably detect TDF-related renal disorders and can be used as reference tests. More accurate and affordable methods to monitor bone toxicity are needed for paediatric and adolescent populations. Research to optimize drug tolerability and safe use in children is crucially needed. Implementation research is needed to assess newly available point-of-care creatinine clearance tools.

Toxicity profiles of INSTIs need further exploration and surveillance in resource-limited settings, especially their association with hepatotoxicity, risk factors for severe reactions and use during pregnancy and breastfeeding. The risk of hepatotoxicity and adverse reactions when co-administered with other potentially hepatotoxic drugs to treat comorbidities needs further assessment.

More data are needed on the presence of the HLA-B*5701 allele associated with ABC HSRs, notably in children and in Asian populations.

There is a critical need for continuing active toxicity surveillance to accompany implementation of lifelong ART for pregnant and breastfeeding women. Further research is needed to assess the extent and consequences of adverse pregnancy outcomes with preconception ART, whether there are differences by type of ART regimen and the ultimate effects on neonatal and infant mortality and to better understand the pathogenesis and determine whether there are potential interventions to reduce these outcomes.

More data are needed on the effects of in utero TDF exposure on infant bone development and growth and maternal toxicity. More data are also needed to determine whether use of TDF during breastfeeding increases the normal bone mineral density loss observed during breastfeeding (lactation is associated with bone mineral density loss that stabilizes after lactation) and, more importantly, whether if accelerated loss of bone mineral density is found, it reverses when breastfeeding stops or persists. This is a key question because TDF use could result in excess bone fragility among women during breastfeeding or in the future.

4.6.7 Drug substitutions for ARV drug toxicity

Drug regimen or single-agent substitutions may be required to manage drug toxicity and to avoid drug interactions. Delaying substitutions or switches when there are severe adverse drug reactions may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure.

When drug interruptions are required, such as for severe and life-threatening adverse reactions, it is important to consider the various half-lives of ARV drugs. For example, when an NNRTI needs to be discontinued, a staggered approach should be followed, in which the use of the NRTI backbone is prolonged for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

4.7   Key ARV drug interactions

Pharmacological interactions can reduce the efficacy of ART and/or increase ART-related toxicities. Major ARV drug interactions are summarized in Table 4.14 and described in more detail in Annex 13. Providers should be aware of all drugs that people are taking when ART is initiated, including alternative medicine products such as herbal remedies and dietary supplements as well as new drugs that are added during treatment maintenance.

Antituberculosis drugs

WHO *Treatment of tuberculosis guidelines* include key considerations for managing concomitant TB and HIV therapy *(452)*. A key contraindicated drug combination is rifampicin with PIs. When people with HIV-related TB are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV (*see* section 4.8.1 "Second-line ART for adults and adolescents"). For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered. For patients who are coinfected with HIV and extensively drug-resistant or multidrug-resistant (XDR/MDR) TB, there is limited information on the drug interactions of ARV drugs with new drugs such as bedaquiline and delamanid. As bedaquiline is primarily metabolized by CYP3A4, concomitant use with EFV and PIs can interfere with drug concentrations and should be undertaken with extreme caution and close clinical monitoring; alternative ARV options should be considered *(453)*. Rifampicin is known to significantly lower plasma concentrations of DTG, and increasing the dose to a twice-daily schedule may be necessary, but there are very few studies and limited clinical experience with this combination, particularly in individuals living with HIV and active TB (*see* section 4.4.1 "First-line ART for adults").

Drugs for hepatitis C

Potential drug interactions should be considered when using ARV drugs and DAAs for HCV infection. Simeprevir and the combination of ombitasvir + paritaprevir + ritionavir plus dasabuvir should not be co-administered with any PI or NNRTI. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways *(454,455)*. Although access to DAAs is still limited in many settings, ribavirin and pegylated interferon alpha-2a are being less frequently used to treat HCV infection. Administration of both agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfected with HCV and HIV who are using AZT may need to be switched to TDF. A complete list of drug–drug interactions is available at www.hep-druginteractions.org.

Antifungal agents

Itraconazole and ketoconazole are often used to treat fungal infections. Studies have shown that NVP may decrease the concentrations of these antifungal agents to subtherapeutic levels. Alternative antifungal agents (such as flucytosine and fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV.

Antimalarial drugs

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria *(456)*. One such recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant increase in liver transaminases. Halofantrine and lumefantrine should not be used with PIs. Alternative artemisinin-based combination therapies (such as artestunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.

Opioid substitution therapy

WHO recommends methadone and buprenorphine for treating opioid dependence *(457)*. Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People taking methadone and NNRTIs should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

Hormonal contraceptives

ARV drugs have the potential to either decrease or increase the levels of steroid hormones in hormonal contraceptives *(458)*. There may be drug interactions between some NNRTIs and RTV-boosted PIs with hormonal contraceptives, which can reduce the effectiveness of both the hormonal contraceptive and the ARV drug. There are generally fewer concerns regarding interactions of hormonal contraceptives with NRTIs and newer NNRTIs (*see* Annex 13). The contraceptive efficacy of injectable formulations of either intramuscular or subcutaneous depot medroxyprogesterone acetate (DMPA) is unaffected by ARV drugs and can be used without restriction *(459)*. There is a potential for reduced efficacy of long-acting progestogen-only implants when a women is also on ART containing EFV. If women receiving ART decide to initiate or continue using hormonal contraceptives, consistently using condoms and other contraceptive methods is recommended both to prevent HIV transmission and unintended pregnancy. WHO recommendations released in 2014 on the use of hormonal contraception by women receiving ART are available at www.who.int/reproductivehealth/publications/family_planning/MEC-5/en.

Antihistamines

Concomitant use of boosted PIs and NNRTIs with some antihistamine agents (such as astemizole and terfenadine) has been associated with severe and life-threatening reactions, such as cardiac arrhythmia. Alternative antihistamine agents include loratidine and cetirizine.

Statins

WHO recommends statins for people with a 10-year cardiovascular risk exceeding 30% *(460)*. Boosted PIs may lead to increased concentrations of lovastatin and simvastatin,

which may increase the risk of serious adverse events such as myopathy, including rhabdomyolysis. Alternative cholesterol-lowering agents should be used to prevent severe toxicity in people with HIV.

Other interactions

DTG should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin or mineral supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medications containing polyvalent cations *(445)*.

Table 4.14. Key ARV drug interactions and suggested management

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and pegylated-interferon alpha-2a	Substitute AZT with TDF
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the dose of LPV/r or substitute with three NRTIs (for children)
	Halofantrine and lumefantrine	Use an alternative antimalarial agent
	Lovastatin and simvastatin	Use an alternative cholesterol-lowering agent
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
DTG	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg- or Zn-multivitamin supplements; mineral supplements, cation-containing laxatives and Al-, Ca- or Mg-containing antacids. Monitor for virological efficacy
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies, as EFV may lower efficacy of some long-acting hormonal contraceptives
	Astemizole and terfenadine	Use an alternative antihistamine agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
NVP	Rifampicin	Substitute NVP with EFV
	Methadone	Adjust the methadone dose as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	Itraconazole and ketoconazole	Use an alternative antifungal agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA

This table was developed using the University of Liverpool's drug interaction charts, which can be found online at www.hiv-druginteractions.org and www.hep-druginteractions.org. A more comprehensive table of ARV drug interactions is available in Annex 13.

AZT zidovudine, ATV atazanavir, DAA direct-acting antiviral (agent), DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, TDF tenofovir.

4.8   What ART regimen to switch to (second- and third-line ART)

Table 4.15. Preferred second-line ART regimens for adults, adolescents, pregnant women and children

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r[c]
		2 NRTIs + DTG		
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r
Children	**Less than 3 years**	2 NRTIs + LPV/r	2 NRTIs[b] + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs[b] + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs[b] + LPV/r	2 NRTIs[b] + RAL[d]
	3 years to less than 10 years	2 NRTIs + LPV/r[a]	2 NRTIs[b] + EFV	2 NRTIs[b] + RAL[d]
		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + LPV/r	2 NRTIs[b] + ATV/r[d]

[a]   ATV/r can be used as an alternative PI for children older than 3 months of age.

[b]   If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

[c]   RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

[d]   DRV/r can be used as an alternative PI option in special situations.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, RAL raltegravir.

4.8.1 Second-line ART for adults and adolescents

Table 4.16. Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen[a]	
Adults and adolescents	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r [b,c]
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r [b,c]
Pregnant or breastfeeding women	Same regimens as recommended for adults and adolescents	
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) [d]
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)[b]	

[a] ABC and didanosine (ddI) can be used as NRTI back-up options but add complexity and cost without clinical advantages.

[b] DRV/r can be used as an alternative PI option.

[c] RAL + LPV/r can be used as an alternative second-line regimen (conditional recommendation, low-quality evidence).

[d] Standard LPV/r and RTV-boosted saquinavir (SQV/r) doses with an adjusted dose of RTV (that is, LPV 400 mg/ RTV 400 mg or SQV 400 mg /RTV 400 mg twice daily) can be used as alternative options.

3TC lamivudine, ATV atazanavir, AZT zidovudine, d4T stavudine, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, TDF tenofovir.

Recommendations

- Second-line ART in adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a ritonavir-boosted protease inhibitor (PI).

- The following sequence of second-line NRTI options is recommended:

  – After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.

  – After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.

- Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (strong recommendation, moderate-quality evidence).

- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (strong recommendation, moderate-quality evidence).

- **Heat-stable fixed-dose combinations of DRV/r can be used as an alternative boosted PI option for second-line ART (conditional recommendation, low-quality evidence).**   NEW

- **A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen (conditional recommendation, low-quality evidence).**   NEW

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that second-line adult ART regimens should include two NRTIs and a boosted PI *(9)*. Those guidelines placed a high value on using simpler second-line regimens, ideally as heat-stable formulations and FDCs. The preferred PI/r options for second-line ART were the heat-stable FDCs of ATV/r or LPV/r. RTV-boosted darunavir (DRV/r) could be used in special situations, but was recommended as a preferred third-line drug, as it was not available as a heat-stable FDC boosted with low-dose RTV at that time and because of its higher price compared with other options. The drugs used in first-line therapy should determine the choice of NRTI backbone in second-line regimens.

Since 2013, several studies exploring different strategies for second-line ART have been published, including those focused on the use of drug classes other than PI and NRTI, NRTI-sparing regimens and PI dose-optimization strategies *(461–465)*.

As first-line ART should preferably be based on an NNRTI, PI-based regimens are recommended for second-line therapy. Of the PI options, ATV/r and LPV/r are preferred. DRV/r has been used for second-line therapy in high-income settings *(466,467)*. However, several factors precluded DRV/r being recommended as a preferred option in the WHO

2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* These included limited comparative studies on its use as a second-line option, the high cost compared with other PI drugs and limited availability as an FDC. As a result, DRV/r has more frequently been used in third-line regimens in resource-limited settings *(468)*.

Rationale and supporting evidence

As in the case of first-line ART, WHO emphasizes a public health approach to second-line ART with a limited number of preferred regimens that can be used across different populations, including adults, adolescents, children, pregnant or breastfeeding women and people coinfected with TB, HBV and HCV. Less toxic, more convenient, tolerable, durable and efficacious heat-stable FDCs are also needed *(469)*.

The recommendations on second-line regimens for people with HIV and TB and with HIV and HBV remain unchanged from 2013.

NRTI backbone for second-line ART in adults and adolescents

Choice of second-line regimens should be consistent with ART-optimizing principles, in particular, availability as FDCs, tolerability and resistance mutation risk, based on the NRTIs used in the first-line regimen *(9)*. If a thymidine analogue NRTI (AZT or d4T) was used in the failing first-line regimen, TDF should be used in the second-line regimen. If a non-thymidine analogue NRTI was used in first-line ART (TDF), AZT should be used in the second-line regimen. Other NRTI drugs such as ABC and ddI are acceptable as potential back-up options in special situations but are not recommended as preferred alternatives, as they have no specific advantage and add complexity and cost.

PI options for second-line ART in adults and adolescents

A systematic review and network meta-analysis was undertaken to determine whether DRV/r-based regimens are comparable to currently recommended boosted PI options in second-line regimens with respect to safety and efficacy *(470)*. The analysis was restricted to patients failing NNRTI-based first-line regimens. Four randomized controlled trials *(464,471–473)* and two observational cohort studies *(474,475)* showed low- to very low-quality evidence that a DRV/r-containing regimen is not distinguishable from ATV/r- or LPV/r-containing regimens in terms of viral load suppression, mortality and grade 3/4 adverse events. However, there were no direct or indirect comparisons involving DRV/r-containing regimens with other outcomes.

The analysis also evaluated whether once-daily DRV/r regimens were equivalent to twice-daily DRV/r regimens, but no comparisons of frequency of administration and dosage were found in the studies with patients for whom NNRTI-containing regimens are failing. When the definition of study population was expanded to include treatment-experienced patients for whom any ART regimen fails (i.e. including patients on third-line regimens), five randomized controlled trials *(476–480)* showed that the estimated virological efficacy of DRV/r 800 mg/100 mg once daily was comparable to DRV/r 600 mg/100 mg twice daily (moderate-quality evidence), but the confidence intervals were too large to determine equivalence. For all other outcomes, the estimated effects favoured once-daily dosage, but the statistical analysis was not significant (low-quality evidence). Despite limited data, lower once-daily doses of DRV/r were found to be inferior

in terms of viral suppression and treatment discontinuation, though not statistically significant (low-quality evidence).

Considering the body of evidence in the review, there is inadequate new information to support a change in the recommendations on preferred boosted PI options and DRV/r dosing established in the WHO 2013 guidelines. Additional research in this area is required. DRV/r continues to be recommended as an alternative option to LPV/r or ATV/r for second-line ART.

INSTIs for second-line ART in adults and adolescents

In the same network meta-analysis, two randomized controlled trials investigated the comparative efficacy of RAL + LPV/r and 2 NRTIs + LPV/r *(464,465)*. The review showed moderate- to low-quality evidence supporting the equivalence of the NRTI-sparing regimens (i.e. INSTI + PI/r) when compared to 2 NRTI + ATV/r or LPV/r regimens. Apart from higher increases in CD4 cell counts in patients using RAL + LPV/r, there were no statistically significant differences in the evaluated outcomes. However, credible intervals tended to be narrow enough to suggest equivalence. No comparisons between RAL + LPV/r and 2 NRTI + DRV/r were available.

While evidence in the review allowed for inferences to be drawn about the use of NRTI-sparing regimens for second-line ART, it did not allow for inferences on the use of 2 NRTI + INSTI second-line regimens. The absence of such evidence can be explained by the low threshold for viral drug resistance with this regimen *(263)*, limiting the use of currently available INSTIs with simple NRTI backbones in patients for whom ART is failing.

Considerations for second-line regimens in TB and hepatitis B coinfection

For people with active TB disease taking rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions with rifampicin and significant reductions in PI plasma concentrations *(481–484)*. In these circumstances, rifabutin can be used in place of rifampicin and concomitantly administered with all boosted PIs in their standard doses. Rifabutin can be taken at an adjusted dose of 150 mg once daily or 300 mg three times a week *(485)*; careful monitoring is important for the occurrence of adverse events, particularly neutropaenia *(486)*. If rifabutin is not available, LPV/r may be used by doubling the daily dose (i.e. LPV/r 800 mg/200 mg twice daily) or with an adjusted, super-boosted dose of RTV (i.e. LPV/r 400 mg/400 mg twice daily), but this is frequently associated with high levels of toxicity and requires close clinical and laboratory monitoring *(483,487,488)*. The recommendation to use LPV/r 800 mg/200 mg twice daily is based on low-quality evidence and is associated with similar to slightly lower levels of toxicity when compared with LPV/r 400 mg/400 mg twice daily *(486,487)*. However, the double dosing option may be less complex and more feasible, as LPV/r is widely available as a single heat-stable formulation, whereas RTV is not.

For people coinfected with HIV and HBV whose first-line regimen contained TDF + 3TC (or FTC), these NRTIs should be continued in the second-line regimen for the anti-HBV activity and to reduce the risk of hepatic flares, regardless of the selected second-line regimen, which should be AZT + TDF + 3TC (or FTC) + a boosted PI *(489)*.

There are limited studies on the efficacy and safety of INSTI-containing second-line regimens in patients with TB and HBV coinfection. Despite the overall lower potential of

Table 4.17. Comparative analysis: ATV/r versus LPV/r versus DRV/r

Major parameters	ATV/r	LPV/r	DRV/r
Consistency with paediatric regimens	No[a]	Yes	No[b]
Number of pills per day (standard dose as a fixed-dose combination)	1	4	2–4
Convenience (once- versus twice-daily regimen)	Once daily	Twice daily	Once or twice daily
Safety in pregnancy	Yes	Yes	Yes
Gastrointestinal intolerance (diarrhoea)	Not frequent	Common	Not frequent
Availability of co-formulations (as heat-stable fixed-dose combinations)	Yes	Yes	No[d]
Use with a TB treatment regimen that contains rifampicin	No	Yes[c]	No
Hyperbilirubinaemia	+	–	–
Dyslipidaemia	±	+	±
Accessibility in countries (registration status)	Moderate	High	Low
Availability of generic formulations	Yes	Yes	No

[a] Approved only for children older than 3 months.

[b] Approved only for children older than 3 years.

[c] Can be used with dose adjustment.

[d] A generic heat-stable FDC of DRV/r (400/50 mg tablet) is expected to be available in late 2016.

INSTIs for drug interactions compared with PIs, rifamycin can significantly reduce the levels of RAL and DTG, and dose adjustments may be necessary *(275,490,491)*.

Implementation considerations

Clinical and programmatic simplification can be promoted in the sequencing from first- to second-line ART. If AZT- or d4T-based regimens are failing, a second-line regimen with once-daily dosing with boosted PI and NRTI components (such as TDF + 3TC [or FTC] + ATV/r) should be used. If a TDF-based regimen is failing, twice-daily dosing with boosted PI and NRTI components (such as AZT + 3TC + LPV/r) should be used.

Use of DRV/r as a boosted PI option and NRTI-sparing regimens such as RAL + LPV/r increase the cost of second-line ART and have not shown better performance when compared with the current standard of care (i.e. 2 NRTI + ATV/r or LPV/r). Heat-stable FDCs of DRV/r are expected to be available only in late 2016, but with good potential for price reduction through generic competition *(281)*. For these reasons, these options are recommended as alternative choices for second-line ART.

Key research gaps

Additional research is required to better understand choice and sequencing strategies for PI options in second- and third-line ART. Several ongoing studies comparing various drugs and ARV classes will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches. The different drug toxicity profiles of ATV/r, DRV/r and LPV/r, the contraindication of using ATV/r and DRV/r with rifampicin and the lack of WHO approval for the use of ATV/r and DRV/r in younger children are highlighted in Table 4.17. Further investigation is needed of the role of boosted DRV in second- and

third-line regimens, including optimal dosing in adults and children, FDCs with other boosting agents and INSTIs, and sequencing strategies. Several trials are under way to examine induction and maintenance using PI/r monotherapy or in combination with 3TC as maintenance therapy. The potential of including rifabutin as part of FDCs for TB treatment also needs to be explored.

4.8.2 Second-line ART for children

Recommendations

- After failure of a first-line LPV/r-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen (conditional recommendation, very low-quality evidence).

- After failure of a first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL (conditional recommendation, very low-quality evidence).

- After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred (conditional recommendation, very low-quality evidence).

- After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC (strong recommendation, low-quality evidence).

- After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) (strong recommendation, low-quality evidence).

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Of the 1.5 million children estimated to be in need of ART by 2020, up to 20% are expected to experience virological failure at some point *(355)*. Recommending potent and effective second-line regimens for infants and children is difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This challenge highlights the importance of choosing potent and effective first-line regimens and the need for optimal adherence to ensure their durability and effectiveness *(492)*.

The WHO 2013 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend a PI boosted with RTV and combined with two NRTIs as the second-line treatment for children for whom a regimen of two NRTIs plus an NNRTI fails *(9)*. For infants and young children who had used a first-line, PI-based regimen, a new NRTI backbone and an NNRTI were recommended for second-line ART, as NNRTIs were the only new drug class available. In addition, data from randomized controlled trials among older children *(314)* provided indirect evidence supporting the safe

Table 4.18. Summary of recommended first- and second-line ART regimens for children

	Children (including adolescents)	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	AZT or ABC+ 3TC + RAL[a]
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV or RAL
		AZT + 3TC + LPV/r	ABC or TDF[b] + 3TC + EFV or RAL
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + ATV/r or LPV/r[c]
		TDF[b] + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC[c] (or FTC) + ATV/r or LPV/r[c]

[a] If RAL is not available, no change is recommended unless in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than 3 years, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population.

[b] TDF may be given only to children older than 2 years.

[c] ATV/r can be used as an alternative to LPV/r in children older than 3 months. However, the limited availability of suitable formulations for children younger than 6 years, the lack of an FDC and the need for separate administration of the RTV booster should be considered when choosing this regimen.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir, TDF tenofovir.

use of an NNRTI-based second-line regimen. However, concerns remain about the effectiveness of this approach, given the potential for re-emergence of archived resistance as a result of NNRTI exposure during breastfeeding and postnatal prophylaxis.

Since 2013, safety and dosage trials have been completed for RAL, which is now approved by stringent regulatory authorities for use in children older than 4 weeks *(336,353)*. In addition, while a DRV co-formulation with RTV is not commercially available for either adults or children, a single-entity paediatric DRV formulation that can be used in children 3 years and older has become available in a few countries in sub-Saharan Africa through a limited donation programme *(493)*.

Rationale and supporting evidence

A systematic review undertaken to assess clinical outcomes for drugs used in second- and third-line ART *(494)* identified 13 cohort and seven single-arm studies. All drugs under consideration were reported to be effective and well tolerated. However, it was not possible to establish a clear preference based on efficacy due to a lack of comparative data.

After reviewing the data for adults and children and considering factors such as the availability of a heat-stable FDC, optimal daily dose, regimen harmonization with adults, cost and availability of alternatives, the main recommendations of the WHO 2013 guidelines were maintained. RAL-based regimens have been added as a second-line option when an LPV/r-based first-line regimen fails for infants and children.

For children for whom a first-line PI-based regimen fails, INSTIs offer advantages over

NNRTIs, including the possibility of potent, palatable formulations without pre-existing resistance that can be used from 4 weeks of age. However, due to the current limited availability of RAL, it is important to strengthen adherence and maintain EFV as a viable option for children who are 3 years and older, as NNRTIs are the only new drug class that can be introduced. Data from a randomized controlled trial among older children *(314)* provides indirect evidence supporting the safe use of an NNRTI-based second-line regimen, but concerns remain about this approach for infants and young children. Based on the suboptimal performance of NVP-based regimens, the limited data available to inform the use of EFV in children younger than 3 years *(339,340)* and the potential re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group *(495)*.

Increasing evidence suggests that, in young children for whom LPV/r-based regimens have failed, selection of major PI mutations is rare and accumulation of thymidine analogue mutations is very limited *(346,496–499)*. In this context, and if RAL-containing regimens are unavailable, children younger than 3 years of age with treatment failure should be maintained on LPV/r until the age of 3 years. However, a more rapid switch should be considered in situations where failure results from poor adherence because of the poor palatability of LPV/r or in cases of advanced HIV disease. In these cases, children younger than 3 years should be switched to an NVP-based regimen and close monitoring provided to ensure adequate adherence.

For children for whom a first-line NNRTI-based regimen fails, PI-based regimens remain the recommended choice for second-line therapy, as they are less costly and more broadly available than newer drugs such as RAL and DTG. LPV/r and ATV/r are the preferred options.

Reviews of clinical trials and observational and pharmacovigilance studies did not provide any direct comparison between LPV/r, ATV/r and DRV/r. Despite its side-effect profile and limited role in TB and HIV coinfection, ATV/r is likely to be a good alternative to LPV/r for children older than 3 months due to less frequent gastrointestinal side-effects, a more favourable lipid profile, the potential for once-daily dosing and lower cost. However, acceptability may be lower due to ATV-related hyperbilirubinaemia, which – although usually mild and transient – is found in 50% of cases *(500)* as well as the lack of co-formulated FDCs containing ATV/r. Validation studies are urgently needed to develop appropriate paediatric ATV/r formulations.

DRV/r may be appropriate, given its efficacy, high genetic barrier to resistance and good safety profile *(500)*. However, there is no suitable co-formulation with RTV, it is significantly more expensive in the absence of a donation programme *(493)* and it is contraindicated in children younger than three years. For these reasons, DRV/r is not recommended for second-line use but could be considered in the future should a generic paediatric formulation become available. DRV/r can be considered for third-line therapy where it is available.

Because unboosted PIs such as fosamprenavir (FPV), DRV and ATV and other PIs such as indinavir (IDV)/r, SQV/r, FPV/r and tipranavir (TPV)/r are associated with reduced viral suppression, high pill burden and/or a higher frequency of side-effects, their use is discouraged *(9)*.

The sequencing of NRTIs was assessed for both PI and NNRTI failures, based on

optimizing principles for ARV drugs and the need to maximize antiviral activity in the context of selection of resistance mutations. If a thymidine analogue NRTI drug (AZT or d4T) was used in the failing first-line regimen, ABC or TDF should be used in the second-line regimen. If a non-thymidine analogue NRTI drug (ABC or TDF) was used in the failing first-line regimen, AZT should be used in the second-line regimen. The use of ddI in second-line regimens is no longer recommended; continuation of 3TC even where 3TC resistance is likely is the preferred option. HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication capacity and may induce some degree of resensitization to AZT or TDF based on in vitro data *(354,501)*.

Key research gaps

More evidence is needed to inform the choice of second-line regimens, particularly for young children for whom an LPV/r-based first-line regimen fails. Validation studies to assess simplified dosing for ATV/r and DRV/r FDCs are critical to ensure the availability of effective alternatives. Innovative second-line strategies such as using a PI combined with INSTIs or induction and maintenance approaches using boosted PI monotherapy should also be investigated among children. Further studies to examine the role and feasibility of genotyping to inform second-line choice in the context of a public health approach would also be of value.

4.8.3 Third-line ART

Recommendations

- National programmes should develop policies for third-line ART (conditional recommendation, low-quality evidence).

- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs (conditional recommendation, low-quality evidence).

- Patients on a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen (conditional recommendation, very low-quality evidence).

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection:r ecommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

In 2010, WHO made recommendations on third-line ART in a context of limited evidence to guide treatment of patients for whom second-line therapy fails *(65)*. Although there were few studies with newer agents, cohort data showed high mortality among people for whom second-line ART had failed *(502)*. Salvage regimens were recommended with new drugs such as DRV/r, etravirine (ETV) and RAL with or without previously used ARVs that potentially maintained residual virological activity, particularly from the NRTI class *(503–505)*. These recommendations were maintained in 2013 based on additional trial data *(506–509)*, but the need for more clinical and operational research to guide the

establishment of strategies and public health policies on third-line ART was emphasized *(9)*.

Rationale and supporting evidence

Recent data from several randomized controlled trials and observational cohorts are available for DRV/r-, ETV-, DTG- and RAL-containing regimens in treatment-experienced adults, but most studies have been conducted in middle-to-high or high-income settings *(430,510–515)*. Many of these ARV drugs were effective in prospective studies in children and adolescents *(494)*. Taken together, the data support the efficacy of new agents such as INSTIs, second-generation PIs and NNRTIs in people for whom second-line ART fails. However, in ART-experienced patients for whom first- and second-line regimens have already failed, multiple resistance to NRTI agents with reduced virological efficacy is common, and there is some uncertainty about whether maintaining or recycling previously used NRTIs provides clinical benefit through reduction in viral fitness and/or in vitro enhancement of susceptibility caused by some mutations, combined with some residual antiviral activity of these drugs *(516–518)*. Furthermore, as NRTI agents are often associated with cumulative toxicity, their maintenance in third-line ART may not be optimal and may involve increased pill burden and risk of drug interactions. Avoiding NRTIs in third-line regimens is now more feasible due to the increasing availability of new ARV drug classes with a different resistance profile.

A systematic review and network meta-analysis was undertaken to determine whether NRTI-sparing new regimens (i.e. regimens that do not include NRTIs and that contain new drugs with a minimal risk of cross-resistance to previously used regimens) are comparable to NRTI-containing new regimens in those for whom first- and second-line therapy has failed *(470)*. Three comparative studies were relevant and included NRTI-sparing and NRTI-containing new regimens for patients for whom both NNRTI- and PI-containing regimens had failed. One study was a phase III, open-label trial with 360 patients *(519)*. The other two studies were prospective observational cohorts with 122 patients and 689 patients, respectively *(520,521)*. Only limited data are available on third-line ART for children, adolescents or pregnant women. In the absence of data among these populations, it is reasonable to extrapolate from adult studies, but pharmacokinetic and safety data on new drugs are particularly critical for children and pregnant women.

The analysis showed that NRTI-sparing and NRTI-containing regimens were comparable with respect to viral suppression. Efficacy with respect to change in CD4 cell count favoured NRTI-containing regimens, but this difference was not statistically significant. For other outcomes such as mortality, AIDS-defining illnesses, serious adverse events, serious treatment-related adverse events, treatment discontinuation, discontinuation due to adverse events and risk of drug resistance, all estimates favoured NRTI-sparing regimens but also failed to do so in a statistically significant manner. The data suggest that NRTI-sparing regimens may have better tolerability but that further evidence with highly treatment-experienced patients is needed.

Because there is limited evidence to show that NRTI-sparing regimens are as effective as NRTI-containing salvage regimens, the WHO 2013 recommendations for third-line use are maintained in 2015. Further data on the pharmacokinetics, safety and efficacy of salvage regimens in children, adolescents and pregnant women are needed. Countries must strike a balance between the need to develop policies for third-line ART and the continued

expansion and optimal use of first-line and second-line ART. Many countries also face financial constraints that limit the adoption of third-line regimens. Table 4.19 summarizes potential options for third-line regimens depending upon the preferred options used previously in first- and second-line therapy.

Table 4.19. Summary of sequencing options for first-, second- and third-line ART regimens in adults, adolescents, pregnant women and children

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (>10 years)	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a]	DRV/r [b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTI + DRV/r[b]	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r [b] + 2 NRTIs ± NNRTI
		2 NRTI + DRV/r	Optimize regimen using genotype profile
Pregnant or breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r[a]	DRV/r[b] + DTG[c] (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r[b]	
Children (0–10 years	2 NRTI + LPV/r	If less than 3 years: 2 NRTIs + RAL[d]	RAL (or DTG)[f] + 2 NRTIs
			DRV/r[g] + 2 NRTIs
		If older than 3 years: 2 NRTIs + EFV or RAL	DRV/r[g] + RAL (or DTG)[f] ± 1–2 NRTIs
	2 NRTI + EFV	2 NRTIs + ATV/r[e] or LPV/r	

[a] RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

[b] In PI-experienced patients, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

[c] Safety and efficacy data on the use of DTG in adolescents younger than 12 years and pregnant women are not yet available.

[d] If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence, specifically because of poor palatability of LPV/r. In this case, switching to a second-line NVP-based regimen should be considered. Based on approval of the use of EFV in children less than 3 years of age, an EFV-based regimen could be considered as an alternative. However, more data are needed to inform how best to use EFV in this population (*see* Table 4.18).

[e] ATV/r can be used as an alternative to LPV/r in children older than 3 months of age. However, the limited availability of suitable formulations for children younger than 6 years of age, the lack of an FDC and the need for separate administration of RTV booster should be considered when choosing this regimen.

[f] RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently approved only for children 12 years and older; however, studies are ongoing to determine dosing in younger children, and approval for lower age groups is expected in the near future

[g] DRV/r should not be used in children younger than 3 years of age.

ATV atazanavir, DRV darunavir, DTG dolutegravir, EFV efavirenz, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir.

Implementation considerations

WHO estimates that less than 1% of people taking ART globally are using third-line regimens, but the demand for third-line regimens will increase as access to viral load monitoring and use of first- and second-line ART continue to expand *(239)*. The cost of third-line drugs is either higher than first- and second-line regimens or has not been established, which may limit the adoption of third-line regimens in many countries with limited resources. Although developing a policy on access to third-line ART is desirable, it should not compromise access to first- and second-line ART.

Special considerations for children, adolescents and pregnant women

There have been limited studies on the use of many newer ARV drugs as part of third-line regimens in children and adolescents and during pregnancy and breastfeeding; pharmacokinetic and safety data are particularly lacking. As a result, strategies that balance the benefits and risks need to be explored when second-line treatment fails.

A systematic review and network meta-analysis conducted to inform these guidelines showed overall good efficacy and tolerability of newer drugs in treatment-experienced patients *(494)*. However, no head-to-head comparison was identified to fully assess the clinical advantages of one drug over others. Given the limited evidence available, DRV and DTG are recommended for use in third-line regimens for children *(355)*. There is uncertainty about whether these drugs should be used in combination or as part of a standard NRTI-backbone regimen. DRV cannot be used in children younger than 3 years and is provided as a single drug through a donation programme only to selected countries *(493)*. In addition, no paediatric FDC of DRV with RTV is available. DTG is currently approved for adolescents from 12 years, but the availability of this drug is expected to be limited. A safety and dose-finding trial (IMPAACT 1093 study) is under underway, and its completion in 2016 is expected to support paediatric registration by stringent regulatory agencies. RAL provides an alternative option in children for whom PI-based second-line ART fails and should be considered when DTG cannot be used (Table 4.18).

Children for whom a second-line regimen fails with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, attention should be paid to preventing OIs, symptom relief and pain management.

There are limited data on the use of newer third-line drugs in women who are pregnant or breastfeeding. The current edition of the Antiretroviral Pregnancy Registry reports only 200 documented in-utero exposures to any of the INSTIs, although this is likely to increase with expanded use of DTG as a first-line therapy *(442)*. There are no animal data to suggest fetal toxicity with any of the INSTIs, but in the absence of well-controlled studies in pregnant women, as well as pharmacokinetic data to inform dosing of INSTIs during pregnancy, DTG should be used in pregnancy only if clearly indicated. For DRV, sufficient numbers of first-trimester exposures have been reported to detect at least a twofold increase in risk of birth defects, no such increases have been reported to date. In the case of a pregnant woman needing third-line ART, it may be warranted to use both DRV and DTG, as the benefits are likely to outweigh any potential risks (Table 4.19).

Research gaps

Further research into a range of areas is needed to guide third-line ART strategies for resource-limited settings. Priorities include the monitoring of critical outcomes for people taking second-line ART, once-daily dosing for DRV/r and RAL as alternatives to NRTI-based regimens in second-line ART, developing heat-stable formulations of DRV/r and evaluating the pharmacokinetics, safety and efficacy of new drugs in children, adolescents and pregnant women. The need to assess the pharmacokinetics and safety of DTG in pregnant women is particularly urgent. Pharmacovigilance research is also needed, including studies on the long-term safety of and potential interactions with drugs used for TB, malaria, hepatitis and opioid substitution therapy. As the epidemic matures in resource-limited settings, pilot studies are urgently needed on implementing third-line ART in settings with limited capacity and resources.

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CLINICAL GUIDELINES: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

5

5 CLINICAL GUIDELINES: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

5.1   Introduction

Various coinfections, comorbidities and other concomitant health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of ARV drugs. This section provides a brief overview of the most common and important conditions. It summarizes selected key recommendations from existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions; it does not cover their management in detail. Sources are provided for relevant, previously published recommendations. These recommendations were not reviewed during the 2015 guideline development process.

Evidence reviews were undertaken in 2015 with regard to presumptive treatment for tuberculosis (TB), depression and cardiovascular disease in people living with HIV. Although no formal recommendation on presumptive TB treatment is made, guidance is provided. New recommendations are presented for the screening and management of cardiovascular disease and depression in people living with HIV.

5.2   Prevention, screening and management of common coinfections

5.2.1 Co-trimoxazole prophylaxis

Background and rationale

Co-trimoxazole (CTX) is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) used to treat a variety of bacterial, fungal and protozoan infections. CTX prophylaxis is a feasible, well-tolerated and inexpensive intervention to reduce HIV-related morbidity and mortality in people living with HIV. CTX is an off-patent drug and is widely available in resource-limited settings.

In 2006, the first WHO guidelines on CTX prophylaxis in resource-limited settings recommended CTX prophylaxis as an integral component of HIV care *(1)*. These guidelines were reviewed in 2014 and updated in the context of expanded access to and earlier initiation of ART *(2)*. In recent years, new evidence has emerged showing that with expanded access to ART, there is a broader benefit of CTX prophylaxis beyond the prevention of some AIDS-associated opportunistic diseases (*Pneumocystis jirovecii* pneumonia [PCP] and toxoplasmosis) and the reduction of HIV-associated mortality in people with low CD4 cell counts. These benefits relate to prevention of malaria and severe bacterial infections (SBIs) in adults and children with HIV.

Recommendations

Co-trimoxazole prophylaxis for adults

Co-trimoxazole (CTX) prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count ≤350 cells/mm^3 (strong recommendation, moderate-quality evidence).

In settings where malaria and/or severe bacterial infections (SBIs) are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (conditional recommendation, moderate-quality evidence).

Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression (conditional recommendation, low-quality evidence).

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage (conditional recommendation, moderate-quality evidence).

Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count (strong recommendation, high-quality evidence).

Co-trimoxazole prophylaxis for HIV-infected infants, children and adolescents

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage, and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a CD4 count ≤350 cells/mm^3 (strong recommendation, high-quality evidence).

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood, irrespective of whether ART is provided (conditional recommendation, moderate-quality evidence).

In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children five years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and with a CD4 count > 350 cells/mm^3 (strong recommendation, very low-quality evidence).

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding (strong recommendation, very low-quality evidence).

Source: Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

The effectiveness of CTX prophylaxis in reducing death among people starting ART with a CD4 cell count at or below 350 cells/mm^3 and/or WHO clinical stage 3 or 4 disease is supported by moderate-quality evidence from nine observational studies *(3–11)*. In addition, a new expanded recommendation for use of CTX prophylaxis is based on a recent systematic review showing the effectiveness of CTX prophylaxis in reducing mortality, SBIs, malaria and hospitalization in adults and adolescents with HIV, regardless of clinical and immunological parameters *(12)*. One randomized clinical trial in children with HIV showed survival benefits regardless of age and CD4 cell count and also supports the expansion of CTX prophylaxis in paediatric populations, particularly in settings with a high prevalence of malaria and/or SBIs *(13,14)*.

Continuation of CTX prophylaxis regardless of ART status, age, CD4 cell count or WHO clinical stage in settings with a high prevalence of malaria and/or SBIs is also recommended based on data from randomized controlled trials, which show significant reduction in the risk of hospitalization, malaria and diarrhoea among adults and children with HIV in settings with a high prevalence of malaria and/or SBIs *(15–17)*. In addition, the recommendation to continue CTX prophylaxis in settings with a high prevalence of malaria and/or SBIs may simplify HIV management, forecasting and supply management issues.

The risks and benefits of continuing versus stopping CTX prophylaxis after viral suppression induced by ART were also evaluated in settings with a low burden of malaria and SBIs. Two studies found that the rates of PCP and death were similar in people on ART who achieved viral suppression and had CD4 cell counts above 100 cells/mm^3 in study arms *(18,19)*. In these settings, discontinuation of CTX prophylaxis in adults based on clinical, immunological and virological parameters indicative of ART immune recovery can be considered, although the quality of the evidence is low to very low *(2)*. However, in settings with a low prevalence of malaria and/or SBI, and limited or no access to CD4 testing, CTX prophylaxis should not be discontinued.

The recommendation on the use of CTX prophylaxis during pregnancy in women and adolescents living with HIV to prevent malaria complications and avoid simultaneous intermittent preventive treatment is maintained, based on a systematic review showing that CTX prophylaxis is not inferior to intermittent preventive treatment of malaria in pregnancy with respect to mortality, low birth weight, placental malaria, maternal deaths and severe adverse events *(20)*. The recommendation to discontinue CTX prophylaxis at the end of the risk period for transmission in HIV-exposed uninfected infants is also maintained, as there is insufficient evidence available to establish the clinical benefit of CTX prophylaxis in HIV-exposed uninfected infants.

Table 5.1 summarizes the criteria for initiation and discontinuation of CTX prophylaxis in adults, adolescents, pregnant women and children with HIV.

Table 5.1. Criteria for initiation and discontinuation of co-trimoxazole prophylaxis

Population	Recommendation	
	Criteria for initiation of co-trimoxazole prophylaxis	**Criteria for discontinuation of co-trimoxazole prophylaxis**
Adults (including pregnant women) with HIV	• Initiate in all with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm[3][a] • **In settings with a high prevalence of malaria and/or severe bacterial infections**[b]**:** initiate in all regardless of WHO clinical stage or CD4 cell count	• May be discontinued in those who are clinically stable,[c] with evidence of immune recovery and/or viral suppression on ART[d,e] • In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued
Children and adolescents with HIV	• Initiate in all regardless of WHO clinical stage or CD4 cell count • **As a priority:** (1) initiate in all less than 5 years of age, regardless of WHO clinical stage or CD4 cell count; (2) initiate in all older than 5 years of age and with severe /advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm^{3}	• **In settings with a high prevalence of malaria and/or severe bacterial infections:** should be continued until adulthood • **In settings with a low prevalence of both malaria and severe bacterial infections:** may be discontinued for those older than 5 years of age who are clinically stable, with evidence of immune recovery[f] and/or viral suppression on ART
HIV-exposed uninfected infants	• Initiate in all starting at 4–6 weeks after birth	• Until the risk of HIV transmission ends or HIV infection is excluded[g]
People living with HIV and TB[h]	• Initiate in all with active TB regardless of CD4 cell count	• Until criteria for discontinuation in adults or children are met

[a] This group is also prioritized for ART initiation (as recommended for ART in the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection).

[b] Settings where malaria and/or SBIs are highly prevalent includes low- and middle-income countries with high rates of mortality among children less than 5 years old (http://www.who.int/gho/child_health/mortality/mortality_under_five/en).

[c] Clinically stable adults are defined as those individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events.

[d] CD4 count >350 cells/mm^{3}, with viral load suppression, is considered indicative of immune recovery (some countries may adopt a threshold of CD4 count >500 cells/mm^{3}).

[e] WHO recognizes that in settings with a low prevalence of malaria and SBIs where CTX is used primarily as prophylaxis for some AIDS-associated opportunistic infections (PCP and toxoplasmosis), guidelines exist for discontinuing CTX in adults with HIV infection when there is evidence of viral suppression and immune recovery at CD4 cell counts >200 cells/mm^{3} and being on ART for at least 1 year.

[f] Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm^{3}, with viral load suppression.

[g] In settings with a high malaria transmission, consideration may be given to extend CTX prophylaxis in HIV-exposed uninfected infants up to 2 years of age.

[h] Recommendation maintained from: WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders. Geneva: WHO; 2012.

Implementation considerations

Some of the major barriers to CTX implementation include supply chain and management issues leading to stock-outs; imposing costs on patients for medication and/or monitoring; inadequate training, supervision, and/or mentoring of health-care workers; low coverage of HIV testing and counselling; and lack of coordination across programmes. National programmes can implement CTX prophylaxis policy and guidelines more effectively through the approaches shown in Box 5.1.

Box 5.1. Steps to improve the implementation of co-trimoxazole prophylaxis policy and guidelines at the national level

- Adapt WHO guidelines to national context.
- Strengthen national and local drug supply management systems to ensure sustained availability of CTX at health-care facilities.
- Secure financing for providing CTX prophylaxis to ensure that no charges for CTX are imposed on patients.
- Coordinate with malaria programmes at a country level with regard to recommendations related to intermittent preventive treatment of malaria in pregnancy and seasonal malaria chemoprophylaxis in children less than 5 years.
- Provide CTX prophylaxis to eligible people at TB, maternal, newborn and child health (MNCH) and opioid substitution therapy (OST) services.
- Scale up training and sensitization of health-care workers.
- Increase knowledge of CTX prophylaxis at the community level.
- Ensure that a human rights framework is used (e.g. people with HIV should always consent to the use of CTX prophylaxis).
- Ensure that high-quality CTX formulations are provided.
- Toxicity monitoring should be done for adverse reactions, particularly in the context of chronic CTX prophylaxis use.
- Assess adherence to policies and impact of CTX prophylaxis on population health.

5.2.2 Tuberculosis

Background

TB is the most common cause of death in hospitalized adults and children living with HIV, accounting for about a third of all mortality *(21)*. A systematic review of autopsy studies among adults who had had HIV showed a pooled prevalence of almost 40% in the cadavers, with just under half of the cases previously undetected *(22)*.

Routine TB symptom screening for people with HIV, using an algorithm containing fever, cough of any duration, weight loss and night sweats, will help to identify people who should either be expedited for TB diagnosis or given preventive TB therapy. The combined use of isoniazid preventive therapy (IPT) and ART has been shown to have both TB prevention and mortality benefits, including in people with a higher CD4 count *(23,24)*. The timely initiation of ART and implementation of the "Three I's" for HIV/TB (increased TB case-finding, IPT and infection control) are critical to prevent TB and mortality from HIV-associated TB.

Diagnosis of HIV-associated TB using smear microscopy, a widely available method, is very challenging in people with HIV, resulting in delayed diagnoses and misdiagnoses. WHO-approved nucleic acid-based molecular tests (e.g. Xpert MTB/RIF) improve the yield and speed of diagnosis, and need to be scaled up in all HIV clinical settings. This section presents the review of evidence and relevant recommendations on the use of urine lipoarabinomannan (LAM) antigen test for diagnosis and presumptive TB treatment for people living with HIV who are severely immunocompromised. A recent review of evidence on the timing of ART for TB patients is described in section 4.3.5.

TB diagnosis and treatment

Recommendations

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in adults and children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB (strong recommendation, adults: high-quality evidence; children: very low-quality evidence).

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid specimens from patients suspected of having TB meningitis (strong recommendation, very low-quality evidence).

- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence).

Source: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: WHO policy update. Geneva: World Health Organization; 2013 (http://www.who.int/tb/laboratory/xpert_policyupdate/en).

- Except as specifically described below for people with HIV infection with low CD4 counts or who are seriously ill,[a] urine lateral flow (LF)-LAM should not be used for the diagnosis of TB (strong recommendation, low-quality evidence).

- LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary), who have a CD4 count less than or equal to 100 cells/mm^3, or people living with HIV who are seriously ill,[a] regardless of CD4 cell count or with unknown CD4 cell count (conditional recommendation, low-quality evidence).[b]

- LF-LAM should not be used as a screening test for active TB (strong recommendation, low-quality evidence).

Source: The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV: Policy guidance. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf).

- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of a rifampicin-containing treatment regimen. The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high-quality evidence).

[a]   "Seriously ill" is defined as four danger signs: respiratory rate >30/min, temperature >39°C, heart rate >120/min and unable to walk unaided.

[b]   This recommendation also applies to adults living with HIV who are outpatients with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/mm³ or who are seriously ill[a] regardless of CD4 count or with unknown CD4 count, based on the generalization of data from inpatients. This recommendation also applies to children living with HIV, with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalization of data from adults, while acknowledging that data are very limited and that there are concerns regarding low specificity of the LF-LAM assay in children.

Source: WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en).

Early identification of TB among people with HIV through careful assessment of symptoms and signs, diagnosis using proper investigation (i.e. Xpert MTB/RIF) and prompt initiation of anti-TB treatment is important to improve survival and quality of life as well as reduce transmission of TB in the clinic and the community.

All people living with HIV should be regularly screened for TB using a clinical symptom-based algorithm. Those who report any one of the symptoms may have active TB and should be evaluated for TB and other diseases. Xpert MTB/RIF should be used as the initial diagnostic test in adults and children suspected of having HIV-associated TB. Xpert MTB/RIF should also be used as a preferred initial diagnostic test for cerebrospinal fluid investigation in people with HIV presumed to have TB meningitis.

Diagnosis of TB in people with HIV should always be expedited and anti-TB treatment initiated as soon as possible. In peripheral settings where TB investigations are not available, clinical assessment and judgement should be used to provide presumptive TB treatment for select individuals who are seriously ill. Diagnostic algorithms for individuals living with HIV who are suspected of having TB are in Annexes 14 and 15.

Tests based on the detection of mycobacterial LAM antigen in urine have emerged as potential point-of-care tests for TB. LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. The LF-LAM assay (Alere Determine™ TB LAM Ag) is a commercially available strip test for active TB.

In 2015, evidence was reviewed regarding the accuracy of LF-LAM and its use as a screening or diagnostic tool for TB in people with HIV. Sixteen unique studies were identified that assessed the diagnostic accuracy of LF-LAM for TB in people with HIV with signs or symptoms of TB (TB diagnostic tool) or in people with HIV regardless of signs or symptoms of TB (TB screening tool) *(25)*. The review suggested that, in general, LF-LAM should not be used for either the diagnosis or the screening of active TB in adults with HIV. However, because the sensitivity and specificity of the test were highest in adults with CD4 counts at or below 100 cells/mm³ in inpatient settings, LF-LAM may be used to assist in the diagnosis of active TB in adult inpatients with HIV who are

presumed to have TB and who have a CD4 cell count at or below 100 cells/mm^3. LF-LAM could be performed for seriously ill HIV-positive adult patients with danger signs, regardless of CD4 count, in both in-hospital and outpatient settings. This recommendation also applies to children based on the generalization of data from adults but recognizing that data are limited and that there are concerns regarding the low specificity of LF-LAM in children.

TB patients with known HIV-positive status and TB patients living in HIV-prevalent settings should receive daily isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid alone for four months. Pulmonary and extrapulmonary disease should be treated with the same regimens. However, it is noted that some experts recommend 9–12 months of treatment for TB meningitis, given the serious risk of disability and mortality, and 9 months of treatment for TB of bones or joints, because of the difficulties in assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In TB meningitis, ethambutol should be replaced by streptomycin.

Presumptive treatment of TB for people living with HIV

The rationale for presumptive TB treatment is to prevent the death of people with HIV in situations where expedited diagnosis of TB is not possible or feasible due to the clinical condition of the patient or limited access to TB diagnostic services. While there is no case definition of presumptive TB, WHO algorithms include initiation of TB treatment for people with HIV in peripheral facilities based exclusively on clinical suspicion (without TB investigations) for seriously sick patients (with respiratory distress) based on the judgement of the clinician *(26)*. This approach is based on expert opinion and emphasizes that every effort should be made to confirm the diagnosis of TB after initiation of presumptive treatment and that treatment should be stopped only if there is bacteriological, histological or strong clinical evidence of an alternative diagnosis.

In 2015, a systematic review was performed to assess the role of presumptive treatment for people living with HIV, with a particular focus on its efficacy in reducing mortality as well as the risk of severe adverse events following treatment. A total of 2563 citations were identified, together with three ongoing randomized controlled trials *(27–29)* and one cluster randomized trial of presumptive anti-TB treatment. The REMEMBER trial is a multicountry study that compares the provision of ART and TB treatment with ART and IPT in people with HIV with a CD4 count below 50 cells/mm^3 and presumed not to have active TB. The trial showed no evidence of reduced mortality, reduced incidence of AIDS-associated illnesses or increased viral suppression as a result of presumptive therapy in individuals in whom TB was not suspected and in whom it had been ruled out by extensive investigations.

Based on the available evidence, WHO makes no new recommendation on presumptive TB treatment for people with HIV and notes the importance of further research on this issue, including research on the clinical predictors for selecting people with HIV for presumptive treatment and whether nurses or clinical officers can initiate it. Nevertheless, expert opinion continues to support presumptive TB treatment in peripheral health facilities in HIV-prevalent settings for people with HIV who are seriously ill due to suspected TB. The algorithm in Annex 15 may help to facilitate presumptive TB treatment.

Extrapulmonary TB in people living with HIV

The risk of extrapulmonary TB is higher in people living with HIV, especially in those with lower CD4 cell counts *(30)*. People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death. The commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). Pericardial and meningeal TB are less frequent forms of extrapulmonary TB but are more likely to result in fatal outcomes *(31)*.

The diagnosis of extrapulmonary TB is challenging. In people living with HIV with advanced immunosuppression, lack of pulmonary findings is not uncommon and disseminated TB can manifest as non-specific febrile illness. Extrapulmonary TB can be suspected in all HIV-positive individuals presenting with TB symptoms. Furthermore, symptoms suggesting a specific organ involvement, such as breathlessness (pleural effusion/pericarditis), enlarged glands in the neck or armpit (lymphadenitis) and chronic headache or altered mental status (meningitis) should prompt further investigation for extrapulmonary TB *(31)*.

Bacterial confirmation is often difficult due to a low sensitivity of smear microscopy and difficulty in obtaining samples from extrapulmonary sites. If possible, extrapulmonary specimens should be obtained. For patients with suspected TB meningitis, Xpert MTB/RIF is the preferred initial diagnostic test for cerebrospinal fluid *(32)*. If lymphadenitis is suspected, Xpert MTB/RIF may be used to test for samples obtained from lymph node biopsies or fine-needle aspiration *(33)*. LF-LAM may also assist in the diagnosis because these people living with HIV are likely to have low CD4 cell counts *(25)*. The accurate diagnosis of extrapulmonary tuberculosis is complex and difficult, particularly in peripheral health facilities with limited support and diagnostic infrastructure. Therefore, presumptive TB treatment should be initiated for patients with danger signs according to the latest clinical algorithms (Annexes 14 and 15).

Timing of ART for adults and children with TB

Early initiation of ART in TB patients living with HIV is critical for reducing mortality. Section 4.3.5 provides more detailed information and recommendations on the co-treatment of TB and HIV.

Isoniazid preventive therapy (IPT)

Recommendations

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (strong recommendation, moderate-quality evidence).

- Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals regardless of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women (strong recommendation, high-quality evidence).

- Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test status and among whom active TB disease has been safely ruled out should receive at least 36 months of IPT. IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy (conditional recommendation, moderate-quality evidence).

- Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB. Children living with HIV who have poor weight gain, fever or current cough or contact history with a TB case may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, they should be offered IPT regardless of their age (strong recommendation, low-quality evidence).

- Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care (strong recommendation, moderate-quality evidence).

- In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease (strong recommendation, low-quality evidence).

- All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional six months (conditional recommendation, low-quality evidence).

Source: Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44472/1/9789241500708_eng.pdf).

Isoniazid 300 mg given daily prevents the progression of latent TB infection to active clinical disease. The combined use of IPT and ART has also been shown to have both TB prevention and mortality benefits, including in people with higher CD4 counts *(23,24)*.

TST should not be a requirement for initiating IPT for people with HIV. People with HIV whose TST status is unknown should be started on IPT after symptom-based screening for TB. However, given those TST-positive patients who are not receiving ART benefit more from IPT than those who are TST negative, the test is encouraged where feasible.

Infection control

Recommendations

Administrative (facility-level infection control committee and protocols)

- A triage system should be in place to identify people suspected of having TB and minimize diagnostic delays with rapid diagnostics, e.g. Xpert MTB/RIF.
- Separate people with suspected or confirmed TB.
- Ensure cough etiquette and respiratory hygiene.
- Minimize the time spent in health-care facilities (e.g. through community-based approaches).

(all administrative recommendations: strong recommendation, low-quality evidence).

Health workers and caregivers

- Inform and encourage health workers with TB symptoms to undergo TB diagnostic investigation as well as HIV testing and counselling.
- Provide a package of care for HIV-positive workers (ART and IPT) and relocation for health-care workers living with HIV to a lower-risk area.

(all health worker recommendations: strong recommendation in settings with a high prevalence of HIV and conditional with a low prevalence, high-quality evidence).

Use of particulate respirators

- Protective equipment (particulate respirator masks that meet or exceed N95 standards set by the CDC/NIOSH or the FFP2 standards that are CE certified) should be provided for health-care workers caring for patients with infectious TB (suspected or confirmed) (strong recommendation, low-quality evidence).

Environmental

- Ventilation (i.e. natural and/or mechanical) (strong recommendation, low-quality evidence).
- Upper-room ultraviolet germicidal irradiation (conditional recommendation, low-quality evidence).

Source: WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (http://www.who.int/tb/publications/2009/9789241598323/en).

Health-care facilities and congregate settings can present a high risk for acquiring TB (including MDR-TB) for people living with HIV as well as for health-care workers. National TB programmes and national HIV programmes should provide managerial direction for implementing TB infection control. Each health-care facility should have a TB infection control plan that includes administrative, environmental and personal protection measures as well as measures for health workers and caregivers to reduce TB transmission within the facility. Periodic evaluation of infection control practices is essential for ensuring that appropriate measures are in place. Facility-level assessment of TB infection control should be incorporated into the routine supervisory activities of all health facilities providing care for people living with HIV. A standardized essential checklist for periodic evaluation of infection control practices can serve as a tool for such an assessment and can help measure progress over time. An example of such a checklist that can be adapted by countries to suit the context can be found in Annex 16.

To reduce the transmission of TB to the family and the community, key information should also be provided to the patient and family members. This should include advice on cough etiquette, sleeping alone, avoiding congregate settings and public transport while smear-positive and spending as much time as possible outdoors where feasible.

Multidrug-resistant TB and HIV

Recommendation

- Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line antituberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of antituberculosis treatment (strong recommendation, very low-quality evidence).

Source: Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf).

MDR-TB is TB that does not respond to at least isoniazid and rifampicin. Patients with both HIV and MDR-TB face complicated clinical management, fewer treatment options and poorer treatment outcomes *(34)*. Systematic reviews have shown a worrying association between HIV and primary MDR-TB *(35,36)*. Outbreaks of MDR-TB among people with HIV have been documented in hospital and other settings, especially in eastern Europe and in southern African countries with a high HIV prevalence *(37)*. Factors contributing to the occurrence of drug-resistant TB include failure to recognize drug resistance allowing further transmission, inadequate isolation procedures in health-care facilities and congregate settings and inadequate treatment.

Extensively drug-resistant TB (XDR-TB) is a form of TB that is resistant to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance. Although the association between HIV and XDR-TB remains unclear, the rapid and deadly spread of XDR-TB among people living with HIV has been observed *(38,39)*. As with MDR-TB, nosocomial outbreaks involving people with HIV have been reported, suggesting a need for intensified efforts to ensure infection control in health-care settings *(40–42)*.

Because unrecognized drug-resistant TB is associated with very high mortality in people with HIV, Xpert MTB/RIF is recommended as the initial diagnostic test in adults and children suspected of having HIV-associated TB. Those found to have MDR-TB or rifampicin resistance should be further tested for second-line anti-TB drug resistance. People with HIV who have MDR-/XDR-TB should start ART as soon as possible, within eight weeks of starting TB treatment.

WHO recently issued recommendations on the use of the novel anti-TB drugs delamanid and bedaquiline, which may also be used by people living with HIV, although bedaquiline should be used with caution and proper clinical judgement in people aged over 65 years, people with diabetes, HIV, hepatic or severe renal impairment or people who use alcohol or other substances, given that data on efficacy and safety under such conditions are very limited or unavailable *(43)*. In general, there is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line anti-TB drugs. However, people with HIV tend to have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reactions increases with the degree of immunosuppression. The complexity of ARV regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring. Detailed information on the use of second-line anti-TB drugs, including delamanid and bedaquiline, are available in the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (http://www.who.int/tb/publications/pmdt_companionhandbook/en).

Appropriate TB infection control measures in all facilities caring for people with HIV and efforts to optimize adherence and completion of TB treatment are important to help reduce the incidence of MDR-TB. MDR-TB can also be minimized by strengthening HIV prevention, improving collaboration between HIV and TB programmes and focusing attention on the groups at the highest risk of MDR-TB and HIV, such as people who inject drugs and people exposed in prison and other congregate settings.

Additional relevant guidance

- Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (www.who.int/tb/challenges/hiv/ICF_IPTguidelines/en/index.html).

- Treatment of tuberculosis: guidelines for national programmes, fourth edition. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf).

- Improving the diagnosis of and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization; 2007 (www.who.int/hiv/pub/tb/pulmonary/en).

- Xpert MTB/RIF implementation manual – technical and operational "how-to". Practical considerations. Geneva: World Health Organization; 2014 (http://www.who.int/tb/publications/xpert_implem_manual/en).

- Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/77741/1/9789241504492_eng.pdf).

5.2.3 Cryptococcal disease

Cryptococcal meningitis is a common opportunistic infection and a leading cause of death in people with HIV before and after ART is initiated, especially in sub-Saharan Africa and South-East Asia *(44–48)*. The main reasons for this high death rate include delayed presentation, together with poor availability and high cost of treatment *(49–52)*. Furthermore, there are no standardized guidelines applicable to resource-limited settings for the diagnosis and management of cryptococcal disease.

A rapid advice on diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children was published by WHO in 2011. The advice covers diagnosis, screening and prevention of cryptococcal infection; induction, consolidation and maintenance regimens; monitoring and managing toxicities; timing of ART; and discontinuation of maintenance regimens *(53)*. These recommendations encourage earlier diagnosis and early treatment with amphotericin B–based regimens as part of a minimum package of toxicity prevention, monitoring and management, prompt management of raised intracranial pressure and systematic evaluation of a clinically deteriorating patient. They also provide guidance on timing of ART initiation and discontinuation of maintenance treatment.

Infection control

Recommendations

Diagnosis of cryptococcal disease

Prompt lumbar puncture with measurement of CSF opening pressure and rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach (strong recommendation, moderate-quality evidence).

Prevention of cryptococcal disease

The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm^3 and who are CrAg negative or where CrAg status is unknown is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely (strong recommendation, high-quality evidence).

The use of routine serum or plasma CrAg screening in ART-naive adults , followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:
a. patients with a CD4 count less than 100 cells/mm^3; and
b. where this population also has a high prevalence (>3%)[a] of cryptococcal antigenaemia.
(conditional recommendation, low-quality evidence).

Induction, consolidation and maintenance antifungal treatment regimens

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week antifungal regimens are recommended in order of preference.

a. Amphotericin B + flucytosine (strong recommendation, high-quality evidence).

b. Amphotericin B + fluconazole (strong recommendation, moderate-quality evidence).

c. Amphotericin B short course (5–7 days) + high-dose fluconazole (to complete 2 weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two-week induction period (conditional recommendation, low-quality evidence).

d. Fluconazole high dose + flucytosine, when amphotericin B is not available (conditional recommendation, low-quality evidence).

e. Fluconazole high dose alone, when amphotericin B is not available (conditional recommendation, low-quality evidence).

For the consolidation phase treatment of HIV-infected adults, adolescents and children with cryptococcal meningitis or disseminated non-meningeal disease, the following eight-week antifungal regimen is recommended:

Fluconazole 400–800mg/day after a two-week induction with amphotericin B regimen (6–12 mg/kg/day up to 400–800 mg/day if below 19 years).

Fluconazole 800 mg/day after induction treatment with short-course amphotericin B or fluconazole-based induction regimen (fluconazole 12 mg/kg/day up to 800 mg/day if below 19 years).

(strong recommendation, low-quality evidence).

For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents and children, oral fluconazole 200 mg daily (6 mg/kg/day up to 200 mg/day if below 19 years) is recommended (strong recommendation, high-quality evidence).

For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded). Fluconazole 800 mg/day (or 12 mg/kg/day if below 19 years) for two weeks, then 400 mg/day (or 6 mg/kg/day up to 400–800 mg/day if below 19 years) for eight weeks, and continued maintenance with fluconazole 200 mg/day is recommended. The optimal antifungal regimen in this population remains to be determined (conditional recommendation, low-quality evidence).

Prevention, monitoring and management of amphotericin B toxicity

In HIV-infected adults receiving amphotericin B–containing regimens for treatment of cryptococcal disease, a minimum package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B–related toxicities of hypokalaemia and nephrotoxicity (strong recommendation, moderate-quality evidence).

Timing of ART initiation

Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS that may be life threatening. (conditional recommendation, low-quality evidence).

In HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and after 4 weeks of induction and consolidation treatment with amphotericin B–containing regimens combined with flucytosine or fluconazole, or after 4–6 weeks of treatment with a high-dose oral fluconazole induction and consolidation regimen (conditional recommendation, low-quality evidence).

Discontinuation of azole maintenance treatment (secondary prophylaxis)

In HIV-infected adults and adolescents with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal maintenance treatment is recommended based on the following criteria:
a. If HIV viral load monitoring is not available
    When patients are stable and adherent to ART and antifungal maintenance therapy for at least one year and
b. If HIV viral load monitoring is available
    Patient stable and adherent to ART and antifungal maintenance treatment for at least one year and with CD4 count greater than or equal to 100 cells/mm^3 (two measurements six months apart) and a suppressed viral load. (conditional recommendation, low-quality evidence).

In HIV-infected children aged between 2 and 5 years with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of antifungal treatment maintenance is recommended if the child is stable and adherent to ART and antifungal maintenance treatment for at least one year and with a CD4 cell count percentage greater than 25% or absolute count greater than 750 cells/mm^3 (two measurements six months apart) (strong recommendation, low-quality evidence).

Maintenance therapy for cryptococcal disease should NOT be discontinued in children less than two years (strong recommendation, low-quality evidence).

[a] The prevalence threshold above which screening is cost-effective was 1% using LFA in a recent study (Meya D, Rajasingham R, Rolfes M, Birkenkamp K, Boulware D. Cost benefit of integrating cryptococcal antigen screening and preemptive treatment into routine HIV care. In: International AIDS Conference, Washington DC, 22–27 July 2012 [Abstract MOAB0102]). The prevalence cost-effectiveness threshold is likely to vary depending on the cost of the antigen assay used (latex agglutination [LA] vs. LFA) and cost of drug treatment.

> Maintenance treatment for cryptococcal disease should be restarted if CD4 count drops to 100 cells/mm^3 or below in HIV-infected adults and adolescents (or CD4 cell count less than or equal to 25% or 750 cells/mm^3 in children aged between two and five years), or if a WHO stage 4 clinical event occurs, irrespective of patient age (strong recommendation, low-quality evidence).
>
> *Source:* Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/cryptococcal_disease2011/en).

5.2.4 Hepatitis B and C

Chronic hepatitis B virus (HBV) infection affects 5–20% of the 36 million people living with HIV worldwide, and hepatitis C virus (HCV) affects 5-15%, rising to 90% among people who inject drugs. The burden of coinfection is highest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B *(54–56)*.

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV in some regions, including among people on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for people with HIV who are coinfected with hepatitis B and/or hepatitis C.

Management of HIV and hepatitis B coinfection

HIV coinfection has a profound impact on the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality and decreased treatment response compared with people who do not have HIV *(57–62)*.

The 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs* recommended providing ART to all people coinfected with HIV and HBV regardless of CD4 count for those with evidence of severe chronic liver disease.[1] This recommendation has now been superseded by the new recommendation in 2015 to treat all people with HIV regardless of CD4 cell count. Nevertheless, in settings where prioritization is required, people coinfected with HIV and HBV and evidence of severe chronic liver disease should be considered a priority for ART. WHO recommends that adults, adolescents and children with chronic hepatitis B and clinical evidence of cirrhosis (or cirrhosis based on the non-invasive APRI test score >2 in adults) should be treated regardless of alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) status or HBV DNA levels. WHO guidelines for the prevention, care and treatment of people with chronic hepatitis B infection *(63)* provide recommendations on who should receive HBV treatment and recommend the use of NRTIs or entecavir for this treatment.

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[1] Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, spontaneous bacterial peritonitis, variceal haemorrhage and hepatic encephalopathy), sepsis or liver insufficiency (jaundice).

The recommended NRTI drugs for ART – TDF with 3TC or FTC – are active against HBV *(64)*. However, of these, only TDF is recommended in the WHO HBV guidelines for patients with HBV monoinfection. Furthermore, treatment of HIV-HBV coinfection without the use of TDF in the regimen may lead to flares of hepatitis B due to ART-associated immune reconstitution. Similarly, treatment discontinuation, especially of 3TC, has been associated with HBV reactivation, ALT flares and, in rare cases, hepatic decompensation. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs.

The risk of HBV infection may be higher in HIV-infected adults. All people newly diagnosed with HIV should therefore be screened for hepatitis B surface antigen (HBsAg) and vaccinated if non-immune.

Management of HIV and hepatitis C coinfection

Hepatitis C virus (HCV)-related liver disease progresses more rapidly in people coinfected with HIV. Treatment of HCV is therefore a priority for people with HIV/HCV coinfection.

The decision to initiate treatment for HCV is more complex than in those with HCV monoinfection, because response rates are lower, the risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in people with advanced immunosuppression (CD4 count below 200 cells/mm^3). The newer, all-oral direct-acting antiviral HCV regimens (DAAs) produce similar rates of sustained virological response regardless of HIV status.

Careful consideration of drug–drug interactions is important to avoid toxicity and to ensure the efficacy of regimens used to treat both HIV and HCV. Further information regarding choice of anti-HCV regimen, including potential drug–drug interactions with ARV drugs, is provided in the 2014 WHO Global guidelines for the screening, care and treatment of persons living with hepatitis C infection *(65)*, HCV treatment using older regimens (pegylated interferon and ribavirin) generally yielded low rates of success among HCV/HIV coinfected patients, but outcomes for HCV therapy with DAAs in people with HIV coinfection are comparable to those with HCV monoinfection. Updated WHO guidelines for the treatment of people with HCV infection, including management of HCV in HIV-coinfected patients, will be released in 2016. The newer all-oral DAAs also have fewer drug–drug interactions than earlier interferon-based regimens (*see* Annex 13).

The decision to start ART among people coinfected with HCV should follow the same principles as in HIV monoinfection. Potential harmful effects of ARV drugs include their hepatotoxic effects. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine, didanosine, nevirapine or full-dose ritonavir (600 mg twice a day) *(66)*. For most HIV/HCV coinfected people, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

Additional guidance

- Guidelines for the screening, care and treatment of persons with hepatitis C infection. Updated version, April 2016. Geneva: World Health Organization; 2016 (http://www. who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en).

- Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/ hepatitis/hepatitis-b-guidelines/en).

- Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/hepatitis/ en/index.html).

5.2.5 Malaria

There is significant geographical overlap between HIV and malaria. People living with HIV have increased risk of more frequent and higher-density infection, severe malaria and malaria-related death, depending on the malaria transmission intensity of the area.

Key interventions to control malaria include early diagnosis, prompt and effective treatment with artemisinin-based combination therapies and use of insecticide-treated nets and indoor residual insecticide spraying to control the vector mosquitoes. In areas of stable malaria transmission, people with HIV (as for the general population) should routinely use insecticide-treated bed-nets or have access to indoor residual spraying to reduce their exposure to malaria. Intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis are also recommended in areas of high transmission. Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to patients with HIV or HIV-exposed infants who are taking CTX prophylaxis.

People with HIV who develop malaria should receive prompt, effective antimalarial treatment. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test. However, absence or delay of parasitological diagnosis should not delay the immediate start of antimalarial treatment.

Some drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and PIs). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving AZT or EFV should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of the increased risk of neutropaenia in combination with AZT and hepatotoxicity in combination with EFV.

Recommendation

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage (conditional recommendation, moderate-quality evidence).

Source: Guideline on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Recommendations for a public health approach. December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_dec2014/en).

Good practice statement

In people who have HIV and uncomplicated *P. falciparum* malaria, avoid artesunate + sulfadoxine-pyrimethamine if they are being treated with co-trimoxazole and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

Intermittent preventive treatment for malaria in pregnancy should not be provided in addition to CTX prophylaxis.

Source: Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en).

Additional guidance

- Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en).

- WHO policy recommendation: seasonal malaria chemoprevention (SMC) for *Plasmodium falciparum* malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization; 2012 (www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/index.html).

- Intermittent preventive treatment for infants using sulfadoxine–pyrimethamine (SP-IPTi) for malaria control in Africa: implementation field guide. Geneva: World Health Organization; 2011 (www.who.int/malaria/publications/atoz/whoivb11_07/en/index.html).

- WHO website: www.who.int/topics/malaria/en

5.2.6   Sexually transmitted infections and cervical cancer

The epidemiological synergy between HIV and sexually transmitted infections (STIs) is well established, and they frequently coexist *(67)*. Most of these infections are asymptomatic, especially among women. However, even asymptomatic STIs can cause complications, be transmitted to sexual partners and enhance HIV transmission. It has been shown that infection with *N. gonorrhoeae* substantially increases shedding of HIV-1 from the male genital tract in seminal fluid *(68)*. It has also been shown that herpes simplex virus (HSV) is associated with increased acquisition and transmission of HIV *(69–72)*. HIV infection may also alter the natural history of STIs. HIV infection has been found to change the natural history of HSV infection, resulting in more frequent recurrences in coinfected individuals, many of which are subclinical *(73)*. In addition, serious clinical manifestations of HSV, human papillomavirus (HPV), syphilis and other STIs are observed among people with advanced HIV disease.

A systematic review showed that the prevalence of STI among people with HIV on ART was as high as people not on ART, suggesting that STI coinfection could undermine efforts to use ART for prevention unless STIs are appropriately treated *(74)*. It is necessary to appropriately screen, diagnose and treat STIs, especially among the most vulnerable populations and people living with HIV. STI services should be an important part of comprehensive HIV care among adults and adolescents.

WHO guidelines on treatment of specific STIs (gonorrhoea, chlamydial infection, syphilis and HSV) are in the process of being updated. Existing recommendations on STI case management and screening for sex workers and men who have sex with men are given in the resource list below.

Cervical cancer is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer *(75–77)*. The risk and persistence of HPV infection increases with low CD4 count and high HIV viral load. Women living with HIV should be followed closely for evidence of precancerous changes in the cervix, regardless of whether they are taking ART or their CD4 count or viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. All women with HIV should therefore be screened for cervical cancer regardless of age. Immediate management for precancerous and cancerous lesions should be provided. WHO guidance covers HPV vaccination and prevention, screening and treatment and palliative care of cervical cancer *(78)*. To date, concerns about the safety or reduced efficacy among women who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.

Additional resources

WHO guidance on STIs

- Sexually transmitted and other reproductive tract infections: a guide to essential practice. Geneva: World Health Organization; 2005 (http://www.who.int/reproductivehealth/publications/rtis/9241592656/en).

- STI treatment for specific STIs. Geneva; World Health Organization. Guideline revision in process.

- Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en).

- Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings. Geneva: World Health Organization; 2008 (www.who.int/hiv/pub/prev_care/OMS_EPP_AFF_en.pdf).

- Global strategy for the prevention and control of sexually transmitted infections: 2006–2015. Breaking the chain of transmission. Geneva: World Health Organization; 2007 (www.who.int/reproductivehealth/publications/rtis/9789241563475/en/index.html).

- Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/sex_worker/en).

- Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/guidelines/msm_guidelines2011/en).

- Management of sexually transmitted infections – regional guidelines. New Delhi: WHO Regional Office for South-East Asia; 2011 (http://www.searo.who.int/entity/hiv/documents/9789290224105/en).

Other STI guidelines

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Cervical cancer

- Comprehensive cervical cancer control: a guide to essential practice, second edition. Geneva: World Health Organization; 2014 (http://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en).

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5.2.7 Vaccines for people living with HIV

Immunizations are an important component of the HIV care package in many international guidelines, and people living with HIV should be assessed for eligibility for vaccination at all stages of care *(79–81)*.

Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, notably when the CD4 count is above 200 cells/mm^3. People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines. Inactivated vaccines, although safe, can be less effective in this group and may require supplemental doses or revaccination after ART-induced immune reconstitution. Transient increases in plasma HIV-RNA load have also been reported after the administration of several vaccines. Available evidence indicates that these transient increases do not have clinical significance *(82,83)*.

In general, HIV-exposed infants, children and adolescents with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules *(84,85)*. In adults living with HIV, immunization against some diseases such as influenza, hepatitis B, pneumococcal disease and tetanus are frequently indicated. Other immunizations may be recommended based on age, risk factors or travel plans.

For currently recommended vaccination schedules and detailed guidance on immunization for all age groups, see WHO recommendations for routine immunization – summary tables at www.who.int/immunization/policy/immunization_tables/en/index.html.

For position papers on each vaccine, and statements about their use in people with HIV, see (www.who.int/immunization/documents/positionpapers/en/index.html).

5.2.8 HIV-related skin and oral conditions

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's CD4 count declines below 200 cells/mm^3. As a result, skin and oral conditions affect up to 90% of adults and children with HIV in resource-limited settings. Adverse drug reactions of the skin are also 100 times more common in people living with HIV compared to the general population, and their prevalence increases as immunodeficiency worsens. Skin and oral manifestations of HIV infection can aggravate stigma in some societies, as physical signs in the form of skin diseases, such as papular pruritic eruptions, which suggest the possibility of HIV infection, could make the affected person more vulnerable to discrimination.

Certain systemic diseases, such as Kaposi sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance and psychological stress. In the case of candidiasis, it can cause pain on swallowing, limiting a person's ability to take ARV drugs.

Due to a lack of services to promptly diagnose and manage skin and oral conditions, many people attempt to conceal the skin disease or avoid social contact. These could affect their health-seeking behaviour, leading to a negative impact on their self-esteem and quality of life. Skin and oral conditions are among the most common management problems faced by health-care workers caring for patients with HIV infection.

In 2014, WHO released guidelines for the treatment of common HIV-associated skin and oral conditions in low- and middle-income countries. These guidelines are applicable for all adults, pregnant women, adolescents and children living with HIV and recommend HIV testing for all those with unknown HIV status presenting with the discussed skin conditions. If the HIV status is known, they should be evaluated for initiation of ART.

ART is the initial treatment of choice for a number of these conditions (e.g. Kaposi sarcoma, papular pruritic eruption, eosinophilic folliculitis, molluscum contagiosum).

Additional resources

• Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/136863/1/9789241548915_eng.pdf?ua=1&ua=1).

5.3 Prevention, screening and management of other comorbidities and chronic care for people living with HIV

5.3.1 Assessment and management of noncommunicable diseases

General

Several studies have demonstrated that, compared to the general population, people living with HIV are at increased risk of developing a range of chronic noncommunicable diseases (NCDs), including cardiovascular disease (CVD), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), kidney disease and cancers *(86–91)*.

The intersection of HIV and NCDs is strongly influenced by increasing survival due to effective ART, lifestyle factors, long-term complications of ART and other disease conditions associated with ageing *(92,93)*. Both HIV and NCDs require health systems that can deliver effective acute and chronic care and support adherence to treatment. Chronic HIV care provides the opportunity for assessment, monitoring and managing NCDs, especially through primary care. Integrating interventions, such as nutrition assessment, dietary counselling and support, smoking cessation, exercise promotion, blood pressure monitoring and – where available – cholesterol management as part of HIV care can help to reduce the risks of NCDs among people with HIV and improve HIV treatment outcomes *(94,95)*.

WHO has defined a package of essential NCD interventions (WHO PEN) and published recommendations on assessment and management of the major NCDs from the primary care level to the district hospital level. The interventions are mainly focused on assessment and management of CVD risk, including high blood pressure, type 2 diabetes, chronic respiratory diseases (asthma and COPD) and early identification of breast and cervical cancer. More information and additional guidance on WHO PEN and management of NCDs are available in the following resources:

• Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva: World Health Organization; 2010 (www.who.int/ cardiovascular_diseases/publications/pen2010/en).

• Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings. Geneva: World Health Organization; 2012 (http://apps.who. int/iris/bitstream/10665/76173/1/9789241548397_eng.pdf).

Assessment and management of cardiovascular diseases

NEW

Recommendation

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for the general population[a] (conditional recommendation, very low-quality evidence).

[a] The WHO PEN protocol targets the following populations for CVD screening: age >40 years, smokers, people with known hypertension or diabetes mellitus, waist circumference >90 cm in women and >110 cm in men and family history of diabetes mellitus or premature CVD. See more about PEN at www.who.int/cardiovascular_diseases/ publications/ pen2010/en.

NEW

Good practice statement

Strategies for the prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as high blood pressure, smoking, obesity, unhealthy diet and lack of physical activity should be applied to all people living with HIV.

Background and rationale

Several studies have demonstrated that people with HIV have an increased risk of CVD compared to HIV-negative people in the same age ranges and that CVD accounts for an increasing proportion of mortality observed in this population *(96,97)*. Large cohort studies have confirmed that the risk of both myocardial infarction and cerebrovascular disease is 40–70% higher among people with HIV than among age- and gender-matched HIV-uninfected controls *(98–103)*. This association has been reported both in people on ART and in those who are treatment naive. Similar findings have also been reported in children and adolescents with HIV *(104)*. The mechanisms underlying the association between HIV and CVD are multifactorial and include HIV-related chronic immune

activation and inflammation, immunodeficiency and higher burdens of traditional CVD risk factors among people living with HIV *(105–109)*.

Findings from cohort data have shown that the role of ART in CVD risk and exposure to some classes of ARV drugs (PIs) causes lipid abnormalities and may increase the risk of premature CVD *(110–113)*. Associations between NRTIs and CVD risk remain the subject of debate. Although recent and cumulative exposure to some NRTIs such as ddI and ABC has been associated with increased relative risk for CVD *(114–117)*, other reviews have not found such an association *(118,119)*. However, regardless of the class of ARV drug used, it is clear that treatment with ART is beneficial compared with no treatment. Several studies have demonstrated an increased risk of CVD events among people discontinuing ART *(120)* and in people with detectable viral load *(96)*. It has been hypothesized that the increased attributable risk among people with HIV is due to increased immune activation and chronic inflammation, which remain abnormally high among people with HIV even after viral suppression *(121,122)*; both are associated with preclinical and clinical atherosclerosis. The overall beneficial role of ART on HIV morbidity and mortality has therefore been demonstrated to outweigh potential CVD risks in people with HIV.

CVD screening for people with HIV has been recommended in several HIV clinical guidelines, and several risk tools for calculating CVD probability have been used *(123–127)*. Several studies have demonstrated that incorporation of routine CVD screening for people with HIV could improve health outcomes and be cost-effective *(128–130)*. A systematic review on the use of validated tools to identify people at highest CVD risk for primary prevention shows that there is potential to lower CVD mortality and the incidence of cardiovascular events; this was particularly evident in studies with high-intensity interventions *(131)*. However, despite the overall consensus that the current CVD screening tools designed for the general population have a moderate discriminatory power to identify people with HIV at high risk for CVD events or eligibility for therapeutic interventions, these tools frequently underestimate the CVD risk in people with HIV and need to be adjusted or validated in HIV-infected populations *(132–139)*. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group has described a CVD risk algorithm that incorporates some HIV-specific factors such as CD4 cell count and ARV drug use, which has reported better accuracy in predicting serious CVD events *(140–142)*. While this is an important step towards improving CVD risk prediction in people, it still has limitations because the study populations – all in high-income settings – have different genetic and behavioural CVD risk profiles from the majority of people living with HIV in the world. In addition, as in the case of studies reporting less direct risk predictions, the D:A:D: instrument can also significantly overestimate and underestimate CVD risk *(135–137)*.

Implementation considerations

No specific WHO recommendation for the management of CVD in people with HIV has been made in previous guidelines. However, since 2010, WHO has defined a package of essential NCD interventions (WHO PEN), along with recommendations on screening for and treating NCDs in the general population. The WHO PEN *(143)* has several programmatic advantages in the context of resource-limited settings, as it integrates other major NCDs in addition to CVD, can be implemented at the primary health-care level, can be managed by non-physicians, consists of a minimal package and has good discrimination to identify those with high CVD risk. However, the systematic review did

not identify any studies assessing the impact or use of WHO PEN interventions in people with HIV with any outcomes relevant to low- and middle-income countries. Studies on WHO PEN-based interventions in the general population from low- and middle-income countries were found, showing that the PEN protocol and universal risk assessment are cost-effective *(144–146)*. Furthermore, an evaluation of the short-term outcomes of PEN in pilot districts indicated a significant reduction in CVD risk and a healthy lifestyle in the target population *(139)*.

Disparities in CVD care among people with HIV have been reported. In two studies, people with HIV were significantly less likely to receive aspirin for CVD prevention than those without HIV *(147,148)*. Other data on medical management and outcomes following acute myocardial infarction showed that people with HIV received significantly fewer cardiovascular procedures and/or therapeutics than people without HIV *(149)*. Regular assessment and management of CVD risk among people with HIV is expected to result in better and more equitable care.

One major remaining barrier to equitable access to CVD prevention and care for people with HIV is the lack of quality data assessing proven CVD therapies in this population. For example, prospective trials on the use of statins for people with HIV have generally been small in size and have not assessed hard clinical end-points *(150)*.

Integrated multiple disease campaigns conducted in Lesotho and Uganda (SEARCH consortium), which included CVD screening and HIV testing, demonstrated the feasibility of integrated screening for communicable diseases and NCDs in community-based HIV programmes *(151,152)*. Improved diagnosis and linkage to care for CVD conditions have been shown to also improve linkage to HIV care and ART *(153)*. CVD/HIV integrated pilot services have been implemented in Kenya, Nigeria and Zambia since 2012 and shown to be feasible and acceptable, with CVD service integration implemented within the context of an HIV chronic care model *(154)*.

Research gaps

Further research is needed to unravel the complex pathophysiology of atherogenesis in people with HIV, to elucidate the relationships between traditional and HIV-associated CVD risk factors and to investigate how ART alters these interactions. Studies on the impact of early ART on CVD development, particularly in adolescents and children with HIV, are also needed. Clinical studies to assess methods of risk prediction and risk-reduction strategies for CVD applicable to people with HIV would be of great use. There is a need to validate simplified CVD screening protocols and risk-assessment algorithms that include HIV-specific risk factors to improve accuracy. Use of co-therapies for CVD such as statins, aspirin, antihypertensive drugs and metformin and measurement of their impact on HIV mortality are also important. Assessments of the unique pathophysiology, related risk factors and optimal management of downstream CVD complications associated with HIV, such as heart failure and malignant arrhythmia, are also needed. Such studies should be conducted in both high-income and resource-limited countries.

5.3.2 Assessment and management of depression in people living with HIV

NEW

Recommendation

Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV (conditional recommendation, very low-quality evidence).

People living with HIV are at high risk of mental, neurological and substance-use disorders *(155)*. Systematic reviews from both from low- and high-income countries showed that depression is one of the most prevalent mental health comorbidities in people with HIV *(156,157)*. A systematic review conducted in 2015 reported depression prevalence rates as high as 80% among people with HIV, but with wide variation across studies, which is attributed to the screening and diagnostic criteria used *(158)*. Depressive symptoms have been reported as common in many studies in sub-Saharan Africa, where the HIV burden is also high *(159,160)*.

People living with HIV who have depression are less likely to achieve optimal treatment adherence. Although chronic HIV care settings provide an opportunity to detect and manage depression among people living with HIV, it is often overlooked and unrecognized by health-care providers. Treatment or lack of it for mental health disorders can affect general health, adherence to ARV drugs and retention in care and may lead to potential side-effects and drug interactions being overlooked *(160–164)*.

The WHO Mental Health Gap Action Programme (mhGAP), first published in 2008 and updated in 2015, provides evidence-based comprehensive guidelines on the diagnosis and management of a range of mental, neurological and substance use disorders, including developmental and behavioural disorders in children and adolescents. It focuses on nine priority mental health conditions, including the diagnosis and management of depression *(165)*. Implementation of mhGAP through primary care would improve the detection and management of depression in adults when compared to standard-of-care approaches *(166)*.

A systematic review conducted to support the guideline update in 2015 *(167)* aimed to determine whether routine screening and management of depression (specifically with mhGAP criteria) improve ART adherence and treatment outcomes in people with HIV. No studies were identified explicitly reporting on mhGAP for this specific population.

Indirect evidence from a systematic review on the accuracy of using screening tools to identify depression in people living with HIV in all settings identified 18 studies, using 25 different screening instruments, compared to criterion standards for diagnosing depression *(168)*. Studies included a total of 5209 unique participants, and criterion-diagnosed depression prevalence ranged very widely by region and population. Multiple index test and criterion standards were assessed and the review evaluated each test's area under the curve (AUC) as a summary measure of accuracy (AUC above 0.9 is

considered to be highly accurate; 0.7–0.9 to be moderately accurate; 0.51–0.69 to be of low accuracy) *(168)*). Although several instruments showed very good or even excellent performance in diagnosing depression in people with HIV, the overall quality of evidence is very low. The Guideline Development Group, citing acceptability and feasibility from end-users and lack of harm, made a conditional recommendation.

Though depression is more common among people with HIV compared to the general population, there is less consistent and limited evidence to show that management of depression improves HIV treatment outcomes. However, management of depression improves mental health and general well-being in people with HIV.

The limited data on HIV and mental health service delivery models indicate that integration supports efficiency and does not increase costs of care. A narrative review from South Africa and sub-Saharan Africa suggests that integration of mental health care into existing health systems is an effective and cost-efficient approach to expanding access to mental health services for people with HIV in resource-limited settings *(169)*. There is also an ongoing study on the cost-effectiveness of screening and treatment of depression among people with HIV in sub-Saharan Africa *(170)*. However, more evidence is needed on effective models of HIV–mental health service integration in various settings *(171)*.

A survey of national HIV programme managers *(172)* found that 38% of respondents reported that mental health screening is performed in some HIV care settings, with referral for treatment when indicated. Forty-three per cent did not have mental health screening and treatment available for people with HIV. None of the countries reported countrywide implementation of mental health screening and treatment services in all HIV care settings. The top three challenges identified by programme managers for integration of mental health services in HIV care settings are shortage of human resources, skills and capacity of health-care providers and lack of funding. WHO estimates that up to 85% of people with severe mental disorders and 56% of people with depression in low- and middle-income countries do not have access to treatment *(173)*.

Implementation considerations

Screening for depression may support adherence to ART, retention in care and viral load suppression and improve the quality of life. If implemented, depression should be managed according to national standards or mhGAP. Integration or linkage to mental health services should be implemented in settings where health-care infrastructure and trained human resources are available. Implementation of treatment for depression among people with HIV may require task-shifting, building health worker capacity, national adaptation of screening tools and simplification of tools for use by non-specialized primary care providers.

Research gaps

There are several research gaps related to screening and treatment for mental health disorders and depression among people living with HIV:

• Current estimates of HIV and depression are inaccurate due to the wide variability in reports.

- Packages of care for common mental disorders are likely to be most effective among people living with HIV in low- and middle-income countries.

- The long-term impact of depression interventions in relation to HIV outcomes needs to be studied.

- The optimal time-points for mental health interventions need to be identified.

5.3.3 Drug use and drug use disorders

People living with HIV who use drugs may experience a range of disorders related to drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated with a range of diseases and infections, including viral hepatitis, TB, septicaemia and bacterial endocarditis, in addition to HIV.

WHO, the United Nations Office on Drugs and Crime (UNODC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend a comprehensive package of nine interventions for HIV prevention, treatment and care for people who inject drugs; these are needle and syringe programmes, OST, HIV testing and counselling, ART, preventing and treating STIs, condom programmes, targeted behaviour change communication, preventing and treating viral hepatitis and preventing, diagnosing and treating TB.

Additional guidance

- WHO, UNODC, UNAIDS. Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users – 2012 revision. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/idu/targets_universal_access/en/index.html).

- Community management of opioid overdose. Geneva: World Health Organization; 2014 (http://www.who.int/substance_abuse/publications/management_opioid_overdose/en).

- Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (http://whqlibdoc.who.int/publications/2009/9789241547543_eng.pdf).

- Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (www.who.int/hiv/pub/guidelines/hepatitis/en/index.html).

- Policy guidelines for integrating collaborative TB and HIV activities within the comprehensive package of harm reduction for people who inject drugs. Geneva: World Health Organization; 2016 (In press).

5.3.4 Nutritional care and support

Nutrition for adults and adolescents living with HIV

Low energy intake combined with increased energy demands due to HIV infection *(174–176)* and related infections may lead to HIV-related weight loss and wasting. In addition, altered metabolism, reduced appetite and higher incidence of diarrhoea may

lower nutrient intake and absorption and lead to nutrient losses. These effects may all be compounded in low-income and food-insecure contexts. Low body mass in adults (body mass index less than 18.5 kg/m^2) and weight loss and wasting in children are all independent risk factors for HIV disease progression and mortality *(177,178)*. Nutritional assessment (anthropometry, clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored across the care continuum. Malnourished HIV-infected patients, especially in food-insecure contexts, may require food supplements in addition to ART to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection and/or while on ART should trigger further assessment and appropriate interventions.

WHO is revising recommendations for nutritional care and support of adolescents and adults living with HIV, including pregnant and lactating women.

Nutrition for children living with HIV

Nutritional assessment is essential to identify malnutrition and growth faltering early. Infants and children should undergo initial nutritional assessment (evaluation of nutritional status, diet and symptoms) and then be weighed and have height measured at each visit, and monitored with reference to WHO or national growth curves. Growth monitoring should also be integrated into the assessment of ART response *(179)*. If poor growth is identified, then further assessment should be performed to determine the cause, and plan an appropriate response. The 2009 guidelines for an integrated approach to the nutritional care of children living with HIV provide details of nutritional interventions.

Additional guidance

- Nutrition assessment, education, counselling and support for adolescents and adults living with HIV: A programming guide. Food and nutrition in the context of HIV and TB. Geneva: World Food Programme, PEPFAR, USAID, UNAIDS 2014. (http://reliefweb.int/sites/reliefweb.int/files/resources/wfp271543.pdf).

- Guidelines on HIV and infant feeding 2010: principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010 (http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf).

- Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months–14 years): handbook. Preliminary version for country introduction. Geneva: World Health Organization; 2009 (http://whqlibdoc.who.int/publications/2009/9789241597524_eng_Handbook.pdf).

- WHO, FAO. Nutritional care and support for people living with HIV/AIDS: a training course. Geneva: World Health Organization; 2009 (www.who.int/nutrition/publications/hivaids/9789241591898/en/index.html).

5.3.5 Palliative care: symptom management and end-of-life care

Through all stages of HIV disease, and when receiving treatment, people living with HIV may experience various forms of pain and other discomfort. Care providers should identify and treat the underlying cause where possible, while also controlling the pain. Further, effectively managing the side-effects of ART is important to support adherence. WHO is currently in the process of developing guidelines for palliative care.

Additional guidance

- IMAI district clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization; 2011 (www.who.int/hiv/pub/imai/imai2011/en).

5.3.6 General care for people living with HIV

Countries should establish a package of general HIV care interventions, in addition to ART, for people living with HIV to reduce HIV transmission, prevent illness and improve their quality of life. General care includes basic HIV prevention, promoting the health of people living with HIV, and screening, prophylaxis and management of HIV-related coinfections and comorbidities. WHO has produced summary guidance on general care and prevention interventions *(180–182)*, and recommends a package of 13 prevention interventions for adults and adolescents living with HIV in resource-limited settings *(1)*. These are (1) psychosocial counselling and support; (2) disclosure and partner notification; (3) CTX prophylaxis; (4) TB counselling, screening and preventive therapy; (5) preventing common fungal infections; (6) treatment of STIs and supporting reproductive health needs, including prevention of and screening for cervical cancer; (7) preventing malaria (CTX, bed-nets and particularly preventing malaria among pregnant women); (8) the use of vaccines for the prevention of pneumococcal disease, influenza, hepatitis B and yellow fever; (9) provision of adequate nutrition; (10) family planning services; (11) prevention of mother-to-child HIV transmission; (12) needle and syringe programmes for people who inject drugs; and (13) water, sanitation and hygiene.

A general care package will vary according to the epidemic type, populations affected and prevalence of coinfections, other comorbidities and health conditions. Table 5.2 provides an overview of the elements of a general care package for people living with HIV. In the era of universal treatment for all people with HIV, the time between HIV diagnosis, enrolment into care and initiation of ART may be addressed in one visit or in an expedient manner to reduce loss to follow-up and provide life-saving ART as soon as possible. WHO no longer recommends the need for preparation visits prior to ART initiation; many of the care aspects outlined in Table 5.2 can be accomplished once ART has started.

Table 5.2. Overview of key elements of general care over the continuum of HIV care for people living with HIV

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching of ART regimen
General care					
WHO clinical staging Past and current HIV- related conditions	✔	✔	✔		
Preparing people for ART	✔	✔	✔		
Preparing, assessing and supporting adherence	✔	✔	✔	✔	✔
Current medications		✔	✔	✔	✔
Pregnancy status Family planning and contraception	✔	✔	✔	✔	✔
Support for disclosure and partner notification	✔	✔	✔	✔	✔
Risk reduction counselling and combination HIV prevention approaches	✔	✔	✔	✔	✔
Assessing, preventing and managing noncommunicable diseases	✔	✔	✔	✔	✔
Screening for and managing mental health problems and substance use **Psychosocial counselling and support**	✔	✔	✔	✔	✔
Managing pain and symptoms	✔	✔	✔	✔	✔
Nutritional assessment and counselling	✔	✔	✔	✔	✔
Nutritional, growth and development assessment in children and adolescents Infant and child feeding	✔	✔	✔	✔	✔

Table 5.2. (continued)

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching of ART regimen
Preventing and treating coinfections					
Co-trimoxazole preventive therapy	✔	✔	✔	✔	✔
Intensified TB case-finding	✔	✔	✔		✔
Isoniazid preventive therapy		✔	✔		
Screening for cryptococcal infection and fungal prophylaxis		✔	✔		
Screening for hepatitis B and C		✔	✔		✔
Malaria prevention (insecticide-treated bed-nets and prophylaxis)	✔	✔	✔	✔	✔
Screening for sexually transmitted infections	✔	✔	✔	✔	✔
Prevention of and screening for cervical cancer		✔	✔	✔	✔
Assessing for vaccine-preventable diseases	✔	✔	✔	✔	✔

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SERVICE DELIVERY

6

6 SERVICE DELIVERY

6.1   Introduction

Less than 30% of people diagnosed with HIV in resource-limited settings navigate the full continuum of care *(1,2)*. Worldwide, less than 50% of adults are retained in care four years after initiation of antiretroviral therapy (ART) *(3)*. Simple and standardized first-line ART now directly supports adherence, decentralization, task shifting to nurse-led teams and community delivery and more efficient procurement and supply management. In 2013, for the first time, WHO published operational recommendations on how to implement clinical recommendations on the use of antiretroviral (ARV) drugs. These guidelines further expand on the implementation aspects of the clinical recommendations and present 10 new recommendations, three good practices, consensus-derived definitions and a new framework for ART service delivery intended to help countries and programme managers improve the quality and efficiency of services.

This chapter provides guidance in three service delivery areas:

1. Differentiated care:
   - addressing the diversity of needs of people in care
   - community ARV drug delivery approaches.

2. Recommendations to strengthen the continuum of treatment and care:
   - linkage from HIV testing to enrolment in care
   - retention
   - adherence
   - frequency of clinic visits and medication pickup
   - task shifting
   - decentralization
   - integration
   - adolescent-friendly health services.

3. Considerations for continuity and high quality of service delivery:
   - quality service delivery
   - ensuring a stable supply chain of ARV drugs
   - laboratory and diagnostic services.

New service delivery recommendations made in 2015 are included with recommendations from the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. The inclusion criteria of all systematic reviews conducted to support the decision-making process included adults, key populations, pregnant and breastfeeding women, children and adolescents. In general, there were limited data to inform specific recommendations for these important populations. However, learning from programme implementation has helped to highlight specific challenges and some potential solutions to improve service delivery.

Applicability of service delivery recommendations

In contrast to most clinical interventions, service delivery interventions are generally highly context specific in terms of both relative effectiveness and relative importance in a given context. Consistent with the burden of disease, much of the evidence supporting the recommendations in this chapter comes from studies undertaken in sub-Saharan Africa. Nevertheless, for the majority of interventions, evidence was also available from other regions. Where this is not the case, the need for evidence from a broader range of settings has been indicated in the corresponding section as a research gap.

Many of the recommendations in the service delivery section are conditional and represent interventions that have been shown to have benefit in some settings and thus represent approaches that programme managers can consider in designing their care packages.

6.2 Differentiated care

It is estimated that 95% of HIV service delivery is currently facility based *(4)*. In nearly all countries, the delivery of HIV care in the initial phase of rapid scale-up has been based on a "one-size-fits-all", clinic-based model, largely undifferentiated for individual needs *(5)*. As national guidelines evolve towards initiating ART for all people living with HIV regardless of clinical and immunological status *(6)*, HIV programmes will be challenged to manage an increasingly diverse set of patient needs. There is now a growing cohort of patients who have been on treatment for several years. At the same time, there is a need to expand timely access to ART for those who have yet to start. While implementation of the recommendations in these guidelines will mean that more people will start earlier, programmes must also retain the capacity to respond to the needs of patients who present with advanced disease, and are at heightened risk of morbidity and mortality *(7)*.

During a scoping consultation on care packages for people living with HIV, WHO reviewed the growing diversity of patient needs and assessed how programmes can treat and care for people differentially within a public health approach *(8)*. Broadly, four groups of patients with specific needs can be identified. First, people who present when well, potentially with higher CD4 cell counts, may require additional and targeted

adherence and retention support in order to commit to lifelong ART. Second, people presenting to care with advanced disease require a fast-tracked clinical and care package to initiate ART and prevent death and reduce ill health. A third group of individuals are those who are already on ART but need careful monitoring to ensure timely action as required; this may include clinical care, additional adherence support and timely switch to second-line ART regimens in the case of treatment failure. A final group of stable individuals are likely to represent the majority of people on ART and they can safely reduce the frequency of clinic visits, potentially receiving ART in community settings. Such an approach can relieve overburdened health-care settings and enable more attention to be paid to patients with more complex conditions who require prompt diagnosis and treatment of opportunistic infections, enhanced adherence support, viral load testing and potential changes of regimen, HIV drug resistance testing or other specialized care *(8)*. Receiving care closer to their home can also reduce direct and indirect costs related to transport and long facility waiting time for patients and their families. While these four groups have distinct needs, patients may move between the groups over the course of their lifetime in care.

Table 6.1. Diversity of care needs for people living with HIV

People living with HIV	Care package elements
People presenting when well	Adherence and retention support
People with advanced disease	Clinical package to reduce mortality and morbidity
Stable individuals	Reduced frequency of clinic visits and community ART delivery models
Unstable individuals	Adherence support, viral load testing, switch to second- or third-line ART if indicated, monitoring for HIV drug resistance (HIV-DR)

The care package elements for people living with HIV (Table 6.1) are a minimum and may be expanded according to the epidemic, clinical setting and health-care system. These packages are further supported by the differentiated care framework, which proposes the delivery of care in facilities for those who need clinic-based services, with less frequent clinical contact for those who are stable. Differentiating between the service needs of those who are unwell – either because they present late for care or due to treatment failure – and those who are stable on ART, and determining where and how those services are to be delivered, are key to maximizing treatment outcomes and efficiencies. A number of national HIV programmes have already adopted differentiated approaches to care as they scale up ART.

The differentiated care framework (Fig. 6.1) is characterized by four delivery components: (i) the types of services delivered; (ii) the location of service delivery; (iii) the provider of services; and (iv) the frequency of services. How these components are combined into a service delivery framework will vary across countries and populations, but the common intention should be to improve acceptability and care outcomes *(5)*.

Two key groups of people require specific approaches that will involve different resource requirements – people who present late to care and people who are stable on ART. To

Figure 6.1. Key factors in differentiated approaches to HIV care *(5)*
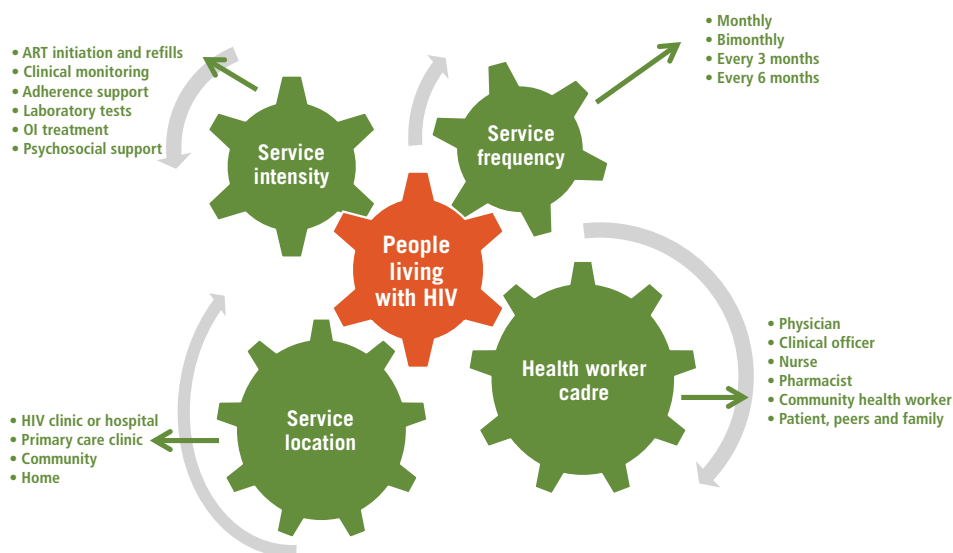
support differentiated care approaches for these two groups, the following WHO consensus definitions and related package of care were reached in a Delphi survey of experts.[1]

People with advanced disease are defined as those presenting to care with a CD4 count below 200 cells/mm^{3} or WHO disease stages 3 and 4. The package of care for these people should include the following:

- rapid initiation of ART (once the risk of immune reconstitution inflammatory syndrome [IRIS][2] is ruled out);

- systematic screening for *Cryptococcus* antigen;

- screening and treatment for tuberculosis (TB) or isoniazid preventive treatment (IPT) as indicated;[3]

- screening for toxoplasmosis and co-trimoxazole (CTX) prophylaxis; and

- intensive follow-up.

Stable individuals are defined as those who have received ART for at least one year and have no adverse drug reactions that require regular monitoring, no current illnesses or pregnancy, are not currently breastfeeding and have good understanding of lifelong adherence and evidence of treatment success (i.e. two consecutive viral load measurements below 1000 copies/mL). In the absence of viral load monitoring, rising

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[1] The Delphi technique is aimed at generating consensus. It solicits opinions from groups in an iterative process of questions. After each round, the responses are summarized and redistributed for discussion in the next round. Through a process of convergence involving the identification of common trends and inspection of outliers, a consensus is reached.

[2] Immune reconstitution inflammatory syndrome (IRIS): IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART. It occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after starting therapy.

[3] This is recommended for all people living with HIV but should be prioritized for patients presenting with advanced disease.

CD4 cell counts or CD4 counts above 200 cells/mm^3, an objective adherence measure, can be used to indicate treatment success. The package of care for stable individuals can include the following:

• less frequent (3–6-monthly) clinic visits;

• less frequent (3–6-monthly) medication pickup;

• community-based care; and

• cessation of CD4 count monitoring if viral load testing is available.

While less frequent clinic visits are recommended for stable individuals, rapidly growing children (0–5 years old) and adolescents will need to be monitored more frequently for treatment dosing/weight changes and adherence support.

6.3　Models of community ARV delivery

To accommodate the growing number of stable individuals on ART and improve retention in care and health outcomes, innovative models of community ARV delivery have been developed. WHO reported on their emerging importance in 2014 *(9)*, and they are shown in Table 6.2. Several implementing organizations – notably Médecins Sans Frontières (MSF) together with health ministries – have been pioneers in developing these models. Outcomes have been reported for four countries in sub-Saharan Africa and

Table 6.2. Summary of strategies for alternative community delivery of long-term ART *(10)*

Health service driven　　　　　　　　　　　　　　　　　　　Patient driven

Key objective	Appointment spacing and fast-track ARV refill	At enrolment into care		Community ART distribution points	Community ART groups
		Facility-based clubs	Community-based clubs		
Patient perspective					
Reduce costs (time and transport)	Yes	Yes	Yes	Yes	Yes
Increase peer support	No	Yes	Yes	Yes	Yes
Enhance community participation	No	Potentially	Potentially	Potentially	Yes
Health-care perspective					
Reduce workload					
Nurse	Yes	Yes	Yes	Yes	Yes
Pharmacist	Yes	Yes	No	Yes	Yes
Counsellor/health-care worker/peer supporter	N/A	No	No	No	No
Maintain and improve health care					
Retention	Yes	Yes	Yes	Yes	Yes
Improve self-management of patients	Yes	Yes	Yes	Yes	Yes

the impact assessed through routine programme data *(10)*. Models of interest include appointment spacing for clinical and drug refill visits in Malawi, peer educator-led ART refill groups in South Africa, community ART distribution points in the Democratic Republic of the Congo and patient-led community ART groups in Mozambique. All these approaches were found to reduce the burden for patients (reduced time and cost of travel to clinic and less income loss) and the health system (reduced clinic attendance), while maintaining high retention in care (more than 90% retained in care across multiple time points). The success of community ART models depends on sufficient and reliable support and resources, including a flexible and reliable drug supply, access to quality clinical management, a reliable monitoring system that can follow patients in and out of the community to the clinic and a nationally supported cadre of lay health workers.

6.4   Linkage from HIV testing to enrolment in care

6.4.1   Interventions to ensure timely linkage

NEW

Recommendation

Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV (strong recommendation, moderate-quality evidence).

The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis:

- streamlined interventions to reduce time between diagnosis and engagement in care, including (i) enhanced linkage with case management, (ii) support for HIV disclosure, (iii) patient tracing, (iv) training staff to provide multiple services and (v) streamlined services (moderate-quality evidence);

- peer support[a] and navigation approaches for linkage (moderate-quality evidence); and

- quality improvement approaches using data to improve linkage (low-quality evidence).

[a]   Peer support includes peer counselling.

Background

Patient attrition following an HIV diagnosis is a huge global challenge, contributing to delayed ART initiation, avoidable morbidity and mortality, suboptimal treatment outcomes, increased cost of care and preventable HIV transmission. In sub-Saharan Africa, it is estimated that 57% (42–70%) of people who are diagnosed are linked to HIV care *(11)*. A retrospective cohort analysis in South Africa identified that 25% of newly diagnosed people were not linked to care, and 35% who were linked never initiated ART *(12,13)*. Data from community-based cohorts in seven African countries suggest that the majority of deaths among people with HIV occur prior to starting

ART *(14)*. Decreasing loss to follow-up by early initiation of ART is estimated to reduce mortality by 6–14% *(13)*.

Multiple factors may hinder successful linkage to care, including distance from HIV care sites, transport costs, disclosure-related concerns, stigma and long waiting times at the facility *(15)*. Men and young people tend to be less likely to be linked to HIV care. As programmes expand access to HIV testing services, it is essential that linkage to HIV care be improved through interventions that support people in the initial steps of the continuum of care. Such interventions may vary based on the local context, including the health-care delivery system, geography and target population.

Rationale and supporting evidence

A systematic review identified 60 studies from 16 countries that evaluated the effect of 63 interventions on improving linkage of newly diagnosed patients to HIV care *(16)*. The majority of the studies were observational and targeted adults and pregnant women living with HIV in Africa (80%). Three main areas of intervention were identified: (i) streamlined interventions; (ii) peer support and navigation approaches; and (iii) quality improvement approaches. Almost all the studies reviewed were conducted in the context of 2013 WHO ART eligibility criteria, which by definition was characterized by longer pre-ART care prior to ART initiation. Initiating all people living with HIV will significantly reduce the period of time between HIV diagnosis and ART initiation; as such, many of the interventions outlined below may need to refocus on accelerating ART initiation as well as engagement in care.

Streamlined interventions

Four studies evaluated packages of service delivery interventions to streamline care; two were randomized controlled trials and two observational studies with pre–post designs. Overall, there was moderate-quality evidence of increased ART initiation and engagement in care among those eligible.

Multifaceted interventions to reduce time between diagnosis and engagement in care and ART initiation included (i) enhanced linkage with case management, (ii) support for HIV disclosure, (iii) patient tracing for those who failed to engage in care, (iv) training staff to provide multiple services and (v) streamlined services to accelerate time to initiation. These were shown to be associated with increased rates of ART initiation *(16)*. Such promising approaches should be considered as part of routine care to improve ART uptake. However, because the studies evaluated multiple system interventions, the improvements reported cannot readily be attributed to any specific action but rather to the multifaceted interventions as a whole. Due to high variability surrounding equity and the feasibility of the use of incentives to improve linkage, this intervention was not included in the recommendation; however, it should be noted that multifaceted, streamlined services may employ incentives to improve linkage to care and initiation of ART in selected populations.

Peer support and navigation

The systematic review identified seven cohort studies demonstrating that peer support and navigation interventions were effective in increasing linkage to care *(16)*. The specific interventions evaluated included home visits, peer support, including for navigating the health-care system, and enhanced counselling. The evidence for peer support and

navigation interventions was overall of moderate-quality for increasing linkage to care due to the observational nature of the studies. In the reviewed studies, peer navigators assisted patients to link from community-based testing services to health-care settings where HIV care is provided. No studies identified any significant harmful effect of the interventions.

Counselling interventions were identified in eight included studies (seven cohort studies and one individual randomized controlled trial). Specific interventions included one-on-one post-test counselling, group counselling and counselling delivered by trained community members. All interventions demonstrated a significant increase in clinic enrolment, although none demonstrated any increase in ART initiation.

Quality improvement

Five quality improvement (QI) intervention studies (one cluster randomized controlled trial and four cohort studies) demonstrated significant benefits for linkage to care. Four of these studies with the largest benefits were all implemented in programmes to prevent mother-to-child transmission of HIV *(16)*. All QI initiatives employed in the interventions focused on the use of facility data and addressing locally specific barriers to linkage. Overall quality was low due to the risk of bias in the individual studies. Interventions included educational outreach training sessions for health workers, policy and protocol changes and improved data collection.

Other approaches

The systematic review also identified very low-quality evidence demonstrating the effect of integrating services within HIV care settings – provision of ART in TB treatment settings and maternal and child health settings – on reducing time between diagnosis and ART initiation. These findings are consistent with existing WHO recommendations (*see* section 6.10 "Integrating and linking services"). CD4 cell count testing at the point of care can also be used to prioritize patients for urgent linkage to care and ART initiation (*see* section 6.4.2 "CD4 cell count testing at the point of care").

The WHO Consolidated guidelines on HIV testing services also identify good practices to increase linkage to care, developed by reviews of published studies and programmatic experience *(17)*. These are valuable and are consistent with the new recommendations listed above to improve linkage and are derived from the testing perspective. WHO recommends that all HIV testing services should adhere to the five C's – consent, confidentiality, counselling, correct test results and connection (linkage to prevention, treatment and care services) (*see* section 2.1 "Clinical guidelines: HIV diagnosis – Introduction"). Taken together, the new recommendations and good practices outline a comprehensive set of interventions with demonstrated benefit to improve linkage from testing to care and ART initiation.

Cost and cost–effectiveness

The costs of specific interventions will vary depending on the components of the intervention and the context for implementation. None of the studies identified in the systematic review reported estimates of the direct cost or cost–effectiveness of interventions. Effective linkage to HIV care following an HIV diagnosis potentially improves programme effectiveness, supports earlier ART initiation and reduces loss to

Good practices for linkage from HIV testing services *(17)*

- Comprehensive home-based HIV testing, which includes offering home assessment and home-based ART initiation

- Integrated services, where HIV testing, HIV prevention, treatment and care, TB and sexually transmitted infection (STI) screening and other relevant services are provided together at a single facility or site

- Providing on-site or immediate testing for CD4 cell count with same-day results

- Providing assistance with transport, such as transportation vouchers, if the ART site is far from the HIV testing service site

- Decentralized ART provision and community-based distribution of ART

- Support and involvement of trained lay providers who are peers and act as peer navigators, expert patients/clients and community outreach workers to provide support, and identify and reach people lost to follow-up

- Intensified post-test counselling by community health workers

- Using communication technologies, such as mobile phones and text messaging, which may help with disclosure, adherence and retention, particularly for adolescents and young people

- Providing brief strengths-based case management, which emphasizes people's self-determination and strengths, is client-led and focuses on future outcomes, helps clients set and accomplish goals, establishes good working relationships among the client, the health worker and other sources of support in the community and provides services outside of office settings

- Promoting partner testing may increase rates of HIV testing and linkage to care, as may approaches that encourage male involvement in prevention of mother-to-child transmission (PMTCT) settings

- Intimate partner notification by the provider, with permission, is feasible in some settings; it identifies more HIV-positive people and promotes their early referral to care

follow-up before treatment initiation, thus resulting in potential cost savings along the continuum of care.

Equity and acceptability

A qualitative evidence synthesis identified 25 studies of interventions to support linkage to care *(18)*. Key areas of convergence included counselling and support interventions that highlighted the importance of positive interactions with health-care workers and case managers (high confidence) and family and peer support (moderate confidence). For service delivery interventions, process and discussion of implementation of interventions

(high confidence) and task-shifting interventions (high confidence) all were acceptable to improve linkage. HIV programmes need to address barriers to linkage to HIV care and ART initiation. This is particularly important for populations that face multiple barriers, both structural and individual, to accessing HIV services.

Population considerations

Children

There is historically poor linkage and retention among children, especially for infants tested using early infant diagnosis (EID) within programmes for PMTCT of HIV. Of the two studies identified in the systematic review *(16)* that evaluated interventions delivered at the time of EID (one individually randomized controlled trial and one cohort study), both demonstrated significantly increased ART initiation with the use of technology (automated text messages to providers and mothers and provision of rapid results using short message service/Global System for Mobile Communications/General Packet Radio Service (SMS/GSM/GPRS) printers [*see* section 6.4.3 "Laboratory connectivity"]). The recommendation and good practice statements should be considered relevant for this population, given the lack of demonstrated harm and potential benefit. In addition, point-of care EID should be utilized to improve linkage to care (*see* section 2.5.3 "Point-of-care technologies for the diagnosis of HIV infection in infants and children") and family-centred service delivery models considered.

Adolescents

Developmental changes during adolescence may mean that not all adolescents have the ability to come to terms with an HIV diagnosis. Adolescents may also have limited awareness of their own health needs and of the availability of services, in addition to limited experience and confidence in navigating the health services. Consent requirements can also restrict access to treatment and care. One randomized controlled trial was identified in the systematic review *(16)* demonstrating that peer support groups resulted in significantly increased linkage to care for this age group. Other linkage mechanisms involving outreach to the adolescent patient should also be considered for this population. These include peer-based interventions, community-based services, support groups and use of mobile technology, social media or call centres. All linkage mechanisms should be introduced at the point of HIV testing for young people living with HIV.

Research gaps

Evaluation is needed of packages of strategies aimed at improving linkage to care to build a stronger evidence base, including packages developed in the era of initiating ART for all people living with HIV regardless of CD4 cell count. Future studies should disaggregate effects of these strategies by sex, key populations and age. Costing studies and cost–effectiveness analyses are needed to better inform national policy decisions.

6.4.2 CD4 cell count testing at the point of care

> NEW
>
> ### Recommendation
>
> CD4 cell count testing at the point of care can be used to prioritize patients for urgent linkage to care and ART initiation (conditional recommendation, low-quality evidence).

Background

WHO and national guidelines have progressively recommended earlier initiation of ART at higher CD4 cell counts, and in all regions, ART is being started at increasingly higher CD4 cell counts *(19,20)*. Nevertheless, it is recognized that it may not be possible to immediately implement the recommendation to initiate ART for all people with HIV regardless of CD4 count in all settings. In addition, across all regions, many people start ART too late, with median CD4 cell counts at ART initiation in sub-Saharan African still below 200 cells/mm^3 *(21)*. This is partly explained by late HIV diagnosis and delays in linking people to care following a positive diagnosis. Once linked to care, long turnaround times for laboratory results have contributed to delays in ART initiation and loss to follow-up *(1,17,22)*. Therefore, while there may be a reduction in the need for CD4 count testing over time, CD4 count testing at the point of care remains a potentially important approach to increase access to clinical monitoring and decrease turnaround times. Many countries in sub-Saharan Africa have implemented CD4 count testing at the point of care, and several reports suggest that it can reduce loss to follow-up and time to ART initiation *(22)*.

Rationale and supporting evidence

A systematic review identified 30 studies, mainly conducted in Africa, which assessed the impact of CD4 count testing at the point of care on turnaround time of results, loss to follow-up, ART initiation rate and timing compared to conventional laboratory-based CD4 count testing *(23)*. The review identified significant reductions in turnaround times for results returned to the provider using CD4 count testing at the point of care (median 0.1 day) compared to conventional laboratory-based CD4 testing (11 days). Time between HIV diagnosis and ART initiation was also lower (9 days compared to 32 days) *(23)*. The findings were heterogeneous, with a variable degree of risk of bias in the studies. Overall, low-quality evidence indicated that CD4 testing at the point of care improves each step of the treatment cascade from testing to ART initiation.

Studies of cost–effectiveness in low-income settings have concluded that CD4 count testing at the point of care is cost-effective, even in settings where an initial investment in point-of-care devices is required, as this is offset by the health benefits of reduced morbidity and mortality *(24,25)*. Many countries have piloted or implemented at-scale strategies for CD4 count testing at the point of care, including through task-shifting approaches. A number of studies have also reported that trained and supervised non-laboratory staff, including laypeople, can undertake blood finger-prick testing and

carry out point-of-care diagnostic tests *(19)*, including point-of-care CD4 count testing *(26)*, and this can facilitate the conduct of CD4 count testing at the point of care.

A conditional recommendation was made acknowledging that the use of this intervention will be highly context specific. Consideration was given to the forecasted reduction in the need for CD4 cell count testing over time as the recommendation to initiate ART regardless of CD4 cell count is fully implemented.

Equity and acceptability

Providing CD4 count testing at the point of care is judged to improve equity by bringing it closer to where patients reside and improving access to testing in rural settings. CD4 count testing at the point of care is acceptable to people living with HIV and preferred to laboratory-based testing *(27,28)*. The acceptability to health workers is similarly positive due to the ease of use and interpretation of results *(28)*.

Implementation considerations

It is anticipated that many countries will adopt a phased approach to implementing the policy of ART initiation at any CD4 cell count recommended in these guidelines. Nevertheless, HIV programmes should retain the capacity to perform CD4 cell count assays at baseline and in case of treatment failure, as this remains one of the best predictors of disease progression and mortality risk *(29)*.

Appropriate placement of point-of-care instruments is a key factor, based on considerations such as volume, distance, loss to follow-up and cost. Careful consideration should be given to human resource requirements and quality assurance (QA). The connectivity functions of point-of-care CD4 testing instruments are critical to monitoring QA as well as supply management and programme monitoring and evaluation. Point-of-care programmes should be integrated into existing laboratory and clinical programmes to ensure synergy, strengthening and linkage to care and treatment.

Research gaps

Given the changing role of CD4 count measurement for initiation and monitoring recommended in these guidelines, models for how best to use existing CD4 count testing equipment, including point-of-care CD4 count testing, will be important.

6.4.3 Laboratory connectivity

NEW

Recommendation

Electronic communication can be considered to transfer test results and reduce delays in acting on the results of early infant diagnosis and other essential laboratory tests (conditional recommendation, low-quality evidence).

The decentralization of HIV care services to primary-care settings has allowed for expanded access to treatment and improved outcomes. One challenge to delivery of care at peripheral facilities has been to ensure rapid and reliable turnaround of laboratory results. Sample transportation networks can result in delays in or losses of results, which in turn can delay clinical decision-making. While this can be partly overcome through the use of devices at the point of care, in situations where these devices are unavailable, alternative approaches are needed to ensure that delays in turnaround time of essential laboratory results, in particular for EID, are minimized. Early identification of HIV-infected infants is critical to enable timely initiation of ART.

SMS/GSM/GPRS printers represent a potential solution, whereby laboratories can transmit messages to the clinic site in real time via standard telecommunication networks. A number of countries have well-established programmes using SMS/GSM/GPRS printers, including Kenya, Mozambique, Rwanda, South Africa, Zambia and Zimbabwe. Several other countries are in the implementation and pilot phases of SMS/GSM/GPRS printer use.

Rationale and supporting evidence

A systematic review was conducted focusing on the potential for electronic result delivery systems to reduce turnaround time of early infant HIV diagnostic test results *(30)*. Mortality among HIV-positive infants is highest during the first three months, and early HIV diagnosis and prompt ART initiation can significantly reduce this risk *(31)*. Turnaround times using traditional paper-based systems can extend to around two months, leading to loss to follow-up of mothers and their infants and increased infant mortality if treatment is delayed.

The review identified 11 retrospective cohort studies, all conducted in Africa. The use of SMS/GMS/GPRS printers reduced average turnaround time by 17 days (from 68 to 51 days), with several studies reporting a turnaround time of less than 20 days *(30)*. The evidence was graded as low quality due to the absence of randomized study designs and lack of data on clinical impact. Because it is possible that similar efficiencies could be gained for other laboratory test results, electronic result delivery systems could be used for other tests such as CD4 count testing, viral load testing and other non-HIV-related testing.

No formal cost–effectiveness analysis has been conducted; however, the cost of the intervention is likely to be offset by the substantial health benefits related to earlier identification of HIV-positive infants. This premise is also considered relevant for other essential laboratory tests.

Equity and acceptability

SMS/GMS/GPRS printers have been well accepted and widely implemented in many countries for return of laboratory results. The technology has the potential to improve access to results in rural settings and, as such, could improve equity. Focus groups conducted with women living with HIV who had given birth within the past 3 years suggest that any intervention to speed up identification of HIV-infected infants has the potential to reduce anxiety of mothers and is therefore highly acceptable *(32)*.

Implementation considerations

Adequate cellular phone network coverage, maintenance, troubleshooting and systems for ensuring the supply of sufficient credit and printer consumables are all key to ensuring coverage and uninterrupted service. Implementation should take into account the need to ensure data security and patient confidentiality. Resources for adequate training of health workers and provision of consumables need to be allocated to avoid interruption of service.

Research gaps

Further studies should assess the clinical impact of SMS/GSM/GPRS printers on infant ART initiation rates, loss to follow-up, mortality and morbidity. It would be useful to assess the utility and impact of the use of SMS/GSM/GPRS printers and other technologies that return results for a range of essential laboratory results.

6.5   Retention in care

NEW

Recommendations

Programmes should provide community support for people living with HIV to improve retention in HIV care (strong recommendation, low-quality evidence).

The following community-level interventions have demonstrated benefit in improving retention in care:

- package of community-based interventions[a] (children: low-quality evidence; adults: very low-quality evidence)
- adherence clubs[b] (moderate-quality evidence)
- extra care for high-risk people (very low-quality evidence)

[a] Patient advocates, treatment and peer support interventions providing adherence and psychosocial support in the community.
[b] Peer support, distribution of ARV drugs and assessment by non-clinical or lay providers.

Background

Poor patient retention undermines programme and patient outcomes, including achieving sustained viral suppression. The global effort to increase the number of people on ART needs to ensure that people taking ART are retained in chronic care for life. Systematic reviews show that retention rates are estimated to be as low as 64% to as high as 94% at 12 months after ART initiation *(33,34)*. Several countries report a lower than 60% retention rate after 3 years on ART, with high loss to follow-up representing unknown outcomes. Retention in ART programmes is a major challenge in all settings and across populations, specifically paediatric and adolescent populations, postpartum women and men. Multiple factors may play a role in loss to follow-up, including distance to health facilities, lack of transport or inability to cover travel expenses, stigma and disclosure-related issues, being too sick and lack of understanding of the need for lifelong care.

Rationale and supporting evidence

A systematic review *(35)* identified six studies (one randomized controlled trial and five cohort studies) that evaluated community-level interventions to strengthen retention in HIV care: a package of community-based interventions, adherence support clubs and provision of extra care for high-risk patients. A strong recommendation was made despite the overall low quality of evidence due to the balance of benefit greatly outweighing potential harm, the degree of acceptability to people living with HIV and the programmatic benefits of implementing interventions that result in positive patient and programmatic outcomes.

Package of community-based interventions

Community-based interventions identified with beneficial impact on retention in HIV care included: support centred on the needs of the individual, counselling and psychosocial support by lay adherence counsellors or patient advocates and family and peer support. The lay counsellors or patient advocates assisted patients by linking health facilities with communities, providing counselling and patient-centred support and visiting patients in their home environment. One cohort study *(36)* included children and adolescents (aged <16 years) and demonstrated significantly increased retention at 36 months with overall low quality of evidence. Bringing services closer to communities through decentralization has also improved retention in HIV care and has been recommended by WHO since 2013 (*see* section 6.9 "Decentralization") *(37)*.

Adherence clubs

The systematic review identified one retrospective cohort study *(38)* evaluating the impact of facility-based adherence clubs on loss to follow-up or death at 40 months, with a significant reduction compared to standard care. No studies were identified in the review evaluating the impact of adherence clubs on outcomes for adolescents or children.

Extra care for high-risk people

The systematic review identified one cohort study from Kenya that evaluated the impact of nurses and non-clinical health workers providing weekly or biweekly contact with patients with advanced HIV infection (i.e. CD4 count <100 cells/mm³) on mortality *(39)*. Stable individuals on ART met for brief assessments by a non-clinical health worker, referral to a nurse where necessary, in addition to peer support and distribution of ART every 2 months. The study also included a yearly follow-up review with a clinician. Long-term follow-up and death were significantly reduced at 40 months, with an overall very low quality of evidence.

Cost and cost–effectiveness

The cost of implementing community-level interventions varies by setting and depends on whether community-based health programmes are already established. Generally, costs related to training and remunerating lay providers are much less than the cost of care provided at facility level and care provided by health workers. Cost related to community support, peer support and support by patient advocates is often related to training and orienting these cadres and support groups.

Equity and acceptability

A qualitative evidence synthesis *(40)* highlighted key interventions that were acceptable, related to improving retention in HIV care. These included lay health workers providing support (moderate confidence), particularly if they were also living with HIV; family and friend support (moderate confidence); mobile health (mHealth) interventions (moderate confidence) and developing positive and non-judgemental relationships with those implementing the intervention (moderate confidence).

Population considerations

Pregnant and breastfeeding women

For pregnant women living with HIV, the transition from antenatal care and maternal, newborn and child health (MNCH) services to ART care is a potential point for loss to follow-up. A systematic review *(41)* identified 10 studies (one cluster randomized controlled trial, three individual randomized controlled trials and six cohort studies) that evaluated interventions to improve postpartum retention of women living with HIV. The majority of the studies reported outcomes in the immediate postpartum period. There was moderate-quality evidence to support the use of phone calls and SMS/GSM/GPRS to improve retention in the early postpartum period (6–10 weeks). Given the paucity of data on the long-term impact of these interventions, limited conclusions can be derived from this result. There is also very limited evidence on the cost–effectiveness of interventions to improve retention in care of postpartum women. However, a systematic review attests to the positive impact of various mHealth approaches *(42)*. Given the low costs of technologies such as SMS or phone, it can be inferred that this would likely be a cost-effective intervention.

A review of country programme experience of delivery of ART in antenatal care settings shows a range of practices to address women who transition from MNCH-based services to HIV care clinics. This transition period is often a critical point in which a substantial number of women and their infants discontinue care. Several countries are implementing interventions with evidence of benefit, including assigning district-level focal points, active patient tracing and financial support for transportation. Many programmes are implementing community-based interventions: peer support such as mothers-to-mothers programmes and peer adolescent support groups for adolescent pregnant women living with HIV. Structured counselling sessions and telephone reminders may also have the potential to support the process of transition.

Children

Caregivers are responsible for understanding the importance of retaining children in care, especially younger children. Disclosure to children typically occurs late, making it challenging to discuss the importance of follow-up. WHO recommends age-appropriate disclosure to children *(43)*. Solutions include:

- supporting caregivers to attend for regular follow-up; and
- reinforcing to caregivers the importance of the process of disclosing to the child, which can begin early with age-appropriate messaging and tools.

Adolescents

Frequent clinic visits, time spent waiting for services and having to miss school discourages adolescents' engagement in care. Negative attitudes of health workers, concerns regarding privacy and confidentiality and limited opportunity to discuss their concerns also act as barriers to retention for younger people. Distance to facilities and out-of-pocket expenses may restrict their engagement. Service delivery models beyond the facility, which support adolescents to engage in care, such as peer-based interventions and community-based services, should be considered. Peer interventions are highly valued by young people. Adolescent-friendly health services should be implemented to improve quality (*see* section 6.11 "Delivering HIV services to adolescents").

Consider:

• providing adolescent services at specific times or in separate areas with flexible appointment systems that accommodate school hours;

• comprehensive services that address multiple needs, including psychosocial support and sexual and reproductive health (SRH); and

• close monitoring of adolescents' engagement in care, rapid proactive follow-up and implementation of strategies for re-engagement.

Men

A systematic review *(44)* identified 69 studies demonstrating that men had a 37% increased risk of death while on ART compared to women, after adjusting for baseline characteristics. This is partly explained by the fact that men tend to be diagnosed later and are more likely to start ART late. In several settings, initiatives to improve men's engagement in care have focused on engaging them in services for PMTCT. Innovative service delivery models are essential to improve men's access to HIV care services and ART initiation. Programmes need to routinely disaggregate data by sex in order to better monitor access to and outcomes of treatment for both men and women.

Implementation considerations

There is no single model of community or peer support that works in all settings, and programmes need to adapt such interventions to the local context. Some patients may choose not to receive services in the community due to concern over stigma and discrimination. Community interventions require linkage with health facilities for smooth transfer and referral of patients, when necessary, and strategic planning and resourcing for sustainability. Community-level programmes still need to be integrated into national health sector plans in many settings.

Research gaps

Implementation research and evaluation of the different models of community-level support in different contexts are necessary to further guide programmes. Innovative approaches and effective strategies are needed to support transitioning across different care-delivery points for men, postpartum women, adolescents and children. Further data on the cost of implementing community-level interventions in different settings will guide national policy.

6.6   Adherence

NEW

Recommendations

Adherence support interventions should be provided to people on ART (strong recommendation, moderate-quality evidence).

The following interventions have demonstrated benefit in improving adherence and viral suppression:

- peer counsellors (moderate-quality evidence)
- mobile phone text messages (moderate-quality evidence)
- reminder devices (moderate-quality evidence)
- cognitive-behavioural therapy (moderate-quality evidence)
- behavioural skills training and medication adherence training (moderate-quality evidence)
- fixed-dose combinations and once-daily regimens (moderate-quality evidence).[a]

[a]   Refer to section 4.4.2 "Fixed-dose combinations and once-daily regimens" for detail.

Background

Adherence to ART is the primary determinant of viral suppression and the risk of transmission, disease progression and death *(45–47)*. Suboptimal adherence is a major challenge worldwide and is associated with a diversity of patient- and programme-related causes. Individual factors may include forgetting doses, being away from home, changes in daily routine, depression or other illness and substance or alcohol use. Adherence to ART may also be challenging in the absence of supportive environments for people living with HIV and in the presence of HIV-related stigma and discrimination. Medication-related factors may include adverse events and the complexity of dosing regimens, such as those for children. Health system factors include distance to health services, long waiting times to receive care and obtain prescription refills, receiving only one month's supply of drugs, pharmacy stock-outs and the burden of direct and indirect costs of care *(48,49)*.

Specific population groups face additional challenges to adherence, and these should be considered when implementing the recommended interventions.

Pregnant and postpartum women

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. It is estimated that around a quarter of pregnant women have inadequate ART adherence, and this is higher during the postpartum period *(50)*. Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other individual factors include suboptimal understanding of HIV, ART and PMTCT, lack of partner disclosure and support, and fear

of stigma and discrimination. Service delivery barriers include poor-quality clinical practices, gaps in provider knowledge and training, poor access to services and health worker attitudes *(51,52)*.

Adolescents

It is estimated that over one third (38%) of adolescents globally are suboptimally adherent to ART, with substantial regional variation *(53)*. In addition to common challenges to adherence, adolescents face specific challenges, including psychosocial issues such as peer pressure, the perceived need to conform and inconsistent daily routine *(54,55)*. Adolescents are often left out of decisions and have limited opportunities to discuss their concerns, and there is limited availability of adolescent-specific treatment literacy and adherence counselling tools. For adolescents who are transitioning from paediatric to adolescent care, additional challenges may include assuming increased responsibility for their own care, issues relating to disclosure to peers or partners, difficulties in navigating the health-care system, lack of links between adult and paediatric services and inadequately skilled health workers *(56)*.

Infants and young children

Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV, and suboptimal HIV care and treatment for family members could result in suboptimal care for the child. Other challenges include lack of nutrition support, limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements and difficulties in swallowing tablets *(57–59)*.

People with mental health conditions and substance use

People with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART *(60,61)*. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate medical therapies for people with mental disorders can help to improve adherence. WHO recommends that assessment and management of depression should be included in care services for all people living with HIV (*see* section 5.3.2 "Assessment and management of depression in people living with HIV").

Use of alcohol and other substances may also contribute to poor adherence to ART. Alcohol and substance use can lead to forgetfulness, poor organization and diversion of monetary resources *(62,63)*. Treatment of depression and management of substance use disorders can improve HIV treatment outcomes *(64,65)*. WHO recommends treatment of depression and substance use disorders regardless of HIV status. Other key services for people with HIV who use drugs, such as needle and syringe programmes and drug substitution therapy, provide further opportunities to support adherence.

Key populations

In many settings, key populations face multiple challenges related to stigma and discrimination that can affect access to health services, all of which may impact negatively on adherence *(66,67)*. WHO Consolidated guidelines on HIV prevention,

diagnosis, treatment and care for key populations include specific considerations for adherence support for these populations.

Rationale and supporting evidence

A systematic review and network meta-analysis identified 84 randomized controlled trials of interventions to improve adherence *(68)*. Forty-seven trials reported on overall viral suppression and 71 on adherence. The review found overall moderate-quality evidence to support a range of interventions that demonstrate the benefits of improving adherence and viral suppression. Interventions were grouped by components of similarity, given below:

• Peer counsellors: there is direct evidence of higher levels of adherence compared to standard care.

• Mobile phone text messages: text messages sent to the client's phone one way or two ways. There is direct evidence that text messages result in higher adherence compared to standard care.

• Reminder devices: interventions using calendars, alarms, system devices for disease management assistance and pagers. There is direct evidence that supporters and device reminders result in increased viral suppression.

• Cognitive-behavioural therapy: there is direct evidence of a higher rate of viral suppression compared to standard care.

• Behavioural skills training: provision of training or medication adherence training sessions. These included module-based interventions and those designed to improve life skills, attitudes, behaviour and knowledge.

The benefits significantly outweigh any potential harm for all interventions identified. Peer counsellors are generally considered to be a low-cost intervention and, in some settings, have been highly cost-effective. Interventions such as cognitive-behavioural therapy and behavioural skills training require initial increased investment for training and resources. Reminder devices, telephone interventions and mobile phone text messages are low cost in the majority of low- and middle-income countries. Cost–effectiveness will vary depending on the setting and epidemic context. A strong recommendation was made by the Operational Guideline Development Group, given the potential benefits for patient outcomes, feasibility in a variety of settings and low cost.

Supportive interventions

Several interventions may also be of value in addressing specific challenges that impact on adherence and/or viral suppression. Nutritional assessment, care and support are essential components of HIV care. HIV programmes should ensure that existing national policies on nutritional support are observed to maximize adherence to ART and achieve optimal health outcomes, particularly in food-insecure settings. Nutritional support could include nutritional counselling, cash transfers, subsidizing food costs and/or food vouchers. Studies suggest that providing nutritional support to people receiving ART reduces the risk of non-adherence among food-insecure individuals *(69)*.

Financial support can reduce the risk of non-adherence *(70)*. Programmes and care providers should consider a broader programmatic approach to reducing the costs of care for people living with HIV. This includes avoiding out-of-pocket payments at the

point of care (such as drugs, diagnostics and clinical services), supporting transport costs, decentralizing care and reducing the frequency of health facility visits. Programmes need to consider the ethical and equity implications of providing financial support and non-monetary incentives for people living with HIV. Standardized criteria for supporting people receiving ART may need to be developed based on national income levels.

Equity and acceptability

A qualitative evidence review *(71)* of the acceptability of interventions to improve adherence identified intervention-specific themes. These included educational programmes for individuals and families (high confidence), mobile phone text messages (high confidence), health worker outreach (moderate confidence) and complex interventions (low confidence). Confidentiality and privacy and strengthening social networks were identified as cross-cutting themes from a total of 31 studies. Interventions may be more acceptable if they consider local cultural customs and religious beliefs. Peer-based interventions are generally well accepted, in particular among adolescents, who find that hearing experiences and learning from others facing the same challenges is critical for supporting adherence and engagement in care *(72)*.

Implementation considerations – monitoring adherence

Effective monitoring of adherence requires a combination of approaches based on human and financial resource capacity, acceptability to people with HIV and health workers and an understanding of the local context.

Viral load monitoring

Viral load monitoring is considered the gold standard for monitoring adherence and confirming treatment response. Although treatment failure is often caused by lapses in adherence to ART, it may also result from other factors, including drug resistance, malabsorption, drug–drug interactions and other patient-, disease- and drug-associated effects. Other approaches to monitoring adherence should therefore be considered as a way to provide additional information about possible causes of virological failure or to support adherence monitoring in settings where viral load testing is not available. WHO recommends that, following an initial high viral load (>1000 copies/mL), an adherence intervention be carried out prior to conducting a second viral load test. This has been shown to lead to re-suppression in over 70% of patients *(73)*. Viral load monitoring also has a high potential to motivate adherence.

Pharmacy refill records

Pharmacy refill records provide information on when people pick up their ARV drugs *(74,75)*. Pharmacy records are more reliable than self-reporting *(76)* and are already a part of national monitoring and evaluation frameworks in many settings.

Self-reporting

Self-reported data are easy to collect and can be a useful adjunct to estimating non-adherence but are subject to recall bias *(77)*. Counselling on the importance of remembering ART doses and an environment that promotes and enables honest reporting of non-adherence are critical components of monitoring adherence to ART in routine care settings.

Pill counts

Counting the remaining pills in bottles may help to assess adherence. Pill counts usually take place at routine health-care visits. However, some people discard tablets prior to health-care visits, leading to overestimated adherence. Counting pills also requires health-care personnel to invest significant time and may not be feasible in routine care settings. Pill count has been found to perform better when combined with self-reported adherence *(78)*.

Research gaps

Further research is needed to determine:

- optimal ways to proactively monitor adherence and identify through simple triage those patients in greatest need of adherence support;

- interventions to support adherence in populations at heightened risk of suboptimal adherence (children and adolescents, pregnant women, men who have sex with men, people who inject drugs);

- potential synergistic effects of combining two or more interventions that could impact individual, social support and health system factors; and

- the effectiveness of long-acting ART in improving adherence and viral suppression.

6.7   Frequency of clinical visits and medication pick-up

NEW

Recommendations

- Less frequent clinical visits (3–6 months) are recommended for people stable on ART (strong recommendation, moderate-quality evidence).[a]

- Less frequent medication pickup (3–6 months) is recommended for people stable on ART (strong recommendation, low-quality evidence).[b]

[a]   When routine clinical consultations are due, they should be coordinated with planned medication pickup to reduce visit frequency.
[b]   ARV supply management should be strengthened to ensure availability of ARV medicines and prevent stock-outs in the context of less frequent medication pickup.

Background

In the early period of ART scale-up in low- and middle-income settings, the majority of people seeking HIV care presented with advanced disease, often requiring intensive clinical management *(79)*. This led to the typical practice of monthly visits to health facilities for clinical review *(80)*. As guidelines now recommend treatment at earlier stages of the disease, there is a growing appreciation that, with effective ART and good adherence, people can have a near-normal life expectancy *(81–83)*. HIV programmes are providing ART to increasing numbers of people who are stable on ART, and there is a need to rationalize the delivery of care to reduce the burden on health systems, particularly in countries with a high HIV prevalence. Frequent clinical visits also place a

burden on people taking ART, and the opportunity and financial costs of travelling to the clinic have been associated with an increased risk of poor adherence and poor retention in care *(84)*. Correspondingly, approaches to reducing the frequency of clinical visits, including community ART dispensing, have been associated with improved retention *(85,86)*.

Rationale and supporting evidence

Because clinical visits and medication pickup are often linked, both were assessed in a combined systematic review that found eight studies (one cluster randomized controlled trial, two randomized controlled trials and five cohort studies) from Kenya, Malawi, South Africa, Uganda and the United States, providing comparative data on the impact of reduced frequency of clinical visits. Overall, the review found that reduced frequency of clinical visits among stable individuals was associated with significantly better retention, with no difference in mortality outcomes. The same review identified three studies from Malawi, South Africa and Spain, which reported that reduced frequency of ART refills was also associated with improved retention in care. The studies also reported a positive trend towards improved adherence *(87)*. There was no evidence that reduced frequency of ART refills led to additional complications or disengagement from care.

The strong recommendation to reduce the frequency of clinical visits and drug refills is supported by the expanding availability of ART and the fact that people are presenting to care earlier and require less intensive clinical care. This trend is expected to continue as countries move towards initiating ART for all people living with HIV regardless of CD4 cell count. In addition, there is substantial cost to people and health services of monthly clinical visits for those who are stable on ART. Reducing the frequency of clinical and ART pickup visits will be cost saving for both patients and health services. All cost analyses conducted within the systematic review point towards reduced cost per patient with reduced visits.

Equity and acceptability

Implementation of these recommendations is likely to improve equity as it relieves the burden placed on people to attend for frequent clinical assessments and to pick up drugs. This burden is greatest on people in rural areas (distance to travel) and those with very low income (costs associated with time off work). This recommendation is supported by the reported acceptability by young people and adults, citing increased convenience and fewer interruptions of daily schedules.

Implementation considerations

Reduced frequency of clinical and ART pickup visits has already been implemented for HIV and other chronic diseases in a variety of low- and middle-income settings. In implementing these recommendations, programmes need to consider coordinating routine clinical consultations with planned medicine pickup to reduce visit frequency. ARV drug procurement and supply management should be strengthened to ensure availability of ARV drugs and prevent stock-outs in the context of less frequent medication pickup (*see* section 6.10 "Integrating and linking services").

In some settings, consideration is being given to implementing even less frequent (i.e. annual) clinical visits for people who are stable on ART. While there is currently no published evidence to support this approach as a formal recommendation in these guidelines, it is recognized that this may be a reasonable approach in certain contexts and for certain populations.

Population considerations

Pregnant and breastfeeding women

Pregnant or breastfeeding women on ART may require closer follow-up and more frequent visits than other populations. Psychosocial support and counselling requirements may need to be considered, especially with regard to infant feeding and postpartum care. Differential care models should be used from the beginning of pregnancy until the end of the breastfeeding period.

Children

The needs of the children evolve as they grow, especially during rapid phases of growth and development, early adolescence and around the time of disclosure. Differential care models should be modified to the child's needs. Growth monitoring is an important component of paediatric HIV care and is necessary for dose adjustment of ART. This should be emphasized within the differential care model.

Adolescents

Rapid development may impact on adherence, retention and support requirements for adolescents. The evolving capacities and emerging independence of adolescents need to be recognized as well as the involvement of caregivers. Busy and changing daily routines and competing priorities can make frequent visits challenging for adolescents. Close monitoring of adolescents' engagement in care, rapid and proactive follow up and implementation of strategies for re-engagement are critical. Facilitating independence and self-management can support differential care for adolescents. Peers and other community-based services can also facilitate early identification of adolescents requiring additional support and follow-up. (*See* section 6.11 "Delivering HIV services to adolescents".)

Research gaps

Further evidence of the feasibility and benefits of increasingly spaced clinical visits and medication pickup (greater than 6 months) is needed, and this should be studied across various patient populations.

6.8   Task shifting and task sharing

Recommendations

- **Trained and supervised lay providers can distribute ART to adults, adolescents and children living with HIV (strong recommendation, low-quality evidence).**

- Trained non-physician clinicians, midwives and nurses can initiate first-line ART (strong recommendation, moderate-quality evidence).

- Trained non-physician clinicians, midwives and nurses can maintain ART (strong recommendation, moderate-quality evidence).

- Trained and supervised community health workers can dispense ART between regular clinical visits (strong recommendation, moderate-quality evidence).

These recommendations apply to all adults, adolescents and children living with HIV.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

The number of available health workers remains inadequate in many settings with a high burden of HIV. Task shifting and task sharing involve the redistribution of tasks within health workforce teams. Specific tasks are reassigned to health workers with shorter training and fewer qualifications to optimize the available human resources. Although increasing the number of health-care personnel is also crucial, clinical tasks need to be shared and shifted to ensure that enough health workers are available.

In 2013, WHO made recommendations on task shifting relating to initiation, maintenance and dispensing of ART. These recommendations are supported by a systematic review of four randomized controlled trials and six observational studies *(88)*. Overall, the data showed no difference in mortality and some evidence of reduced rates of loss to follow-up when nurses or non-physician clinicians initiated or maintained people on ART or when community health workers maintained people on ART relative to physicians performing these tasks. The quality of care in these studies was ensured by providing training, mentoring and supervision for nurses, non-physician clinicians and community health workers, clear referral pathways and effective monitoring and evaluation systems *(88)*.

These guidelines provide a new recommendation for trained and supervised lay providers to distribute ART to adults, adolescents and children living with HIV. Several high HIV-burden settings are experiencing a critical shortage of pharmacy personnel to undertake this task. Apart from the absolute shortage of such staff, pharmacy personnel tend to be concentrated in urban settings, large hospitals and private pharmacies,

accentuating shortages in rural and primary-care settings *(89–91)*. Community distribution of ART for stable individuals can ease the burden of care on people with HIV and health services by reducing the frequency of clinical consultation and drug pick-up visits. Additionally, retrospective cohort studies from Uganda, the United Republic of Tanzania and Zambia demonstrate that community ARV distribution results in significantly less patient attrition than health facility-based services *(92)*.

Rationale and supporting evidence

Indirect evidence from a systematic review comparing dispensing of ARV drugs by non-pharmacists compared to pharmacists identified two cluster randomized trials that compared the outcomes of community-based HIV care with clinic-based care *(93)*. The first trial evaluated patient outcomes (viral load, CD4 count, opportunistic infections and change in ART regimen) when ART was provided in community settings by community care counsellors living with HIV compared to clinic-based ART delivery where care was provided by health professionals. In the community-based settings, ART was distributed by community care counsellors who were trained and mentored for patient triaging, referral when necessary and distribution of ARV drugs prefilled by pharmacy personnel. People receiving community-based care had been on ART for more than six months and had no clincial conditions and high levels of self-reported adherence to treatment *(94)*. People in the standard-of-care arm visited health facilities on a monthly basis, picked up their ARV drugs from a health facility pharmacy and were provided care by health workers. The second trial evaluated virological failure among those accessing ART from lay providers in the community compared to the standard ART care delivery by health professionals at health facilities *(95)*.

The meta-analysis identified no difference in mortality and virological failure between people who received care from a community-based team and those who received care from health professionals at a health facility. Fewer people were lost to follow-up in the community-based care group. Both groups demonstrated high levels of self-reported medication adherence, with no statistical differences between the groups. The overall quality of evidence is low. The lay providers were also part of a wider community-based intervention with additional confounders that supported the success of the intervention, not solely the distribution of ART.

A strong recommendation was made that trained and supervised lay providers can distribute ART to adults, adolescents and children living with HIV despite the low quality of evidence, considering existing programme experience of trained and supervised community health workers and lay workers providing and performing other tasks within the HIV testing, treatment and care continuum. Additionally, there are important examples within the broader health sector where community health workers, with minimal training, are entrusted to provide curative and preventive care in maternal and child health services, malaria diagnosis and treatment and TB care.

Potential benefits and harm

The public health benefits of lay providers distributing ART are an overall increase in the number of providers to overcome the shortage of facility personnel, reduced clinic congestion and services provided closer to communities, which support retention in care. Where ARV drug supply and stock management are not reliable, distributing ARV drugs outside health facilties may increase distribution sites and potentially aggravate stock-

outs. Neither of the two studies in the systematic review included people with comorbidities or children. While the recommendation is relevant to these populations, necessary dose adjustments, as the child grows, can be safely done during clinic visits, with maintenance treatment provided at the community level.

Cost and cost–effectiveness

There may be initial increased costs for training and other costs associated with introduction of community ART distribution. However, studies report substantial costs to patients when they are required to travel to centralized health services to collect medication. A study from Uganda reported that the cost to people receiving hospital-based care was three times higher than for people who received home-based care *(95)*.

Equity and acceptability

A qualitative evidence synthesis identified that task shifting can enhance linkage to care and treatment adherence and assists HIV programmes to cope with shortages of professional health workers *(18)*. Strengthened relationships between people with HIV and local communities can empower individuals. In Malawi, people from the community were hired as pharmacy attendants to pre-package and distribute ARV drugs to enhance the capacity of pharmaceutical services, an approach that has facilitated visit spacing and reduced waiting times and health providers' workload at health facilities *(96)*.

Implementation considerations

Both initial and ongoing training and mentoring, supportive supervision and administrative planning have been critical to the success of programmes that have implemented task shifting. Programmes adopting these recommendations need to train and establish a system for routine supportive supervision of health workers, including lay providers. Adopting task shifting and sharing strategies often requires the revision of regulatory frameworks and national policies so that new cadres of health workers can perform new tasks. WHO recommends that all health workers, including lay providers, should be adequately remunerated *(97)*, and programme experience indicates that it is difficult to sustain health services based on volunteerism alone. National regulatory bodies, professional associations and other stakeholders need to be involved when addressing the scope of practice, roles and responsibilities of health workers.

It is important that the local supply chain system take into account task shifting and sharing responsibilities, and community models of ARV drug delivery to ensure adequate stock. The supply management logistic information system needs to incorporate all ARV drug distribution outlets, including community lay providers' distribution sites (*see* section 6.13 "Procurement and supply management systems for HIV health products").

> NEW
>
> ### Good practice statement
>
> Trained and supervised non-laboratory staff, including laypeople, can undertake blood finger-prick for sample collection.

WHO recommends that trained and supervised lay providers be used to provide safe and effective HIV testing services using rapid diagnostic tests (*see* section 2.3.1 "Pre- and post-test services: overview). A systematic review *(98)* was conducted to evaluate the outcomes of shifting tasks of finger-prick specimen collection for HIV-related diagnostic tests to non-laboratory staff (i.e. clinicians, nurses and midwives) and lay providers compared to laboratory professionals doing the same task. The review identified 27 studies (observational and technical evaluations), the majority based in sub-Saharan Africa (88%). The study results were inconsistent due to various cadres of health workers, test types utilized and the outcomes assessed. All of the studies reported a high degree of acceptability by clients and health workers, which was consistent with findings from the qualitative evidence synthesis on the acceptability of task shifting (*see* recommendations for task shifting). The inconsistent study results, high risk of bias and limitations of the reported data reduce the ability to make definitive conclusions from the systematic review alone.

A good practice statement was developed on task shifting for conducting blood samples by finger-prick testing, due to the overall benefits outweighing any potential harm. Nurses, midwives and clinicians readily perform HIV testing and are involved in EID sample collection and CD4 point-of-care testing in many settings, which form the basis of this good practice statement. Expanding finger-prick testing to lay providers will support increased access to essential diagnostics and decentralization of HIV care. In several settings, trained and supervised lay providers are already conducting HIV testing and performing sample collection using the finger-prick method. No harm was identified from this approach; however, a system of quality assurance is necessary for effective and safe implementation. The WHO *Consolidated guidelines on HIV testing services* provide additional considerations and key steps for successful implementation related to performing testing and sample collection by lay providers (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en).

Building human resource capacity

As HIV treatment and care have been scaled up in the past decade, in-service training has assumed a key role in rapidly upgrading the competencies of health-care providers. All health workers, including community health workers and lay providers, need to be regularly trained, mentored and supervised to ensure high-quality care and timely implementation of updated national policies. Given the rapidly evolving knowledge on HIV care and treatment, countries need to consider a system for supporting health workers' continuing education, including through clinical mentoring and regular supportive supervision *(99)*. The use of new technologies, such as computer-based self-learning, distance education, online courses and phone-based consultation, may supplement classroom in-service training and enable efficient use of health workers' time and other resources. It is equally important to strengthen the HIV treatment and care components of existing pre-service courses for health workers graduating and receiving certification in a range of disciplines. Health-care workers also need to be equipped to manage HIV as a chronic condition, work in a team and implement new national guidelines and protocols.

Programme managers should also support the development and implementation of policies to create a suitable environment for recruiting, retaining, remunerating and motivating health workers in rural or remote areas, where turnover and attrition may be considerably higher than in urban settings.

In many countries, people living with HIV, community workers and volunteers are involved in delivering HIV testing, counselling, care, treatment and social support services. People with HIV are also involved in training health workers as expert trainers. Involving people living with HIV in both training health workers and delivering HIV services may have the additional benefit of overcoming HIV-related stigma and discrimination.

Research gaps

Research is needed to determine the feasibility and safety of further task shifting to improve access to treatment, including initiation and maintenance of ART at the community level, with spaced clinical visits to a health facility.

High-quality evidence is lacking for the initiation of second-line ART by trained non-physician clinicians, midwives and nurses. Further research in this area would identify the benefits and harm of implementing this approach in settings where there are clinician shortages.

6.9   Decentralization

Recommendations

Decentralization of HIV treatment and care should be considered as a way to increase access to and improve retention in care:

- initiation of ART in hospitals with maintenance of ART in peripheral health facilities (strong recommendation, low-quality evidence);

- initiation and maintenance of ART in peripheral health facilities (strong recommendation, low-quality evidence); and

- initiation of ART at peripheral health facilities with maintenance at the community level (strong recommendation, moderate-quality evidence).[a]

a   Community level includes external outreach sites, health posts, home-based services or community-based organizations. Frequency of clinical visits will depend on health status.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en/.

Background

The rapid scale-up of ART programmes has posed significant challenges to health systems in high-burden, resource-limited settings. In many settings with a high burden of HIV infection, clinics have long waiting times due to the volume of patients needing care. Decentralizing

HIV treatment and care reduces waiting times for people receiving care in facilities and brings HIV services closer to people's homes. Decentralizing HIV treatment and care also strengthens community engagement by linking community-based interventions with health facilities and can optimize access to services, care-seeking behaviour and retention in care. People living with HIV, affected communities and community-based interventions play a key role in providing HIV testing, treatment, care and support.

Rationale and supporting evidence

This recommendation, made in 2013, is supported by a systematic review identifying 16 studies (two cluster randomized trials and 14 cohort studies) assessing models of decentralized HIV treatment and care. The review provides evidence that decentralization of HIV care, either from hospitals to health centres or from health centres to community-based care, improves patient access and retention in care without compromising clinical outcomes. All but one of the studies was carried out in sub-Saharan Africa, and the benefits of decentralization may differ in different contexts *(100)*.

Implementation considerations

The optimal model for ART decentralization (partial or full) depends on the local context, including the burden of HIV infection and the health-care delivery system. Programmes should determine which clinical and laboratory services will be available at what level of the health-care delivery system.

Programme managers should consider the values and preferences of those receiving care, the number of people likely to attend decentralized settings and whether decentralization brings services closer to people who would otherwise travel long distances to receive ART.

Decentralization should be accompanied by efforts to strengthen linkage and referral systems. Community-based treatment programmes should be linked with regular care at health facilities and with adequate laboratory facilities, diagnostics, monitoring and evaluation and drug and supply management systems.

Standards of care should be defined for each level of the health system. The role of each level should match its capacity, and the lines of authority and accountability should be clear and well understood. In many settings, decentralizing ART requires task shifting to ensure an appropriate mix of health workers at peripheral facilities. An appropriate regulatory framework (laws, regulations, policies and guidelines) is needed to allow tasks to be performed by different cadres of health workers.

Adaptations may be needed for specific populations. HIV care and treatment services for pregnant and postpartum women and HIV-exposed and -infected children can be provided in decentralized settings and is a preferred option where the HIV burden is high and a large number of women and children access health services in primary care settings. In settings with a low HIV burden, a centralized service delivery model with community linkage may be more appropriate. Some groups, such as adolescents and key populations, may choose to receive HIV services in a facility that is not close to their homes due to stigma and disclosure-related concerns. In such settings, programme managers should incorporate the values and preferences of their clients in designing appropriate service delivery models.

6.10 Integrating and linking services

Chronic care requires integrating and linking related services to ensure comprehensive and consistent patient management over time, including provision of related services in the same settings, systems to share information and effective referrals across settings and providers. Integrating and linking services are likely to reduce missed opportunities for initiating ART, enhance adherence support and optimize retention in care.

6.10.1 Delivering ART in maternal and child health-care settings

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Recommendation

In generalized epidemic settings, ART should be initiated and maintained in eligible[a] pregnant and postpartum women and in infants at maternal and child health-care settings, with linkage and referral to ongoing HIV care and ART, where appropriate (strong recommendation, very low-quality evidence).

[a] All people living with HIV are now eligible for initiating ART at any CD4 cell count.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

Access to ART for pregnant and breastfeeding women with HIV remains a challenge, as does provision of essential services to HIV-exposed and -infected infants and ensuring that services for PMTCT reach pregnant adolescents, female sex workers and women who inject drugs.

Because many women living with HIV access health services only at the time of pregnancy, maternal and child health settings provide a key opportunity to provide access to ART *(101,102)*. In most generalized HIV epidemic settings, maternal and child health services are provided at the primary care level, where pregnant women and children predominantly access health services. WHO recommends offering HIV testing to pregnant women through provider-initiated approaches as an essential component of MNCH services (*see* section 2.6.2 "Other priority populations: pregnant women"). WHO also recommends couple and partner HIV testing for all pregnant women and their partners in maternal and child health-care services in generalized HIV epidemics, and that such testing should be considered for key populations in concentrated and low-level epidemics *(17)*.

ART should be available in maternal and child health clinics or easily accessible in a linked model of service delivery. Countries with generalized epidemics may consider a phased approach to providing ART in maternal and child health settings, which may effectively transform such settings into ART sites, giving priority to facilities with the largest burden of HIV, and building health systems to ensure uninterrupted ART and adherence and retention.

Not all maternal and child health settings will have the capacity to provide long-term HIV treatment and care for women, their partners and children. These settings will need to assess the best time for transitioning and linking mothers and their infants to chronic HIV care. Issues to consider in the assessment may include the capacity and quality of HIV care in the maternal and child health-care setting, acceptability and proximity of alternative HIV care settings and HIV burden.

Rationale and supporting evidence

The systematic review conducted to support this recommendation in 2013 evaluated the impact of providing HIV treatment and care to women in maternal and child health-care settings compared to referral to ART clinics in generalized epidemic settings. One cluster randomized trial and three observational studies showed that integrated services improved uptake of and adherence to ART during pregnancy, but outcomes for maternal mortality, morbidity, immune response, infant HIV testing uptake and mother-to-child transmission were comparable *(103–107)*. Providers felt that integrated services increased efficiency, decreased waiting time for clients and improved relationships between providers and patients, resulting in less stigmatization and improved care and adherence to treatment *(108)*. Given the potential to improve access and provide acceptable services to increase adherence and retention, this is a strong recommendation despite the very low quality of evidence. The alternative to providing ART in maternal and child health settings is to refer women and infants to HIV care facilities. Referral-based models may further require women and infants to receive care at separate service delivery points, potentially resulting in decreased linkage and coverage of ART.

6.10.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings

Recommendations

In settings with a high burden of HIV and TB, ART should be initiated for people living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART (strong recommendation, very low-quality evidence).

In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made (strong recommendation, very low-quality evidence).

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

In 2014, ART coverage was less than 40% among the total number of people estimated to have fallen ill with HIV-associated TB in 20 of the 41 countries with the highest burden of HIV and TB *(109)*.

Since 2010, WHO has recommended that ART be initiated for all people living with HIV and active TB patients, regardless of CD4 cell count. TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of starting TB treatment (*see* section 4.3.5 "Timing of ART for adults and children with TB"). CTX prophylaxis is also recommended for all people living with HIV and active TB, regardless of CD4 cell count (*see*, section5.2.1 "Co-trimoxazole prophylaxis"). These recommendations are intended to facilitate expanded ART coverage for people living with HIV and TB and to support the diagnosis and treatment of active TB. TB infection control measures (*see* Annex 16) are crucial in HIV care settings to minimize the risk of nosocomial transmission of TB.

Rationale and supporting evidence

A systematic review conducted to support these recommendations in 2013 *(110)* evaluated the effectiveness of delivering ART in TB treatment settings. The review identified 19 observational studies, many of which showed increased uptake and timeliness of ART initiation. However, data on mortality and TB treatment success were inconsistent. The systematic review evaluating the effectiveness of delivering TB treatment in HIV care settings identified five observational studies. Two studies reported decreased mortality and another showed comparable mortality rates. TB treatment success rates and ART uptake were comparable across studies *(110)*. In making the recommendations, the quality of evidence was considered along with programmatic risks and benefits.

6.10.3 ART in settings providing opioid substitution therapy

Recommendation

ART should be initiated and maintained in eligible[a] people living with HIV at care settings where opioid substitution therapy (OST) is provided (strong recommendation, very low-quality evidence).

[a]   All people living with HIV are now eligible for initiating ART at any CD4 cell count.

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Background

These guidelines recommend the same ART eligibility criteria for all individuals living with HIV, regardless of drug use behaviour. WHO recommends opioid substitution therapy (OST) (with methadone or buprenorphine) for the treatment of opioid dependence, combined with psychosocial support *(111)*. Where available, treatment of opioid dependence should be integrated and administered in conjunction with ART for those who need it. Although there is some evidence to suggest that OST improves HIV treatment outcomes among people living with HIV who inject drugs, OST should not be a

prerequisite for initiating or maintaining ART for people who use opioids. The provision of ART in settings providing OST may expand access to ART for people who inject drugs.

Given the high incarceration rates of people who inject drugs, efforts should be made to ensure that ART is available as part of prison health services. Continuity of treatment and care need to be maintained through appropriate referrals when people return to the community.

Rationale and supporting evidence

A systematic review conducted to support this recommendation in 2013 identified one randomized trial and three observational studies evaluating the effect of delivering ART in settings providing OST. Most of these studies had small sample sizes. Some studies observed trends of improved viral suppression and reduced mortality, while others found comparable rates of viral suppression and mortality *(112–114)*.

This recommendation supports expansion of ART by delivering the service in settings providing OST. OST should be provided free of charge or covered by public health-care insurance and should be accessible to all those in need, including in prisons and other closed settings. HIV programmes will need to continue to work closely with other service providers to ensure successful implementation of this recommendation. Guidance on maintaining effective OST programmes is available in the WHO Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1).

6.10.4 STI and family planning services in HIV care settings

NEW

Recommendation

Sexually transmitted infection (STI) and family planning services can be integrated within HIV care settings (conditional recommendation, very low-quality evidence).

Background

There is significant overlap in the demographics and risk profile among people accessing HIV treatment and care services and SRH services. WHO recommends the routine offer of HIV testing services for people with an STI in all epidemic settings and for family planning clients in generalized epidemic settings. Data from countries across sub-Saharan Africa confirm high rates of unintended pregnancy (51–84%) among women living with HIV *(115–118)*. There is also a higher unmet need for family planning services among women living with HIV enrolled in HIV care compared to the general population.

A study in Uganda found that 75% of women living with HIV had an unmet need for family planning, more than double the unmet need reported by women who did not have HIV (34%) *(119)*. A limited but growing body of evidence suggests that many women in

Asia who are living with HIV lack access to family planning services and experience disproportionately high rates of unintended pregnancy and abortion *(120)*. Adolescent women are more likely to have unintentional pregnancies, detectable viral loads during pregnancy and higher mother-to-child transmission rates compared to adult mothers *(121)*. Access to adolescent-friendly family planning services should be prioritized for this group.

STI and family planning services can be delivered in conjunction with chronic HIV care at primary care settings. Integration and linkage of these services potentially expands access to all of them. The diagnosis of syphilis in pregnant women is increasingly integrated with HIV testing services, and the dual elimination of mother-to-child transmission of HIV and syphilis is a global public health objective.

Rationale and supporting evidence

A systematic review identified three studies (one retrospective cohort and two comparative cross-sectional studies) from low- and middle-income countries. These evaluated the impact of providing family planning services on contraceptive use in HIV care settings and the rate of unplanned or unintended pregnancy among people enrolled in HIV care *(122)*. All the studies reported improved contraceptive use compared to referral to an external maternal and child health or family planning clinic. One cluster randomized trial examining the integration of family planning into HIV care and treatment services in Kenya found that integration was feasible, inexpensive to implement and cost-effective *(123)*. The review did not identify any studies that evaluated delivery of STI services in HIV care settings. The overall quality of evidence is very low due to the observational nature of the studies and the lack of data on delivery of STI services in HIV care settings in low- and middle-income countries. There is evidence that integrated service delivery is cost-effective and leads to economies of scale *(124–126)*.

A conditional recommendation was made that STI and family planning services can be integrated within HIV care settings, considering existing programme experience, potential for cost savings and evidence of feasibility and acceptability. Provision of integrated services will improve access and expand the opportunity to provide STI and family planning services to a key population of adults and adolescents.

Equity and acceptability

A qualitative evidence review identified 10 studies from Uganda, Ghana, Kenya, Malawi, Swaziland and Zambia *(127–136)*. A global community dialogue and focus groups were also conducted in Bangladesh, Burundi, Ethiopia, Myanmar and Uganda to evaluate the perceptions of people living with HIV about the delivery of STI and family planning services in HIV care settings. Three studies evaluated the perceptions of health-care providers. Overall, integration of STI and family planning services into HIV care settings is the acceptable and preferred model of service delivery by people living with HIV and service providers. Many people living with HIV expressed a preference to receive family planning services in an "HIV-only" environment.

Feasibility

Delivery of comprehensive, integrated HIV and SRH services is already part of national policy in several high HIV-burden settings *(137)*. Feasibility and models of integrating STI and family planning services in HIV care settings is often context specific. Effective implementation of integrated services at national scale requires an enabling environment, including collaboration across programmes, particularly in human resources and supply management, supportive supervision and joint programme planning, monitoring and evaluation. Major challenges cited by health-care providers and programme managers include poor patient record-keeping, key commodity stock-outs, client misconceptions about the side-effects of some contraceptive methods and an increased workload for health workers, especially in database management.

Implementation considerations

It is essential to provide follow-up to postpartum women living with HIV and their HIV-exposed infants, both for HIV and for routine postpartum and child health care. Initial follow-up of the infant is usually scheduled at the first immunization visit at 4–6 weeks. Follow-up for the mother should ideally be scheduled at the same time and should include a postpartum check-up, family planning counselling and review of ARV drug regimen and adherence support *(138)*. Family-based care, in which the mother, her baby and partner receive care in the same place, should be promoted as much as possible.

For adolescents living with HIV, HIV care presents an opportunity for the provision of comprehensive SRH information and services, including safe sex practices, prevention and management of other STIs, sex and sexuality education and family planning services. Sex and sexuality should be treated in a positive, non-judgemental way with all adolescents, regardless of their HIV status. Integrated service delivery models also present an opportunity to provide comprehensive services to key populations.

6.10.5 Care transition

An effective continuum of HIV care ensures that patients are retained as they transition between different health-care services and providers. Care transitions may be negatively affected by stigma and discrimination, fear of disclosure to new providers and anxiety or inconvenience resulting from changes in providers, their practice style and location. Examples of such changes include adolescents transitioning from paediatric care to adult care; pregnant and postpartum women transitioning from maternal and child health services to HIV care; patients transitioning from hospitals to primary care facilities; patients transitioning from facility-based to community-based services; and patients in correctional facilities transitioning to general outpatient care. Effective planning and support for patients are needed to ensure that these transitions occur as smoothly as possible.

6.11 Delivering HIV services to adolescents

Recommendations

- **Adolescent-friendly health services should be implemented in HIV services to ensure engagement and improved outcomes (strong recommendation, low-quality evidence).**   **NEW**

- Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV (conditional recommendation, very low-quality evidence).

- Training of health-care workers can contribute to treatment adherence and improvement in retention in care of adolescents living with HIV (conditional recommendation, very low-quality evidence).

- Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV status to others and empowered and supported to determine if, when, how and to whom to disclose (conditional recommendation, very low-quality evidence).

Source: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

Background

These guidelines recommend ART initiation in all adolescents (10–19 years old) living with HIV, regardless of CD4 count or clinical stage of disease (*see* section 4.3.3 "When to start ART in adolescents (10–19 years of age)"). There is a growing cohort of adolescents living with HIV, which includes those infected from birth and those who have acquired HIV later in childhood and adolescence. While there is still a lack of health outcome data for this age group, emerging evidence indicates that adolescents living with HIV are underserved by current HIV services and have significantly worse access to and coverage of ART *(139)*. Adolescents are at high risk of loss to follow-up both before and after ART initiation; people aged 15–24 years and those attending services for the PMTCT of HIV are particularly at risk *(140–146)*.

Rationale and supporting evidence

All adolescents, including those living with HIV, face significant barriers to accessing health services, due to inadequate health literacy, limited ability to navigate health systems, legal requirements for parental or caregiver consent, and insufficient resources to pay direct and associated service costs *(147,148)*. Adolescents face significant levels of stigma and discrimination, particularly those from key populations, among whom criminalization of behaviour such as sex work, drug use and same-sex activity further perpetuates social exclusion and hinders access to health and support services *(149,150)*.

Poor quality of services also limits adolescent engagement in health care. Adolescents often perceive health services as unacceptable due to concerns about confidentiality and

negative health provider attitudes *(150,151,153)*. Services are often not organized to accommodate adolescent needs and routines and have inconvenient service schedules, inflexible appointments and unwelcoming environments *(150,151)*. Without sufficient consideration and support, adolescents can be lost between paediatric and adult services. The rapid developmental and social changes that occur during adolescence exacerbate the impact of such barriers and can have a profound impact on the way adolescents engage with health services *(151)*.

Due to their unique needs, adolescents living with HIV require quality comprehensive services and care to support access, retention and adherence. This includes psychosocial support, SRH and mental health care *(151,152)*. The WHO quality-of-care framework provides a useful working definition of adolescent-friendly health services (Box 6.1) *(153,154)*. Additionally, global standards for quality health-care services for adolescents have been developed to support implementation (Box 6.2) *(155)*.

> ## Box 6.1. WHO-defined characteristics of adolescent-friendly health services
>
> **Equitable:** all adolescents, not just certain groups, are able to obtain the health services they need.
>
> **Accessible:** adolescents are able to obtain the services that are provided.
>
> **Acceptable:** health services are provided in ways that meet the expectations of adolescent clients.
>
> **Appropriate:** the right health services that adolescents need are provided.
>
> **Effective:** the right health services are provided in the right way and make a positive contribution to the health of adolescents.

A systematic review *(156)* was conducted to assess the effectiveness of adolescent-friendly health services for adolescents living with HIV compared to standard care. Due to the limited evidence available, the review was expanded to include the general adolescent population and young people up to and including 24 years of age. Adolescent-friendly health services were defined according to the WHO characteristics and the global standards for quality health-care services for adolescents. Eleven randomized control trials *(157–167)* and eight observational studies *(168–175)* from four of the six WHO regions were identified. Four studies focused on adolescents living with HIV; the remainder focused on SRH, HIV prevention, mental health, diabetes, general health and smoking cessation. All studies included two or more of the WHO characteristics, and global standards for quality health-care services for adolescents. Only one study included all WHO characteristics and no study addressed all global standards.

Young people engaged in adolescent-friendly health services compared to standard care showed small but significant improvements in various outcomes, including health

outcomes (lower pregnancy rates); health-care utilization (presentation at a clinic for mental health, HIV counselling and testing and outpatient visits); uptake (HIV testing); knowledge (HIV and STI acquisition, pregnancy prevention and sexual health); attitudes (towards sex and HIV testing); sexual risk-reduction behaviour (condom use); self-efficacy (condom use or diabetes management); and service acceptability. No differences were seen with respect to healthy lifestyle or quality of life outcomes. Among HIV-positive young people exposed to adolescent-friendly health services compared to the standard care, there were small but significant improvements with respect to short-term viral load reduction and long-term ART adherence. The overall quality of evidence is low. A strong recommendation was made despite low-quality data, citing the promising improvement in outcomes, the existing programme experience, and evidence of feasibility and acceptability by the end users.

Cost and cost–effectiveness

No studies have assessed the resource requirements or cost–effectiveness of adolescent-friendly health services within HIV service settings. However, a cost modelling study and a retrospective cost analysis for adolescent-friendly health services in low- and middle-income countries reported that, although additional resources are required to ensure delivery of quality adolescent-friendly health services, investments to implement and scale up these services – in particular, services providing multiple interventions – appear to have value and impact for adolescents *(176,177)*.

Equity and acceptability

Adolescent-friendly approaches aim to ensure that all adolescents obtain the health services that they need, that policies and procedures are in place to facilitate provision of health services to adolescents and that all health service providers treat adolescents with equal care and respect, regardless of HIV status, behaviour or other characteristics.

A global consultation of 470 young people living with HIV and a situational analysis of over 200 facilities in the WHO African Region was undertaken to prepare for the development of these guidelines *(150,178)*. Additional inputs were also considered from two unpublished, multicountry longitudinal qualitative studies with 147 adolescents living with HIV *(179)*.

Key acceptability themes and suggested strategies for improving service delivery focused on empowered and solution-oriented information and support; opportunities for open and honest discussion; skills development on SRH and HIV disclosure from an early age; comprehensive care that addresses issues beyond HIV, including support for adolescents from key populations; flexible scheduling of clinic visits to accommodate school hours; free services closer to home and community-based services; dedicated hours and spaces for adolescents; peer-led interventions and services; and an adolescent-competent workforce.

Feasibility

The programmatic and facility-level feasibility of adolescent-friendly health services was explored. The situational analysis of facilities assessed the availability of appropriate HIV treatment services for adolescents *(181)*. Thirty-five per cent of facilities reported that adolescent patients were attended to separately from adult and/or paediatric patients through the use of dedicated schedules, staff or spaces. A case study of a government

ART clinic in KwaZulu-Natal province in South Africa found that it is feasible to provide adolescent-friendly health service approaches in an HIV service setting. Although financial costs were low, consideration needs to be given to ensure engagement of stakeholders, including adolescents, adolescent-specific training, minimal provider rotation and adequate time for planning of restructured services. A survey of HIV programme managers highlighted the lack of appropriately trained health service providers and the need for greater preparation of health-care services as key challenges in delivering HIV services to adolescents *(180)*.

Experience in Zimbabwe has identified several requirements for scaling up adolescent-friendly HIV services. These include a national, multisectoral, coordinated response; adolescent-sensitive policies and guidelines; meaningful involvement of adolescents; training and sustained mentorship of health service providers; community systems strengthening; linking community interventions with health facilities; and a national monitoring and evaluation framework with disaggregation and clear indicators for adolescents.

Implementation considerations

The global standards for quality health-care services for adolescents provide an approach to implementing health-care services for adolescents (Box 6.2) *(152)*. The standards outline the desired level of care and what needs to be done for the standards to be achieved.

Further actions to implement the standards at the national, district and facility levels are outlined within the implementation guide *(158)*. These standards and actions are relevant to HIV services for adolescents.

HIV-specific implementation considerations include the following:

- aligning approaches for HIV service delivery with WHO and national adolescent-friendly health service standards, protocols and activities;
- including implementation of adolescent-friendly approaches in HIV health service supervisory and monitoring systems;
- ensuring training, research and personal development opportunities for health service providers on adolescent HIV treatment and care;
- engaging service providers, adolescents and other key stakeholders to identify acceptable and feasible activities;
- implementing adolescent-friendly health service approaches in all HIV services used by adolescents, including antenatal care for pregnant adolescents living with HIV;
- establishing linkages and referral pathways to ensure a comprehensive continuum of care, especially for the transition from paediatric to adult HIV services; and
- addressing the needs and vulnerabilities of adolescents from key populations *(181).*

Box 6.2. Global standards for quality of health-care services for adolescents

Adolescent health literacy	**Standard 1.** The health facility implements systems to ensure that adolescents are knowledgeable about their own health and that they know where and when to obtain health services.
Community support	**Standard 2.** The health facility implements systems to ensure that parents, guardians and other community members and community organizations recognize the value of providing health services to adolescents and support the provision and utilization of services by adolescents.
Appropriate package of services	**Standard 3.** The health facility provides a package of information, counselling, diagnostic, treatment and care services that fulfil the needs of all adolescents. Services are provided in the facility and through referral, linkages and outreach.
Provider competencies	**Standard 4.** Health-care providers demonstrate the technical competence required to provide effective health services to adolescents. Both health-care providers and support staff respect, protect and fulfil adolescents' rights to information, privacy, confidentiality, non-discrimination, non-judgemental attitude and respect.
Facility characteristics	**Standard 5.** The health facility has convenient operating hours, a welcoming and clean environment and maintains privacy and confidentiality. It has the equipment, medicines, supplies and technology needed to ensure effective service provision to adolescents.
Equity and non-discrimination	**Standard 6.** The health facility provides quality services to all adolescents irrespective of their ability to pay, age, sex, marital status, education level, ethnic origin, sexual orientation or other characteristics.
Data and quality improvement	**Standard 7.** The health facility collects, analyses and uses data on service utilization and quality of care, disaggregated by age and sex, to support quality improvement. Health facility staff is supported to participate in continuous quality improvement.
Adolescents' participation	**Standard 8.** Adolescents are involved in the planning, monitoring and evaluation of health services and in decisions regarding their own care as well as in certain appropriate aspects of service provision.

Source: http://www.who.int/maternal_child_adolescent/documents/global-standards-adolescent-care/en

Additional guidance

Adolescent HIV testing, counselling and care: implementation guidance for health providers and planners. Geneva: World Health Organization; 2014 (http://www.who.int/maternal_child_adolescent/documents/hiv-testing-counselling/en).

HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

Global standards for quality health-care services for adolescents: a guide to implement a standards-driven approach to improve the quality of health-care services for adolescents. Geneva: World Health Organization; 2015 (http://www.who.int/maternal_child_adolescent/documents/global-standards-adolescent-care/en).

Interagency Working Group on Key Populations: technical brief series on young key populations (http://www.who.int/hiv/pub/toolkits/hiv-young-msm/en).

Research gaps

Research should contribute to a better understanding of how to implement adolescent-friendly health services at a programmatic level and the cost–effectiveness of these approaches in HIV services in low- and middle-income countries. Research on the service delivery needs of adolescents living with HIV should examine the minimum package of care; models of delivery at different service levels, including for key populations and pregnant adolescents living with HIV; the integration of SRH in ART services for adolescents; interventions to support safe disclosure; treatment literacy; interventions to address mental health; and the impact of provider training and peer interventions.

6.12 Improving the quality of HIV care services

Background

This section provides brief guidance for programme managers and health-care providers on improving the quality of HIV care services. It focuses on key principles, approaches and interventions, highlighting QA and quality improvement (QI) practices based on implementation and programme experience. HIV programmes should also be innovative in addressing local challenges and aim to strengthen programme monitoring and the routine use of programme data to improve the quality of services. Quality of care emphasizes that services should be effective in achieving desired health outcomes and that health-care practices should be people-centred and safe *(182)*. The *WHO global strategy on people-centred and integrated health services* outlines the strategy and provides an overview of evidence and good practices *(183,184)*. Strategies to improve the quality of HIV care services are needed both at the programme management level and at health facility and community levels where HIV care services are provided *(185)*. If an intervention is to achieve the desired health outcomes, it needs to be evidence based, of high quality and achieve a level of coverage that brings desired outcomes at the population level.

Rationale for strengthening the quality of HIV care services

Quality care means that people living with HIV receive the care they require to maintain their health and quality of life. For HIV programmes and health-care providers, quality HIV care optimizes programme effectiveness and efficiency. For policy-makers and funding agencies, quality care is an important requirement for maintaining health at the population level and ensuring the optimal use of available resources.

HIV programmes should plan to provide quality HIV care services from the outset by incorporating quality in the national policy, strategic plan, strategic information framework and operational and service delivery plans. Quality of care should not be seen as an additional activity to routine HIV services or a short-term project to redress implementation issues and gaps; it should be incorporated into daily activities at all levels, from service delivery to national programme management.

The WHO global strategy on people-centred and integrated health services

The *WHO global strategy on people-centred*[a] *and integrated health services*[b] represents a fundamental shift in the way health services should be funded, managed and delivered. Without a people-centred and integrated health services approach, health care will become increasingly fragmented, inefficient and unsustainable. The strategy proposes that all people have access to health services provided in a way that responds to their needs and that are equitable, safe, effective, efficient, timely and of an acceptable quality.

Within the context of HIV care service delivery, people-centred care includes:

• building health-care providers' skills for effective communication with people;

• providing information and supporting people to make informed decisions and for their active engagement in their own care and self-management;

• offering a patient appointment system and acceptable frequency of facility visits;

• avoiding long health facility waiting times during clinical consultations, medication pick-up or laboratory services;

• coordinating care when people require multiple services (e.g. TB and HIV treatment, family-centred care); and

• providing comprehensive integrated services, as appropriate and relevant.

[a]   People-centred health services involve an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants as well as beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways. People-centred care requires that people have the education and support they need to make decisions and participate in their own care. It is organized around the health needs and expectations of people rather than diseases.

[b]   Integrated health services are health services that are managed and delivered in a way that ensures that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services at the different levels and sites of care within the health system and according to their needs, throughout their whole life.

Source: WHO global strategy on people-centred and integrated health services (http://www.who.int/servicedeliverysafety/areas/people-centred-care/en).

WHO, the participants of a scoping consultation on strengthening quality of HIV clinical services and members of the Operational Guideline Development Group developed the following good practice statements for HIV care services that are reflective of the broader WHO global strategy on people-centred and integrated health services *(187)*.

NEW

Good practice statements

HIV programmes should:

- provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families to play an active role in their own care by informed decision-making;

- offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection, and to improve health outcomes and quality of life in general; and

- promote efficient and effective use of resources.

Components of quality assurance and quality improvement

QI is the process of improving services and care through the routine use of patient and programme data. Several contextual factors, such as leadership and teamwork, also have a bearing on the quality of HIV care. Programme managers and health-care providers need to continuously monitor the quality of HIV care services (Fig. 6.2). This can be done by comparing implementation against set standards, analysis and use of routinely collected data at facility level and consultation with service users or community networks on the needs, values and preferences related to HIV care services that they receive. Some quality interventions require broader system-level interventions to ensure sustained improvement. For example, the delivery of community ART, triaging patients to reduce clients' waiting time for clinical consultation and use of lay providers in patient education and counselling all require a supportive programme and resources for sustained implementation. Lessons from the QI process in HIV care service delivery and management should feed back into subsequent policy and programme formulation and planning processes.

Enablers of quality improvement

HIV programmes should provide a national framework for strengthening the quality of HIV care services. The framework should also facilitate accountability and resource mobilization at different levels of the health-care delivery system. Integration of quality HIV care in national policies and strategic plans can also facilitate partnership with other health programmes and stakeholders, including professional associations, funding agencies, research institutions, communities and networks of people living with HIV. A national framework should also highlight the needs of marginalized people or groups, address resource needs to reach underserved populations and address health worker capacity to bridge gaps in quality. Comprehensive quality-of-care activities should include both QA and QI activities. Fig. 6.2 summarizes enablers for delivering high-quality HIV care services.

Fig. 6.2. Key enablers of quality HIV care services

HIV care quality incorporated in the national policy and programme framework

Quality assurance and quality improvement integrated in the management and delivery of HIV care services at health facilities and community levels

ENABLERS OF QUALITY HIV CARE SERVICES

Defined package of HIV care services to offer, including for which population and at what level of the health-care delivery system

Community engagment for strengthening the quality of HIV care services, advocacy and demand creation; and community literacy on quality

Several key considerations for integrating QI of HIV care into national policies, programmes and strategic plans are given below.

• Ensure involvement of stakeholders, including networks of people with HIV, communities and health-care workers, for building a common understanding on strengthening quality HIV care services and efficient use of resources.

• Identify elements of national policies and strategies to address the quality of HIV care services and HIV-related stigma and its impact on accessing HIV care services.

• Prioritize strategies for QA and QI of HIV care (Fig. 6.3).

• Identify nationally harmonized key indicators and reporting requirements for monitoring the quality of HIV care.

• Define roles and responsibilities of stakeholders at different levels of the health-care delivery system in strengthening the quality of HIV care services.

• Allocate resources for the development of mechanisms to support QI; for management and information systems that report, monitor and improve the quality of HIV care services; and for alignment of performance with implementation of evidence-based good practices.

• Include high-quality, people-centred HIV care service delivery in the principles, values and strategies of national polices and the HIV strategic plan.

• Set standards for evidence-based HIV care through national guidelines by defining the package of HIV care services to be offered, including at what level of the health-care delivery system and for which population or geographical location.

• Provide a national monitoring framework for continuous QI of HIV care services and assure that the practice of care adheres to national, evidence-based guidelines and standards.

Fig. 6.3. Process of building a strategy for continuous quality improvement

ASSESMENT AND EVALUATION
- **Involvement of stakeholders**
- **Situation analysis to identify gaps**
- **Confirm set goals**

STRATEGIES
- **Goals for quality improvement**
- **Choosing interventions for quality improvement**

IMPLEMENTATION
- **Implementaton process**
- **Monitoring progress**
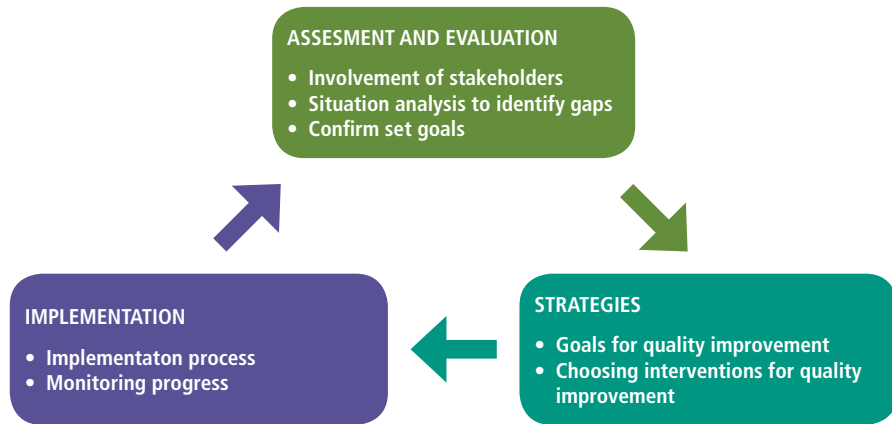
6.13 Procurement and supply management systems for HIV health products

6.13.1 Overview

This section provides operational guidance on procurement and supply management (PSM), with a focus on how PSM systems can respond to new recommendations in these guidelines. Comprehensive advice on the general management of PSM systems is readily available in existing publications and training materials. References to relevant publications and materials are provided at the end of this section.

The overarching objective of PSM systems is to support national policy with the adequate and continuous availability of the most effective, heat-stable, fixed-dose, quality-assured ARV drug formulations, diagnostics and other consumables at service delivery sites, in the right quantities, at the lowest possible cost and in a timely manner.

The new recommendation that ART should be initiated in all people living with HIV regardless of CD4 cell count will require an integrated national strategic response that considers the resources available and enables strong PSM systems at all levels of the health system. In addition, the fact that all people living with HIV need to be on ART will accelerate the scaling up of ART programmes. Procurement managers and ART programme managers will need to work together to ensure that the national supply system is forecasting, procuring and distributing the quantities of ARV drug and other health commodities required to meet the increasing national demand and the 90–90–90 target.

While there are no major changes in the ART regimens recommended in these guidelines, new drugs are recommended as components of alternative regimen choices, with potentially important implications for PSM.

6.13.2 Implementation considerations

Most national HIV programmes will need to plan a phased approach to the adoption of the new recommendations, notably the expansion of ART to all people living with HIV and the introduction of pre-exposure prophylaxis (PrEP) for groups at substantial risk of HIV infection. Where programme resources are already stretched, unplanned adoption of these new recommendations with the associated increase in demand for drugs and diagnostics may lead to stock-outs and imbalances.

Challenges and opportunities associated with implementing new WHO recommendations include the following:

• product selection;

• quantification and demand forecast;

• procurement planning and execution, including delivery and timeliness of orders;

• the ability of global supply to cope with the increasing global demand;

• storage and distribution, including logistics constraints;

• monitoring of consumption and demand changes;

• frequency of ARV drug pickup;

• information flow between stakeholders at different levels;

• costs and opportunities for cost saving;

• shelf-life of ARV drugs;

• risk of stock-outs if procurement does not meet demand; and

• risk of expired health products if the quantities procured have been overestimated.

National HIV programmes should consider establishing a stakeholder working group to develop a plan to address these issues, with participation by health policy-makers, implementers, PSM specialists and representatives from central medical stores management and the finance ministry.

Selecting pharmaceutical and diagnostic products

• Medicines should be selected in accordance with national ART guidelines and programme needs.

• National ART guidelines should provide guidance on alternative regimens in case of drug toxicities and treatment failure or stock-outs (e.g. lopinavir/ritonavir [LPV/r] versus atazanavir (ATV)/r; lamivudine (3TC)-containing versus emtricitabine (FTC)-containing formulations).

• It is recommended that the overall number of ARV drug regimens be minimized in order to optimize treatment and sourcing. According to WHO country surveys conducted in

2015, 30% of reporting countries use over 10 different first-line ARV drug regimens in adults and adolescents.

• Before new products are included in national essential medicines lists, registration and intellectual property status should be verified to ensure that the product can be imported.

• If a selected ARV drug is not on the national list and/or registered in the country, HIV programme managers should coordinate with the national drug regulatory authority and request that these drugs be put on the list and registered. Pharmaceutical companies also have a responsibility to register products in countries where they market their products.

• Drugs no longer recommended by WHO for any ARV drug treatment regimen should be removed from the national ART guidelines and essential medicines lists, and plans should be made to transition patients to more effective regimens, using existing stocks as appropriate.

• The synchronized introduction of new guidelines with planning for forecasting, procurement and distribution will minimize the wastage of products that are being phased out and shortages of newly recommended products.

• National essential medicines lists should be optimized for paediatric ARV drug formulations following the detailed guidance on preferred paediatric products provided in the Interagency Task Team (IATT) Paediatric ARV Optimal Formulary available at http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf.

Quantification and forecasting of demand

To assess the volume of products required to meet programme demand, PSM managers need to know:

• the number of patients on treatment, disaggregated by age group;

• the ARV drug regimens in use by those patients;

• proposed changes in ARV drug regimens, if any;

• the expected rate of scale-up of treatment, i.e. the increase in numbers of patients on each regimen in a given period of time;

• the numbers of rapid test kits required to identify people with HIV in line with scale-up targets;

• the forecasted uptake of PrEP; and

• the frequency of ARV drug pickup by patients.

The process of quantification of needs can be highly complex. Good practice suggests that quantification should be undertaken annually, projecting for at least two years with a quarterly or semi-annual review to determine if any significant upward or downward adjustments are needed. Assuming that financial resources are available, PSM managers can then plan ahead and place long-term orders while allowing sufficient flexibility to adjust for potential changes in the pace of scale-up, regimen switching and/or other unforeseen events affecting consumption.

When demand for a specified period has been quantified, procurement managers should develop a supply plan that takes into account:

- the months of stock currently available;

- the existing orders yet to be fulfilled by vendors;

- the budget available for new orders;

- the volume of new orders required to satisfy the forecasted demand, including provision of a safety buffer stock; and

- the required delivery dates for new shipments.

It is recommended that this process of supply planning be conducted on a quarterly or half-yearly basis to accommodate changes in demand and any delivery delays from suppliers.

Procurement

A uniform and harmonized procurement system is required to efficiently procure quality-assured, affordable ARV drugs and diagnostics. Procurement should be based on selection of appropriate products and forecasted needs, considering consumption, expanding services, phasing in and phasing out of formulations and implementing new recommendations. Transparent procedures should be adopted to achieve best-value procurement and a QA system implemented to procure, store and distribute quality-assured pharmaceuticals, diagnostics and other health products.

National procurement programmes should:

- request that partners supporting the national HIV programme consolidate PSM systems and pool procurement for ARV drugs and diagnostics;

- consider joining other pooled procurement mechanisms to increase economies of scale and minimize the risk of long delivery times observed with small orders (second-line regimens and paediatric ART);

- establish agreed specifications for selected products to ensure a common basis for procurement competition, QA standards of the products, and any special needs such as packaging or identification, with special requirements likely leading to price increases;

- use a competitive process to ensure value for money;

- establish long-term framework contracts against which call-down orders can be placed for commodities in regular and repeated demand, such as medicines and diagnostics. This will reduce procurement transaction costs as well as the time taken from identification of need to fulfilment of order and help to build collaborative relationships between buyers (national procurement managers) and sellers (suppliers);

- wherever possible, implement a multisupplier procurement strategy to support a healthy market and avoid dependence on a single supplier, which will also provide flexibility during periods of supply constraints or where individual suppliers face production or logistical difficulties that lead to delays;

- use a publicly accessible database to facilitate access to information about prices and to support competition; and

- follow the principles described in the United Nations interagency guidelines for donated drugs and WHO model quality assurance system for procurement (MQAS) *(186)*.

National HIV programmes should be aware that other countries and programmes will be ordering the same or similar formulations at the same time, and manufacturers may already have orders that will account for current production, possibly for several months ahead. Working with their suppliers, procurement managers will be able to place their orders according to agreed volumes and delivery schedules. Advice on current production and any existing supply constraints and opportunities may also be available from the organizations and contacts provided at the end of this chapter (*see* section 6.13.6 "Useful PSM resources").

Storage and distribution

Appropriate storage and distribution of HIV medicines, diagnostics and other commodities is essential. The recommendation to offer ART to people with HIV regardless of CD4 cell count will significantly increase commodity volumes and the demands on storage and distribution. Countries may need to plan for new public facilities or examine alternative approaches, including leveraging additional resources by outsourcing to private sector facilities, provided that they are appropriate for storing pharmaceuticals. Neither of these options is a quick fix; contracting with private sector providers may take many months to complete the appropriate tendering, contracting and QA of providers before available facilities can be activated for use. Countries may also wish to explore the potential of existing parallel systems, such as cold-chain facilities in immunization programmes for products that require temperature control.

PSM systems should consider planned programmatic changes in service delivery related to the frequency of clinical visits and location where patients receive their ARV drugs. For example, community distribution of ARV drugs to stable patients and community-based HIV testing may involve another step in the local supply chain and potentially increase the quantity of ARV drugs and diagnostics to be procured and distributed. Changes that impact positively on the amount of stock retained at each level, including by the patient, need to take into account the shelf-life of the ARV drugs. For example, the most common first-line ARV drugs currently have a 24-month shelf-life only, and many rapid test kits have a 12- to 18-month shelf-life only, which may impact storage and distribution plans.

Storage and distribution plans should include:

- QA of products on receipt at the warehouse;
- secure storage facilities appropriate for pharmaceuticals;
- cold storage for products that require temperature control;
- rationalization of the number of storage levels to reduce the length of the supply pipeline;
- inventory control systems with appropriate minimum and maximum levels that trigger reordering;
- regular distribution patterns to service facilities, with increased frequency of potentially smaller deliveries supporting more effective use of existing limited space and distribution capacity; and

- routine data reporting from facilities to monitor usage and identify changes in predicted consumption patterns that may risk excess stocks (which can be reallocated to avoid expiry) or stock-outs.

Ensuring a secure supply for programme flexibility and to avoid stock-outs and expired health products

It is essential to avoid stock-outs in order to prevent treatment discontinuation and achieve ART targets. Recommended actions to avoid the risk of stock-outs include the following.

- There should be close coordination with HIV programme managers and policy-makers to understand the planned progression towards "treat all" targets. Programme managers and clinicians should agree on the speed at which new patients will be started on treatment to ensure that the required commodities are available. A faster-than-planned introduction of new patients will exhaust stocks and cause an increased risk of stock-out; a slower-than-planned introduction risks overstocking and wastage due to expiry of medications.

- A clear understanding is needed of the supply chain implications of any proposed changes in the service delivery model (e.g. community distribution of ARV drugs).

- It is important to ensure that the ARV drug and diagnostics supply chain – especially its distribution system and allocation of commodities by facility – reflects the geography of the HIV epidemic.

- New patients should be initiated on the preferred first-line regimen, unless clinically contraindicated.

- Quantification and ordering should include a rotating safety buffer to compensate for errors in forecasting and potential delivery delays. It is recommended that the buffer be part of the normal stock rotation, not a separate stockpile, to avoid the risk of retaining aged or expiring products. The level of buffer may vary but should cover at least one round of planned deliveries so that any delivery delay will not lead to a stock-out. Forecasts should be revisited at least semi-annually to adjust for variances between forecasts and actual demand and to review demand for the next 12–18 months, adjusting orders as necessary.

- Orders should be placed in advance for timely delivery. Procurement managers should work closely with their suppliers to understand the suppliers' normal delivery periods and plan accordingly. It is recommended that orders be placed at least six months ahead of the required date of delivery, as this will allow adequate time for production and – where volumes allow delivery by sea freight – reduce the cost of shipping. It is also recommended that, where practical, deliveries be staged rather than arriving as a large shipment containing six months or more of stock. Staged deliveries allow for more flexible delivery schedules and enable PSM managers to make the best use of existing storage and distribution capacity.

- PSM managers should be aware of potential and actual constraints in the global market. In 2015, there were some constraints in the availability of important active pharmaceutical ingredients. This impacts the ability of formulators to manufacture and deliver finished products and must be factored into requested delivery times for new orders.

- Special consideration should be given to products that have a low demand, as in the case of many drugs used by adults or adolescents in second- or third-line ART and many paediatric ART regimens. Production of these medicines will be less frequent and many countries will require only low volumes, usually less than a full production batch. Pooled procurement at the national level and cooperation between countries and with suppliers may be appropriate in the case of these products. Buffer stocks may need to be higher to compensate for less regular deliveries and challenges in accurate forecasting of usage and uptake. Examples of such mechanisms include the Pan American Health Organization regional drug facility and the Paediatric ARV Procurement Working Group.

- Where procurement regulations allow, it is recommended that framework contracts be placed to allow for call-down orders. This maximizes the flexibility in delivery schedules, which can be adapted to actual consumption, and reduces the need for frequent repeat procurement and bidding exercises without compromising value for money.

- Several of the above actions will limit the risks of stock-outs as well as expired products (e.g. moving ARV drugs from low-volume treatment sites to high-volume treatment sites). However, when products expire, they should be destroyed according to the approaches and various disposal methods outlined in the WHO *Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies* (http://apps.who.int/iris/bitstream/10665/42238/1/WHO_EDM_PAR_99.2.pdf).

Use and monitoring

Robust information systems ensure the availability of accurate and timely consumption data on ARV drugs and diagnostics and other information required to effectively monitor the performance of the entire supply system and forecast the ARV drugs and diagnostics needed. Monitoring PSM through the effective use of early warning indicators prevents stock-outs and overstocks leading to expiry. Reliable capture and analysis of usage and consumption data from facilities will support a robust bottom-up approach to quantification and forecasting that will reflect changes in demand and support a flexible approach to the introduction of new recommendations in these guidelines.

6.13.3 Special considerations for adult and adolescent ART regimens

The preferred first-line ART regimen remains tenofovir (TDF) in combination with lamivudine and efavirenz, or TDF in combination with FTC and efavirenz (EFV), preferably as fixed-dose combinations (*see* section 4.4 "What to start: first-line ART"). Regimens containing nevirapine (NVP) are retained in the guidelines as an alternative option where clinically required for patients who cannot tolerate or have contraindications to TDF or EFV.

Key changes compared to 2013 are:

- dolutegravir (DTG) and EFV 400 mg/day are recommended as alternative first-line agents;

- darunavir/ritonavir (DRV/r) (as part of a heat-stable fixed-dose combination [FDC]) and DTG are recommended as alternative second-line options (*see* section 4.8.1 "Second-line ART for adults and adolescents"); and

- DTG and raltegravir (RAL) are recommended as potential third-line options (*see* section 4.8.3 "Third-line ART").

Four key challenges for the supply chain arise as a result of the recommended ARV drug regimens.

- The currently approved suppliers of preferred first-line FDC formulations are expected to have sufficient production capacity to satisfy the increased demand for these formulations as the number of patients on treatment increases, provided that increases are carefully phased to avoid sudden spikes in demand. However, short-term supply constraints may arise, highlighting the need for proper planning and maintenance of buffer stocks at the national level.

- Delivery lead times for the recommended first-line drugs may become extended during peak periods of demand. PSM managers should be aware of current lead times and plan their orders and deliveries accordingly.

- Purchasers and implementing partners who are distributing zidovudine (AZT)-based and NVP-based regimens to patients and have stocks and orders in process should consider how to manage their stocks to avoid stock-outs or wastage due to expiry of usable products from overstocking.

- There may initially be limited demand for alternative first-line, second-line or third-line regimens, particularly those containing the newer medicines DTG, DRV/r and RAL. Pooling orders from several buyers is recommended to increase the volumes to be ordered and ensure that suppliers can deliver and adequately respond to the demand.

Transitioning to the recommended preferred regimens and preferred formulations

Programmes should plan carefully and discuss with their suppliers the pace at which increased quantities of TDF- and EFV-based products can be made available. This will require a graduated process of transition to the "test and offer" paradigm and for alternative scale-up targets. To ensure that supply is available to meet the anticipated demand, a phased programme is highly recommended. Suggested approaches are the following.

- Initiate new patients eligible for ART on TDF-based regimens, with preference for FDCs of TDF + 3TC + EFV or TDF + FTC + EFV.

- Include buffer stocks in supply plans and liaise closely with suppliers and the major pooled procurement mechanisms to understand global demand patterns and act accordingly.

Programmes should stop procuring the following:

- Stavudine (d4T): in light of the cumulative mitochondrial toxicity of d4T, it should no longer be procured, and people currently receiving d4T-based regimens should transition to a TDF-based regimen.

- Didanosine (ddI): ddI should no longer be procured as it is no longer recommended as an alternative nucleoside reverse-transcriptase inhibitor (NRTI) in adult and adolescent second-line regimens due to toxicity, lower efficacy and inconvenient dosing requirements.

People currently receiving first-line AZT- and/or NVP-based regimens should be transitioned to the preferred first-line FDCs in a phased manner to enable the use of current stocks and orders and taking into account the speed at which increased deliveries of TDF products can be ordered and delivered.

In areas with a high prevalence of HIV-2 infection, the procurement and use of formulations with two-drug FDCs (TDF with 3TC, TDF with FTC and AZT with 3TC) might be a preferred option, as this provides the flexibility to combine the NRTI backbone with protease inhibitors (PIs) or integrase strand transfer inhibitors (INSTIs) in first- and second-line therapy for people living with HIV-2 infection.

In the case of newer products such as DTG, DRV/r and RAL or existing products of low demand (e.g. for second- or third-line regimens), where feasible and practicable, procurement managers should consider pooling their demand with other domestic programmes, neighbouring countries or other regional programmes and/or collaborating with major purchasers to form a part of total orders that meet manufacturers' production batch sizes. Shelf-life, storage facilities and consumption patterns permitting, PSM managers should also plan to hold larger buffer stocks for essential products in low demand. In the case of newly introduced products, it should also be assumed that initial orders may require longer lead times.

Supply chain considerations for implementation of less frequent ARV drug refills, community ART delivery and lay providers distributing ARV drugs

There are several supply chain issues that programme managers and policy-makers need to consider when adopting and implementing new service delivery recommendations regarding less frequent ARV drug pickup, the use of community ART delivery models and lay providers distributing ARV drugs. PSM managers and policy-makers should examine the current ARV drug supply chain model and its performance to see what adaptations are needed to enable the supply chain to support these new recommendations. As no "one-size-fits-all" supply approach will meet the needs of differentiated care models, the local supply chain must be agile enough to serve a variety of service delivery models, including at the community level. In addition, programme managers should consider taking a phased approach that takes into account the following:

- the additional ARV drugs needed at pickup sites, including the provision of a safety buffer stock;

- the number of patients to be served by multi-month (3- to 6-month) prescribing and the regimens they currently use;

- the capacity of local distribution sites to safely and securely store and handle the additional ARV drugs;

- the additional reporting needed by the logistics information system to track the ARV drugs through these sites, including at community level;

- any ARV drug shelf-life constraints;

- overall supply chain performance where the recommendations will be implemented; and

- incorporation of additional ARV drug requirements in the country's annual quantification, financing, procurement and supply plans.

Besides the quantity of additional products required to implement new recommendations, the manufacturing lead time may influence the pace at which programmes can take new recommendations to national scale.

6.13.4 Special considerations for paediatric ART

These guidelines make no changes to the first-line paediatric ART regimen recommended in 2013 (*see* section 4.4.4 "First-line ART for children three to ten years of age" and section 4.4.5 "First-line ART for children younger than three years of age"). RAL is newly recommended in second-line paediatric ART for children younger or older than 3 years after failure of a first-line regimen containing LPV/r (*see* section 4.8.3 "Third-line ART").

Transitioning to recommended preferred regimens and preferred formulations

In general, these guidelines recommend once-daily FDCs to facilitate procurement and supply chain management, logistics and adherence. Additional logistic and programme factors should be addressed for national programmes to select optimal formulations. To ensure smooth implementation of recommended first-line regimens for children, it is critical for policy-makers and implementers to consider the availability of paediatric ARV drug formulations.

National programmes are urged to limit the procurement of ARV drug products for children to formulations on the Optimal Paediatric Formulary of the IATT on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children. Complying with the IATT Optimal Formulary based on WHO recommendations will help to simplify the supply chain and aggregate global demand to stabilize the global supply of ARV drugs for children.

Programmes should not procure the following paediatric formulations:

- Stavudine (d4T): d4T is no longer recommended due to its cumulative mitochondrial toxicity. Children currently receiving d4T-based regimens should transition to preferred paediatric ART regimens.

- Didanosine (ddI): ddI should no longer be procured as it is no longer recommended as an alternative NRTI in paediatric second-line regimens due to toxicity, lower efficacy and inconvenient dosing requirements.

When available, age-appropriate FDCs for any recommended regimen are preferable.

Dispersible tablets (also known as tablets for oral solution) are the preferred solid oral formulations.

Oral liquid formulations should be avoided in favour of solid oral dosage forms when available:

- FDCs of abacavir (ABC) + 3TC (60 mg + 30 mg and 120 mg + 60 mg) are available as dispersible scored tablets recommended as the preferred option in the Optimal Paediatric Formulary.

- Three formulations of lopinavir (LPV)/r are available for use among young children: LPV/r 100 mg/25 mg heat-stable tablet for children >10 kg who are able to swallow whole tablets; LPV/r pellets 40 mg/10 mg to be taken with soft food such as porridge

(newly available in 2015); and LPV/r oral liquid 80 mg/20 mg per 1 ml for use among infants. The IATT has produced a fact sheet on how to administer and use the new dosage form of oral pellet LPV/r 40 mg/10 mg *(187)*.

In light of the continuing challenges of ensuring the availability of ARV drug formulations for children, the IATT provides guidance on optimal ARV drug products for children to promote a secure and sustainable supply. A new revision took place in December 2015 after these guidelines were finalized, and an updated version will be available at http://www.emtct-iatt.org/resources.

6.13.5 Checklist for introducing new products and phasing out old ones

These guidelines recommend new ARV drug formulations for adults and adolescents as well as for paediatric ART. Introduction of new medicinal or diagnostic products is one of the most complex and unpredictable activities in any HIV programme and, as such, presents a heightened challenge for policy-makers, PSM managers and manufacturers. When planning the introduction of new products, the following PSM-related factors should be taken into account.

- Is the product subject to patent or other intellectual property protection that would restrict access to generic formulations of the product in your country? In many middle-income countries, access to generic versions of ARV drugs is restricted. Should this be the case, advice is available from the Public Health, Innovation and Intellectual Property Team of the WHO Department of Essential Medicines and Health Products.

- Is the product registered for use in your country? If not, consider obtaining a temporary waiver and, in the meantime, accelerate the official registration processes for future procurement. This information should be available from the national drug regulatory authority. While it is the responsibility of the manufacturer to arrange registration, registering a drug can be a lengthy and expensive process.

- What is the forecasted demand for the product, including the anticipated pace of adoption? The pace of adoption is very difficult to forecast accurately, and ordering and delivery schedules must take into account this unpredictability. Faster adoption may lead to stock-outs if the procurement plan has not taken this into account, whereas a slower pace could lead to expiry of stocks if the procurement plan assumed a faster adoption. PSM managers will need to monitor consumption closely and have risk mitigation strategies in place. In case of faster adoption, suppliers should be asked to be prepared to respond to urgent orders. In case of slower adoption, suppliers should be asked to deliver quantities gradually according to country requests until all the quantities ordered are consumed. Ordering in large volumes has the advantage of economies of scale, but suppliers should be flexible enough to send deliveries according to national demand to prevent wastage by expiry. PSM managers are encouraged to work with HIV programme managers in formulating risk mitigation plans to account for the difficulty of accurate forecasting of demand and the pace of adoption.

- How will introduction of the new product impact the use of existing medicines or diagnostics? Unless it is recommended that a product be stopped due to severe toxicity or other reasons, PSM managers should always plan to optimize the use of existing stocks and orders before a full switchover to new products, in order to avoid wastage.

- How will purchase of the new product affect procurement budgets? PSM managers may wish to consult with major global purchasers to gauge the expected price so that quantities of existing and new products can be accommodated within the available budget. In some cases, lack of sufficient funds has delayed a full transition to new products that were more expensive or led to stock-outs of existing products.

- What is the shelf-life of the product and how might this affect the procurement strategy and the in-country distribution of the product? The "first expiry, first out" principle should be applied in stock management and distribution. Products with a shorter shelf-life should be distributed to treatment sites and dispensed as quickly as possible to allow their consumption before their expiry.

- Does the new product require any special handling or storage, such as temperature control? Consider adjusting the capacity and storage conditions of current facilities.

- What is the production status of the new product? What minimum order will the supplier accept and what is the anticipated lead time from order placement to delivery? In the case of products in lower demand, manufacturers may be willing to only commit to production once they are assured of commercially viable orders.

- If small volumes of new products are required, PSM managers should consider collaborating with neighbouring countries or global pooled procurement mechanisms to reach total order volumes that are viable for the manufacturers. This strategy may be particularly appropriate for second- and third-line formulations and for paediatric ARVs.

- Policy-makers and PSM managers may wish to consult with global purchasers and other knowledgeable entities to gain market intelligence on new formulations while they develop strategies to introduce these new formulations through national procurement.

6.13.6 Useful PSM resources

This document does not cover all technical issues related to PSM. The PSM Toolbox contains PSM tools that can be searched by technical area and by publishing organization: http://psmtoolbox.org/en.

6.14 Laboratory and diagnostic services

6.14.1 Overview

Implementing recommendations in these guidelines will require increased access to laboratory and diagnostic services.

To ensure that diagnostic services are accurate and reliable, relevant QA systems need to be developed and strengthened. Within a country, a multiplicity of diagnostic settings may exist, such as laboratories, maternal and child health clinics, HIV testing and counselling sites and community-based testing. A multipronged and networked approach to selecting diagnostics and laboratory systems should therefore be planned and adopted. Because many new diagnostic tests and point-of-care systems are entering the market, the use of only high-quality diagnostics and equipment needs to be ensured. Strategic planning for proper placement and harmonization of testing platforms should be carried out to ensure appropriate use and cost–effectiveness.

Effective laboratory and diagnostic services require sound leadership and governance to enable the following activities *(188)*:

- strengthening and expanding laboratory and diagnostic services;

- supporting a dedicated specimen referral system;

- appropriate availability of CD4 count testing;

- increased access to HIV viral load testing for all people on ART, for monitoring purposes;

- supporting the expansion of diagnostic services to include testing at the point of care;

- training and certifying health-care workers who perform testing;

- ensuring high-quality diagnostics and plans for implementing these, including QA; and

- ensuring appropriate deployment of diagnostic technologies to increase their efficient and optimal use.

WHO and the United States Centers for Disease Control and Prevention (CDC) have developed a handbook on QA approaches to point-of-care testing and for laboratories in low- and middle-income countries *(191)*. Figure 6.4 shows the three-phase approach to QA of laboratory programmes.

Fig. 6.4. Three phases of laboratory quality assurance

Phase 1: Planning quality assurance for HIV-related point-of-care testing

1. Engage leadership
2. Establish the national coordination team for the quality assurance of point-of-care testing
3. Define roles and responsibilities
4. Develop or review policies and incorporate quality assurance into the national plan
5. Define standards for the quality of point-of-care testing
6. Conduct situation analysis
7. Develop and implement the plan
8. Plan financial and human resources
9. Select and assess sites
10. Select products

Phase 2: Implement quality assurance for HIV-related point-of-care testing

1. Improve training and ensure that all point-of-care testers are certified
2. Strengthen and innovate the documentation related to quality assurance
3. Implement quality assurance process control
4. Strengthen the supply chain for quality assurance
5. Supervise and certify the sites

Phase 3: Evaluate, improve and sustain quality assurance for HIV-related point-of-care testing

1. Post-market surveillance
2. Use monitoring data for decision-making
3. Advocacy and communication of best practices
4. Encourage social entrepreneurship and public-private partnerships
5. Increase country ownership
6. Operational research

Plan · Define · Implement · Monitor · Evaluate · Improve

Quality assurance cycle
Ensuring accurate results

Source: WHO, US CDC. Improving the quality of HIV-related point-of-care testing: ensuring the reliability and accuracy of test results. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/toolkits/handbook-point-of-care-testing/en/).

6.14.2 Strengthening and expanding laboratory and diagnostic services

The following areas are important for strengthening the network of laboratory and diagnostic services in order to implement the recommendations in these guidelines:

- national laboratory strategic plans and policies;

- evaluating diagnostics for their performance and operational characteristics to validate testing algorithms (with backup options) before introduction;

- carrying out strategic planning in order to properly place and harmonize testing platforms to ensure appropriate use and cost–effectiveness;

- expanding current laboratory networks to support and monitor the decentralization and integration of testing services and to provide access to testing when diagnostic services are unavailable at service delivery sites;

- allocating appropriate resources to ensure the availability of testing services, including human and financial resources; and

- guidance on operations and service delivery.

6.14.3 Supporting a dedicated specimen referral system

Laboratory referral systems and procedures for collecting and processing specimens need to be strengthened to increase access to viral load and other testing (e.g. CD4 testing at the point of care and EID). Providing for and strengthening a dedicated, efficient, safe and cost-effective specimen referral system requires reliable specimen transport with adequate conditions for whole blood, plasma and dried blood spot specimens as well as for rapidly and dependably reporting test results back to the referring site with linkage to care. Rapid reporting of results is essential for timely care.

6.14.4 Increasing access to HIV viral load testing

These guidelines recommend the use of viral load testing to monitor treatment response and diagnose treatment failure and the use of dried blood spot samples for viral load testing. This will require ongoing strengthening of existing laboratory services and phased expansion of monitoring services in peripheral facilities. It may involve:

- strengthening and leveraging existing EID networks;

- ensuring that laboratories have adequate infrastructure, technical expertise and QA and QI programmes;

- ensuring an appropriate mix of high-volume centralized laboratory testing and testing at the point of care for facilities in remote locations; and

- use of dried blood spot specimens to increase access to viral load testing.

6.14.5 Planning for appropriate use of CD4 count testing as access to viral load testing increases

As countries move to eliminate CD4 count-dependent treatment initiation thresholds and viral load monitoring replaces monitoring with CD4 cell count, it is anticipated that the

demand for CD4 count testing will decrease. As this transition takes place, programme, laboratory and PSM staff should take into account the following programmatic considerations.

- As demand decreases, reductions in CD4 count testing capacity can be staged through several strategies based on site-level demand, age of the instrument and failure rates.

- Although sample referral networks for CD4 cell count and viral load testing may overlap, the sample types require different transport capabilities. Programmes need to ensure adequate network capability for sample referral for viral load testing prior to scaling down CD4 count testing.

- Programme planning should include a realistic transition of financial support from CD4 count testing to viral load monitoring. Cost savings may not be evident immediately, as the cost per test for CD4 count testing will increase as volumes decrease.

- Quantification and forecasting (active supply planning) will be essential to account for commodity shifts. This is particularly important in the early phases of the transition when historical data will not reflect current commodity needs. Supply chain needs, including cold-chain transport and storage, must also be considered during the transition.

- Even in settings with full access to viral load testing, CD4 cell count testing capability will continue to be needed as part of HIV programmes for baseline risk and other clinical assessments. Depending on the context, as the transition to viral load monitoring from CD4 count testing for initiation and monitoring progresses, programmes may wish to consider centralizing the continued use of CD4 count testing.

6.14.6 Expanding diagnostic services to point-of-care settings

Decentralizing laboratory and diagnostic services requires that all aspects of testing be in place before services are implemented. This includes:

- using only high-quality, evaluated and reliable diagnostic tests;

- supervising and monitoring point-of-care testing for quality and reliability;

- implementing a strategy for managing the supply chain and equipment service;

- establishing data management systems for timely identification of quality issues; and

- regional and national data reporting.

6.14.7 Ensuring appropriate deployment of diagnostic technologies

The WHO diagnostic use survey demonstrated that several technologies are available in the countries that reported their diagnostic usage. Their utilization is lower than 50% of their capacity for several reasons:

- Deployment of high-throughput instruments in low-volume settings with no appropriate plan for sample transportation: CDC and WHO have produced a strategic planning manual since the Maputo Declaration on Strengthening of Laboratory Systems to ensure that equipment is deployed in a tiered laboratory network based on the volume of tests at the testing sites (Table 6.3).

Table 6.3. Tiered laboratory network at various levels of the health-care delivery system

Health-care delivery level	Laboratory service	Quality assurance actions	Human resources
National reference laboratory	• Enzyme immunoassays for diagnosis • Higher throughput CD4 count testing • HIV molecular technologies, including HIV viral load testing and quantitative and qualitative early infant diagnosis • HIV resistance testing	• Validating point-of-care testing • Training and certification • Coordinating quality assurance • Proficiency testing • Confirmatory testing • Collecting and analysing data • Taking corrective action	• Senior laboratory specialists • Senior laboratory supervisors • Trainers • Senior technicians
Regional or provincial reference laboratory	• Enzyme immunoassays for diagnosis • Higher throughput CD4 count testing • HIV molecular technologies, including HIV viral load testing and quantitative and qualitative early infant diagnosis	• Rapid diagnostic tests, point-of-care tests for CD4 count, early infant diagnosis and viral load • Coordinating regional training and quality assurance • Collecting and analysing data • Taking corrective action	• Laboratory supervisors • Trainers • Senior technicians
District-level laboratory	• Enzyme immunoassays for diagnosis • Low-throughput CD4 count testing • Chemistry, haematology and microbiology	• HIV rapid diagnostic tests, point-of-care tests for CD4 count testing, early infant diagnosis and viral load • Supervising sites • Corrective action	• Laboratory technicians • Laboratory assistants
Primary care setting	• HIV rapid diagnostic tests and other point-of-care tests • Collecting dried blood spots	• HIV rapid diagnostic tests, point-of-care tests for CD4 count testing • Collecting dried blood spots for point-of-care tests and early infant diagnosis	• First-level trained health workers such as nurses and clinical officers
Community-based and community outreach	• HIV rapid diagnostic tests • Collecting finger-prick samples for testing	• HIV rapid diagnostic tests	• Community health workers

Source: WHO expert meeting report on short, medium, longer term product development priorities for HIV-related diagnostics, 6–7 June 2012, Geneva, Switzerland (http://www.who.int/hiv/pub/meetingreports/hiv_diagnostics/en) and Handbook for improving the quality of HIV-related point-of-care testing: ensuring the reliability and accuracy of test results, 2015 (http://www.who.int/hiv/pub/toolkits/handbook-point-of-care-testing/en).

- Frequent stock-out of reagents: WHO has developed a manual for efficient procurement of essential equipment and laboratory commodities to support national programme managers when they are estimating their procurement (http://apps.who.int/iris/bitstream/10665/180980/1/9789241509183_eng.pdf?ua=1).

- Lack of maintenance and repair needs: maintenance should be embedded in the contractual agreement with the manufacturers supplying diagnostics.

- Lack of installation of purchased equipment due to lack of trained personnel or adequate space for the size of the equipment: prior strategic planning is essential to ensure that appropriate space and a trained laboratory technician are ready when the procured equipment is delivered for use in the country.

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MONITORING AND EVALUATION

7

7 MONITORING AND EVALUATION

7.1 Introduction

As countries adapt and implement these guidelines, monitoring and evaluation (M&E) frameworks and systems will need to collect and analyse information to support the implementation and maximize the impact of the new recommendations. M&E will help programme managers assess the effectiveness of interventions and linkages between services along the cascade of testing, treatment and care for HIV and associated conditions. Such information is essential to detect and respond to bottlenecks or gaps in programme performance and to adequately characterize and respond to patient attrition. Patient monitoring systems are also important to support people receiving treatment over time and as they move between clinics and districts, to ensure retention in care. As programmes mature, monitoring is also essential of individual- and population-level outcomes, such as toxicity and adverse events, drug resistance, viral suppression, mortality, survival and incidence, to assess and optimize the impact of country programmes.

Data can be collected in many ways, including from routinely reported data from all facilities or sentinel sites; district health information systems; population-based surveys; surveillance data; observations from cohorts of people living with HIV; and periodic evaluation. Programme inputs and processes can also be monitored through facility surveys or updated lists of service availability; documenting the availability and training of human resources; and monitoring the availability of HIV medicines and diagnostics at various geographical and facility levels. Special studies can be considered where routine monitoring is not feasible or appropriate.

In considering how best to collect critical data, efforts should be made to review current monitoring systems, such as better linkages between the monitoring of services for TB and ART, and integrating HIV drug resistance (HIV-DR) monitoring into routine health information systems.

Involving civil society in M&E activities is also critical to better understand successes and failures, especially in assessing the determinants, perceptions, values and experiences of people living with HIV, key populations and the broader community in accessing and using services.

7.2 Selection of indicators

The 2015 WHO *Consolidated strategic information guidelines for HIV in the health sector* provide comprehensive guidance on monitoring national and global health sector responses to HIV, including the use of ARV drugs for treatment and prevention *(1)*.

The guidelines propose 50 national, including 10 global indicators to help national HIV programmes monitor and evaluate HIV programme performance and assess its impact along the cascade of prevention, treatment and care.

The 50 **national programme indicators** can be used to describe what the status of the HIV epidemic is and identify how the HIV response could be improved. Countries should select relevant indicators to be included in the national M&E system, as appropriate to the country context and the services that are delivered. Typically, countries will opt to collect most of these indicators to obtain a focused but comprehensive overview that informs tracking and management of their HIV programme. To ensure comparability, WHO recommends that reporting from countries and donors adhere to the same definitions of these indicators, which have been agreed with major partners and in extensive consultation with countries. National programme indicators that are of particular importance to the implementation of these guidelines include those that relate to the following:

• services for key populations;

• post-exposure and pre-exposure prophylaxis (PrEP);

• HIV testing services;

• linkage, enrolment and retention in care;

• provision of ART;

• treatment and care for pregnant and breastfeeding women (prevention of mother-to-child transmission [PMTCT])

• paediatric HIV treatment and care;

• TB/HIV coinfection;

• other comorbidities and coinfections;

• toxicity monitoring;

• HIV-DR;

• viral suppression; and

• impact evaluation (mortality, prevalence and incidence).

Detailed indicator tables for each of these programme areas along the testing, treatment and care cascade may be found in Chapter 2 of the 2015 WHO *Consolidated strategic information guidelines for HIV in the health sector*.

The **10 global indicators** are a subset of the 50 proposed national indicators and provide the essential information needed to identify key issues for improving the health sector response to HIV. Each of these indicators reflects a key step in the HIV prevention, treatment and care cascade. Together, the 10 global indicators represent the **minimum** set of information needed for global reporting. To provide a common platform for global monitoring and comparison among countries, national managers should include the 10 global indicators among the national indicators selected for their M&E framework. The 10 indicators are shown in Table 7.1.

Table 7.1. Ten global monitoring indicators of the health sector response to HIV

Indicator	Relevance to cascade	Rationale for global monitoring	Disaggregation	Sources and issues
1. People living with HIV Number and % of adults and children living with HIV N: Number of people living with HIV D: Population	Target population for the HIV care cascade. Serves as numerator or denominator for several other estimates along the cascade.	Reflects epidemic and service needs	Sex, age, key population,[1] pregnancy status, ART eligibility, HIV prevalence among TB patients (LINK.5), location	NEEDS.1[2] Derived from surveillance, surveys and programme data, "know your epidemic" review, internationally consistent modelling
2. Domestic HIV financing % contribution of domestic public expenditure to total HIV expenditure N: HIV domestic public expenditure D: Total HIV expenditure	Important for the sustainability of financing the response to HIV	Used to assess government commitment and ownership and to identify funding gaps	Key population and other target population, programme categories such as prevention, treatment and care	RES.31 Health accounts and national AIDS spending assessment can help capture expenditures and track trends.
3. Prevention by key population a) for sex workers, % reporting condom use with most recent client b) for men who have sex with men, % reporting condom use at last anal sex with a male partner c) for people who inject drugs, needles and syringes distributed per person d) for general population, % of women and men age 15–49 years who used a condom during last sexual intercourse	Reflects prevention interventions in key population groups and the general population to control transmission risk and prevent new HIV infections	Condom use with non-regular or high-risk sexual partners and clean needle and syringe provision reflect key interventions and can be consistently measured across all countries.	Sex (female, male, transgender), age, location	a) PREV.1.a b) PREV.1.b c) KPOP.2 d) PREV.1.d Collected through surveys. Needs to be interpreted based on coverage and sampling of survey. Include use of PrEP where relevant.

[1] In many settings, key population-specific data cannot be collected from routine programme monitoring; surveys are required.

[2] Indicator labels in this column, such as NEEDS.1, represent specific indicators referred to in the 2015 WHO Consolidated strategic information guidelines for HIV in the health sector.

Table 7.1. (continued)

Indicator	Relevance to cascade	Rationale for global monitoring	Disaggregation	Sources and issues
4. People living with HIV diagnosed % of people living with HIV who have been diagnosed N: Number of people living with HIV who have been diagnosed and received their results D: Number of people living with HIV	Diagnosis and awareness of HIV-positive status are precursors to care and treatment. Also, HIV testing may influence adoption of preventive behaviour among both HIV-positive and HIV-negative people.	HIV testing is key to effective responses to HIV.	Sex, age, key population, pregnant women, TB patients, other target populations, location	HTS.1 The proportion of people living with HIV in specific populations who have been tested should also be globally monitored, including (a) key populations, (b) pregnant women, and (c) TB patients. Information captured through programme data, population-based surveys and key population-focused special surveys
5. HIV care coverage Number and % of people living with HIV who are receiving HIV care (including ART) N: Number of people living with HIV who received HIV care in the past 12 months OR CD4 count or viral load testing OR currently receiving ART D: Number of people living with HIV	Reflects linkage to care by measuring HIV care coverage and progress towards universal access to care (including ART)	Helps to track global trends in coverage of care and treatment across populations of people living with HIV	Sex, age, key population, treatment status (i.e. pre-ART or ART), location	LINK.2 The numerator is based on programme data counting people living with HIV, who receive a clinical or laboratory assessment or are on ART, as proxies for receipt of care. The denominator is usually estimated.
6. Currently on ART Number and % of people living with HIV who are receiving ART N: Number of people living with HIV who are currently receiving ART D: Number of people living with HIV	Measures the extent to which needs for ART are met	Tracks trends in ART coverage nationally and globally	Sex, age, key population, regimen, location	ART 3. The numerator is based on programme statistics; the denominator is usually estimated using an internationally consistent model. For consistency of global reporting, people living with HIV is used as a denominator. For national use, coverage should also be calculated by applying national eligibility criteria to estimate the denominator (ART.2).

Table 7.1. (continued)

Indicator	Relevance to cascade	Rationale for global monitoring	Disaggregation	Sources and issues
7. ART retention % of people living with HIV and on ART who are retained on ART 12 months after initiation N: Number of ART patients alive and on ART at 12 months (or 24, 36, 48, 60 months, etc.) after initiating ART D: Number of patients initiating ART up to 12 months (or 24, 36, 48, 60 months) before the beginning of the reporting year. This includes those who died since starting therapy, those who have stopped therapy and those lost to follow-up as of month 12 (or 24, 36, 48, 60 etc.).	Once on ART, treatment is lifelong. Retention on ART is important to achieve the desired outcomes of the HIV care cascade.	Indicates quality of services and continuing engagement of people living with HIV on ART	Sex, age, pregnancy or breastfeeding at initiation; optional: coinfection with TB also by 24, 36 months and longer periods	ART.5 Follows cohorts of people living with HIV initiating ART. Systematic analysis of those lost to follow-up is required to determine true outcomes, including mortality patterns.
8. Viral suppression % of people living with HIV who have suppressed viral load N: Number of people living with HIV and on ART who have suppressed viral load (<1000 copies/ml). Population level denominator: Number of people on ART in the past 12 months Programme-based denominator: Number of people on ART who had a viral load measurement in the past 12 months	Gauges the proportion of people on ART who have suppressed viral load. A large proportion with suppressed viral load implies a low rate of onward transmission. Viral load suppression among a cohort 12 months after ART initiation should also be monitored (VL.1).	Viral suppression is an indicator of treatment success and reduced potential for transmission.	Sex, age, location	VLS.3 Provides a cross-sectional view of viral load suppression among people on ART. Can also be assessed by time since initiation of ART, as a cohort. Suppressed viral load is defined as <1000 copies/ml.

Table 7.1. (continued)

Indicator	Relevance to cascade	Rationale for global monitoring	Disaggregation	Sources and issues
9. AIDS-related deaths Number of AIDS-related deaths per 100 000 population N: Total number of people who have died of AIDS-related illness in a 12-month period D: Population (100 000)	Measures the ultimate negative outcome of past incidence and care and treatment failure	Shows trends in deaths among people with HIV; can be compared with other causes of death	Sex, age, HIV-positive TB, location	IMP.1 Analysis of sample and site mortality data Ongoing improvement of vital registration will facilitate measurement of this indicator. Number of deaths can be compared to the number of people living with HIV to review trends.
10. New infections Rate of new HIV infections: number of new HIV infections per 1000 uninfected population N: Number of new infections D: 1000 uninfected population, which is the total population minus people living with HIV.	Reflects the impact of HIV prevention and treatment	Important for monitoring epidemic trends, detecting possible shifts in pattern and projecting needs	Sex, age, mode of transmission (for children), key population, other target populations, location	IMP.2 Estimates should be calculated through internationally consistent modelling, cohorts and age-specific HIV prevalence data. Predicts the direction of epidemics.

Source: Consolidated guidelines for strategic information for HIV in the health sector. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en).

7.3 Data collection and disaggregation

Disaggregation of data by age, sex, key population, location and pregnancy and breastfeeding status is critical to assist in the analysis of selected indicators. Disaggregation makes it possible to focus the country's response to achieve maximum impact.

Confidentiality must be maintained for all collection of data, specifically for key populations, who face significant stigma and discrimination. All data should be stored securely and staff collecting and storing data correctly trained to maintain confidentiality.

7.4 Reviewing and strengthening monitoring and evaluation systems

The recommendations in these guidelines may require certain adaptations to the M&E system, including:

- consolidating and prioritizing indicators for consistent reporting, as M&E plans are updated;
- investing in data sources and surveillance priorities to strengthen data;
- planning disaggregation and building analysis capacity to assess data in a linked manner along the health sector cascade;
- using data for decisions within regular programme reviews;
- evaluating the impact of each stage of the cascade on outcomes to prove and improve the response; and
- adapting M&E systems to support outcome assessment for differentiated models of care, including patient identifiers for improved follow-up and tracking.

Chapter 3 of the 2015 WHO *Consolidated strategic information guidelines for HIV in the health sector* provides guidance on the five key sources of strategic information on HIV in the health sector (Box 7.1). The crucial elements for measuring the cascade of care will depend on the integration of different sources of data. Routine patient monitoring and case reporting form the backbone of the data required to measure the cascade of services over time, and as patients move between facilities. Robust M&E systems that can accurately measure the cascade of care and address the new recommendations in these guidelines will require:

- improving the monitoring of enrolment and retention in HIV care;
- accurate accounting of transfers and losses;
- updating data elements required for patient monitoring in line with new recommendations (such as treating all people with HIV regardless of CD4 count, provision of PrEP, changes in regimens, viral load monitoring and frequency of clinic and pharmacy visits);
- revisiting disaggregation categories and links and synergy among systems for monitoring ARV drugs for PMTCT, TB and ART; and
- moving to electronic systems where feasible.

Box 7.1. Overview of the five key sources of strategic information on HIV in the health sector

1. FACILITY AND OUTREACH REPORTING SYSTEMS
(continuously collected minimum datasets)
a. Patient monitoring data: extracted from individual patient records. Data are entered into electronic databases or in paper-based systems, transferred to written registers and aggregated on routine reporting forms. Includes data from laboratory and pharmacy records.
b. Case reporting data: from routine surveillance, based on newly diagnosed HIV cases reported to the central level by health facilities and providers, preferably as individual electronic records with key information (age, sex, transmission mode, CD4 count and viral load at diagnosis).
c. Outreach data: based on records maintained by NGOs conducting outreach and/or community health and outreach workers, who may or may not be linked to a facility, of peer education, HIV testing (or referrals) and linkage to care for specific populations, for example, key populations, pregnant women and HIV-exposed infants, or in specific locations.

2. ADMINISTRATIVE SOURCES
(routine, periodic or one-time data collection)
a. Financial and health systems data: budgets, financial records, health accounts (HA), national AIDS spending assessment (NASA), procurement and supply management system data, human resources data and key policies related to HIV, prevention, treatment and care.
b. Facility list (with unique facility IDs).

3. POPULATION-BASED SURVEYS
(periodically collected)
a. General population: for example, Demographic and Health Survey (DHS), AIDS Indicator Survey (AIS), Multiple Indicator Cluster Survey (MICS)
b. Key populations: integrated biological and behavioural surveillance surveys (IBBS).

4. FACILITY ASSESSMENTS
(periodically collected)
a. Facility census or survey: for example, service availability and readiness assessment (SARA), service provision assessment (SPA), surveys of pre-treatment HIV drug resistance (PDR) and acquired HIV drug resistance (ADR).
b. Sentinel surveillance data collected over time at sentinel sites.

5. VITAL REGISTRATION
(continuous, compulsory recording)
a. Civil registration system data: birth and death records; death records may include information on cause of death.

Source: Consolidated guidelines for strategic information for HIV in the health sector. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en).

The relationship between these five key sources of strategic information and the 10 key global indicators of the cascade is shown in Fig. 7.1.

Figure 7.1. Global indicators for the health sector response to HIV
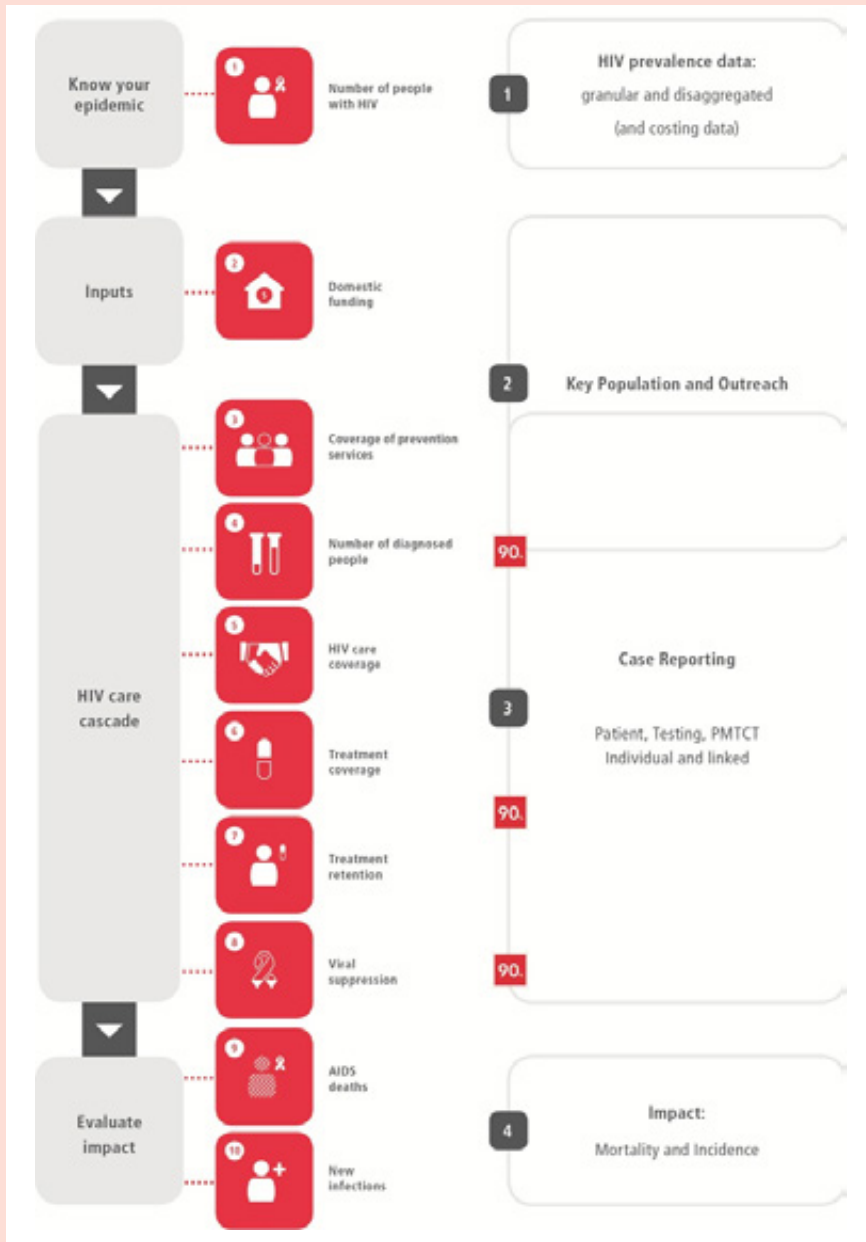
Source: Consolidated guidelines for strategic information for HIV in the health sector. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en).

7.5   Evaluation, including impact and programme performance

The ultimate goal of M&E is to provide data for decision-makers to use at all points of the HIV programme cycle. Regular programme reviews allow data to be used for decisions and help to inform policy to improve the delivery of prevention and treatment services. Routine monitoring should therefore be complemented by systematic evaluations and programme reviews to assess the performance and effects of HIV programmes, either comprehensively or with respect to specific priority areas. Social science and implementation research are also important to assess perceptions and values of service recipients and communities, including the barriers and facilitators that people encounter and their experiences in the delivery and receipt of services.

7.5.1   Analysis of the cascade

The defined indicators support analysis across the cascade of testing, treatment and care for people living with HIV. Cascade analysis helps to identify trends, progress, gaps and bottlenecks in service delivery and to develop solutions and improvements. The cascade shown in the 2015 WHO strategic information guidelines allows individual indicators to be linked to each other and to outcomes and impact. Cascade analysis can be cohort based or cross-sectional.

Information needs vary across levels of the national health-care system, and all national strategic plans for HIV should include an explicit data use plan to assist in the effective use of data for decision-making.

Regular programme reviews should assess each stage of the testing, prevention and treatment cascade to identify and measure progress, gaps and relations to trends in incidence and mortality.

7.6   Other key monitoring considerations

7.6.1   ARV toxicity monitoring

People taking ART may develop toxicity to one or more ARV drugs or to other drugs that they are taking. The major ARV-related toxicities are described in section 4.6.2. As more people experience earlier and prolonged exposure to ARV drugs, toxicity monitoring needs to become a basic component of treatment and prevention programmes. ARV-associated toxicities are among the most common reasons reported for non-adherence to ART, treatment discontinuation or substitution of drugs. Routine monitoring provides data on the incidence and clinical significance of serious ARV toxicities and their impact on adherence, patient outcomes and retention. WHO recommends that routine monitoring be complemented by active sentinel toxicity surveillance through special studies and surveys at sentinel sites.

WHO recommends that countries use a standardized approach to integrate toxicity monitoring into national M&E systems. This approach defines a minimum set of data elements for reporting on the magnitude of toxicities and their impact on treatment discontinuation.

Routine monitoring for ARV toxicity

The key indicator for routine toxicity monitoring is "the percentage of patients on ART with treatment-limiting toxicity, defined as life-threatening illness, death, hospitalization, disability or resulting in treatment discontinuation or substitution". In 2015, WHO designated this indicator for national programme monitoring. Disaggregation by ART regimen, sex, age, pregnancy, TB/HIV coinfection and, if data are available, key population, using data collected from patient clinical records and ART registers, provides additional information on populations at higher risk for toxicity due to environmental and behavioural factors, comorbidities and concomitant use of other medications. It is also important that toxicity be assessed in the context of overall reasons for treatment adherence and loss to follow-up.

Surveillance for ARV-related toxicity

When more data are needed to inform policy and improve treatment outcomes, WHO recommends strengthening surveillance of key ARV drug toxicities at sentinel sites. WHO provides guidance on conducting special studies in two main areas:

- active surveillance for specific ARV drug toxicities in existing sentinel cohorts. There is a benefit to nesting active toxicity surveillance within existing cohorts set up in a country for M&E purposes, as these cohorts have a reliable system for capturing clinical and toxicity data. A focus on one drug or the incidence of key toxicities will improve the accuracy of the assessment.

- surveillance of ARV toxicity during pregnancy and breastfeeding: this involves a prospective pregnancy-exposure registry for toxicity among pregnant women and neonates, a birth defects surveillance system for assessing birth outcomes, and prospective monitoring of cohorts of mother–infant pairs for toxicity from birth through the breastfeeding period.

WHO offers technical guidance and assistance on toxicity monitoring for routine M&E or through special surveys at http://www.who.int/hiv/topics/arv_toxicity/en/index.html.

A supplement to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs published in March 2014 includes specific chapters on incorporating toxicity surveillance into ART programmes and ARV toxicity surveillance during pregnancy and breastfeeding *(2)*. WHO has also developed a series of technical briefs on ARV toxicity monitoring *(3)*.

Special considerations for pregnant and breastfeeding women

WHO recommends that routine monitoring of ARV drug toxicity during pregnancy and the breastfeeding period focus on three areas:

- maternal adverse outcomes: monitoring treatment-limiting toxicities associated with ART in pregnant women;

- adverse birth outcomes: monitoring toxicity in the fetus in utero, manifesting as stillbirths, preterm births, low birth weight, major congenital anomalies or early infant deaths;

- adverse infant and child outcomes: monitoring health outcomes in infants and young children exposed to ARV drugs via breast milk, particularly any impact on growth and development. Adverse birth outcomes may be routinely monitored by integrating an additional indicator into the national M&E system. If preterm deliveries (<37 weeks) are

reported at a frequency equal to or higher than a rough estimate of their expected incidence, a formal assessment is warranted.

7.6.2 Drug resistance surveillance

As ART is scaled up, the emergence of significant population-level HIV-DR has become a global concern. HIV-DR threatens the effectiveness of ART and sustained reductions in HIV-related morbidity and mortality. As documented in WHO's global report on HIV-DR in 2012 *(4)*, levels of drug resistance have been slowly increasing. Resistance has not yet reached the level that endangers the effectiveness of ART programmes, but the trend is of concern and signals of high levels of resistance to NNRTI drugs among PLHIV starting ART are starting to emerge. Efforts to slow the development of HIV-DR are a priority. WHO recommends that HIV-DR prevention and assessment be integrated into every national HIV programme.

Routine monitoring of early warning indicators for HIV-DR

Comprehensive HIV-DR surveillance involves both routine monitoring with early warning indicators (EWIs) of performance of the ART programme in treatment facilities and conducting periodic HIV-DR surveys in specific populations. The WHO HIV-DR strategy *(3)* (developed in 2005 and revised in 2015) promotes the monitoring of key EWIs and using them for quality improvement. The EWIs are clinic-level quality-of-care indicators that alert clinic and programme managers to conditions favouring virological failure and the emergence of population-level resistance. Drug resistance may not necessarily result immediately if an indicator shows poor performance; however, achieving the best possible performance as measured by these indicators will help to minimize preventable HIV-DR and maximize long term population-level viral suppression. EWIs are included in the ART and viral suppression indicators recommended by WHO.

The EWIs of HIV-DR are:

- on-time ARV drug pickup (proxy for adherence)
- retention on ART at 12 months
- ARV drug stock-out
- viral load suppression at 12 months after ART initiation
- coverage of viral load testing.

WHO has recommended methods for making site-specific estimates of EWIs through a sampling of patient records. This guidance will be updated in 2016 to elaborate on operationalization of EWI data collection, including methods that will allow for nationally representative estimates through a random sampling of clinics providing ART.

The primary source used for EWI reporting should be routine programme data. However, routine data may not be optimally available. If the coverage of routine data is less than a certain percentage representative of the eligible population (such as the 70% or 80% used as a cut-off in some settings), clinic-level EWI results should not be aggregated to create a national estimate. Depending on the level of coverage of routine data, results may be useful at a subnational level for informing and improving local performance. Indicator analysis and action plans based on the results support optimization of HIV treatment and minimize the emergence of HIV-DR.

HIV drug-resistance surveys

In addition to routine monitoring of EWIs, periodic surveys in specific populations are important to inform the selection of regimens and the frequency of viral load monitoring monitoring and should be included in national HIV strategic plans. WHO provides detailed guidance on how to perform surveys for HIV-DR *(3)*. These periodic surveys allow nationally representative assessments of the prevalence of HIV-DR and tracking its evolution in four populations:

• people initiating ART (PDR), to inform the national choice of first-line ART, PrEP regimens and recommended frequency of viral load measurement (http://www.who.int/hiv/pub/drugresistance/pretreatment_drugresistance/en) *(6)*;

• people already on ART (ADR), to inform the selection of second-line regimens, with a survey in this population also providing nationally representative estimates of retention in treatment and viral load suppression (http://www.who.int/hiv/pub/drugresistance/acquired_drugresistance/en) *(5)*;

• people recently infected with HIV (transmitted HIV-DR), to document and characterize the transmission of drug-resistant virus;

• infants under 18 months of age, to inform selection of the first-line regimen for children.

WHO recommends that countries prioritize PDR and ADR surveys, and assess PDR every three years, for example, in years 1, 4 and 7, and ADR assessment in years 2, 5 and 8. Alternatively, the two survey types can be combined and conducted concomitantly. Countries should consider how best to sequence the surveys depending on the type of the epidemic and on the status and coverage of the national ART programme. HIV-DR data should be available to support national decision-making, especially when updating adult and paediatric ART guidelines.

The HIV drug resistance surveillance guidance 2015 update provides additional information on developing national strategies for monitoring HIV-DR *(3)*.

Comprehensive information on HIV-DR is available on the WHO website at http://www.who.int/hiv/topics/drugresistance/en/index.htm.

References

1   Consolidated strategic information guidelines for HIV in the health sector. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en/, accessed 5 October 2015).

2   Supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; March 2014. See Chapter 12. Surveillance of the toxicity of antiretroviral drugs during pregnancy and breastfeeding and Chapter 13. Surveillance of the toxicity of antiretroviral drugs within ART programmes. (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en/, accessed 19 October 2015).

3   HIV Drug Resistance Surveillance Guidance: 2015 UPDATE (http://apps.who.int/iris/bitstream/10665/204471/1/9789241510097_eng.pdf?ua=1) .

4   WHO HIV drug resistance report 2012. Geneva: WHO; 2012 (http://www.who.int/hiv/pub/drugresistance/report2012/en/, accessed 12 October 2015).

5   Surveillance of HIV drug resistance in adults receiving ART. Concept note. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/topics/drugresistance/protocols/en/, accessed 19 October 2015).

6   Surveillance of HIV Drug Resistance in adults initiating antiretroviral therapy. Concept Note. Geneva: World Health Orgnanization: 2014 (http:77www.who.int/hiv/).

PUBLICATION, DISSEMINATION AND EVALUATION

8

8 PUBLICATION, DISSEMINATION AND EVALUATION

8.1   Publication

These guidelines will be updated in full or in part every three years. As the evidence base or user needs change, consideration will be given to producing technical updates on specific subjects.

The guidelines will be disseminated as a print publication and electronically on the WHO website. The web supplements will contain all supporting documentation and evidence. A policy brief summarizes the new recommendations (http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en) and is supported by a variety of fact sheets on key topics. Dissemination will be supported by publication of selected systematic reviews and evidence in peer-reviewed journals.

8.2   Dissemination and implementation

WHO headquarters will work closely with the regional and country offices and implementing partners to ensure communication and country adaptation of the guidelines through regional and subregional meetings. As countries consider how to optimally implement these guidelines, the budgetary, human resource requirements and other health system implications should be analysed to identify which inputs and systems are currently available, and areas that require additional investment. Checklist 17.1 (Annex 17) outlines the critical issues for consideration. The implementation considerations included with each recommendation should be referred to in this process. All decisions should be made through open and informed processes involving all stakeholders and the meaningful engagement of people living with HIV (*see* checklist 17.2 [Annex 17]). Broad stakeholder engagement in policy design, implementation and M&E will help to ensure that the national adaptation of these guidelines results in HIV programmes that are legitimate, acceptable, effective, equitable and address community needs.

Treatment, care and support and national responses need to be considered within the broader health and development context. The sustainability and effectiveness of HIV programmes can be greatly enhanced by creating and strengthening linkages with other health and non-health programmes to achieve broad development gains *(1)*. National programmes need to identify an essential package of high-impact HIV interventions that cover the full continuum of HIV prevention, diagnosis, treatment and care services, include it in the national health benefit package and fund it at least partially through the national health financing system. The package needs to be adapted for different populations, locations and settings and regularly reviewed and updated as necessary. Realizing that it may not be possible to fund and implement the full range of

interventions and services immediately, an approach of progressive realization and phase-in of essential interventions should be adopted, progressively expanding the range of services offered and the populations covered and reducing out-of-pocket expenses for users.

The recommendations included in these guidelines will need to be considered within the context of the full range of HIV interventions and services, and more broadly, the overall national health benefit package. Where dedicated national HIV budgets exist, there will be a need to prioritize how HIV interventions are implemented. Where there is no dedicated national HIV budget, the priority of HIV interventions will need to be considered across all "essential" health interventions. To assist with this, there needs to be a clear set of criteria that can be used within the range of HIV interventions and services, and more broadly, for the whole national health benefit package.

WHO has developed a framework to assist with the sequence of implementation of HIV and other similar communicable disease programmes (Fig 8.1). The framework provides a structured approach to implementation considerations in the context of programme needs and available resources. Implementation tools will be published in conjunction with this guidance and will include useful tools for costing and planning, and country case studies.

Fig. 8.1. A logical framework for implementing policies in health and HIV
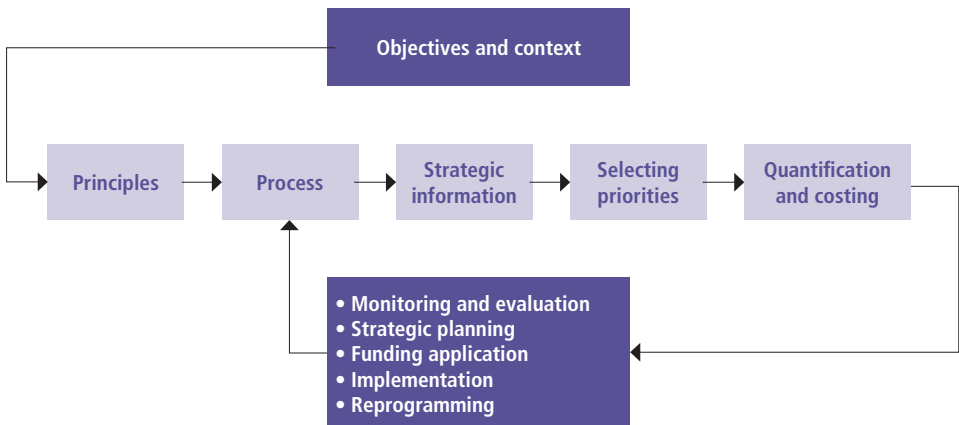
The ultimate aim of selecting, adapting and implementing the recommendations in these guidelines is to reach and sustain universal coverage of services so as to have the greatest impact on the epidemic. Countries are therefore encouraged to set ambitious targets and make every effort to reach them. However, disparities in the coverage of services, limitations in capacity, resource considerations and quality concerns often require a phased approach or sequencing to implement new recommendations. Sequencing should ensure that implementation of each recommendation builds on another to achieve sustained scale-up and high-quality services.

8.3 Useful tools for planning

Estimating the costs associated with implementing new recommendations is a key step in the roll-out process. Several costing tools and resources are available to assist countries in estimating the costs and budgeting for HIV and related interventions and services, as outlined below. Annex 18 provides greater detail on models for costing and planning and provides four examples of how costing assisted with implementation choices in countries.

Spectrum *(2)* is a suite of models and analytical tools to support decision-making. It comprises several software applications, including AIM (AIDS Impact Model) and Goals (Cost and Impact of HIV Interventions). The AIM and Resource Needs modules can be used to estimate the impact of key new recommendations on AIDS-related mortality, the number of infant infections and treatment needs and costs. The key data needed to generate these estimates are demographic projections, incidence trends and historical data on the number of people receiving ART, the number of pregnant women receiving PMTCT interventions and the unit costs of ART for adults and for PMTCT. All countries already have AIM files prepared as part of their national epidemiological estimates, so interested countries could rapidly apply both modules.

The Goals module can be used to estimate the number of adult HIV infections averted by ART under different eligibility criteria and rates of scaling up. The key inputs required are the distribution of the adult population by risk group (such as stable couples, those with casual partners, female sex workers, male clients of sex workers, men who have sex with men, transgender people and people who inject drugs); sexual behaviour by risk group (number of partners per year, acts per partner and condom use); and needle-sharing among people who inject drugs. Goals models already exist for about 25 countries, and other countries have compiled these data in the context of modes of transmission studies.

OneHealth is a software tool designed to strengthen health system analysis and costing and to develop financing scenarios at the country level. It is specifically designed to assess health investment needs in low- and middle-income countries and provides planners with a single framework for planning, costing, impact analysis, budgeting and financing of strategies for all major diseases and health system components. Both Spectrum and OneHealth are available for download free of charge *(3)*.

WHO and collaborating organizations have recently developed a variety of tools to assist with drug quantification and supply management. Several are available for download *(4–6)*, with a description of their main purposes and programmatic focus. A flexible tool for costing investments in critical enablers (such as integrated treatment and rights literacy programmes, legal services, stigma and discrimination reduction programmes, training for health-care workers and law enforcement) has also been developed and can be downloaded for free, along with a user guide *(7,8)*.

Optima *(9)* is a tool for HIV epidemic projection, and HIV response prioritization as well as evaluation. Optima is a mathematical model of HIV transmission and disease progression, integrated with an economic and financial analysis framework and a formal mathematical optimization routine. Analyses determine the optimal approach to getting as close as possible to defined objectives (e.g. national strategic plan targets) within political, ethical and logistical constraints.

AIDS Epidemic Model (AEM) is a tool that reflects the primary subpopulations and transmission modes driving HIV epidemics.

8.4   Evaluation

An evaluation process of this guideline will be conducted, building on the 2014 and 2015 evaluation surveys, to identify the uptake of the recommendations in the guidelines into national policies and programmes. Data will be made available within the WHO country intelligence database, which is updated every six months to reflect both change in policy and implementation diffusion for all low- and middle-income countries and selected high-income countries.

References

1   Making fair choices on the path to universal health coverage: final report of the WHO Consultative Group on Equity and Universal Health Coverage. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/112671/1/9789241507158_eng.pdf?ua=1, accessed 30 September 2015).

2   Avenir health [website] Spectrum software (http://www.avenirhealth.org/software-spectrum.php, accessed 9 December 2015).

3   OneHealth Tool. Geneva: World Health Organization; 2014 (http://www.who.int/choice/onehealthtool/en/, accessed 1 November 2015).

4   Global Price Reporting Mechanism [online database]. Geneva: World Health Organization; 2013 (http://apps.who.int/hiv/amds/price/hdd, accessed 1 November 2015).

5   PSM Toolbox [website]. Geneva: Procurement and Supply Management Toolbox; 2013 (http://www.psmtoolbox.org, accessed 1 November 2015).

6   Avenir Health [website]. Glastonbury, CT: Avenir Health; 2015 (http://www.avenirhealth.org/, accessed 1 November 2015).

7   The human rights costing tool (HRCT): a tool to cost programmes to reduce stigma and discrimination and increase access to justice. Geneva: UNAIDS; 2012 (http://www.unaids.org/en/media/unaids/contentassets/documents/data-and-analysis/tools/The_Human_Rights_Costing_Tool_v_1_5_May-2012.xlsm, accessed 1 November 2013).

8   The user guide for the human rights costing tool: costing programmes to reduce stigma and discrimination and increase access to justice in the context of HIV. Geneva: UNAIDS; 2012 (http://www.unaids.org/en/media/unaids/contentassets/documents/data-and-analysis/tools/The_Human_Rights_Costing_Tool_v_1_5_May-2012.xlsm, accessed 1 November 2015).

9   Optima HIV optimization and analysis tool [website] (http://optimamodel.com/, accessed 9 December 2015).

ANNEXES

ANNEX 1

Declaration of interests, Clinical Guideline Development Group, June 2015

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Elaine Abrams ICAP, Columbia University (Co-Chair)	Region of the Americas	United States	0	1 Participation in advisory board GSK/ViiV Healthcare US$ 4500	0	1 Principal investigator for implementation science study; Merck donated ARV drugs
Serge Eholie University Felix Houphouet-Boigny (Co-Chair)	African Region	Côte d'Ivoire	0	0	0	0
Renaud Becquet INSERM-Bordeaux University	European Region	France	0	0	0	0
Alexandra Calmy Geneva University Hospital	European Region	Switzerland	0	0	1 Travel grant, research grants (unrestricted), support for the metabolic clinic. AbbVie, Janssen, Cilag, Gilead, Boehringer, Ingelheim. MSD, BMS, ViiV Healthcare Sw.fr. 10 000 each	
Pedro Cahn Fundacion Huesped	Region of the Americas	Argentina	0	1	1 Research grants Abbvie, Merck, ViiV Healthcare Served on advisory boards for Merck, ViiV Healthcare and Abbvie	
Sergio Carmona NHLS	African Region	South Africa	0	0	1 Research grants to research unit (multiple) Technical advisory board, CROI 2014, Abbott, US$ 1000 Speaker, IAS 2014, Abbott, travel cost only	

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	Financial non-significant Non-financial significant
								Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	Principal investigator for TEMPRANO study	0	Non-financial significant
								Partial exclusion from the decision-making process or voting for relevant PICOs; did not chair discussion on when to start A1.1 and A1.3
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant
								Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	Financial significant
								Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	Financial significant
								Conditional participation through disclosure of his interests Institutional research support only

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Mohammed Chakroun Teaching Hospital and University of Monastir	Eastern Mediterranean Region	Tunisia	0	0	0	0
Nikoloz Chkhartsihvili Infectious Diseases, AIDS and Clinical Immunology Research Center	European Region	Georgia	0	0	0	0
Martin Choo Asia Pacific Network of People Living with HIV	South-East Asia Region	Malaysia	0	1 Consulting community consultations to support WHO 2016 ARV guidelines US$ 6000	0	0
David Cooper Kirby Institute	Western Pacific Region	Australia	0	0	1 Research support from BMGF, Gilead, ViiV Healthcare, Merck to employer	0
Mark Cotton Stellenbosch University	African Region	South Africa	0	0	1 National Institutes of Health research grant – employer	0
Aleny Couto Ministry of Health, Mozambique	African Region	Mozambique	0	0	0	0
Wondwossen Amogne Degu Addis Adaba University School of Medicine	African Region	Ethiopia	0	0	0	0
Charles Flexner Johns Hopkins University	Region of the Americas	United States	0	1 Current consulting fees: Merck, US$ 19 000 Mylan Pharmaceuticals, US$ 13 000 Per diem for consulting services related to drug development or clinical pharmacology	1 Unrestricted grant to Johns Hopkins University (employer) for investigator support	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	1 Unpaid invited presentation at 2015 Social Forum by the United Nations Human Rights Council	1 Person living with HIV who depends on HIV treatment for survival and well-being	0	Financial non-significant Non-financial non-significant
0	0	0	0	0	0	1 Site investigator for ENCORE and site investigator for START	0	Financial significant Non-financial significant / Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	Financial significant / Conditional participation through disclosure of his interests Institutional research support only
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant / Partial exclusion from the decision-making process or voting for relevant PICOs

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Peter Fonjungo United States Centers for Disease Control and Prevention	Region of the Americas	United States	0	0	0	0
Carlo Giaquinto University of Padova	European Region	Italy	0	1 Advisory board, ViiV Healthcare, €2500 Gilead, €2500	1 Research support to research unit 2014–current: Gilead, BMS, Jenssen, ViiV Healthcare	0
Diane Havlir University of California, San Francisco	Region of the Americas	United States	0	0	1 Research support from National Institutes of Health to support UCSF faculty salary Research support	0
Charles Holmes Centre for Infectious Disease Research in Zambia and Johns Hopkins University	Region of the Americas	United States	0	1 Consulting on content and strategy for continuing medical education, US$ 10 000	1 Research support pending from BGMF to employer, US$ 40 000	0
John Idoko National Agency for the Control of AIDS	African Region	Nigeria	0	0	0	0
Andreas Jahn ITECH	African Region	Malawi	0	0	0	0
Quarraisha Abdool Karim CAPRISA	African Region	South Africa	0	0	0	1 Honorarium of US$ 2000 from Gilead
Nagalineswaran Kumarasamy YRGCARE Medical Centre, VHS, Chennai	South-East Asia Region	India	0	0	0	0
Karine Lacombe Sorbonne-University and INSERM AP-HP	European Region	France	0	1 Board adviser, BMS, Gilead, MSD, Abbvie, Janssen, US$ 10 000	1 Board adviser, BMS, Gilead, MSD, Abbvie, Janssen, US$ 10 000	1 Board adviser, BMS, Gilead, MSD, Abbvie, Janssen, US$ 10 000

| Declaration of conflict of interest | | | | | | | | Conflicts and management plan |
| Investment interests | | Intellectual property | | Public statements and positions | | Additional information | Tobacco products | |
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	Participant from funding source
0	0	0	0	0	0	0	0	Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
0	0	0	0	0	0	0	0	Financial non-significant
0	0	0	0	0	0	0	0	Financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	1 Patent for use of tenofovir to prevent HSV-2 infection	0	0	0	1 Principal investigator for CAPRISA OO4 and CAPRISA 008 and principal investigator for HPTN 077	0	Financial non-significant Non-financial significant Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Loyce Maturu AFRICAID ZANDIRI	African Region	Zimbabwe	0	0	0	0
Dorothy Mbori-Ngacha UNICEF	African Region	South Africa	0	0	0	0
Landon Meyer University of Cape Town	African Region	South Africa	0	0	0	1 Alere Health Care, US$ 20 000 in equipment
Lynne Mofenson Elizabeth Glaser Pediatric AIDS Foundation	Region of the Americas	United States	0	0	0	0
Angela Mushavi Ministry of Health and Child Care, Zimbabwe	African Region	Zimbabwe	1 Employed by Elizabeth Glaser Pediatric AIDS Foundation and seconded to Ministry of Health and Child Care	0	0	0
Angelina Namiba Positively UK	European Region	United Kingdom	0	0	0	0
Shinichi Oka National Centre for Global Health and Medicine	Western Pacific Region	Japan	0	0	0	0
Ryan Phelps United States Agency for International Development	Region of the Americas	United States	0	0	0	0
Andrew Prendergast MRC University of London	European Region	United Kingdom	0	0	0	0
Elliot Razies United States Centers for Disease Control and Prevention	Region of the Americas	United States	0	0	0	0
George Siberry United States National Institutes of Health	Region of the Americas	United States	0	0	0	0

Declaration of conflict of interest								Conflicts and management plan	
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work				
0	0	0	0	0	0	0	0	None	
0	0	0	0	0	0	0	0	None	
0	0	0	0	0	0	0	0	Financial significant	
								Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only	
0	0	0	0	0	0	0	0	None	
0	0	0	1 Coordinate PMTCT and HIV care and treatment for children in Zimbabwe and interested technically in the outcome of the meeting	0	0	1 The outcome of the meeting leads to revised WHO recommendations for PMTCT and HIV care and treatment for children and will affect the programme in Zimbabwe	0	Financial non-significant Non-financial non-significant	
0	0	0	0	0	0	0	0	None	
0	0	0	0	1 Travel to meeting supports by employer	0	0	0	Financial non-significant	
0	0	0	0	1 Travel to meeting supports by employer	0	0	0	Financial non-significant Participant from funding source	
0	0	0	0	0	0	0	0	None	
0	0	0	0	0	0	0	0	Participant from funding source	
0	0	0	0	0	0	1 Contribution towards travel costs	0	Financial non-significant	

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Annette Sohn TREAT ASIA – amfAR	South-East Asia Region	Thailand	0	0	1 Research and training grants to institution Medicine donation for research study on hepatitis C to research unit only	
Bukiki Sylvere Biziyaremye ITPC West Africa	African Region	Côte d'Ivoire	0	0	0	0
Denis Tindyebwa ANECCA	African Region	Uganda	0	0	0	0
Francois Venter Wits RHI	Region of the Americas	South Africa	0	1 Travel support to IAS, Gilead and Mylan, US$ 2000	1 Principal investigator for BMGF low-dose stavudine; principal investigator for low-dose darunavir; SA MRC investigator for PrEP and TandT in sex workers; Gilead and Mylan, donation of drug	1
Heather Watts Office of the Global AIDS Coordinator, United States Department of State	Region of the Americas	United States	0	0	0	0
Benjamin Young International Association of Providers of AIDS Care	Region of the Americas	United States	0	0	1 Research support, Merck and Co., Gilead Sciences and ViiV Healthcare	1 Advisory boards, Bristol Myers Squibb, Merck and Co. and ViiV Healthcare
Oleg Yurin Central Research Institute of Epidemiology	European Region	Russian Federation	0	0	0	0
Fuji Zhang NCAIDS Chinese CDC	Western Pacific Region	China	0	0	0	0
Methodologist[a]						
Nandi Siegfried Independent clinical epidemiologist	African Region	South Africa	0	1 Consulting as methodologist for WHO, 2011–2015, remuneration >US$ 40 000	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	Financial significant
								Conditional participation through disclosure of interests Institutional research support only
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	1 Advisory boards, Janssen, Tibotech and Mylan, US$ 500 to US$ 1000 per meeting	1 Speaking honoraria, Merck, GSK, US$ 500 per meeting	0	0	0	0	Financial significant and Non-financial significant interest
								Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	Participant from funding source
0	0	0	0	0	0	0	0	Financial significant interest
								Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial non-significant

Key
Declaration of conflict of interest
None – no conflict declared on conflict of interest form or at start of the Clinical Guideline Development Group meeting in June 2015.
0 – no conflict declared.
1 – conflict declared with public disclosure statement.

Management plans
Conditional participation: Continued involvement in the meeting and publicly disclose the expert's interest at the start of the meeting and in the report of the meeting and relevant publications or work products.

Partial exclusion: Limited involvement: (a) exclude expert from the portion of the meeting or work in which a conflict of interest has been identified and/or exclude the expert from participating in the decision-making process. Reported interest to be publicly disclosed to other meeting participants and in the report of the meeting and relevant publications or work products. Partial exclusion was carefully monitored in the meeting.
Total exclusion: Expert was excluded from the meeting altogether.

[a] Methodologists facilitated decision-making and were not involved in voting.

ANNEX 2

Declaration of interests, Operational Guideline Development Group, June 2015

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Anthony Harries International Union Against Tuberculosis and Lung Disease (Co-chair)	European Region	United Kingdom	0	0	0	0
Fabio Caldas de Mesquita Ministry of Health, STI, AIDS and Viral Hepatitis Department (Co-chair)	Region of the Americas	Brazil	0	0	0	0
Tsitsi Apollo Ministry of Health and Child Care, Zimbabwe	African Region	Zimbabwe	0	0	0	0
Helen Ayles London School of Hygiene and Tropical Medicine/ ZAMBART	European Region	United Kingdom	0	0	0	0
Ferenc Bagyinszky European AIDS Treatment Group	European Region	Germany	0	0	0	0
Joe Barker Office of the Global AIDS Coordinator and Health Diplomacy, United States Department of State	Region of the Americas	United States	1 Employee of United States Government: United States Centers for Disease Control and Prevention. Seconded to OGAC since 2013. Salary paid for by PEPFAR funds.	0	1 See Employment and consulting.	0
David Barr Fremont Center	Region of the Americas	United States	0	0	0	0
John Blandford United States Centres for Disease Control and Prevention	Region of the Americas	United States	0	0	0	0
Thomas Cai AIDS Care China	Western Pacific Region	China	0	0	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	1 Requested to make statements in regards to equity, epidemiology, monitoring and evaluation and surveillance on behalf of PEPFAR to partner governments and other multilateral organizations.		1 All official travel paid by PEPFAR.	0	Financial non-significant Participant from funding source
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None Participant from funding source
0	0	0	0	0	0	0	0	None

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Karen Cohen University of Cape Town	African Region	South Africa	0	0	0	0
John Crowley United States Agency for International Development	Region of the Americas	United States	0	0	0	0
Francois Dabis Université de Bordeaux	European Region	France	0	0	0	0
Carol El-Hayek Burnet Institute	Western Pacific Region	Australia	0	0	0	0
Carlos Falistocco Argentina Presidente del GCTH	Region of the Americas	Argentina	0	0	0	0
Ruby Fayorsey ICAP Columbia University	Region of the Americas	United States	0	0	0	0
Robert Ferris United States Agency for International Development	Region of the Americas	United States	1 Full-time direct-hire United States Government employee	0	0	0
Elvin Geng University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Lucy Ghati National Empowerment Network of People living with HIV/ AIDS Kenya	African Region	Kenya	0	0	0	0
Diana Gibb MRC Clinical Trials Unit at University College London	European Region	United Kingdom	0	1 ViiV Healthcare Paediatric Advisory Board Mylan Advisory Board, US$ 5000	1 Funding support from ViiV Healthcare for ARROW virology sub-study	1 Drugs from ViiV Healthcare, Gilead, CIPLA and Merck for REALITY trial, CIPLA for CHAPAS 2and 3, ViiV Healthcare for ARROW trial

Declaration of conflict of interest									Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work				
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None Participant from funding source
0	0	0	0	0	0	Principal investigator, large treatment trial	0		Non-financial significant Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	1 Direct hire United States Government employee, represents USAID on global HIV issues	1 United States Government/ USAID paid full travel costs	0		Financial non-significant Participant from funding source
0	0	0	0	0	0	Principal investigator large treatment trial	0		Non-financial significant Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Eric Goemaere Médecins Sans Frontières South Africa	African Region	South Africa	0	0	0	0
Christopher Hoffman Johns Hopkins University	Region of the Americas	United States	0	0	0	1 Dinner and train ticket for advisory board Gilead, <US$ 400
Ilesh Jani Instituto Nacional de Saude	African Region	Mozambique	0	0	0	0
Medhi Karkouri CHU Ibn Rochd/ Faculte de Medicine de Casablanca	Eastern Mediterranean Region	Morocco	0	0	0	0
Bekezela Bebbie Khabo Ministry of Health, Zimbabwe	African Region	Zimbabwe	0	0	0	0
Siti Nadia National AIDS Program, Ministry of Health, Indonesia	South-East Asia Region	Indonesia	0	0	0	0
Jean Nachega University of Pittsburgh	Region of the Americas	United States	0	0	1 National Institutes of Health/NIAID to Stellenbosch University, US$ 7 520 583 and £192 590 Wellcome Trust to Stellenbosch University, US$ 9 400 000	0
Hai Nguyen Huu Viet Nam Authority of HIV/AIDS Control	South-East Asia Region	Vietnam	0	0	0	0
Sabin Nsanzimana Rwanda Biomedical Center	African Region	Rwanda	0	0	0	0
Daniella Mark PATA	African Region	South Africa	0	0	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Gitau Mburu International HIV/ AIDS Alliance	European Region	United Kingdom	0	0	0	0
Irene Mukui Ministry of Health, National AIDS and STI Control Program	African Region	Kenya	0	0	0	0
Bora Ngauv Ministry of Health	Western Pacific Region	Cambodia	0	0	0	0
Nataliya Nizova SI Ukrainian Center for Socially Dangerous Disease Control of the Ministry of Health of Ukraine	European Region	Ukraine	0	0	0	0
Rosanna Peeling London School of Hygiene and Tropical Medicine	European Region	United Kingdom	0	0	0	0
Trevor Peter Clinton Health Access Initiative	African Region	Botswana	0	0	0	0
Yogan Pillay Department of Health, South Africa	African Region	South Africa	0	0	0	0
Asia Russell HealthGAP	African Region	Uganda	0	0	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	1 Senior adviser for HIV and health systems at the International HIV/AIDS Alliance. Providing expertise implementation of community-based testing, prevention, treatment and care and to advocate and support country policies related to HIV prevention, treatment and care	0	0	0	Non-financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	Principal investigator, diagnostics trials	0	Non-financial significant Partial exclusion from the decision-making process or voting for relevant PICOs
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None

Name, institution	WHO region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Kenly Sikwese African Community Advisory Board	African Region	Zambia	0	0	1 AFROCAB received grants for community consultation on ARV and HIV/TB/HBV diagnostic access and increasing community participation in clinical trials. Funding from ViiV Healthcare, Gilead and Janssen. US$ 30 000	0
John Stover Avenir Health	Region of the Americas	United States	0	0	0	0
Frits van Griensven Thai Red Cross AIDS Research Center	South-East Asia Region	Thailand	0	0	0	0
Brian van Wyk University of the Western Cape	African Region	South Africa	0	0	0	0
Stefano Vella Istituto Superiore di Sanità	European Region	Italy	0	0	0	0
Nicola Willis Africaid	African Region	Zimbabwe	0	0	0	0
David Wilson World Bank	Region of the Americas	United States	0	0	0	0
Gautam Yadav India HIV/AIDS Alliance	South-East Asia Region	India	0	0	0	0
Anna Zakowicz AHF Europe Global Network of People Living with HIV and AIDS	European Region	Ukraine	0	0	0	0
Methodologist[a]						
Paul Garner Liverpool School of Hygiene and Tropical Medicine	European Region	United Kingdom	0	0	0	0

| Declaration of conflict of interest | | | | | | | | | Conflicts and management plan |
| Investment interests | | Intellectual property | | Public statements and positions | | Additional information | Tobacco products | | |
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work				
0	0	0	0	0	0	1 AFROCAB seeking further support from Janssen, Gilead, ViiV Healthcare and Merck to provide financial support for core operations and country access programmes. Further support is being support from ViiV Healthcare to support access programmes for key populations and youth.	0		Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
0	0	0	0	0	0	1 Travel paid to meeting	0		Financial non-significant
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None

Key
Declaration of conflict of interest
None – no conflict declared on conflict of interest form or at start of the Clinical Guideline Development Group meeting in June 2015.
0 – no conflict declared.
1 – conflict declared with public disclosure statement.

Management plans
Conditional participation: Continued involvement in the meeting and publicly disclose the expert's interest at the start of the meeting and in the report of the meeting and relevant publications or work products.

Partial exclusion: Limited involvement: (a) exclude expert from the portion of the meeting or work in which a conflict of interest has been identified and/or exclude the expert from participating in the decision-making process. Reported interest to be publicly disclosed to other meeting participants and in the report of the meeting and relevant publications or work products. Partial exclusion was carefully monitored in the meeting.

Total exclusion: Expert was excluded from the meeting altogether.

[a] Methodologists facilitated decision-making and were not involved in voting.

ANNEX 3

Declaration of interests, external contributors to the systematic reviews

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Andrew Anglemyer California State University Monterey Bay	Region of the Americas	United States	0	0	0	0
Mohsin Ali Icahn School of Medicine at Mount Sinai	Region of the Americas	United States	0	0	0	0
Stefan Baral Johns Hopkins School of Public Health	Region of the Americas	United States	0	0	0	0
Sarah Beckham Johns Hopkins School of Public Health	Region of the Americas	United States	0	0	0	0
Sara Beste Consultant, University of Masachusetts	Region of the Americas	United States	0	0	0	0
Chris Beyer Johns Hopkins School of Public Health	Region of the Americas	United States	0	0	0	0
Caroline Boeke Clinton Health Access Initiative	Region of the Americas	United States	0	0	0	0
Kimberley Bonner Médecins Sans Frontières	European Region	Switzerland	0	0	0	0
Xavier Bosch-Capblanch Swiss Tropical and Public Health Institute	European Region	Switzerland	0	0	0	0
Lisa Butler Boston University Children's Hospital	Region of the Americas	United States	0	0	0	0
Brian Chang Icahn School of Medicine at Mount Sinai	Region of the Americas	United States	0	0	0	0
Mark Clowes University of Sheffield	European Region	United Kingdom	0	0	0	0
Desire Dahourou Centre Muraz ANRS	African Region	Burkina Faso	0	0	0	0
Jon Deeks University of Birmingham	European Region	United Kingdom	0	0	0	0
Rashida Ferrand London School of Hygiene and Tropical Medicine	European Region	United Kingdom	1 The Wellcome Trust Research Fellowship	0	1 Wellcome Trust funding £1.5 million – to support salary and research costs	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for a commercial entity or organization	Office or position to represent interest relating to the subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	1 Travel costs to conference reimbursed by the Icahn School of Medicine	0	Financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	Travel costs to conference reimbursed by the Icahn School of Medicine	0	Financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Institutional research support

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Hana Azman Firdaus University of California, San Francisco – Global Health Sciences	Region of the Americas	United States	0	0	0	0
Virginia Fonner Johns Hopkins Bloomberg School of Public Health	Region of the Americas	United States	0	0	0	0
Matthew Fox Boston University	Region of the Americas	United States	0	0	1 Grants to research retention in HIV care and associated interventions: National Institutes of Health, World Bank, USAID US$ 1 000 000	0
Pascal Geldsetzer Harvard T.H. Chan School of Public Health	Region of the Americas	United States	0	0	0	0
Antonio Jose Grande University of Oxford Enhance Reviews LtD	European Region	United Kingdom	0	0	0	0
Lindsay Harris Clinton Health Access Initiative	Region of the Americas	United States	0	0	0	0
Matthew Hickey University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Hacsi Horvath University of California, San Francisco – Global Health Sciences	Region of the Americas	United States	0	0	0	0
Kristin Hunt Johns Hopkins School of Public Health	Region of the Americas	United States	0	0	0	0
Julie Jesson Inserm U897, Bordeaux University	European Region	France	0	0	0	0
Amrita Jesurasa University of Sheffield	European Region	United Kingdom	0	0	0	0
Artemisia Karkourou Enhance Reviews Ltd	European Region	United Kingdom	0	0	0	0
Steve Kanters Global Evaluative Sciences	Region of the Americas	Canada	0	0	0	0
Ingrid Katz Boston University Children's Hospital	Region of the Americas	United States	0	0	0	0
Ryan Keating University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Erica Lazarus Consultant, Perinatal HIV Research Unit	African Region	South Africa	0	0	0	0
Andrew Lee University of Sheffield	European Region	United Kingdom	0	0	0	0
Aimee Leidich University of California, San Francisco	Region of the Americas	United States	0	0	0	0

Declaration of conflict of interest									Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for a commercial entity or organization	Office or position to represent interest relating to the subject of the meeting or work				
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		Financial significant Institutional research support
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Valeriane Leroy University of Bordeaux, Inserm U897-ISPED	European Region	France	0	0	0	0
Mary Lou Lindegren Boston University Children's Hospital	Region of the Americas	United States	0	0	0	0
Divya Mallampati Consultant, Northwestern University	Region of the Americas	United States	0	0	0	0
Peter MacPherson University of Liverpool	European Region	United Kingdom	0	0	1 Wellcome Trust Clinical PhD Fellowship, 2009–2010 Academy of Medical Sciences clinical lecturer starter grant 2014–2017	0
Susan Mallett University of Birmingham Enhance Reviews Ltd	European Region	United Kingdom	0	0	0	0
Edward Mills Global Evaluative Sciences	Region of the Americas	Canada	0	0	0	0
Jason Nagata Stanford University School of Medicine	Region of the Americas	United States	0	0	0	0
Matthew Neilson University of Sheffield	European Region	United Kingdom	0	0	0	0
Eleanor Ochodo Stellenbosch University Enhance Reviews Ltd	African Region	South Africa	0	0	0	0
Amy Penn University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Marta Prescott Clinton Health Access Initiative	Region of the Americas	United States	0	0	0	0
Jay Rajan University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Sydney Rosen Boston University	Region of the Americas	United States	1 Employed as full-time professor and research is related to subject of the project	0	1 Principal investigator of several research grants related to the subject of this topic: USAID, United States National Institutes of Health and Bill & Melinda Gates Foundation	1 Paid travel to meetings has been provided by several organizations: USAID, United States National Institutes of Health and Bill & Melinda Gates Foundation, WHO

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for a commercial entity or organization	Office or position to represent interest relating to the subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Institutional research support
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial and non-financial significant

Institutional research support |

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
George Rutherford University of California, San Francisco – Global Health Sciences	Region of the Americas	United States	0	0	0	0
Karla Soares-Weiser Enhance Reviews Ltd	European Region	United Kingdom	0	0	0	0
M. Eugenia Socias Global Evaluative Sciences	Region of the Americas	Argentina	0	0	0	0
Amitabh Suhtar Consultant, WHO	Western Pacific Region	Viet Nam	0	0	0	0
Kelly Taylor University of California, San Francisco	Region of the Americas	United States	0	0	0	0
Olalekan Uthman Global Evaluative Sciences Warwick Medical School	European Region	United Kingdom	0	0	0	0
Brittany Urick Clinton Health Access Initiative	African Region	Kenya	0	0	0	0
Lara Vojnov Clinton Health Access Initiative	African Region	United Republic of Tanzania	0	0	0	0
Matthew Wiens Global Evaluative Sciences	Region of the Americas	Canada	0	0	0	0
Taryn Young Enhance Reviews Ltd Stellenbosch University	African Region	South Africa	0	0	0	0

Key
Declaration of conflict of interest
None – no conflict declared on conflict of interest form or at start of the Clinical Guideline Development Group meeting in June 2015.
0 – no conflict declared.
1 – conflict declared with public disclosure statement.

Management plans
Conditional participation: Continued involvement in the meeting and publicly disclose the expert's interest at the start of the meeting and in the report of the meeting and relevant publications or work products.
Partial exclusion: Limited involvement: (a) exclude expert from the portion of the meeting or work in which a conflict of interest has been identified and/or exclude the expert from participating in the decision-making process. Reported interest to be publicly disclosed to other meeting participants and in the report of the meeting and relevant publications or work products. Partial exclusion was carefully monitored in the meeting.
Total exclusion: Expert was excluded from the meeting altogether.

Declaration of conflict of interest									Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for a commercial entity or organization	Office or position to represent interest relating to the subject of the meeting or work				
0	0	0	0	0	0	1 Travel to Geneva to attend Clinical Guideline Development Group meeting concurrent with another project. Travel paid by Itad Ltd under contract with the Global Fund to Fight AIDS, Tuberculosis and Malaria	0		Financial non-significant
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None
0	0	0	0	0	0	0	0		None

ANNEX 4

Declaration of interests, Core Group

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Elaine Abrams ICAP, Columbia University (Co-Chair, Clinical Guideline Development Group)	Region of the Americas	United States	0	1 Participation in advisory board GSK/ViiV Healthcare, US$ 4500	0	1 Principal investigator for implementation science study: Merck donated ARV drugs
Tsitsi Apollo Ministry of Health and Child Care, Zimbabwe	African Region	Zimbabwe	0	0	0	0
Janet Tatenda Bhila Y+ AFRICAID Zandiri	African Region	Zimbabwe	0	0	0	0
Serge Eholie University Felix Houphouet-Boigny (Co-Chair)	African Region	Côte d'Ivoire	0	0	0	0
Waffa El Sadr ICAP, Columbia University	Region of the Americas	United States	0	1 Attended pharmaceutical board meeting, ViiV Healthcare,US$ 3000	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	Financial non-significant Non-financial significant

Partial exclusion from the decision-making process and voting for relevant PICOs A1.1 and A1.3

Comments interpreted in the context of conflict of interest |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| 0 | 0 | 0 | 0 | 0 | 0 | Principal investigator for TEMPRANO study | 0 | Financial significant Institutional

Non-financial significant

Partial exclusion from the decision-making process and voting for relevant PICOs; Did not chair discussion on when to start A1.1 and A1.3

Comments interpreted in the context of conflict of interest |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Financial non-significant |

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Paul Garner Liverpool School of Tropical Medicine	European Region	United Kingdom	0	0	0	0
Timothy Hallett Imperial College	European Region	United Kingdom	0	1 Bill & Melinda Gates Foundation, World Bank and University of Washington and New York University, US$ 20 000 over 2 years	1 Bill & Melinda Gates Foundation, UNAIDS, RUSH Research, support to institution, US$ 8 million	0
Anthony Harries International Union against TB and Lung Disease	European Region	United Kingdom	0	0	0	0
Salim Abdool Karim CAPRISA	African Region	South Africa	0	0	0	0
Yogan Pillay Department of Health, South Africa	African Region	South Africa	0	0	0	0
Rebecca Matheson ICW	African Region	Kenya	0	0	0	0
Fabio Mesquita Department of STDs, AIDS and Viral Hepatitis	Region of the Americas	Brazil	0	0	0	0
Julio Montaner BC-CFE, University of British Columbia	Region of the Americas	Canada	0	0	1 Supported by grants to institution by British Columbia Ministry of Health Grants from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb and Gilead Sciences, Janssen, Merck and ViiV Healthcare	1 Financial support from United States National Institutes of Health, IAS, UNAIDS, WHO, ANRS, IAPAC, UNICEF, MAC AIDS Fund and OSF
Natalia Nizova Ukraine Centre for Social Disease Control	European Region	Ukraine	0	0	0	0

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	Director of DFID-funded research programme – effective health care based on reliable research summaries	0	Non-financial significant
0	0	0	0	0	0	0	0	Financial significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None
0	0	1 Patent for effect of tenofovir gel on HSV	0	0	0	0	0	Non-financial significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
								Financial significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None

Name, institution	Region	Country	Declaration of conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Douglas Shaffer Office of the United States Global AIDS Coordinator	Region of the Americas	United States	0	0	0	0
Nandi Siegfried Independent clinical epidemiologist (methodologist, Clinical Guideline Development Group)	African Region	South Africa	0	1 Consulting as methodologist for WHO, 2011–2015, remuneration >US$ 40 000	0	0
Kenly Sikwese African Community Advisory Board AFROCAB	African Region	Zambia	0	0	1 Grants for community consultation, ViiV Healthcare , Gilead and Janssen to institution, US$ 30 000, US$ 35 000	0
David Sinclair Liverpool School of Tropical Medicine	European Region	United Kingdom	0	0	0	0
Annette Sohn TREAT ASIA/amfAR	South-East Asia Region	Thailand	0	0	1 Research and training grants to institution Medicine donation for research study on hepatitis C to research unit only	0
Stefano Vella Istituto Superiore di Sanità	European Region	Italy	0	0	0	0

Key
Declaration of conflict of interest
None – no conflict declared on conflict of interest form or at the start of the Clinical Guideline Development Group meeting in June 2015.
0 – no conflict declared.
1 – conflict declared with public disclosure statement.

Management plans
Conditional participation: Continued involvement in the meeting and publicly disclose the expert's interest at the start of the meeting and in the report of the meeting and relevant publications or work products.
Partial exclusion: Limited involvement: (a) exclude expert from the portion of the meeting or work in which a conflict of interest has been identified and/or exclude the expert from participating in the decision-making process. Reported interest to be publicly disclosed to other meeting participants and in the report of the meeting and relevant publications or work products. Partial exclusion was carefully monitored in the meeting.
Total exclusion: Expert was excluded from the meeting altogether.

Declaration of conflict of interest								Conflicts and management plan
Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None Participant from funding source
0	0	0	0	0	0	0	0	Financial non-significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	1 AFROCAB is seeking further support from Janssen, Gilead, ViiV Healthcare and Merck to provide financial support	0	Financial significant Institution Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None

ANNEX 5

Declaration of interests, Expert Review Group

Name, Institution	Region	Country	Declaration of Conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Jared Baeten University of Washington	Region of the Americas	United States	0	0	1 Grant support from the Bill & Melinda Gates Foundation, United States National Institutes of Health and USAID related to PrEP to research unit, >US$ 70 million	1 PrEP medication donated to research unit by Gilead Sciences without other monetary support
Suna Balkan Médecins Sans Frontières	European Region	France	0	0	0	0
Carlos Caceres Universidad Peruana Cayetano Herredia	Region of the Americas	Peru	0	0	0	0
Frank Chimbwandira Ministry of Health, Malawi	African Region	Malawi	0	0	0	0
Simon Collins HIV i-Base	European Region	United Kingdom	0	0	0	0
Frances Cowan University College London, CeSHHAR Zimbabwe	European Region	United Kingdom	0	0	0	1 Principal investigator on ART as prevention trial among female sex workers in Zimbabwe. Gilead donated drugs for PrEP

		Intellectual property		Public statements and positions		Additional information	Tobacco products	**Conflicts and management plan**
Investment interests								
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	1	0	0		Financial significant Institutional research support Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	Coordinator of network for multidisciplinary studies in ARV-based HIV prevention. The network has received support from WHO and UNAIDS. This network is about fair consideration of knowledge and does not promote any specific product.		Financial non-significant
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Non-financial significant Comments interpreted in the context of conflict of interest

Name, Institution	Region	Country	Declaration of Conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Mitzy Gafos University College London	European Region	United Kingdom	0	0	0	0
Alison Grant London School of Hygiene & Tropical Medicine	European Region	United Kingdom	0	0	0	0
Juan Vicente Guanira Investigaciones Medicas en Salud	Region of the Americas	Argentina	0	0	0	0
Jessica Haberer Massachusetts General Hospital, Harvard University	Region of the Americas	United States	0	1 Consulting work for FHI 360, US$ 500. Consulting work for WHO on PrEP adherence, US$ 9900 Consulting work for United States National Institutes of Health on behavioural science consulting group, US$ 6700 annually	0	1 Research support from United States National Institutes of Health to institution (including salary support), principal investigator Bill & Melinda Gates Foundation, including salary support, principal investigator and co-investigator
Hakima Himmich Association Lutte Control le Sida	Eastern Mediterranean Region	Morocco	0	0	0	0
Rohan Hazra National Institutes of Health, United States Department of Health and Human Services	Region of the Americas	United States	0	0	0	0
Sarah Huffam National Centre for HIV AIDS Dermatology and STI	South-East Asia Region	Cambodia	0	1 Consultant employed to write the Cambodian national HIV management guidelines	0	0
Jonathan Kaplan United States Centres for Disease Control and Prevention	Region of the Americas	United States	0	0	0	0

Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	**Conflicts and management plan**
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant Comments interpreted in the context of conflict of interest
0	0	0	0	0	0	0	0	None Participant from funding source

Name, Institution	Region	Country	Declaration of Conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Michael Kiragu LVCT Health	African Region	Kenya	0	0	1 Research project received donation of drugs valued at US$ 20 000, principal investigator of PrEP demonstration project	0
James McIntyre Anova Health Institute	African Region	South Africa	0	0	0	0
Lisa Nelson United States Centres for Disease Control and Prevention, Office of the Global AIDS Coordinator, PEPFAR	Region of the Americas	United States	0	0	0	0
Nicole Ngo-Giang-Huong Institut de Recherche pour le Développement	South-East Asia Region	Thailand	0	0	0	0
Joselyn Pang Malaysian AIDS Council	South-East Asia Region	Malaysia	1 Managed TREAT Asia Pediatric HIV Observational Database (TApHOD) sponsored by United States National Institutes of Health, NICHD and Austrian AIDS Life Association, 2007–2012	0	1 See entry under employment US$ 3.7 million	0
Anastasia Pharris European Centre for Disease Prevention and Control	European Region	Sweden	0	0	0	0
Anton Pozniak Chelsea and Westminster NHS Foundation Trust Hospital	European Region	United Kingdom	0	0	1 Research into drugs via institution and pharmaceutically sponsored meetings and travel ViiV Healthcare, Merck, BMS, Gilead and Janssen	1
Gayle Sherman University of Witwatersrand	African Region	South Africa	0	0	0	0
Kwasi Torpey Family Health International (FHI360)	African Region	Nigeria	0	0	0	0

Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	**Conflicts and management plan**
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	Non-financial significant Financial significant

Comments interpreted in the context of conflict of interest |
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	None Participant from funding source
0	0	0	0	0	0	0	0	None
0	0	0	0	0	0	0	0	Financial significant

Comments interpreted in the context of conflict of interest |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| 0 | 0 | 0 | 0 | 0 | 1 Member of BHIVA and EACS guidelines committees | 0 | 0 | Financial significant Institutional research support

Comments interpreted in the context of conflict of interest |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | None |

Name, Institution	Region	Country	Declaration of Conflict of interest			
			Employment and consulting		Research support	
			Employment	Consulting	Research support	Non-monetary support
Valdilea Goncalves Veloso Oswaldo Cruz Foundation	Region of the Americas	Brazil	0	0	0	0
Iryna Zablotska Kirby Institute	Western Pacific Region	Australia	0	0	1 Research support for project from Gilead, A$ 40 000	1 Supply of medication for PrEP demonstration study PRELUDE
Vincent Wong USAID	Region of the Americas	United States	1 USAID	0	0	0

Key
Declaration of conflict of interest
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Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	Conflicts and management plan
Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			
0	0	0	0	0	0	0	0	None
								Financial significant Institutional research support

Comments interpreted in the context of conflict of interest |
| 0 | 0 | 0 | 0 | 0 | 0 | 1 Travel paid by USAID (employer) | 0 | Financial non-significant Participant from funding source |

ANNEX 6

Testing strategy for HIV diagnosis in high-prevalence settings

Perform A1

A1+

A1–
Report HIV-negative

Perform A2

A1+ A2–

A1+ A2+
Report HIV-positive

Repeat A1 and A2

A1– A2–
Report HIV-negative

A1+ A2–

Perform A3

A1+ A2– A3+
Report HIV-inconclusive
(retest in 14 days)

A1+ A2– A3–
Report HIV-negative,
if A1 is second- or
third-generation assay

Report HIV-inconclusive,
if A1 is fourth-generation assay
(retest in 14 days)
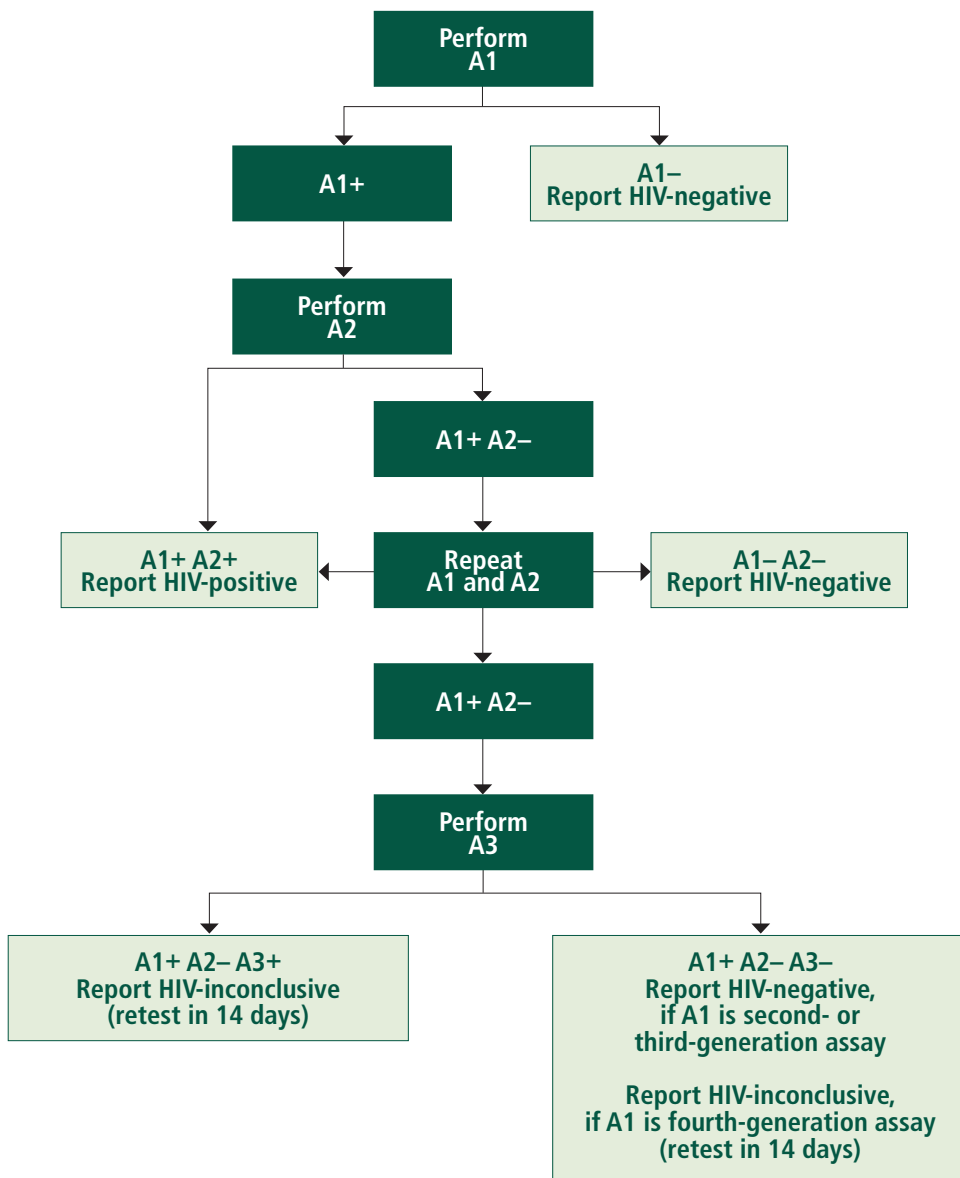
ANNEX 7

Testing strategy for HIV diagnosis in low-prevalence settings

```
                    ┌─────────────┐
                    │   Perform   │
                    │     A1      │
                    └─────────────┘
              ┌────────────┴────────────┐
        ┌───────────┐          ┌──────────────────┐
        │    A1+    │          │       A1–        │
        └───────────┘          │ Report HIV-negative │
              │                └──────────────────┘
        ┌───────────┐
        │  Perform  │
        │    A2     │
        └───────────┘
      ┌───────┴───────┐
┌───────────┐   ┌───────────┐          ┌──────────────────────────┐
│  A1+ A2+  │   │  A1+ A2–  │          │       A1+ A2–            │
└───────────┘   └───────────┘          │   Report HIV-negative,   │
      │               │                │   if A1 is second- or    │
      │         ┌───────────┐          │   third-generation assay │
      │         │  Repeat   │──────┐   │                          │
      │         │ A1 and A2 │      │   │  Report HIV-inconclusive,│
      │         └───────────┘      │   │ if A1 is fourth-generation assay │
      │               │            │   │     (retest in 14 days)  │
      │         ┌───────────┐      │   └──────────────────────────┘
      │←────────│  A1+ A2+  │      │   ┌──────────────────────────┐
      │         └───────────┘      └──→│       A1– A2–            │
┌───────────┐                          │   Report HIV-negative    │
│  Perform  │                          └──────────────────────────┘
│    A3     │
└───────────┘
  ┌────┴────┐
┌──────────┐ ┌──────────────┐
│ A1+ A2+  │ │  A1+ A2+ A3– │
│   A3+    │ │  Report HIV- │
│ Report   │ │  inconclusive│
│ HIV-     │ │ (retest in   │
│ positive │ │  14 days)    │
└──────────┘ └──────────────┘
```
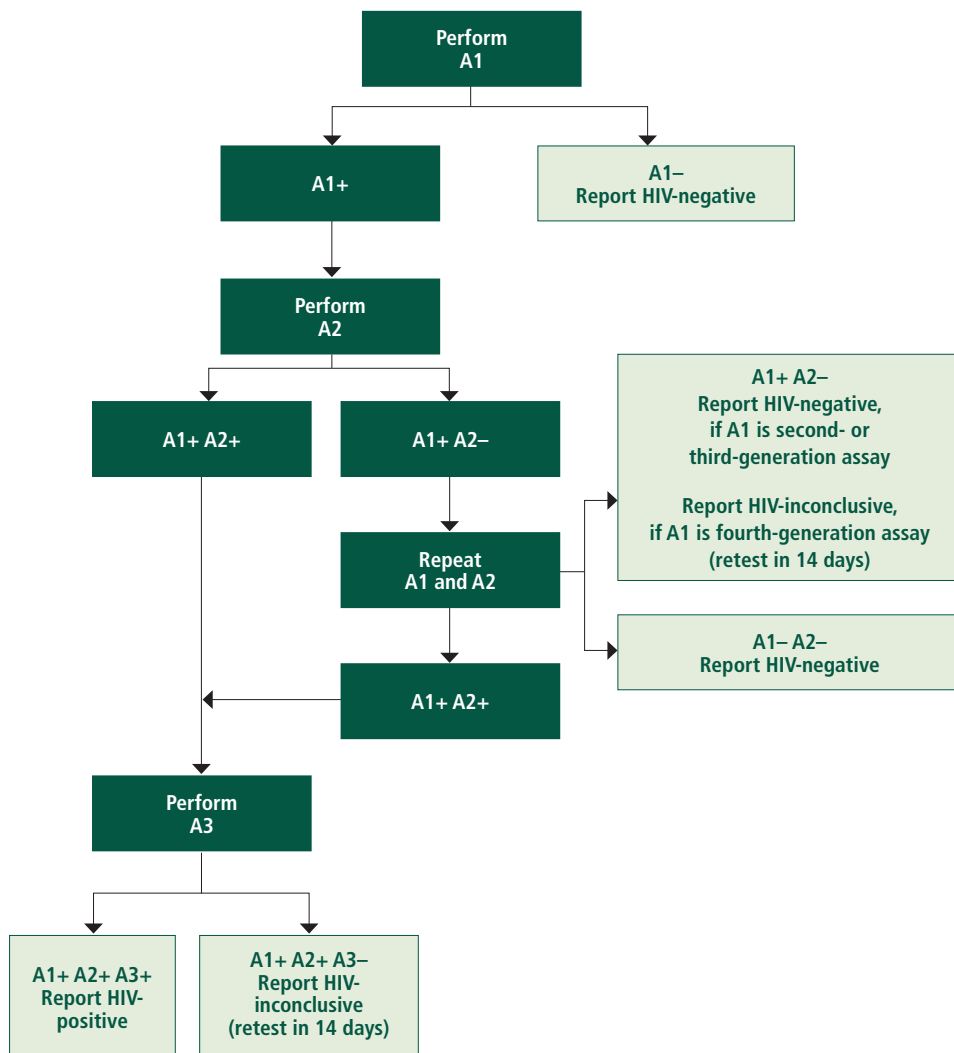
ANNEX 8

Testing strategy for early infant diagnosis

Establishing the presence of HIV infection in HIV-exposed infants and children less than 18 months of age in resource-limited settings.
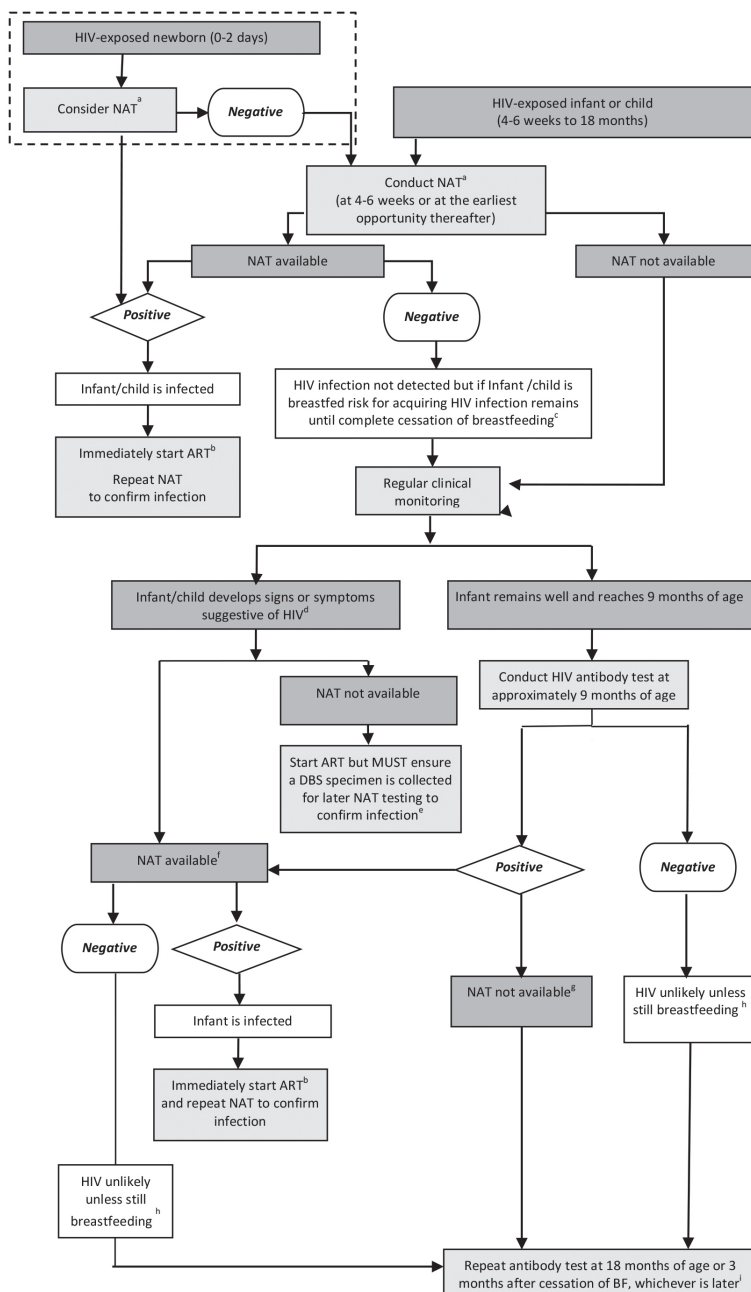
Important Notes:

[a] Based on these revised Guidelines addition of NAT at birth to the existing testing algorithm can be considered. POC NAT can be used to diagnose HIV infection at birth, but positive results should be confirmed using laboratory-based NAT assays, because of limited experience with POC assays close to birth.

[b] Start ART, without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase and re-testing after a first positive NAT is important to avoid unnecessarily treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be done before interrupting ART.

[c] For children who were never breastfed additional testing following a negative NAT at 4-6 weeks is included in this algorithm to account for potential false-negative NAT results.

[d] Signs and symptoms suggestive of HIV (oral thrush, recurrent or severe bacterial infections such as pneumonia or sepsis, FTT/wasting or AIDS indicator condition http://www.who.int/hiv/pub/paediatric/infants2010/en/).

[e] If infant presents with signs and symptoms of HIV disease (see footnote d above) but NAT is unavailable, consider starting ART, especially if an antibody test is conducted and result positive at 9 months or later. A DBS specimen must be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis, because subsequent diagnostic testing while already on ART might be difficult to interpret.

[f] If infant presents with signs and symptoms of HIV disease (see footnote d above) consider starting ART while waiting for NAT result. However, another DBS specimen should be collected prior to starting treatment for later NAT testing to confirm HIV diagnosis.

[g] Regular and periodic monitoring should be ensured while waiting for NAT to be available or for antibody testing to be conducted at 18 months. If infant presents with signs and symptoms of HIV disease should be managed as described previously (see footnote e).

[h] The risk of HIV transmission remains as long as breastfeeding continues. If the 9 months antibody testing is conducted earlier than 3 months after cessation of breastfeeding, infections acquired in the last days of breastfeeding may be missed so retesting at 18 months should be ensured for final assessment of HIV status.

[i] If breastfeeding beyond 18 months, final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants < 18 months of age positive antibody testing requires NAT to confirm infection. If infant is > 18 months, negative antibody testing confirms infant is uninfected; positive antibody testing confirms infant is infected

ANNEX 9

Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women

The WHO 2015 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* recommend that all pregnant and breastfeeding women with HIV initiate ART and continue ART as lifelong treatment. Countries planning for this transition, and those working to expand and strengthen their programme, may find it useful to refer to this readiness assessment checklist, which addresses a range of issues from national policy to facility readiness. The checklist and discussion guide, were developed by the United States President's Emergency Plan for AIDS Relief and are included as part of the larger *IATT toolkit: expanding and simplifying treatment for pregnant women living with HIV: managing the transition to option B/B+* of the Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children.

- Checklist: www.emtct-iatt.org/wp-content/uploads/2013/03/Toolkit-Section-2.pdf

- Full toolkit: www.emtct-iatt.org/toolkit

Recommended timing of action:

Before implementation

Early in implementation

During implementation

Political commitment and policy endorsement	Completed	In process	Not yet started
Commitment to Global Plan goals (national and subnational)			
Full-time health ministry staff responsible for PMTCT (national and possibly subnational)			
Functional technical working group inclusive of stakeholders from maternal, newborn and child health, PMTCT and HIV treatment, including health workers and people living with HIV			
National and subnational endorsement of ART for all pregnant and breastfeeding women			
National guidelines updated to incorporate offering ART to all pregnant and breastfeeding women			
Financial considerations	**Completed**	**In process**	**Not yet started**
Costing of current PMTCT strategy			
Costing of ART for all pregnant and breastfeeding women, both short and long term			
Conduct resource gap analysis			
Increased programme funding needs reflected in budget			
Demonstration of national financial commitment			

Service delivery model	Completed	In process	Not yet started
Defining the minimum package of services to provide ART to all pregnant and breastfeeding women			
Assessing system capacity (infrastructure, human resources and commodities) to decentralize ART to maternal, newborn and child health settings, including absorbing women with HIV and their families			
Timing and location of transition between PMTCT and long-term treatment services has been determined (including consideration of lifelong ART provision within maternal, newborn and child health)			
Systematic identification of ART clients who become pregnant and linkage to maternal, newborn and child health			
Testing and treating partners and family members within maternal, newborn and child health			
Referral of stable ART clients at current ART facilities to new decentralized ART sites			
Human resource capacity	**Completed**	**In process**	**Not yet started**
National endorsement of task shifting and sharing for ART initiation and maintenance			
Assessment of human resource capacity (nurse, midwife, pharmacy and laboratory) to support ART scale-up			
Core competencies in HIV management for each health worker cadre			
Training strategy for ART provision to support rapid scale-up			
Updating of national in-service and pre service curricula			
Nursing and midwifery scopes of practice support nurse-initiated and -managed ART			
Strategy for retention, retraining and continuing professional development of health workers, especially those providing PMTCT and ART			
ART regimen choice	**Completed**	**In process**	**Not yet started**
Simplifying and harmonizing PMTCT and adult treatment regimens			
Plan for alternate regimen for pregnant women who cannot tolerate first-line ART			
Optimizing first-line regimen for infants			
Establishing a pharmacovigilance system, where appropriate (see discussion guide)			
Supply chain management	**Completed**	**In process**	**Not yet started**
Assessing the supply chain gaps, including quantification, distribution and stock management			
18-month forecast, quantification and supply plan developed			
Stock management of ART in maternal, newborn and child health settings (training, capacity, and security)			
If modifying first-line regimen, plan for using ARVs already ordered			
Revised supply chain management system (consumption, forecasting, and distribution)			

Monitoring, evaluation and data use	Completed	In process	Not yet started
Antenatal care and PMTCT register enables documentation of initiation versus those already on ART			
ART register allows for documentation of pregnancy and breastfeeding status			
Tools and registers in maternal, newborn and child health allow for cohort monitoring of maternal ART retention and exposed infant retention in care			
Pregnant and breastfeeding women initiated on ART in maternal, newborn and child health			
settings are included in site and national level ART M&E systems			
System to track and measure linkage and transition between maternal, newborn and child health and long-term HIV care and treatment for the mother and infant (for example, a mother-baby longitudinal register, unique identifiers)			
Programme evaluation designed to detect early successes and challenges and to assess longer-term maternal and infant outcomes, including mother-to-child transmission			
Routine data quality assurance			
Harmonizing PMTCT and ART monitoring and evaluation systems and data review processes			
Standardized client file or card for pregnant and breastfeeding women living with HIV and exposed infants			
Site supervision and quality management	**Completed**	**In process**	**Not yet started**
Routine site supervision and clinical mentoring for quality of care			
Continuous quality improvement process for the PMTCT programme			
HIV testing and counselling in PMTCT settings	**Completed**	**In process**	**Not yet started**
Quality assurance measures for rapid HIV testing at all PMTCT sites			
Policy decision on treatment of discordant couples			
Couples HIV testing and counselling and follow-up of discordant couples incorporated			
Strategy to link or register male partners with HIV in ART programme			
Counselling on ART initiation and adherence	**Completed**	**In process**	**Not yet started**
Specialized messaging and support services for pregnant and breastfeeding women initiating ART			
Structures to expedite preparation for ART initiation			
Alternative protocols developed for women not needing ART for their own health who decline treatment for life			
Laboratory and clinical monitoring	**Completed**	**In process**	**Not yet started**
Capability for monitoring treatment for toxicity			
Availability of baseline CD4 (point of care or reliable sample transport)			
Algorithm for CD4 and/or viral load monitoring			

Infant diagnosis and treatment	Completed	In process	Not yet started
Early infant diagnosis capacity paralleling the scaling up of PMTCT programmes	(light green)	(light green)	(light green)
Strengthening of the early infant diagnosis cascade – early diagnosis, returning results rapidly, active case finding of infants infected with HIV and initiating treatment	(light green)	(light green)	(light green)
Expand access to treatment for infants	(dark green)	(dark green)	(dark green)
Retention in care and treatment	**Completed**	**In process**	**Not yet started**
System to ensure that all pregnant and postpartum women living with HIV are enrolled in ongoing HIV care and/or treatment			
Models of service delivery that consider harmonized follow-up of mother-infant pairs	(light green)	(light green)	(light green)
Facility- and community-based services to support adherence and trace defaulters	(light green)	(light green)	(light green)
Innovative solutions to improving the accessibility of ART	(dark green)	(dark green)	(dark green)
Family planning	**Completed**	**In process**	**Not yet started**
Assessment of family planning service availability and commodities	(dark green)	(dark green)	(dark green)
Access to and uptake of voluntary family planning services in settings providing ART	(dark green)	(dark green)	(dark green)
Community involvement	**Completed**	**In process**	**Not yet started**
Women living with HIV are engaged in planning, implementation and monitoring at the national, subnational and community levels			
Community-based activities and services to support PMTCT scale-up and retention	(dark green)	(dark green)	(dark green)
Roll-out strategy	**Completed**	**In process**	**Not yet started**
Roll-out strategy has been planned			
Real-time evaluation of implementation to inform further scale-up	(light green)	(light green)	(light green)

ANNEX 10

WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents[a]	Children
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9/L) and/or chronic thrombocytopaenia (<50 × 10^9/L)	Unexplained moderate malnutrition[b] not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) Persistent oral candidiasis (after first six weeks of life) Oral hairy leukoplakia Lymph node tuberculosis; pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dL), neutropaenia (<0.5 × 10^9/L) or chronic thrombocytopaenia (<50 × 10^9/L)
Clinical stage 3	
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis

Adults and adolescents[a]	Children
Clinical stage 4[c]	
HIV wasting syndrome	Unexplained severe wasting, stunting or severe malnutrition[d] not responding to standard therapy
Pneumocystis (jirovecii) pneumonia	
Recurrent severe bacterial pneumonia	*Pneumocystis (jirovecii)* pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site)	Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Extrapulmonary tuberculosis	Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Kaposi sarcoma	
Cytomegalovirus infection (retinitis or infection of other organs)	Extrapulmonary tuberculosis
	Kaposi sarcoma
Central nervous system toxoplasmosis	Cytomegalovirus infection (retinitis or infection of other organs with onset at age older than one month)
HIV encephalopathy	
Extrapulmonary cryptococcosis, including meningitis	Central nervous system toxoplasmosis (after the neonatal period)
Disseminated nontuberculous mycobacterial infection	HIV encephalopathy
Progressive multifocal leukoencephalopathy	Extrapulmonary cryptococcosis, including meningitis
Chronic cryptosporidiosis	Disseminated nontuberculous mycobacterial infection
Chronic isosporiasis	Progressive multifocal leukoencephalopathy
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)	Chronic cryptosporidiosis (with diarrhoea)
Lymphoma (cerebral or B-cell non-Hodgkin)	Chronic isosporiasis
Symptomatic HIV-associated nephropathy or cardiomyopathy	Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Recurrent septicaemia (including nontyphoidal *Salmonella*)	Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy
Invasive cervical carcinoma	
Atypical disseminated leishmaniasis	

[a] In the development of this table, adolescents were defined as 15 years or older. For those younger than 15 years, the clinical staging for children should be used.

[b] For children younger than 5 years, moderate malnutrition is defined as weight-for-height < −2 *z*-score or mid-upper arm circumference ≥115 mm to <125 mm.

[c] Some additional specific conditions can be included in regional classifications, such as *penicilliosis* in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

[d] For children younger than five years of age, severe wasting is defined as weight-for-height < −3 *z*-score; stunting is defined as length-for-age/height-for-age < −2 *z*-score; and severe acute malnutrition is either weight for height < −3 *z*-score or mid-upper arm circumference <115 mm or the presence of oedema.

Source: Adapted from: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, World Health Organization, 2007 (www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf).

ANNEX 11

Doses of recommended antiretroviral drugs

A. Dosages of antiretroviral drugs for adults and adolescents

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400–600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily[a] or 600 mg + 100 mg twice daily[b]
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r: (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily).or, SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir (RAL)	400 mg twice daily

[a] For individuals with no previous use of protease inhibitors.
[b] For individuals with previous use of protease inhibitors.

B. Simplified infant prophylaxis dosing

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birth weight 2000–2499 g[a]	10 mg once daily (1 ml of syrup once daily)	10 mg twice daily (1 ml of syrup twice daily)
Birth weight ≥2500 g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)
>6 weeks to 12 weeks		
	20 mg once daily (2 ml of syrup once daily or half a 50 mg tablet once daily)	No dose established for prophylaxis; use treatment dose 60 mg twice daily 6 ml of syrup twice daily or a 60 mg tablet twice daily

[a] For infants weighing <2000 g and older than 35 weeks of gestational age, the suggested doses are: NVP 2 mg/kg per dose once daily and AZT 4 mg/kg per dose twice daily. Premature infants younger than 35 weeks of gestational age should be dosed using expert guidance.

C. Weight-based dosing for ARV formulations for infants and children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on ARV drugs for which there are indications or formulations for children or sufficient information and evidence to provide guidance on prescribing and dosing among infants, children and adolescents younger than 18 years of age. WHO has undertaken the work to develop and update simplified guidance on ARV drugs for use among children through the Paediatric Antiretroviral Working Group.[1]

For simplification and ease of implementation, doses are expressed per weight band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, careful consideration was given to the usual body surface area of children from low- and middle-income countries in that weight band. The primary source of information for the guidance provided is the manufacturer's package insert. This was supplemented with data from other clinical studies as well as consultations of experts in pharmacology for children. For fixed-dose combinations, a dose-modelling tool (http://www.who.int/hiv/paediatric/generictool/en/index.html) was used to predict the dose delivered for each component drug against the recommended dosing schedule. In some cases, the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to ensure that no child would receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. Pharmacokinetic studies have also confirmed the overall safety of this dosing approach. For simplification, ARV drugs that are no longer considered preferred or alternative options for children have been removed from the dosing guidance.

In the context of future introduction of virological testing at birth, and the shift towards treating infants earlier in an effort to reduce early mortality, these guidelines provide drug weight-based dosing for term infants aged <4 weeks, including those weighing less than 3 kg. However, experience is limited with initiating treatment among newborns living with HIV aged <2 weeks, and few pharmacokinetic data can fully inform accurate dosing for drugs other than AZT among newborns, who are undergoing rapid changes in renal and liver function. The dosing provided in this annex for newborns is aligned with that used in ongoing trials; updates will be provided as soon as trial results are available. In addition, reliable pharmacokinetic data in preterm infants are available only for AZT; there is considerable uncertainty about the appropriate dosing for NVP and 3TC, and LPV/r solution should not be given to preterm infants until they have reached 42 weeks of gestational age, making managing HIV treatment in preterm newborns

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extremely challenging. Dosing for postnatal prophylaxis for HIV-exposed infants is not provided here but can be found in section B of Annex 11.

In 2013, the United States Food and Drug Administration approved the use of EFV among children 3 months to 3 years old and weighing at least 3.5 kg. Although the Clinical Guideline Development Group recognized the opportunity to provide an additional drug option to young children and allow further harmonization across age groups, the Group highlighted the need for further data before recommending EFV as a treatment option among children younger than 3 years. These data are still lacking, and the recommended dosing schedule for EFV was not amended in this version of the dosing guidance.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as additional data or newer formulations become available, but national programmes are advised to consider the most recent product labelling for up-to-date information. Additional information can also be found in specific drug information sheets provided at http://emtct-iatt.org/resources-main.

ARV drugs and formulations are available from several manufacturers, and the available dosage strengths of tablets, capsules and liquid formulations may vary from the information given here. Several optimal dosage forms for children are currently being developed but have not yet received regulatory approval during the writing of these guidelines. National programme managers should ensure that products planned for use are currently available and of appropriate quality and stability. For guidance on the quality assurance of medicines, see the WHO medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/about/en/index.html) and *Access to HIV/AIDS drugs and diagnostics of acceptable quality*, which is available and updated at http://www.who.int/hiv/amds/selection/en/index.html. The current list of WHO prequalified drugs is available at http://apps.who.int/prequal. For the current list of ARV drugs approved and tentatively approved by the United States Food and Drug Administration, see http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118915.htm. For the policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance, see http://www.theglobalfund.org/en/healthproducts/qualityassurance/pharmaceutical.

General principles

The principles followed in developing the WHO simplified tables include the following.

• Using an age-appropriate fixed-dose combination is preferable for any regimen if such a formulation is available.

• Oral liquid or syrup formulations should be avoided where possible. Dispersible tablets (or tablets for oral solution) are the preferred solid oral dosage forms, since each dispersible tablet can be made into liquid at the point of use.

• If suitable dispersible fixed-dose combinations are not available and oral liquids must be used, it is recommended that children be switched to a solid oral dosage form as soon as possible.

• Where children have to use adult formulations, care must be taken to avoid underdosing and overdosing. Using functionally scored tablets is preferable to ensure accurate dosing, especially if adult dosage forms are used. Splitting unscored tablets should be avoided, since uniform distribution of the active drug product cannot be assured in tablet fragments.

- Some tablets such as LPV/r or ATV heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split, dissolved, chewed or crushed, since these products have variable bioavailability when not swallowed whole.

- Different dosing between morning and evening doses should be avoided if possible.

- Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or change weight.

- Country programmes should consider the national regulatory status and local availability status and availability of specific dosage forms when developing national treatment recommendations for children.

- Research is ongoing for several ARV medications to establish dosing guidance for newborns, infants and young children. The age indications for each drug mentioned in the drug pages are based on current evidence and will be updated as new recommendations become available.

Table 1. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children 4 weeks of age and older[a]

Drug	Strength of tablets (mg)	Number of tablets by weight band morning and evening										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC[a]	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/ 150 mg	1	1
AZT/3TC/ NVP[a]	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/ 150 mg/200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/ 300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/ 300 mg	0.5	0.5

[a] For infants younger than 4 weeks of age, see Table 4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

Table 2. Simplified dosing of child-friendly solid and oral liquid formulations for once-daily dosing for infants and children 4 weeks of age and older[a]

Drug	Strength of tablet (mg)	Number of tablets or capsules by weight band once daily					Strength of adult tablet (mg)	Number of tablets or capsules by weight band once daily
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg		25.0–34.9 kg
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200 mg	2
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/ 300 mg	1
ABC/3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/ 300 mg	1
ATV[c]	Capsules 100 mg	–	–	1	2	2	300 mg	2 (100 mg)[d] or 1 (300 mg)
TDF[e]	Oral powder scoops 40 mg/scoop	–	–	3	–	–	300 mg	1 (200 mg)[d] or 1 (300 mg)
TDF[e]	Tablets 150 mg or 200 mg	–	–	–	1 (150 mg)	1 (200 mg)		

[a] For infants younger than 4 weeks of age, see Table 4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] EFV is not recommended for children younger than 3 years and weighing less than 10 kg. The United States Food and Drug Administration approved EFV for use for children younger than 3 years weighing more than 3.5 kg during the finalization of these guidelines (3.5–5.0 kg: two 50-mg capsules; 5.0–7.5 kg: three 50-mg capsules; 7.5–15.0 kg: one 200-mg capsule), but more data are urgently needed to inform recommendations for using EFV in this age group.

[c] ATV is only approved for use for children 3 months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands. The ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children weighing 5–10 kg should be administered 200 mg of ATV powder (4 packets, 50 mg per packet) with 80 mg of RTV oral solution (5 ml). http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206352s003,021567s038lbl.pdf

[d] 200 mg should be used for weight 25.0–29.9 kg and 300-mg tablets for 30.0–34.9 kg.

[e] TDF is only approved for use for children 2 years and older. Target dose: 8 mg/kg or 200 mg/m^{2} (maximum 300 mg). The Paediatric Antiretroviral Working Group developed this guidance to harmonize TDF dosing with WHO weight bands and to reduce the numbers of strengths to be made available. The WHO generic tool was used based on the target dose provided by the manufacturer's package insert. In accordance with the standard Paediatric Antiretroviral Working Group approach, dosing was developed ensuring that a child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

Table 3. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children 4 weeks of age and older[a]

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets or ml by weight-band morning (AM) and evening (PM)											Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg				25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM			AM	PM
Solid formulations															
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg		1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg		1	1
NVP[b]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg		1	1
LPV/r[c]	Tablet[d] 100 mg/ 25 mg	–	–	–	–	2	1	2	2	2	2	100 mg/ 25 mg		3	3
	Pellets[e] 40 mg/ 10 mg	2	2	3	3	4	4	5	5	6	6	100 mg/ 25 mg		3	3
DRV[f]	Tablet 75 mg	–	–	–	–	3	3	5	5	5	5				
RAL	Chewable tablets 25 mg	–	–	–	–	3	3	4	4	6	6	400 mg		1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5	400 mg		1	1
	Granules[g] (100 mg/sachet)	0.25	0.25	0.5	0.5	–	–	–	–	–	–			–	–
Liquid formulations															
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	–	–	–	–	–		–	–
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–		–	–
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–		–	–
NVP[b]	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–		–	–
LPV/r[c]	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–		–	–
DRV[f]	100 mg/ml	–	–	–	–	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–				

[a] For infants younger than 4 weeks of age, see Table 4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medication. For infants who are at least 4 weeks of age but less than 3 kg, the immaturity of renal and hepatic pathways of elimination is less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

[b] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS)-1 trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q et al. Is nevirapine dose escalation appropriate in young African HIV+ children? 20th Annual Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, USA, 3–6 March 2013 (http://retroconference.org/2013b/Abstracts/46904.htm, accessed 15 May 2015). More definitive evidence is expected from an ongoing trial.

[c] LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed.

[d] The adult 200/50 ml tablet could be used for children 14.0–24.9 kg (1 tablet in the morning and 1 tablet in the evening) and for children 25.0–34.9 kg (2 tablets in the morning and 1 tablet in the evening)

[e] The LPV/r pellets formulation should not be used for infants younger than 3 months. More details on the administration of LPV/r pellets is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

[f] DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if the child weighs less than 15 kg and with RTV 50 mg solid formulation for children weighing 15–30 kg.

[g] RAL granules are approved for use for children as young as 4 weeks, but the feasibility and acceptability of such formulations has not been widely investigated, and concerns have been raised regarding administration in resource-limited settings. The bioequivalence of RAL chewable tablets dispersed in liquid is currently being explored, and more guidance will be provided as soon as additional evidence becomes available.

Table 4. Drug dosing of liquid formulations for twice-daily dosing for infants younger than 4 weeks of age[a]

Drug	Strength of oral liquid (mg/ml)	2–3 kg	3–4 kg	4–5 kg
AZT	10 mg/mL	1 mL	1.5 mL	2 mL
NVP	10 mg/mL	1.5 mL	2 mL	3 mL
3TC	10 mg/mL	0.5 mL	0.8 mL	1 mL
LPV/r[b]	80/20 mg/mL	0.6 mL	0.8 mL	1 mL

[a] There is limited experience with initiating treatment among newborns living with HIV <2 weeks of age, with few pharmacokinetic data to fully inform accurate dosing for drugs other than AZT during a time that renal and liver functioning is rapidly maturing , and LPV/r solution should not be given to infants aged <2 weeks, making management of HIV treatment in newborns challenging. In addition, reliable pharmacokinetic data for preterm infants are available only for AZT, with uncertainty of dosing for NVP and 3TC; LPV/r solution should not be given in preterm infants until they have reached 42 weeks of gestational age. This guidance will be updated when more evidence is available from ongoing trials.

[b] Do not use LPV/r solution for infants <2 weeks of age. LPV/r pellets should not be used for infants younger than 3 months. More details on the administration of LPVr pellets is available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

Table 5. Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children who are at least 4 weeks of age

Drug	Strength of tablet or oral liquid (mg or mg/5ml)	Number of tablets or millilitres by weight band once daily					Strength of adult tablet (mg)	Number of tablets by weight band
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg		25.0–34.9 kg
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	400 mg/ 80 mg	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	800 mg/ 160 mg	1
Isoniazid + co-trimoxazole + B6[a]	Tablets (scored) 300 mg/960 mg/25 mg	–	–	–	0.5	0.5	960 mg/ 300 mg/ 25 mg	1

[a] This formulation is currently awaiting regulatory approval, and a scored tablet (480 mg/150 mg/12.5 mg) is also being developed.

IATT formulary

In recent years, a number of improved ARV formulations have become available, such as dispersible, scored fixed-dose combination tablets in place of the traditional liquid formulations. These products have greatly simplified the delivery of HIV care for children in low-income settings; however, the proliferation of options, has resulted in a multiplicity of formulations across regimens and weight bands. Generic manufacturers use economies of scale to maintain affordable pricing, but fragmentation of demand across too many duplicative products creates instability in the reliable supply of ARV dosage forms for children and complicates procurement and supply chain management.

For this reason, the Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children (convened by WHO and UNICEF in collaboration with multiple implementing partners) provides formulary

guidance to programmes on selection of optimal ARV drugs for children defined using a robust set of criteria. The optimal formulary is currently a list of nine products that deliver recommended and appropriate first- and second-line regimens across all children's weight bands. The formulary was first developed in 2011 but is routinely revised to correspond to current WHO guidelines and available products. Programmes are encouraged to procure dosage forms for children that are included in the IATT Optimal Paediatric ARV Formulary. In special circumstances, (such as third-line regimens), the dosage forms included in the IATT ARV Limited-use formulary may be used (http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf).

The need for new formulations

The work of the Paediatric Antiretroviral Working Group and the Paediatric Antiretroviral Drug Optimisation[1,2] groups continues to highlight the urgent need for fixed-dose combination formulations to provide the recommended first-line regimen: LPV/r-containing solid forms suitable for treating younger children and EFV + ABC + 3TC fixed-dose combination for children 3–10 years old. In addition, the availability of co-formulated ATV/r and DRV/r in heat-stable fixed-dose combination formulations is critical to facilitate treatment sequencing and uptake of scaled-up second- and third-line treatment. Several formulations containing approved ARV drugs for children have been formally given priority and are listed in Table 6. Finally, additional formulations containing newer drugs for which there is currently no indication for children were considered, and the central future role of DTG and TAF in optimizing dose, sequencing and harmonization across age groups was highlighted.

Table 6. Simplified dosing for urgently needed ARV drugs for children recommended by the Paediatric Antiretroviral Drug Optimization groups

Drug	Strength of dosage form (mg)	Number of tablets or sprinkle capsules or sachets by weight band											
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg		25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC + 3TC + LPV/r	30 mg/15 mg/40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	
AZT + 3TC + LPV/r	30 mg/15 mg/40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	
DRV/r	120 mg/20 mg	–	–	–	–	2	2	3	3	3	3	4	4
ATV/r[a]	100 mg/33 mg	–		–		1		2		2		–	
ABC + 3TC + EFV	150 mg/75 mg/150 mg					1.5		2		2.5		3	

[a] Dosing for ATV/r at 14.0–19.9 kg has been adjusted since previous versions of this annex to address concerns of potential underdosing of ATV.

In moving towards promoting drug optimization for children and adolescents, WHO will continue to work to simplify prescribing, dispensing and dosing guidance and work with the pharmaceutical industry (originator and generic) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate the scaling up of ART for children.

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[1] PADO1 meeting report http://apps.who.int/iris/bitstream/10665/104264/1/9789241506830_eng.pdf?ua=1.
[2] PADO 2 meeting http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization/en/.

ANNEX 12

Viral load testing strategy

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┌─────────────────────────────┐      ┌─────────────────────────────┐
│ Targeted viral load         │      │   Routine viral load        │
│ monitoring (suspected       │      │   (early detection of       │
│ clinical or                 │      │   virological failure)      │
│ immunological failue)       │      │                             │
└─────────────────────────────┘      └─────────────────────────────┘
              │                                      │
              └──────────────┐        ┌──────────────┘
                             ▼        ▼
                   ┌─────────────────────────┐
                   │     Test viral load     │
                   └─────────────────────────┘
                             │
                             ▼
                   ┌─────────────────────────┐
                   │ Viral load >1000 copies/ml │
                   └─────────────────────────┘
                             │
                             ▼
                   ┌─────────────────────────┐
                   │ Evaluate for adherence concerns │
                   └─────────────────────────┘
                             │
                             ▼
                   ┌─────────────────────────┐
                   │ Repeat viral load testing after 3–6 months │
                   └─────────────────────────┘
                     │                        │
                     ▼                        ▼
          ┌───────────────────┐    ┌───────────────────┐
          │ Viral load        │    │ Viral load        │
          │ ≤1000 copies/ml   │    │ >1000 copies/ml   │
          └───────────────────┘    └───────────────────┘
                     │                        │
                     ▼                        ▼
          ┌───────────────────┐    ┌───────────────────┐
          │ Maintain first-line│   │ Switch to second-line│
          │ therapy           │    │ therapy           │
          └───────────────────┘    └───────────────────┘
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ANNEX 13

Key drug–drug interactions for antiretroviral drugs

	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Antibiotics (including drugs for TB)																		
Rifampicin								1	2	3			4	5	6			
Rifabutin															7			
Rifapentine													8		9			
Isoniazid																		
Pyrazanamide																		
Ethambutol																		
Ethionamide																		
Oxfloxacin																		
Kanamycin																		
Cycloserine																		
Bedaquiline																		
Co-trimoxazole																		
Opioid substitution therapy																		
Methadone																		
Buprenorphine																		
Antiviral drugs (including drugs for hepatitis B, hepatitis C and herpesviruses)																		
Ribavirin			10				11											
Adefovir		12																
Peginterferon alpha-2a			13															
Telaprevir																		
Boceprevir																		
Entecavir																		
Ganciclovir																		
Aciclovir																		
Sofosbuvir																		
Ledipasvir + sofosbuvir																		
Daclatasvir																		
Simeprevir								14	15	16	17	18	19	20				21
Tenofovir	NA																	
Telbivudin																		

	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Antiparasitic drugs																		
Metronidazole																		
Spectinomycin																		
Antimalarial drugs																		
Amodiaquine												22						
Artemisinin																		
Halofantrine								23	24	25	26							27
Pyrimethamine																		
Sulfadoxine																		
Lumefantrine																		
Mefloquine																		
Antifungal drugs																		
Itraconazole																		
Ketoconazole														28				
Voriconazole														29				
Fluconazole											30							
Amphotericin B																		
Flucytosine																		
Antihistamines																		
Astemizole								31	32	33	34	35	36	37				38
Terfenadine								39	40	41	42	43	44	45				46
Fluticasone																		
Hormonal contraceptives																		
Desogestrel																		
Drospirenone																		
Dydrogesterone																		
Estradiol																		
Ethinylestradiol																		
Etonogestrel																		
Levonorgestrel																		
Medroxyprogesterone (intramuscular)																		

	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Medroxyprogesterone (oral)																		
Norethisterone (norethindrone)																		
Norgestimate																		
Ulipristal																		
Antiretroviral drugs																		
Efavirenz												–	47					48
Etravirine												49	–	50				51
Nevirapine								52					53	–				54
Didanosine					–		55											56
Emtricitabine				57														
Zidovudine			–				58											59
Lamivudine						60												61
Stavudine			62		63		–											64
Atazanavir								–					65	66				67
Darunavir									68	–								69
Lopinavir									–	70								71
Abacavir	–																	72
Ritonavir											–							73
Saquinavir								74	75	76								77
Dolutegravir																–		78
Anxiolytic drugs																		
Midazolam (injection)								80	81	82	83	79						
Midazolam (oral)								86	87	88	89	84						85
Triazolam												90						91
Diazepam																		
Gastrointestinal agents																		
Omeprazole								92	95	96	97	98			93			
Cisapride								94										99
Esomeprazole								100							101			
Lansoprazole								102							103			
Pantoprazole								104							105			

Drug	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Rabeprazole								106							107			
Metaclopramide																		
Al-, Mg- and Ca-containing antacids																		
Cardiovascular drugs																		
Amiodarone									108	109	110	115						111
Bepridil								112		113	114							
Flecainide								116	117		118							
Lidocaine										119								
Propafenone								120			121							
Quinidine								122		123	124							125
Dabigatran								126	127	128	129							
Rivaroxaban								130	131	132	133							134
Simvastatin								135	136	137	138							139
Lovastatin								140	141	142	143							144
Lercanidipine								145	146	147	148							149
Pravastatin																		
Amlodipine																		
Bisoprolol																		
Enalapril																		
Hydralazine	—	—	—	—	—	—	—					—	—	—	—	—	—	—
Hydrochlorothiazide								—	—	—	—	—	—	—	—	—	—	—
Bendroflumethiazide								—	—	—	—	—	—	—	—	—	—	—
Methyldopa																		
Antipsychotic and neuroleptic drugs																		
Fluphenazine								150	151	152	153							
Pimozide								154	155	156	157	158						159
Antimigraine agents																		
Ergotamine								160	161	162	163	164	165					166
Dihydroergotamine								167	168	169	170	171	172	173				174

	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Anticonvulsant drugs																		
Carbamazepine													175		176	177		178
Phenobarbital										179			180		181	182		183
Phenytoin										184			185		186	187		188
Oxcarbazepine															189	190		
Gabapentin																		
Valproic acid																		
Recreational drugs																		
Marijuana (cannabis)																		
Cocaine																		
Alcohol																		
Methamphetamines																		
Gamma-Hydroxybutyric acid																		
Ecstasy																		
Amyl nitrate																		
Ketamine																		
LSD (lysergic acid diethylamide)																		
Antidepressant drugs																		
Fluoxetine																		
Amitriptyline																		
Antidiabetic drugs																		
Insulin																		
Gliclazide																		
Glucagon	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Metformin																		
Vitamins and supplements																		
Ascorbic acid (Vitamin C)																		
Colecalciferol (Vitamin D3)																		
Cyanocobalamin (Vitamin B12)																		
Phytomenadione (Vitamin K1)																		
Pyridoxine (Vitamin B6)																		

	ABC	TDF	AZT	3TC	ddI	FTC	d4T	ATV	LPV	DRV	RTV	EFV	ETR	NVP	RPV	DTG	RAL	EVG + COB
Folic acid																		
Retinol (Vitamin A)																		
Riboflavin (Vitamin B$_2$)																		
Thiamine (Vitamin B$_1$)																		
Vitamin E																		
Magnesium																		
Iron																		
Zinc																		
Calcium																		
Other drugs																		
Hydroxyurea					191		192											
Sildenafil – pulmonary arterial hypertension								193	194	195	196							
Sildenafil – erectile dysfunction																		
Allopurinol					197													
Alfuzosin								198	199	200	201							202
Dexamethasone															203			
Piroxicam											204							
St John's wort								205	206	207	208	209	210	211	212	213		214
Orlistat																		

Figure Legend

No clinically significant interaction or interaction unlikely based on knowledge of drug metabolism.

Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

Interaction likely: do not use or use with caution (# indicates cross-reference to interaction explanation).

–   No clear data, actual or theoretical, indicate whether an interaction will occur.

Number	Quality of the evidence	Explanation
1	High	Contraindicated because of decreased atazanavir concentrations. Co-administration of rifampicin (600 mg once daily) and atazanavir + ritonavir (300 + 100 mg once daily) to 16 subjects decreased atazanavir maximum serum concentration (Cmax), area under the curve (AUC) and minimum serum concentration (Cmin) by 53%, 72% and 98% respectively. Co-administration of twice-daily atazanavir alone with rifampicin failed to provide adequate atazanavir exposure, and liver reactions were highly frequent.
2	High	Co-administration of lopinavir with rifampicin is not recommended, since it causes large decreases in lopinavir concentrations, which may, in turn, significantly decrease the lopinavir therapeutic effect. Adequate exposure to lopinavir/ritonavir may be achieved when a higher dose of Kaletra® (400/400 mg twice daily) is used, but this is associated with a higher risk of liver and gastrointestinal toxicity. Therefore, this co-administration should be avoided unless judged strictly necessary.
3	Low	Co-administration is contraindicated, since it may significantly reduce darunavir concentrations.
4	Low	Rifampicin is a potent inducer of CYP450 enzymes. Etravirine should not be used with rifampicin, since co-administration may significantly reduce etravirine plasma concentrations and the therapeutic effect of etravirine.
5	High	Co-administration is contraindicated because of decreased nevirapine concentrations. Co-administration of nevirapine (200 mg twice daily) with rifampicin (600 mg once daily) increased rifampicin AUC (11%) and had no effect on Cmax. Compared with historical controls, there were clinically significant decreases in nevirapine AUC (58%), Cmax (50%) and Cmin (68%). Consider using rifabutin instead. Preliminary data suggest that adequate nevirapine concentrations may be attained among people with low body weight. Dose escalation should not be used when starting nevirapine, and a dose increase may be necessary.
6	High	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly. Co-administration of rilpivirine (150 mg once daily) and rifampicin (600 mg once daily) decreased rilpivirine Cmax, AUC and Cmin by 69%, 80% and 89%, respectively. There was no significant effect on rifampicin Cmax and AUC nor on the Cmax of 25-desacetylrifampicin, but the AUC of the metabolite decreased by 9%. Note: this interaction study was performed with a dose higher than the licensed dose for rilpivirine assessing the maximal effect on the co-administered drug. The recommendation is applicable to the licensed dose of rilpivirine 25 mg once daily.
7	Moderate	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly. Co-administration of rilpivirine (150 mg once daily) and rifabutin (300 mg once daily) decreased rilpivirine Cmax, AUC and Cmin by 35%, 46% and 49%, respectively. Note: this interaction study was performed with a dose higher than the licensed dose for rilpivirine assessing the maximal effect on the co-administered drug. The recommendation is applicable to the licensed dose of rilpivirine 25 mg once daily.
8	Low	Rifapentine is a potent inducer of CYP450 enzymes. Etravirine should not be used with rifapentine, since co-administration may significantly reduce etravirine plasma concentrations and the therapeutic effect of etravirine.
9	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
10	Moderate	Co-administration of ribavirin and zidovudine is not advised. Exacerbation of anaemia has been reported in people coinfected with HIV and HCV receiving ribavirin and zidovudine. Hepatic decompensation (some fatal) has occurred among people coinfected with HIV and HCV receiving combination antiretroviral therapy and interferon-alfa with or without ribavirin. Discontinue zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon-alfa, ribavirin or both.
11	Moderate	Potential interaction that may increase the intracellular triphosphate levels of didanosine, which could cause or worsen clinical toxicities. Increased risk of mitochondrial toxicity. Co-administration is not recommended.
12	Low	Tenofovir and adefovir dipivoxil should not be co-administered. The pharmacokinetics of adefovir were evaluated among 22 people following administration of single doses of adefovir alone and with multiple doses of tenofovir. Adefovir exposure met the definition of pharmacokinetic equivalence (90% confidence interval for the geometric mean ratio of 80% to 125%) when dosed with or without tenofovir. The mean differences in Cmax and AUC were 7% or less.
13	None	People treated with peginterferon and ribavirin with zidovudine are at increased risk of developing anaemia, and the concomitant use of this combination with zidovudine is therefore not recommended.
14	High	A study examining amodiaquine pharmacokinetics following co-administration of efavirenz (600 mg once daily) and amodiaquine + artesunate (600 + 250 mg once daily) among people living with HIV had to be terminated after the first two subjects developed asymptomatic but significant elevation of liver transaminases. Addition of efavirenz increased amodiaquine AUC by 114% (subject 1) and 302% (subject 2). Efavirenz AUCs were similar or above historical data.
15	Low	Halofantrine is extensively metabolized by CYP3A4. Inhibition of halofantrine metabolism could potentially prolong the QT interval. Given the narrow therapeutic index of this drug, combination with PIs is contraindicated.

Number	Quality of the evidence	Explanation
16	Low	Halofantrine is extensively metabolized by CYP3A4. Inhibition of halofantrine metabolism could potentially prolong the QT interval. Given the narrow therapeutic index of this drug, combination with PIs is contraindicated.
17	Low	Halofantrine is extensively metabolized by CYP3A4. Inhibition of halofantrine metabolism could potentially prolong the QT interval. Given the narrow therapeutic index of this drug, combination with PIs is contraindicated.
18	Low	Halofantrine is extensively metabolized by CYP3A4. Inhibition of halofantrine metabolism could potentially prolong the QT interval. Given the narrow therapeutic index of this drug, combination with PIs is contraindicated.
19	High	Note: the prescribing information for the United States of America states that nevirapine and itraconazole should not be co-administered, but the European summary of product characteristics suggests a dose increase for itraconazole. The charts reflect the more cautious option. Co-administration of nevirapine (200 mg once daily for 7 days) and itraconazole (200 mg once daily for 7 days) was studied among 12 people living with HIV. Itraconazole mean AUC and Cmax were significantly reduced: by 61% and 38%, respectively. The pharmacokinetics of nevirapine did not differ significantly. Dose adjustment of itraconazole may be needed because of possible decrease in clinical effect.
20	High	Nevirapine and ketoconazole should not be administered concomitantly because decreased ketoconazole concentrations may reduce its efficacy. Co-administration of nevirapine (200 mg twice daily) with ketoconazole (400 mg once daily) decreased ketoconazole AUC (72%) and Cmax (44%), and Cmin was below the limit of detection for the assay. The effect on nevirapine pharmacokinetics was not significant (15–28% increase in exposure compared with historical data).
21	Moderate	Co-administration with full-dose ritonavir is contraindicated because of reduction in voriconazole concentrations and possible loss of effect. Co-administration with low-dose ritonavir should be avoided unless an assessment of the benefit and risk to the person taking the drug justifies the use of voriconazole. Co-administration of ritonavir (400 mg twice daily) and voriconazole (200 mg twice daily) had no effect on ritonavir AUC or Cmax but decreased voriconazole AUC (82%) and Cmax (66%). Co-administration of voriconazole (200 mg twice daily) and ritonavir (100 mg twice daily) decreased voriconazole AUC and Cmin by 39% and 24%, respectively.
22	Low	Atazanavir/ritonavir should not be used in combination with CYP3A4 substrates that have narrow therapeutic windows, such as astemizole.
23	Low	Co-administration of astemizole and Kaletra® is contraindicated because of the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
24	Low	Co-administration is contraindicated, since it may increase astemizole concentrations, which may result in serious and/or life-threatening reactions such as cardiac arrhythmia.
25	Low	Co-administration is contraindicated, since it is likely to increase astemizole concentrations and the risk of cardiac arrhythmia.
26	Low	Co-administration is contraindicated, since it could inhibit the metabolism of astemizole and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
27	Very low	Etravirine and astemizole should not be co-administered, since it could potentially increase astemizole concentrations and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
28	Very low	Nevirapine and astemizole should not be co-administered, since it could potentially increase astemizole concentrations (through competition for CYP3A4) and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
29	Low	Atazanavir/ritonavir should not be used in combination with CYP3A4 substrates that have narrow therapeutic windows, such as terfenadine.
30	Low	Co-administration of lopinavir and terfenadine is contraindicated because of the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
31	Low	Co-administration is contraindicated, since it may increase terfenadine concentrations which may result in serious and/or life-threatening reactions such as cardiac arrhythmia.
32	Low	Co-administration is contraindicated, since it is likely to increase terfenadine concentrations and the risk of cardiac arrhythmia.
33	Low	Co-administration is contraindicated, since it could inhibit the metabolism of terfenadine and create the potential for serious and/or life-threatening reactions.
34	Very low	Etravirine and terfenadine should not be co-administered, since it could potentially inhibit terfenadine metabolism through competition for CYP3A4 and create the potential for serious and/or life-threatening reactions.
35	Very low	Nevirapine and terfenadine should not be co-administered, since it could potentially inhibit terfenadine metabolism through competition for CYP3A4 and create the potential for serious and/or life-threatening reactions.

Number	Quality of the evidence	Explanation
36	Low	Co-administration decreased etravirine AUC by 41% and C_{max} by 18%. Co-administration is contraindicated, since it significantly decreases etravirine concentrations. Combining two NNRTIs has not been shown to be beneficial. If people switch from efavirenz to etravirine, the inducing effect of efavirenz has been shown to persist up to 14 days after stopping drug intake, resulting in decreases in etravirine AUC, C_{max} and C_{min} (32%, 22% and 42% for once daily; 26%, 19% and 34% for twice daily). The decrease in etravirine is comparable to that determined in the presence of darunavir/ritonavir and is not considered clinically significant.
37	Low	Co-administration decreased etravirine AUC by 41% and C_{max} by 18%. Co-administration is contraindicated, since it significantly decreases etravirine concentrations. Combining two NNRTIs has not been shown to be beneficial. If people switch from efavirenz to etravirine, the inducing effect of efavirenz has been shown to persist up to 14 days after stopping drug intake, resulting in decreases in etravirine AUC, C_{max} and C_{min} (32%, 22% and 42% for once daily; 26%, 19% and 34% for twice daily). The decrease in etravirine is comparable to that determined in the presence of darunavir/ritonavir and is not considered clinically significant.
38	Moderate	Co-administration decreased etravirine AUC by 55% and C_{max} by 36%. Co-administration is contraindicated, since it significantly decreases etravirine concentrations. Combining two NNRTIs has not been shown to be beneficial.
39	Moderate	Co-administration of nevirapine with atazanavir/ritonavir is not recommended, since it increases nevirapine exposure and decreases atazanavir C_{min}. The decrease in atazanavir C_{min} might negatively affect the efficacy of atazanavir.
40	Moderate	Co-administration decreased etravirine AUC by 55% and C_{max} by 36%. Co-administration is contraindicated, since it significantly decreases etravirine concentrations. Combining two NNRTIs has not been shown to be beneficial.
41	Moderate	No significant pharmacokinetic interaction observed. However, co-administration not recommended because of increased risk of peripheral neuropathy, pancreatitis and lactic acidosis.
42	Low	Potential competition for metabolism with other cytidine analogues. Co-administration not recommended.
43	Moderate	Co-administration not recommended because of competition for metabolism with other thymidine analogues.
44	Low	Potential competition for metabolism with other cytidine analogues. Co-administration not recommended.
45	Moderate	Co-administration not recommended because of competition for metabolism with other thymidine analogues.
46	Moderate	No significant pharmacokinetic interaction observed. However, co-administration not recommended because of increased risk of peripheral neuropathy, pancreatitis and lactic acidosis.
47	Low	Co-administration is contraindicated in the prescribing information for the United States of America, but the European summary of product characteristics says they can be co-administered without dose adjustment. Co-administration with atazanavir/ritonavir decreases atazanavir C_{min} by ~40% and increases etravirine AUC. Etravirine should be used with caution with atazanavir or atazanavir/ritonavir.
48	Moderate	Co-administration of nevirapine with atazanavir/ritonavir is not recommended, since it increases nevirapine exposure and decreases atazanavir Cmin. The decrease in atazanavir Cmin might negatively effect the efficacy of atazanavir.
49	Low	Co-administration of darunavir (1200 mg twice daily, with or without 100 mg ritonavir) did not significantly affect lopinavir pharmacokinetics but decreased darunavir AUC by ~40% (relative to data obtained with darunavir/ritonavir 600/100 mg alone). Because of decreased darunavir exposure, appropriate doses of the combination have not been established, and it is not recommended to co-administer lopinavir/ritonavir with darunavir.
50	Low	Co-administration of darunavir (1200 mg twice daily, with or without 100 mg ritonavir) did not significantly affect lopinavir pharmacokinetics but decreased darunavir AUC by ~40% (relative to data obtained with darunavir/ritonavir 600/100 mg alone). Because of decreased darunavir exposure, appropriate doses of the combination have not been established, and it is not recommended to co-administer lopinavir/ritonavir with darunavir.
51	Low	Co-administration is contraindicated, since it could inhibit the metabolism of midazolam and create the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
52	Low	Co-administration of oral midazolam and atazanavir is contraindicated because of potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression. Co-administration of parenteral midazolam should be done with caution and in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Number	Quality of the evidence	Explanation
53	High	Kaletra® must not be co-administered with orally administered midazolam, since it results in increased plasma concentrations of midazolam, thereby increasing the risk of extreme sedation and respiratory depression.
54	Low	Co-administration is contraindicated with oral midazolam, since it may increase midazolam concentrations, which may result in serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. However, the European summary of product characteristics does not contraindicate the use of parenteral midazolam. Co-administration of parenteral midazolam should be done with caution and in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
55	Low	Co-administration of oral midazolam is contraindicated, since midazolam concentrations could increase, thereby increasing the risk of extreme sedation or respiratory depression. Caution is recommended with parenteral midazolam: if it is co-administered, it should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment should be considered, especially if more than a single dose of midazolam is administered.
56	Low	Co-administration is contraindicated, since it could inhibit the metabolism of midazolam and create the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
57	Low	Co-administration of triazolam and atazanavir is contraindicated because of potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
58	Low	Co-administration of triazolam and lopinavir is contraindicated because of the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
59	Low	Co-administration is contraindicated, since it may increase triazolam concentrations, which may result in serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
60	High	Co-administration is contraindicated, since it is increases triazolam AUC by >20-fold and C_{min} by 87%. This has the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
61	Very low	Co-administration is contraindicated, since it could inhibit the metabolism of triazolam and create the potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
62	High	Omeprazole decreased atazanavir AUC by 75%. Co-administration is contraindicated for treatment-experienced patients in the prescribing information for the United States of America and not recommended for all patients in the European summary of product characteristics. If co-administration is assessed to be unavoidable, close clinical monitoring is recommended; doses of omeprazole should not exceed 20 mg and must be taken about 12 hours prior to the atazanavir/ritonavir. The European summary of product characteristics recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.
63	Moderate	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly. When rilpivirine (150 mg once daily) and omeprazole (20 mg once daily) were co-administered, rilpivirine exposure decreased by ~40% and omeprazole exposure decreased by ~14%. Note: this interaction study was performed with a dose higher than the licensed dose for rilpivirine assessing the maximal effect on the co-administered drug. The recommendation is applicable to the licensed dose of rilpivirine 25 mg once daily.
64	Low	Co-administration of cisapride and atazanavir is contraindicated because of potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
65	Low	Co-administration of cisapride and Kaletra® is contraindicated because of potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
66	Low	Co-administration is contraindicated, since it may increase cisapride concentrations, which may result in serious and/or life-threatening reactions such as cardiac arrhythmia.
67	Low	Co-administration is contraindicated, since it is likely to increase cisapride concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
68	Low	Co-administration is contraindicated, since it could inhibit the metabolism of cisapride and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.

Number	Quality of the evidence	Explanation
69	Low	No data are available with esomeprazole; lansoprazole decreased atazanavir AUC by 94%, and omeprazole decreased atazanavir AUC by 75%. Co-administration with proton pump inhibitors is contraindicated for treatment-experienced patients in the prescribing information for the United States of America and not recommended for all patients in the European summary of product characteristics. If co-administration is assessed to be unavoidable, close clinical monitoring is recommended; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken about 12 hours before the atazanavir/ritonavir. The European summary of product characteristics recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.
70	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
71	Moderate	Lansoprazole decreased atazanavir (alone) AUC by 94%; omeprazole decreased atazanavir (+ ritonavir) AUC by 75%. Co-administration with proton pump inhibitors is contraindicated for treatment-experienced patients in the prescribing information for the United States of America and not recommended for all patients in the European summary of product characteristics. If co-administration is assessed to be unavoidable, close clinical monitoring is recommended; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken about 12 hours before the atazanavir/ritonavir. The European summary of product characteristics recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.
72	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
73	Low	No data are available for pantoprazole; lansoprazole decreased atazanavir AUC by 94%, and omeprazole decreased atazanavir AUC by 65–75%. Co-administration with proton pump inhibitors is contraindicated for treatment-experienced patients in the prescribing information for the United States of America and not recommended for all patients in the European summary of product characteristics. If co-administration is assessed to be unavoidable, close clinical monitoring is recommended; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken about 12 hours before the atazanavir/ritonavir. The European summary of product characteristics recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.
74	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
75	Low	Co-administration with proton pump inhibitors is contraindicated for treatment-experienced patients in the prescribing information for the United States of America and not recommended for all patients in the European summary of product characteristics. If co-administration is assessed to be unavoidable, close clinical monitoring is recommended; doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken about 12 hours before the atazanavir/ritonavir. The European summary of product characteristics recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.
76	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
77	Low	Potential for increased amiodarone concentrations. Co-administration contraindicated in European summary of product characteristics. The prescribing information for the United States of America suggests caution and concentration monitoring (if available).
78	Low	Co-administration may increase amiodarone concentrations. The European summary of product characteristics contraindicates co-administration. The prescribing information for the United States of America suggests caution and concentration monitoring of amiodarone.
79	Low	Co-administration is contraindicated, since it is likely to increase amiodarone concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
80	Low	Co-administration with atazanavir has not been studied but may increase bepridil concentrations and has the potential to produce serious and/or life-threatening adverse events. Caution is warranted and concentration monitoring is recommended. Co-administration with atazanavir/ritonavir is contraindicated in the European summary of product characteristics.
81	Low	Co-administration may increase bepridil concentrations. The European summary of product characteristics contraindicates co-administration. The prescribing information for the United States of America suggests caution and concentration monitoring of bepridil.
82	Low	Co-administration is contraindicated, since it is likely to increase bepridil concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
83	Low	Co-administration is contraindicated, since it could inhibit the metabolism of bepridil and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
84		Not stated
85		Not stated
86	Low	Co-administration is contraindicated, since it is likely to increase flecainide concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
87	Low	Co-administration may increase lidocaine concentrations. The European summary of product characteristics contraindicates co-administration. The prescribing information for the United States of America suggests caution and concentration monitoring of lidocaine.

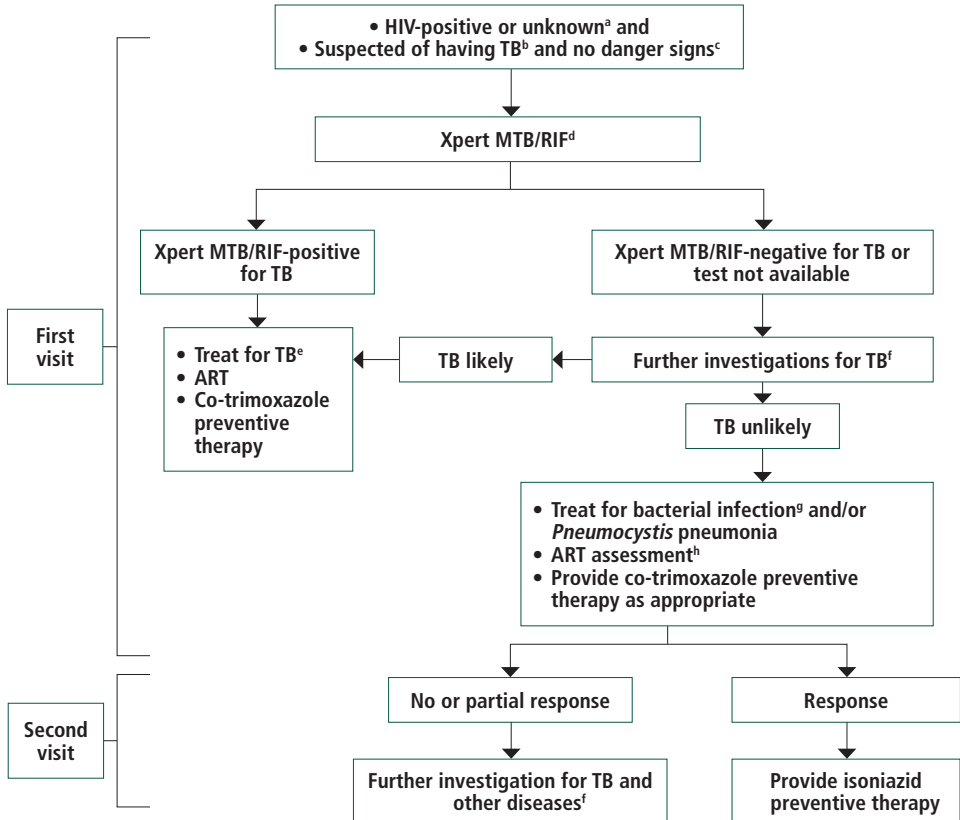| Number	Quality of the evidence	Explanation
88		Not stated
89	Low	Co-administration is contraindicated, since it is likely to increase propafenone concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
90	Low	Co-administration with atazanavir has not been studied but may increase quinidine concentrations and has the potential to produce serious and/or life-threatening adverse events. Caution is warranted and concentration monitoring is recommended. Co-administration with atazanavir/ritonavir is contraindicated in the European summary of product characteristics.
91	Low	Co-administration may increase quinidine concentrations. The European summary of product characteristics contraindicates co-administration. The prescribing information for the United States of America suggests caution and concentration monitoring of quinidine.
92	Low	Co-administration is contraindicated, since it is likely to increase quinidine concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
93	Very low	Co-administration with PIs has not been studied, and co-administration is therefore not recommended.
94	Very low	Co-administration with PIs has not been studied, and co-administration is therefore not recommended.
95	Very low	Co-administration with PIs has not been studied, and co-administration is therefore not recommended.
96	Very low	Co-administration with PIs has not been studied, and co-administration is therefore not recommended.
97	Very low	The use of rivaroxaban is not recommended with HIV PIs. These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree, which may lead to an increased bleeding risk.
98	Very low	The use of rivaroxaban is not recommended with HIV PIs. These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree,. which may lead to an increased bleeding risk.
99	Very low	The use of rivaroxaban is not recommended with HIV PIs. These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk.
100	Very low	The use of rivaroxaban is not recommended with HIV PIs. These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk.
101	Low	Atazanavir and simvastatin should not be co-administered because of potential for serious reactions, such as myopathy, including rhabdomyolysis.
102	Low	Co-administration is contraindicated, since it is expected to markedly increase simvastatin concentrations, which may cause myopathy, including rhabdomyolysis.
103	Low	Co-administration of simvastatin and Kaletra® is contraindicated because of potential for serious reactions such as risk of myopathy including rhabdomyolysis.
104	Low	Co-administration is contraindicated, since it is expected to markedly increase simvastatin concentrations, which could increase the potential for serious reactions, such as myopathy, including rhabdomyolysis.
105	Low	Atazanavir and lovastatin should not be co-administered because of potential for serious reactions, such as myopathy, including rhabdomyolysis.
106	Low	Co-administration of lovastatin and Kaletra® is contraindicated because of potential for serious reactions, such as risk of myopathy, including rhabdomyolysis.
107	Low	Co-administration is contraindicated, since it is expected to markedly increase lovastatin concentrations, which may cause myopathy, including rhabdomyolysis.
108	Low	Co-administration is contraindicated, since it is expected to markedly increase lovastatin concentrations, which could increase the potential for serious reactions, such as myopathy, including rhabdomyolysis.
109	Low	Co-administration is contraindicated with ritonavir-boosted PIs. Strong inhibitors of CYP3A4 (such as ritonavir) could increase concentrations of lercanidipine.
110	Low	Co-administration is contraindicated with ritonavir-boosted PIs. Strong inhibitors of CYP3A4 (such as ritonavir) could increase concentrations of lercanidipine.
111	Low	Co-administration is contraindicated with ritonavir-boosted PIs. Strong inhibitors of CYP3A4 (such as ritonavir) could increase concentrations of lercanidipine.
112	Low	Co-administration is contraindicated with ritonavir. Strong inhibitors of CYP3A4 (such as ritonavir) could increase concentrations of lercanidipine.

Number	Quality of the evidence	Explanation
113	Low	This interaction has not been studied. Concurrent use of other drugs that also prolong the QT interval is likely to potentiate the effect of fluphenazine on QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Rare reports of second- or third-degree atrio-ventricular block among people with underlying structural heart disease and pre-existing conduction system abnormalities or people receiving medicinal products known to prolong the PR interval have been reported among people receiving ritonavir. Ritonavir should be used with caution among such people. Particular caution should be used when prescribing atazanavir in association with medicinal products that can potentially increase the QT interval. Ritonavir-boosted atazanavir could potentially increase levels of fluphenazine via inhibition of CYP2D6 metabolism, increasing the likelihood of adverse events.
114	Low	This interaction has not been studied. Concurrent use of other drugs that also prolong the QT interval is likely to potentiate the effect of fluphenazine on QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Rare reports of second- or third-degree atrioventricular block among people with underlying structural heart disease and pre-existing conduction system abnormalities or among people receiving medicinal products known to prolong the PR interval have been reported among people receiving ritonavir. Ritonavir should be used with caution among such people. Particular caution must be used when prescribing lopinavir/ritonavir and medicinal products known to induce QT interval prolongation. Ritonavir-boosted lopinavir could potentially increase levels of fluphenazine via inhibition of CYP2D6 metabolism, increasing the likelihood of adverse events.
115	Low	This interaction has not been studied. Concurrent use of other drugs that also prolong the QT interval is likely to potentiate the effect of fluphenazine on QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Rare reports of second- or third-degree atrioventricular block among people with underlying structural heart disease and pre-existing conduction system abnormalities or among people receiving medicinal products known to prolong the PR interval have been reported among people receiving ritonavir. Ritonavir should be used with caution among such people. Cardiac side effects including acute prolonged electrocardiogram QT have been observed rarely with darunavir treatment. Ritonavir-boosted darunavir could potentially increase levels of fluphenazine via inhibition of CYP2D6 metabolism, increasing the likelihood of adverse events.
116	Low	This interaction has not been studied. Concurrent use of other drugs that also prolong the QT interval is likely to potentiate the effect of fluphenazine on QT interval. Therefore, concurrent use of these drugs and fluphenazine is contraindicated. Rare reports of second- or third-degree atrioventricular block among people with underlying structural heart disease and pre-existing conduction system abnormalities or among people receiving medicinal products known to prolong the PR interval have been reported among people receiving ritonavir. Ritonavir should be used with caution among such people. Ritonavir could potentially increase levels of fluphenazine via inhibition of CYP2D6 metabolism, increasing the likelihood of adverse events.
117	Low	Co-administration of pimozide and atazanavir is contraindicated because of potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
118	Low	Co-administration of pimozide and Kaletra® is contraindicated because of potential for serious and/or life-threatening reactions such as serious abnormalities of the blood and blood-forming organs or cardiac arrhythmia.
119	Low	Co-administration is contraindicated, since it may increase pimozide concentrations, which may result in serious and/or life-threatening reactions such as cardiac arrhythmia.
120	Low	Co-administration is contraindicated, since it is likely to increase pimozide concentrations and the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
121	Low	Co-administration is contraindicated, since it could inhibit the metabolism of pimozide and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmia.
122	Low	Co-administration of ergotamine and atazanavir is contraindicated because of potential for serious and/or life-threatening events such as acute ergot toxicity.
123	Low	Co-administration of ergotamine and Kaletra® is contraindicated because of potential for serious and/or life-threatening reactions such as acute ergot toxicity.
124	Low	Co-administration is contraindicated, since it may increase ergotamine concentrations which may result in serious and/or life-threatening reactions such as acute ergot toxicity.
125	Low	Co-administration is contraindicated, since it is likely to increase ergotamine concentrations and the potential for serious and/or life-threatening reactions such as acute ergot toxicity.
126	Low	Co-administration is contraindicated, since it could inhibit the metabolism of ergotamine and create the potential for serious and/or life-threatening reactions such as acute ergot toxicity.
127		Not stated
128	Low	Co-administration of dihydroergotamine and atazanavir is contraindicated because of potential for serious and/or life-threatening events such as acute ergot toxicity.
129	Low	Co-administration of dihydroergotamine and Kaletra® is contraindicated because of potential for serious and/or life-threatening reactions such as acute ergot toxicity.

Number	Quality of the evidence	Explanation
130	Low	Co-administration is contraindicated, since it may increase dihydroergotamine concentrations, which may result in serious and/or life-threatening reactions such as acute ergot toxicity.
131	Low	Co-administration is contraindicated, since it is likely to increase dihydroergotamine concentrations and the potential for serious and/or life-threatening reactions such as acute ergot toxicity.
132	Low	Co-administration is contraindicated, since it could inhibit the metabolism of dihydroergotamine and create the potential for serious and/or life-threatening reactions such as acute ergot toxicity.
133	Very low	Etravirineand dihydroergotamine should not be co-administered, since it could potentially inhibit dihydroergotamine metabolism through competition for CYP3A4 and create the potential for serious and/or life-threatening reactions.
134	Very low	Nevirapine and dihydroergotamine should not be co-administered, since it could potentially inhibit dihydroergotamine metabolism through competition for CYP3A4 and create the potential for serious and/or life-threatening reactions.
135	Low	Etravirine should not be used in combination with carbamazepine, since it is expected to decrease plasma concentrations of etravirine.
136	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
137	Low	The European summary of product characteristics contraindicates co-administration, since it may significantly decrease darunavir concentrations. However, the prescribing information for the United States of America predicts no change in darunavir concentrations but decreased phenobarbital concentrations and advises monitoring phenobarbital.
138	Low	Etravirine should not be used in combination with phenobarbital, since it is expected to decrease etravirine concentrations.
139	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
140	Low	The European summary of product characteristics contraindicates co-administration, since it may significantly decrease darunavir concentrations. However, the prescribing information for the United States of America predicts no change in darunavir concentrations but decreased phenytoin concentrations and advises monitoring phenytoin.
141	Low	Etravirine should not be used in combination with phenytoin, since it is expected to decrease etravirine concentrations.
142	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
143	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.
144	Moderate	Co-administration not recommended because of increased risk of hepatotoxicity, peripheral neuropathy and pancreatitis.
145	Moderate	Co-administration not recommended because of increased risk of hepatotoxicity, peripheral neuropathy and pancreatitis.
146	Low	Co-administration of sildenafil (Revatio®) for treating pulmonary arterial hypertension is contraindicated with atazanavir (with or without ritonavir) as a safe and effective dose has not been established.
147	Low	Co-administration of sildenafil (Revatio®) for treating pulmonary arterial hypertension is contraindicated because a safe and effective dose has not been established. There is increased potential for sildenafil-associated adverse events, including visual abnormalities, hypotension, prolonged erection and syncope.
148	Low	Co-administration of sildenafil (Revatio®) for treating pulmonary arterial hypertension is contraindicated with darunavir/ritonavir because a safe and effective dose has not been established.
149	Low	Co-administration of sildenafil (Revatio®) for treating pulmonary arterial hypertension is contraindicated because a safe and effective dose has not been established.
150	Moderate	Co-administration is not recommended as didanosine exposure is increased. If concomitant use is unavoidable, a dose reduction of didanosine may be required and people should be closely monitored.
151	Low	Co-administration is contraindicated, since alfuzosin concentrations may increase which can result in hypotension.
152	Low	Co-administration is contraindicated, since it may increase alfuzosin concentrations, which may lead to severe hypotension.
153	Low	Co-administration is contraindicated, since darunavir/ritonavir may increase alfuzosin concentrations, which may lead to severe hypotension.
154	Low	Co-administration is contraindicated, since it may increase alfuzosin concentrations and lead to severe hypotension.
155	Low	Co-administration is contraindicated with systemic dexamethasone (except as a single dose), since rilpivirine plasma concentrations may decline significantly.
156	Low	Co-administration is contraindicated, since it is likely to increase piroxicam concentrations and the risk of serious respiratory depression or abnormalities of the blood and blood-forming organs.
157	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease atazanavir concentrations and may result in suboptimal levels.

Number	Quality of the evidence	Explanation
158	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease lopinavir concentrations and may result in suboptimal levels. If a person is already taking St John's wort, stop St John's wort and, if possible, check viral levels. Lopinavir and ritonavir levels may increase on stopping St John's wort. The dose of Kaletra® may need adjusting. The inducing effect may persist for at least two weeks after cessation of treatment with St John's wort.
159	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease lopinavir concentrations and may result in suboptimal levels. If a person is already taking St John's wort, stop St John's wort and, if possible, check viral levels. Lopinavir and ritonavir levels may increase on stopping St John's wort. The dose of Kaletra® may need adjusting. The inducing effect may persist for at least two weeks after cessation of treatment with St John's wort.
160	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease lopinavir concentrations and may result in suboptimal levels. If a person is already taking St John's wort, stop St John's wort and, if possible, check viral levels. Lopinavir and ritonavir levels may increase on stopping St John's wort. The dose of Kaletra® may need adjusting. The inducing effect may persist for at least two weeks after cessation of treatment with St John's wort.
161	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease efavirenz concentrations and may result in suboptimal levels. If a patient is already taking St John's wort, stop St John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St John's wort and the dose of efavirenz may need adjusting. The inducing effect of St John's wort may persist for at least 2 weeks after cessation of treatment.
162	Low	Etravirine and products containing St. John's wort should not be co-administered. Co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of etravirine.
163	Low	Co-administration is contraindicated, since St John's wort is expected to substantially decrease nevirapine concentrations and may result in suboptimal levels. If the person is already taking St John's wort, check nevirapine and, if possible, viral levels and stop St John's wort. Nevirapine levels may increase on stopping St John's wort. The dose of nevirapine may need adjusting. The inducing effect may persist for at least two weeks after cessation of treatment with St John's wort.
164	Low	Co-administration is contraindicated, since rilpivirine plasma concentrations may decline significantly.

ANNEX 14

Algorithm for managing people living with HIV who are suspected of having TB (ambulatory)

- For all people with unknown HIV status, HIV testing should be performed according to national guidelines. [a]

- Suspicion of TB is defined by the presence of any one of the following symptoms. [b]
  - For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
  - For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.

- Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided. [c]

- For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood). [d]

- If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing. [e]

- Further investigations for TB include chest X-ray, clinical assessment and a repeat Xpert MTB/RIF using a fresh specimen. Refer a sample for TB culture where feasible. If Xpert MTB/RIF is not available, conduct acid-fast bacillus (AFB) microscopy. AFB-positive is defined as at least one positive smear, and AFB-negative as two or more negative smears. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed. These investigations may require additional visits. A urine lateral flow lipoarabinomannan (LF-LAM) assay should not be performed for people with no danger sign. [f]

- Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used. [g]

- ART should be recommended for all adults, regardless of CD4 cell count or clinical stage. [h]

ANNEX 15

Algorithm for managing people living with HIV and suspected of having TB (seriously ill)

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┌─────────────────────────────────────────────────────┐
│ • HIV-positive or unknownᵃ and                        │
│ • Seriously ill, suspected of having TBᵇ and danger signsᶜ │
└─────────────────────────────────────────────────────┘
                                          ┌──────────────────┐
                                          │ Immediate referral│
                                          │ to a higher level │
                                          │ facility          │
                                          └──────────────────┘
┌─────────────────────────────────────────────────────┐
│ Immediate referral not possible                       │
│ • Xpert MTB/RIFᵈ                                      │
│ • Parenteral antibiotics for treatment of bacterial infectionsᵉ │
│ • Consider treatment for Pneumocystis pneumonia       │
│ • Chest X-ray if available                            │
└─────────────────────────────────────────────────────┘

┌──────────────────────┐        ┌──────────────────────────────────┐
│ Xpert MTB/RIF-positive│        │ Xpert MTB/RIF-negativeᵍ or no test available │
└──────────────────────┘        └──────────────────────────────────┘

┌──────────────────┐   ┌──────────────────────┐   ┌──────────────────────┐
│ • Treat for TBᶠ  │   │ Clinical worsening or no│  │ Improvement after 3–5 days│
│ • ART            │   │ improvement after 3–5 days│ └──────────────────────┘
│ • Co-trimoxazole │   └──────────────────────┘
│   preventive     │
│   therapy        │   ┌──────────────────────┐   ┌──────────────┐
└──────────────────┘   │ • Start presumptive TB│   │ TB Unlikely  │
                       │   treatment           │   └──────────────┘
                       │ • ART                 │
                       │ • Co-trimoxazole preventive│  ┌──────────────────────────┐
                       │   therapy             │   │ • Reassess for other HIV- │
                       │ • Further investigations for TB│ │   related diseases    │
                       │   and other diseasesʰ │   │ • ART assessmentⁱ        │
                       │ • Complete the course of│  │ • Isoniazid preventive therapy│
                       │   parenteral antibiotics│  │ • Co-trimoxazole preventive│
                       └──────────────────────┘   │   therapy                 │
                                                   │ • Complete the course of  │
                                                   │   parenteral antibiotics  │
                                                   └──────────────────────────┘
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[a] For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

[b] Suspicion of TB is defined by the presence of any one of the following symptoms.
  – For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats.
  – For children living with HIV: poor weight gain, fever, current cough or history of contact with a TB case.

[c] Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided.

[d] For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood).
The urine lateral flow lipoarabinomannan (LF-LAM) assay may be used to assist in diagnosing active TB among seriously ill adults and children living with HIV, regardless of CD4 count.
If Xpert MTB/RIF is not available, conduct AFB microscopy. AFB-positive is defined as at least one positive smear and AFB-negative as two or more negative smears. Refer the specimen for TB culture where feasible.

[e] Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used.

[f] If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.
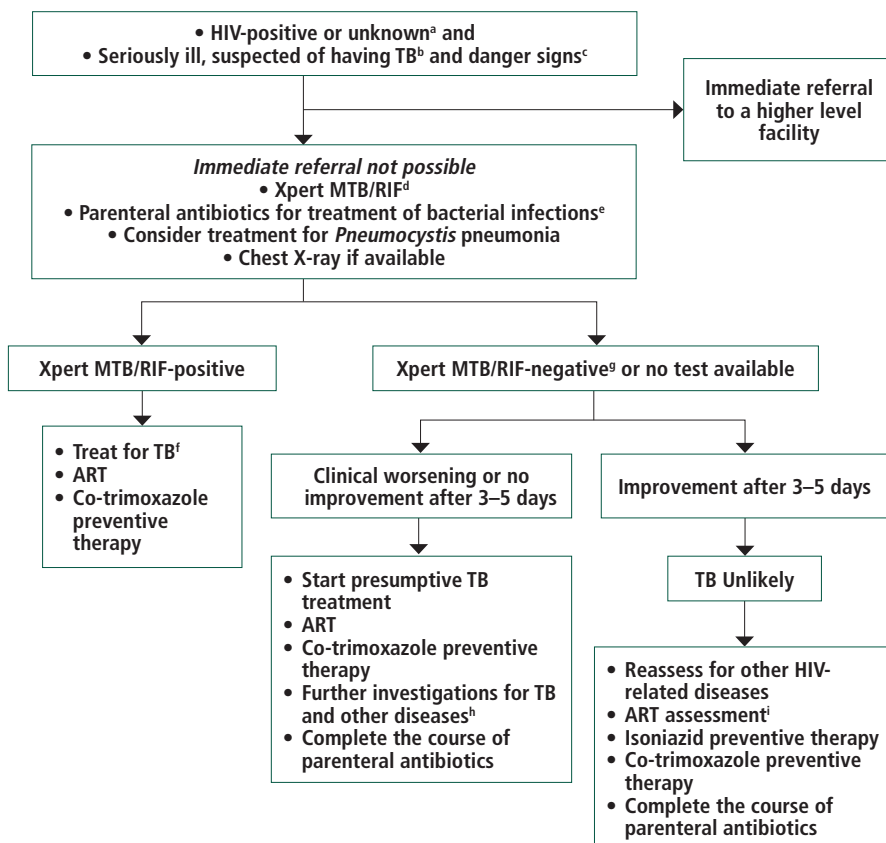
[g] If Xpert MTB/RIF shows negative results, the test can be repeated using a fresh specimen.

[h] Further investigations for TB include chest X-ray, clinical assessment, a repeat Xpert MTB/RIF using a fresh specimen an culture. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

[i] ART should be recommended for all adults, regardless of CD4 cell count or clinical stage.

ANNEX 16

Checklist for periodic evaluation of TB infection control in health facilities

Further information on the purpose of the checklist and guidance for its use is available at: http://www.who.int/tb/areas-of-work/preventive-care/checklist_for_periodic_evaluation_of_tb_infection_control_in_health_facilities.pdf.

Health facility: . . . .

Region/county/district/municipality: . . . .

Type of health facility (such as dispensary, primary health care unit,
ART centre or HIV testing and counselling centre): . . . .

Person completing form and mobile telephone number: . . . .

Date: . . . .

Standards (red font indicates standards needed to be met for measuring global and national indicators)	Yes/no	Means of verification	Recommended action
Part 2: Managerial			
1. There is a written facility-specific infection control plan (that includes TB infection control)		Facility infection control plan	
2. A budget is allocated for TB infection control activities		Budget and expenditure records	
3. A designated person (and committee in larger facilities) is responsible for implementing TB infection control practices in the facility		Job description and interview	
4. The designated TB infection control focal person has received documented TB infection control training or refresher training within the past two years		Training log or human resources record	
5. All clinical staff have received documented TB infection control training or refresher training within the past two years		Training log or human resources record	
6. TB symptoms occurring among staff are immediately investigated and, if TB is diagnosed, it is treated, registered and reported in the confidential occupational health records or in the TB register		Occupational health records or TB register	
Part 2: Administrative			
7. Patients with a cough are identified on arrival at the facility, given guidance on cough etiquette, separated from other patients and fast-tracked through all waiting areas, including consultation, investigations and drug collection		Observation and cough register	
8. All information and education material is systematically checked to prevent the inclusion of stigmatizing or discriminatory language		Language and content of health education material	
9. TB information for patients is readily available and offered by staff		Observation and patient interviews	

Standards (**red** font indicates standards needed to be met for measuring global and national indicators)	Yes/no	Means of verification	Recommended action
10. Supplies are readily available for coughing patients (tissues, surgical masks and cloths) and are being used, and there are medical waste bins for safe disposal		Observation and stock records	
11. A package of HIV and HIV-associated TB prevention and care is available for facility staff on site including (1) confidential HIV testing and post-exposure prophylaxis for all staff, and (2) antiretroviral therapy (ART) and isoniazid preventive therapy for staff members living with HIV		Observation, interviews, occupational health records	
12. There is a tracking mechanism (such as a register) and person responsible for monitoring turn-around time from TB screening to diagnosis and from TB diagnosis to treatment initiation		Records and interview	
13. The median time between screening positive for TB symptoms and actual diagnosis is no more than one day		Cough register and laboratory register or patient records	
14. The median time between actual diagnosis and treatment initiation is no more than one day		TB register or patient records	
15. WHO-recommended rapid diagnostic test, such as Xpert MTB/RIF, is the first TB diagnostic test for people living with HIV		Laboratory register	
16. HIV testing is offered to everyone with presumptive TB, and evaluation for time to ART is carried out for people who test HIV-positive		HIV testing register, TB register, cough register	
Part 3: Environmental			
17. The facility design, patient flow and triage system comply with what is outlined in the infection control plan and/or national infection control policy		Infection control plan/infection control policy and observation	
18. The waiting area is well ventilated (windows and doors open when feasible), and messages on cough hygiene are clearly displayed in all areas frequented by patients		Observation	
19. Patients are not crowded in hallways or waiting areas		Observation	
20. Sputum samples are collected in a well-ventilated, clearly designated area away from others, preferably outdoors		Observation	
21. Diagnosed TB cases who are hospitalized are isolated or grouped according to drug sensitivity status in rooms with adequate natural ventilation or negative pressure		Observation	
Part 4: Personal protective equipment			
22. Respirators are readily available for and being used by staff, particularly for high-risk aerosol-generating procedures and for providing care to patients with diagnosed or suspected infectious multidrug-resistant and extremely drug-resistant TB, in accordance with national guidelines		Observation, stock and stock records	
23. Staff members have been trained in the proper fit and use of respirators		Demonstration and observation	

ANNEX 17

Checklists for decision-making and implementation

Checklists 17.1 to 17.3 provide relevant considerations for decision-making and key elements to consider in assessing health system issues relating to implementing new recommendations. These principles can be a resource for HIV programme managers as they address adopting and implementing these guidelines.

Checklist 17.1. Strategic information for decision-making

1. HIV incidence and prevalence

☐ Which population groups have the highest HIV incidence and prevalence? Relevant criteria include sex, location (urban versus rural), age, income, general population and pregnant women, and key populations (such as men who have sex with men, people who inject drugs, sex workers and prisoners).

☐ What is the HIV seroprevalence among the partners of index cases? What is the incidence of HIV infection in serodiscordant couples?

2. Programme and response analysis

Has the decision-making process taken into account:

☐ the current coverage of HIV testing and counselling disaggregated by relevant stratifiers?

☐ the current coverage of ART disaggregated by relevant stratifiers?

☐ the current coverage of ARV drugs for PMTCT and ART among pregnant women living with HIV?

☐ the median CD4 cell count and HIV disease stage of people initiating ART?

☐ the proportion of people starting ART who are alive and still receiving ART after 12, 24 and 60 months?

☐ the prevalence of viral suppression (and percentage of treatment failure) among people receiving ART after 12 months?

☐ the prevalence of HIV drug resistance among people starting first-line ART and among those already receiving treatment?

3. Equity in access

☐ Based on a review of epidemiological and programme response data, do the recommendations promote greater access to ARV drugs and other services for people with least access or those most in need, including key populations?

4. Alignment between evidence and recommendations

☐ Are the recommendations appropriate for the epidemiological setting in which they will be implemented?

☐ Are the recommendations aligned with and do they support the implementation of the programme's overarching vision, goals and objectives?

☐ Have the recommendations been informed by local and national evidence?

5. Contextual issues

☐ Has the decision-making process taken into account how poverty, gender inequality, education, stigma, discrimination and migration status affect HIV vulnerability and access to services?

☐ Are there any punitive laws and practices, at any levels, related to HIV transmission, sex work, drug use or homosexuality?

☐ Has it been determined how such barriers will be dealt with and how the responses will affect programme planning?

☐ Are there legal or regulatory barriers to adolescents being able to have independent access to HIV testing, counselling, treatment and care?

Checklist 17.2. Process for decision-making

1. Does the process follow principles for sound and appropriate decision-making?

☐ **Publicity**. Is the process transparent and open? Are the evidence and rationale for decisions publicly available?

☐ **Relevance**. Do stakeholders affected by these decisions agree that the rationale rests on relevant reasons, principles and evidence?

☐ **Revisability and appeals**. Can decisions be revised and/or appealed in the light of new evidence and arguments?

☐ **Enforcement**. Are all stakeholders aware of the means to ensure that the conditions of publicity, relevance and revisability are met?

2. Have representatives from all relevant stakeholders been included?

☐ Programme experts and managers, including experts and representatives of sexual and reproductive health, maternal and child health, TB, HIV programmes (ART, HIV testing and counselling and PMTCT), drug dependence and harm reduction

☐ Health care providers, including physicians, nurses and counsellors from adult and child HIV clinics, prison health programmes, maternal and child health, TB clinics and harm reduction and drug dependence services in the public and private sectors

☐ Civil society, including people living with HIV, women and youth groups, religious leaders, people with disabilities and representatives of key populations, including men who have sex with men, transgender people, sex workers and people who inject drugs

☐ Technical specialists, including experts in specific technical areas, such as laboratory services, pharmacy, drug resistance, toxicity management, supply chain and community health

☐ Government partners, including representatives of other relevant ministries (such as finance and planning) and decentralized (such as provincial) authorities, international agencies, faith-based groups, other local nongovernmental and community-based organizations and private-sector service providers

☐ Finance and budget experts, such as programme budget officers and health economists

☐ Academic institutions, including experts in operational research, implementation science, training and supervision

☐ Professional associations of different cadres of health workers, such as physicians, nurses and community health workers

3. Can all stakeholders participate effectively, be heard and influence decision-making?

☐ Is information accessible to all key stakeholders in written and understandable language? Is the process organized to ensure the meaningful participation of all relevant stakeholders? Have the potential social, cultural and legal barriers that deter the meaningful participation of historically marginalized stakeholders been identified and addressed?

4. Transparency regarding the grounds for decisions

☐ Are the decision-making criteria transparent and is the rationale stated explicitly with reference to:
  • scientific evidence, including effectiveness and risk?
  • opportunity costs of interventions, including cost–effectiveness?
  • equity impact (distribution of health benefits and burdens for different groups)?

Checklist 17.3. Implementation checklist of key health system issues

1. Communication, leadership and advocacy

☐ Has it been determined who will be responsible for updating currently existing materials, including service delivery guidelines, protocols, clinical and laboratory standard operating procedures, monitoring and evaluation tools, patient monitoring mechanisms or systems, reference manuals, health worker training materials, job aids, supervisory checklists and materials for public information, education and communication?

☐ Has it been decided how new recommendations will be communicated to (1) local programme managers, including public, not-for-profit and private institutions; (2) health workers; and (3) other relevant stakeholders, such as people living with HIV?

☐ Has it been agreed who will take overall responsibility for advocacy with such stakeholders as political leaders, health personnel and the mass media?

2. Staffing and human resources

☐ Has it been determined how many additional workers are required to implement new recommendations? Which cadres of health workers (physicians, health officers, nurses, midwifes, community health workers and laboratory assistants) are needed and how they can be recruited?

☐ Can task shifting and sharing be used to optimize available human resources and expand service delivery?

3. Drugs and supplies

☐ Are any new medicines (such as ARV drugs) needed to implement the new recommendations? In what quantities?

☐ Has it been determined what systems are required for forecasting needs and procuring medicines and other commodities at the best possible prices?

☐ Has a transition plan been developed to phase out old medicines (such as d4T and ddI) and introduce new ones?

☐ Do supply management systems – especially at the peripheral level – need to be strengthened to manage increased demand?

☐ Is a regulatory process in place to approve and register new medicines and diagnostics in a timely manner?

☐ Are laboratory quality control and external quality assurance systems in place and fully functional?

☐ Do national laws allow for the purchase and importation of all necessary commodities? Do patent issues exist and can TRIPS flexibilities be leveraged to promote access?

4. System organization

☐ Are links and referral systems adequate?

☐ Do services need to be decentralized and/or integrated to support policy implementation? Has the policy been developed in consultation with managers of other relevant programmes (such as TB, maternal and child health and drug dependence services)?

5. Infrastructure

☐ Has the necessary physical infrastructure (such as warehouses, meeting rooms, consultation space, laboratories, pharmacies, administration areas and equipment) and transport infrastructure (such as vehicles) needed to support implementation been identified? Is it available somewhere in the health system or does it require additional investment from the ARV programme?

☐ Is additional communication infrastructure needed, including between health facilities, health workers, laboratories and clients?

6. Costs

☐ Has the total annual investment of implementing new recommendations, including ancillary and other services, been estimated? Have the unit costs for the following programme components been determined?
- ART;
- PMTCT (for women during pregnancy and breastfeeding);
- testing and counselling;
- general HIV care;
- clinical monitoring;
- mentoring, quality assurance and monitoring; and
- community-level services.

7. Funding

☐ Have the sources of funds been identified, such as government budget, social security or health insurance, Global Fund to Fight AIDS, Tuberculosis and Malaria, United States Presidents' Emergency Plan for AIDS Relief, UNITAID and private foundations? (It is important to consider that out-of-pocket expenditure may limit the access to and uptake of interventions)

☐ Are new strategies needed to raise funds to meet estimated investment needs?

☐ Can potential cost savings be achieved through economies of scale or synergy with other interventions and programmes?

8. Monitoring and evaluation

☐ Does the monitoring and evaluation plan clearly identify the facility- and programme-level indicators needed to adequately monitor the coverage of interventions and impact of new recommendations? Have the human resources, equipment and infrastructure requirements been identified?

☐ Are monitoring and evaluation systems interoperable (between the local and central levels and among various donors) to avoid duplication and ensure consistency?

☐ Have the necessary quality control, quality assurance and quality improvement systems been identified and put in place to optimize service delivery?

9. Implementation plan

☐ Does the plan have time-bound targets or objectives? Does the plan contain specific outcomes?

☐ Does the plan clearly identify the roles and responsibilities of the various stakeholders (such as government at the central, provincial and local levels, nongovernmental organizations, technical partners, communities and people living with or affected by HIV) involved in the roll-out process?

ANNEX 18

Models for and country case studies of phased implementation of policies

18.1 Models for costing and planning

In principle, modelling the optimal allocation of available budgets can directly inform the setting of priorities for interventions and resources to maximize population health benefits. Such modelling requires in-depth knowledge of the costs and benefits of all feasible alternatives for all policy areas. Such analyses tend to rely on the available budget being known and fixed. In reality, optimal resource allocation is often more complex. HIV service delivery frequently draws on different budgets, and there may be some degree of transferability between general health care and HIV funding.

An alternative to full budget allocation modelling is a more partial approach that addresses each policy choice in turn. Incremental cost–effectiveness analysis compares the costs and health benefits of mutually exclusive sets of alternatives (such as how to monitor people receiving ART). Cost–effectiveness analysis seeks to compare the cost associated with generating additional health benefits across interventions. Determining whether such interventions can be deemed to provide value for money requires comparison to some benchmark of value. The value of that benchmark is not fully known but is thought to be no more than half of the country's GDP per capita.

Models suggest that moving to rapid ART initiation regardless of CD4 cell count is cost-effective in wide variety of settings. The models usually assume that the retention in care of newly eligible people initiating ART at high CD4 counts will be similar to that of current people receiving ART. Budget implications will vary widely depending on the epidemic context, but the impact of treating all people with HIV could be substantial for many country budgets. The reduction in the number of people newly infected and dying from AIDS-related causes may not make a substantial difference, since relatively few people who are not eligible for ART under the 2013 WHO criteria currently present for care. Given the increases in costs of expanding ART eligibility, it becomes important to examine the potential for cost savings, such as through less frequent clinical visits, which may be informed through viral load monitoring. If used to enable differentiated HIV care, viral load monitoring is expected to be cost-effective even in the most resource-limited settings. Below are four country examples that use cost and cost–effectiveness modelling to assist in defining HIV-related health priorities.

18.2 Case studies

18.2.1 Defining priorities for improving HIV care in western Kenya

The Academic Model Providing Access to Healthcare (AMPATH) programme in western Kenya has collected data on people's routes into care, losses across the cascade and clinical outcomes. A mathematical model was developed, based on these data *(1)* to

examine the cost and impact of a set of interventions acting at different stages of HIV care, including improvements to diagnosis, linkage to care, retention and adherence on ART and immediate ART eligibility and universal treat-all approach. Impact on health was quantified in terms of disability-adjusted life-years (DALYs) averted for 2010–2030, incorporating reduced morbidity from HIV infection and reductions in the number of people newly infected with HIV.

Analysis found that no individual intervention on the cascade would be expected to avert more than 10% of DALYs (Fig. 1). This modest impact is because any single intervention is confounded by other weaknesses in the cascade. Strengthening the retention of the people receiving ART and removing the pre-ART stage of the cascade by initiating ART for all people with HIV as soon as they are diagnosed lead to greater impact than any other single intervention.

However, a combination of interventions (including improved testing and linkage together with pre-ART and ART outreach strategies) was estimated to generate a much larger impact and it is likely (based on provisional estimates of cost) to be cost-effective in averting DALYs. The combination of HIV care interventions was estimated to generate a similar level of health gains to universal testing and treatment over this time frame but at substantially lower cost. Switching to a policy of immediately initiating ART, in addition to a combination of cascade interventions, would lead to even larger health gains.

These results show that moving to a strategy of universal testing and treatment with a leaky cascade would not maximize health benefits in a resource-limited setting, whereas a combination of interventions that strengthen the cascade along with a move to immediate ART initiation could generate substantial and cost-effective health gains.

Fig. 18.1. Incremental improvement in the cost–effectiveness frontier with sequential addition of interventions, based on AMPATH, Kenya cohort, 2015
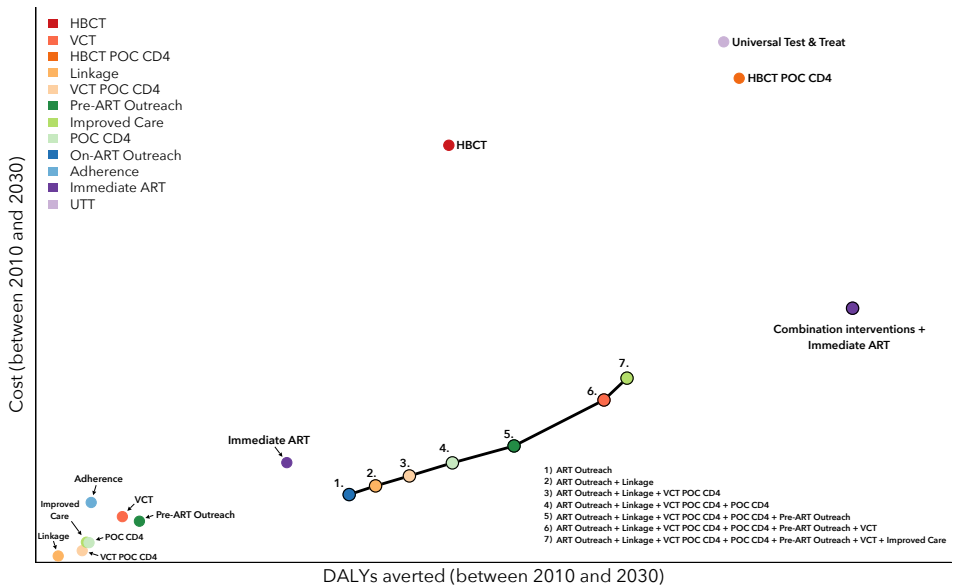
DALYs averted and additional cost of care for individual interventions between 2010 and 2030. Cost is estimated by calculating the additional cost of care relative to baseline between 2010 and 2030 and impact by calculating the number of DALYs averted relative to baseline in the same period. Points linked together indicate combinations of interventions (listed within the figure); otherwise interventions applied individually. The interventions are: home-based counselling and testing (HBCT) of 90% of the population every 4 years, with people more likely to link to care if previously diagnosed; enhanced voluntary counselling and testing (VCT) that increases the rate of testing through VCT by 25%; home-based counselling and testing with point-of-care CD4 testing (HBCT POC CD4) is the same as HBCT but with the addition of POC CD4 testing, which increases the rate of linkage to care; the linkage intervention reduces the risk of not linking to care by 50%; VCT POC CD4 provides POC CD4 testing for everyone testing through VCT, increasing the chance they link to care; pre-ART outreach returns 20% of the people who have been lost from pre-ART care every year; improved care reduces the risk of being lost from pre-ART care by 50%; POC CD4 provides point-of-care CD4 testing to everyone in pre-ART care; on-ART outreach returns 40% of the people lost from ART care every year; adherence reduces the risk of not adhering to ART and failing to achieve viral suppression by 50%; immediate ART removes pre-ART care, providing immediate treatment for all individuals entering care; and universal test and treat (UTT) combines immediate ART with HBCT.
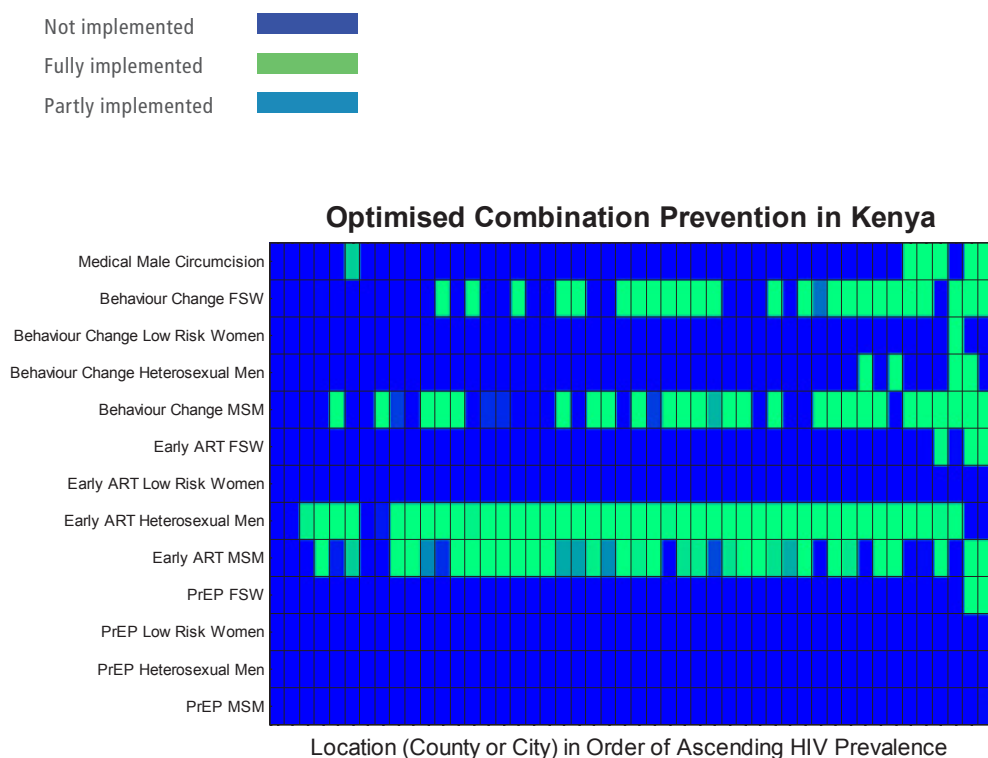
18.2.2 Determining the role of pre-exposure prophylaxis in a comprehensive HIV response in Kenya

A comprehensive HIV prevention programme uses a mixture of interventions most suitable to the population and setting. Pre-exposure prophylaxis (PrEP) offers a highly efficacious means of protecting those in greatest need of HIV prevention. However, its cost and other constraints necessitates making decisions about the circumstances under which PrEP should be part of the HIV prevention services offered. Resources for HIV prevention and treatment should be allocated among potential interventions – including behaviour change communication, male circumcision and HIV testing, among many others – such that available resources generate the greatest possible gains in health and influence the epidemic. In this way, the decision to include PrEP in the services offered depends not only on the attributes of PrEP but also on the patterns of transmission in the population, the cost and effectiveness of other potential interventions and the budget that is available. There is significant heterogeneity in the risk of infection, so "optimal prevention packages" are expected to be specific to particular key populations, geographical locations and age groups.

Mathematical modelling enables information on the epidemic, intervention effectiveness and cost to be drawn together. These models show that PrEP is likely to be included in optimal combination prevention packages for populations with high incidence, in conjunction with other intervention options, and where the budget available for prevention interventions is large. In other situations, greater impact is more likely if available resources are devoted to prevention interventions other than PrEP.

For example, using a subnational model of Kenya *(2)* (Fig. 18.2), the characteristics of a combination prevention strategy are shown that would maximize the impact in reducing the HIV epidemic over 15 years with a prevention budget of US$ 600 million. Each

Fig. 18.2. Interventions used across subnational locations in Kenya in a prospective combination prevention intervention. Locations are presented in order of ascending prevalence

Not implemented

Fully implemented

Partly implemented

Optimised Combination Prevention in Kenya

Location (County or City) in Order of Ascending HIV Prevalence

column represents a different county or major city in Kenya, ordered from lowest to highest prevalence (left to right). Each row represents a different intervention modality by population group (female sex workers, low-risk women, men who have sex with men and heterosexual men). The colour key describes whether interventions are not implemented, partly implemented or fully implemented. Compared with other interventions, PrEP is used in only a few of the higher-prevalence locations and is included only for populations at the higher risk of infection (female sex workers) in the locations of highest prevalence. These populations would also be provided with HIV testing and access to early ART and behaviour change counselling (and condom promotion).

PrEP will be a valuable addition to the set of prevention tools available, but its use should be considered within a wider combination prevention framework that incorporates information on the epidemic and other available intervention and the available budget. This indicates that PrEP is only expected to be cost-effective in some high-prevalence locations among populations at highest risk. However, there will be many other considerations besides these, such as the ethical imperative to protect those with limited other prevention options. Mathematical models are useful tools that can afford insight into this framework and are becoming widely used to address these questions, and the general rules that emerge from existing research provide useful guidance where models have not yet been applied.

18.2.3 Moving to viral load–informed differentiated care in Zimbabwe

In many countries, resources are insufficient to immediately implement all recommended interventions without finding accompanying cost savings.

One important way of saving resources and costs is by implementing viral load–informed differentiated care. This approach involves reducing the frequency with which people visit clinics for assessment if they have had a viral load <1000 cps/ml (in the past year) to 6-monthly or annually, compared with existing more frequent clinical assessments. Currently, the most feasible way to collect viral load samples in most settings is using dried blood spots, which can be sent for laboratory testing using existing networks for early infant HIV diagnosis.

Modelling analyses *(3,4)* find that viral load–informed differentiated care using dried-blood spots if necessary is the most cost-effective approach to monitoring people receiving ART as long as sufficient savings can be realized from reducing the frequency of clinical assessment. Moreover, compared with the current situation in many countries – 6-monthly CD4 count monitoring with a low switch rate to second-line ART when failure criteria are met – viral load–informed differentiated care, if accompanied by a higher switch rate, would lead to both a substantial improvement in people's health (DALYs gained) and reductions in costs.[1]

The HIV programme in Zimbabwe is rolling out the implementation of such a policy of viral load–informed differentiated care in which stable people living with HIV with viral load <1000 cps/ml have an annual clinical assessment and collect their drugs at 3-monthly intervals at pharmacy refill visits *(5)*. The savings resulting from differentiated care will be committed to other priorities in improving the HIV cascade of care.

18.2.4 Setting priorities for programmes in Indonesia using Optima

Optima is a mathematical modelling package that can be used to synthesize information on the HIV epidemic and the effectiveness and cost of potential interventions to reduce number of people dying from AIDS-related causes and the number of people newly infected with HIV *(6)*. The Optima model was used to assess the best use of HIV resources for reducing the number of people newly infected in Indonesia with respect to items in the 2015 WHO guidelines and programmatic components outside the items in the guidelines.

Indonesia has one of the largest HIV epidemics in Asia, and it is currently growing. It is driven by transmission among key populations of people who inject drugs, men who have sex with men and female sex workers in most places and is generalized in Papua New Guinea. ART coverage is currently low (<10% of all people living with HIV on ART).

Although many interventions may be deemed cost-effective in isolation, there may not be the resources available to fund all of them to scale. The figure shows how, for different levels of available budget, the budget would be optimally shared amongst the available interventions and the number of new infections in 2030 that would be expected. With greater budgets, additional programmes can be included:

---

[1] It is estimated that, compared to 6-monthly CD4 count monitoring with a low rate of switching among those meeting the current WHO CD4 failure criteria (0.05 per 3 months), approximately replicating the existing norm in Zimbabwe and other African countries, viral load–informed differentiated care with higher switch rates (0.5 per 3 months) will gain 580 000 DALYs and lead to US$ 140 million in cost savings over a 20-year period in Zimbabwe.

- First, primary prevention among key populations is essential in order to minimize incidence. This is included even when budgets are very low.

- Scaling up ART is the next highest priority and should dominate resource allocations.

  – People living with HIV presenting late (CD4 < 350) or with advanced (CD4 < 200) HIV are to be prioritized. Monitoring would be with CD4 cell count measurement.

  – Targeting key populations – men who have sex with men, people who inject drugs and sex workers – is next priority in ART scale-up

  – Then annual viral load monitoring is to be instigated as routine

  – Then increase eligibility criterion (CD4 < 500)

- When this is achieved, further scaled-up of social and behaviour change communication and non-key population prevention can be included.

- When ART coverage levels start to saturate among those currently diagnosed then

  – Initiate PrEP among key populations

  – Concurrently, start scaling up services to reach and diagnose previously undiagnosed individuals and link more people into care for ART

- Then instigate universal early treatment

- With large resource availability initiate biannual viral load monitoring as routine

If the objective of the HIV response is to minimize the loss of healthy-life years to HIV (thus factoring in incident infections, deaths and loss of health) instead of just minimizing overall new infections, then the order of programme prioritization would shift: In this case, ART would be of highest importance immediately in the same order of treatment-eligibility criteria and prevention programmes for key populations would not start to be funded until the resources available were around 120–140% of the current annual budget.

Overall, the results show that when more resources are available the impact on the epidemic can be greater. There is less extra impact from any marginal increases in resources when overall budgets are greater because (a) with greater resources, the populations targeted increase to include people at lower risk and therefore there is less impact; (b) as coverage levels increase, it becomes increasingly difficult to reach all of the targeted populations. In this framework of optimal allocation of resources, the scale-up early ART for all people, should be done only if there are resources available after having scaled-up primary prevention intervention among key populations, ART for those presenting to care with low CD4 cell counts and early ART for key populations. Similarly, the introduction of PrEP would be included in the framework as resources allow, following the scale-up of ART.

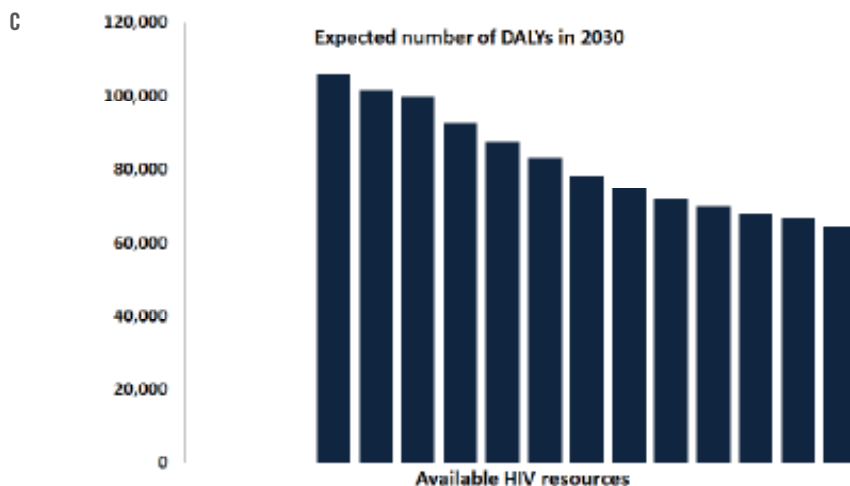Fig. 18.3. Scaling interventions for impact using the Optima model
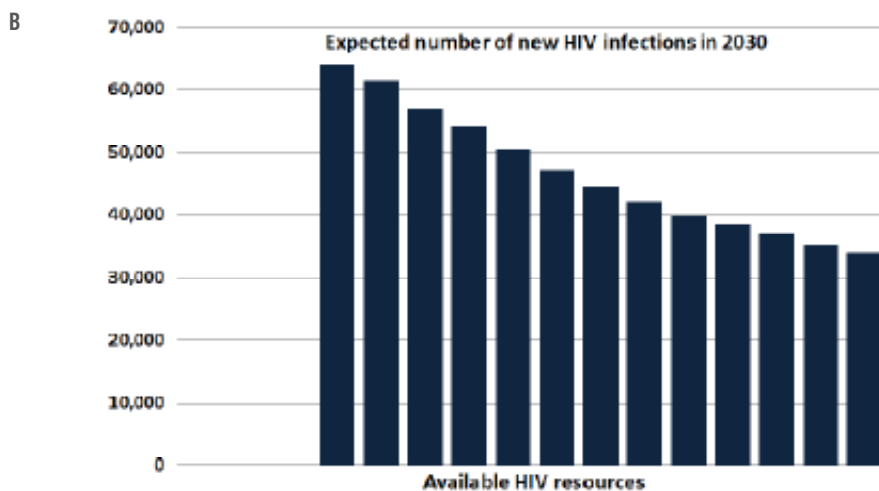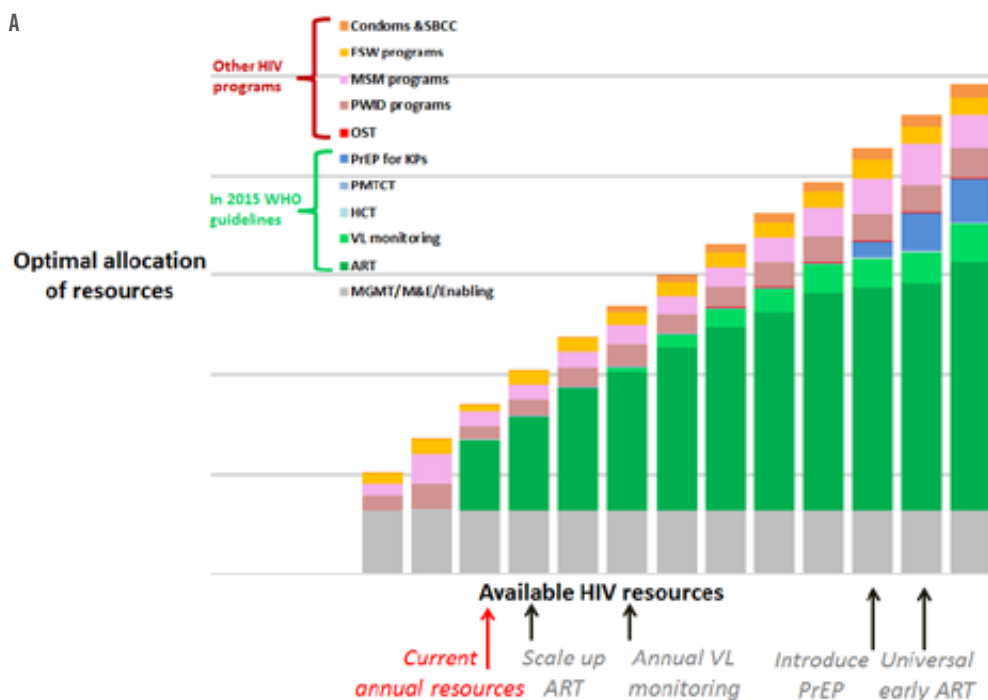
Figure legend: (A) The mathematically estimated optimal allocation of resources to minimize incidence in 2030 versus available HIV resources: Current annual resources in Indonesia refers to ~US$100 million per year; each bar corresponds to a 20% increment in the available HIV resources. (B) The estimated number of new infections in 2030, corresponding to budget allocations as in (A), versus available HIV resources. (C) The estimated number of DALYs in 2030, corresponding to budget allocations as in (A), versus available HIV resources. In these graphs, the Optima model was used to assess optimal budget allocations over the period 2015–2020 in order to minimize new infections by 2030. 3% discounting was employed for both costs and outcomes.

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EXHIBIT 47

Excerpts from the May 3, 2019
Deposition of Sheila Peel Ph.D.

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 1        BEFORE THE UNITED STATES DISTRICT COURT

 2          FOR THE EASTERN DISTRICT OF VIRGINIA

 3                  ALEXANDRIA DIVISION

 4

     RICHARD ROE, ET AL.,              ) Civil Action No.

 5                                     ) 1:18-cv-01565

              Plaintiffs,             )

 6                                     )

         v.                            )

 7                                     )

     PATRICK M. SHANAHAN, ET AL.,      )

 8                                     )

              Defendants.             )

 9   ------------------------------------)

     NICHOLAS HARRISON, ET AL.,        ) Civil Action No.

10                                     ) 1:18-cv-00641

              Plaintiffs,             )

11                                     )

         v.                            )

12                                     )

     PATRICK M. SHANAHAN, ET AL.,      )

13                                     )

              Defendants.             )

14   ------------------------------------)

15                        - - -

16                  FRIDAY, May 3, 2019

17                        - - -

18      Deposition of SHEILA PEEL, PH.D., taken at the

19   offices of Winston & Strawn, LLP, 1700 K Street NW,

20   Washington, D.C., beginning at 9:35 a.m., before

21   Nancy J. Martin, a Registered Merit Reporter,

22   Certified Shorthand Reporter.
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Page 8

1   A.   503 Robert Grant Avenue, Silver Spring,

2   Maryland --

3   Q.   Have you seen --

4   A.   -- 20910.

5   Q.   Sorry. I interrupted.

6   Have you seen the notice of deposition that

7   required your presence here today?

8   A.   I have.

9   MR. SCHOETTES: We're going to mark this as

10   Exhibit 1.

11   (Deposition Exhibit 1 was marked for

12   identification.)

13   BY MR. SCHOETTES:

14   Q.   Is Exhibit 1 the notice of deposition that

15   you've seen for your appearance here today?

16   A.   Yes, sir.

17   Q.   All right. Actually, you can set that aside.

18   You shouldn't be needing that any further.

19   Are you on any medications or other drugs

20   today that would affect your ability to answer

21   truthfully?

22   A.   No.

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1   information you need.

2   BY MR. SCHOETTES:

3   Q.   How did you come to understand what the

4   subjects on which you were going to opine were going

5   to be?

6   A.   There was a general discussion of the case.

7   I performed clinical monitoring, viral load testing

8   support of our HIV infected personnel. Specifically,

9   the U.S. Army and Navy and HIV and for all therapeutic

10   monitoring for antiretroviral therapy for all HIV

11   infected personnel with regards to monitoring of

12   individuals who are HIV infected who may be deployed.

13   Q.   Who may --

14   A.   Be deployed. Sorry.

15   Q.   Did you understand that this disclosure was

16   to include a statement of the subject matter on which

17   you will present evidence and a summary of the facts

18   and opinions to which you are expected to testify?

19   A.   Yes.

20   Q.   I want to better understand where those

21   various things are found in this document. So would

22   you agree that the first three paragraphs, numbered

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1   custody for specimen management, and shipment, which

2   are standard practices. I have no knowledge of

3   whether they have shipped to HDRL a sample from a

4   deployed person. So I can't speak to that practice.

5   Q.   And you can't speak to how the Navy goes

6   about collecting those specimens?

7   A.   No.

8   Q.   What about for the Air Force? First of all,

9   does your lab conduct HIV viral load testing for the

10   Air Force?

11   A.   Upon occasion, yes.

12   Q.   On occasion?

13   A.   On occasion, yes.

14   Q.   But you don't have responsibility for all of

15   it the way you do with the Navy and the Army?

16   A.   Correct.

17   Q.   Can you describe -- do you know any of the

18   logistics for collecting specimens for HIV viral load

19   testing in the Air Force?

20   A.   No. Can we flip -- can I clarify something?

21   Q.   Sure.

22   A.   For your question about whether I know how

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1   before being placed in the centrifuge?

2   A.   It shouldn't be no more than four to six

3   hours.

4   Q.   And just so I understand, I think I

5   understand, but I want to make sure. Cold chain just

6   means being able to maintain a cold temperature for

7   the specimen?

8   A.   Right.

9   Q.   Now let's talk about where it goes from there

10   in terms of where it needs to be transported and by

11   when.

12   A.   Well, it depends on where it's acquired. If

13   there is wet ice available, then you could transport

14   it to a level facility that could freeze it, and then

15   from there it could be transported out of the area.

16   It's going to be where this individual is relative to

17   the laboratory support and capability of where the

18   individual is or where the individual is moved to. So

19   you either move the individual to the laboratory

20   support area or you have to do the best you can for

21   it.

22   Q.   So if you can keep it between 2 and 8 degrees

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1   Celsius -- new question.

2   Does wet ice keep it at between 2 and 8

3   degrees Celsius?

4   A.   It's zero roughly degrees. It's frozen. So

5   it's technically slushy zero degrees.

6   Q.   Okay. So wet ice takes it to the place where

7   the specimen is frozen?

8   A.   Exactly.

9   Q.   And how long would you have before you needed

10   to take it from the 2 to 8 degrees to being frozen?

11   A.   You know, the truth of the matter is I think

12   we would have to -- I'm an evidence-based person. I

13   don't know the answer to that because I could tell you

14   that I require that it be spun, separated, aliquoted

15   and frozen in the states, and I would -- because I am

16   evidence based, I don't know.

17   Q.   Do you know if that evidence base exists? I

18   understand that for purposes of your laboratory and

19   the way you handle specimens in the United States that

20   it is ideal -- or you require that they be aliquoted

21   and then frozen, but do you know if the evidence

22   exists to describe what the window period is before it

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1   if you don't know what equipment is available in the

2   deployed environment?

3   A.   Because I have managed and consulted and

4   engaged providers down range to acquire specimens for

5   incident cases, and it has been an extraordinarily

6   difficult endeavor. One case involved coordination

7   with the Air Force to fly samples to Lackland Air

8   Force base, which were then flown to Washington D.C.,

9   which were then couriered to my laboratory. It

10   involved an enormous number of people to move a person

11   to an area where a phlebotomy could occur and the

12   sample was taken to a place where it could be

13   centrifuged and aliquoted and then moved again to

14   where it could be frozen and shipped, and then we had

15   movement within the United States.

16   There have been individuals who could not be

17   managed in theater who are actually extracted from

18   theater and moved to Germany to Landstuhl, Germany.

19   So it is -- over the course of our experience in the

20   middle east, and particularly from 2003 forward, I

21   have and my laboratory officers who are my lab

22   managers have had to work with their peers in theater

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1   weight constraints, and in that context how that's

2   managed and what is needed which is not already there,

3   if it were added, it is my understanding other things

4   may have to come out.

5   And this is not my area of expertise, but it

6   is -- it does constrain what the military can effect

7   from the medical side of the house in the context of

8   the trauma support, which is going to be the priority

9   relative to something that's more routine. That can

10   be quite constraining.

11   Q. So on the things on the list -- of the things

12   on the list that we have created that are required for

13   HIV blood draw, HIV testing blood draw and then

14   initial processing, and then shipping, what items are

15   unique to HIV testing? HIV viral load testing. Do

16   you need a tube with a particular reagent in it to

17   collect the blood into?

18   A. EDTA tubes are standard. Clinical

19   centrifuges are standard at certain levels.

20   Q. The tubes for aliquoting, standard?

21   A. Not necessarily, no.

22   Q. Okay. So is that an item that is unique to

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1   HIV viral load testing or those secondary tubes also

2   used for other purposes?

3   A.   I am not sure of the total range of test

4   capability in theater. Generally what you are trying

5   to do is spin a centrifuge down on a primary tube and

6   then testing from that primary tube. You don't

7   aliquot off normally. But it may or may not be there.

8   Granted.

9   Q.   And then the wet and the dry ice are both

10   things that are commonly used for other specimens that

11   might need shipping?

12   A.   At a certain level of facility. Certainly

13   not at lower-level facilities.

14   Q.   The pipets and the pipet tips, are those

15   commonly used in a healthcare setting?

16   A.   Yes.

17   Q.   So what is it that you're saying would need

18   to be moved out of a kit or set in order to routinize

19   HIV viral load testing?

20   A.   I think the issue here is where is the

21   individual.

22   Q.   Actually, I want to go back and --

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```
 1        A.   So in the context of needing to be monitored

 2   and how you manage that and move people to that

 3   scenario.  As I said, you either move people to the

 4   lab or you move parts of the component of the lab to

 5   the people.  And we have -- and this is in a deployed

 6   setting.  You have to realize that we're deployed

 7   globally.  CENTCOM is one area.  Africa is another.

 8   South America is yet another still.  Southeast Asia,

 9   another yet.

10           I mean these are different constructs.  Our

11   assets probably in Iraq and Afghanistan are more

12   hardened than they are anywhere else.  So there are

13   areas likely in Africa where there's no power.  So

14   it's not just contextually in the context of talking

15   about capability, we've been talking about CENTCOM,

16   but we're talking about 11 combat commands.  Well,

17   maybe 10 if we exclude North America in the context of

18   moving forces, monitoring forces, where they're

19   deployed, and what their mission set is.  And how we

20   can -- can we move a person, can we not move a person

21   and who is readily available.

22           So there are a lot of military relevant and
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1   A.   No.

2   Q.   So I'm going to offer a hypothetical. Let's

3   say that an individual living with HIV, has a

4   suppressed viral load before they go off to their

5   deployment and it's time for their one monitoring

6   appointment that they'll need while they're on that

7   deployment. And they are serving in a location where

8   there is a role 2 medical treatment facility, and that

9   role 2 treatment medical facility has the necessary

10   medical supplies and personnel to conduct the blood

11   draw.

12   Is there anything that would prevent that

13   specimen from being shipped on a helicopter that is

14   already going to a location where there is a level 3

15   medical treatment facility and the equipment and

16   personnel necessary to do the initial processing of

17   that specimen?

18   MS. CUTRI-KOHART: Objection for several

19   different reasons including the speculative nature of

20   that and the compoundness of the question.

21   But go ahead and answer it to the extent you

22   can.

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1   THE WITNESS: Likely not. I mean, you know,

2   if there's a phlebotomist there and the tubes and the

3   supplies and you can hand off and maintain ambient

4   control, such as the sample doesn't get too hot, you

5   know, you could probably throw it on a helicopter with

6   everybody else and take off.

7   BY MR. SCHOETTES:

8   Q. All right. In determining that in your

9   opinion there are substantial medical logistical

10   challenges to conducting HIV viral load testing, did

11   you compare those challenges with respect to HIV viral

12   load testing to the challenges with respect to other

13   types of testing done in a deployed environment?

14   A. No.

15   Q. Did you compare the challenges you described

16   with respect to HIV viral load testing to the

17   challenges with respect to treatments for other types

18   of conditions in the deployed setting?

19   MS. CUTRI-KOHART: Objection. Scope.

20   But go ahead and answer if you can.

21   THE WITNESS: No.

22   BY MR. SCHOETTES:

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1   integrity possible.

2   Q.   And during your testimony you talked about a

3   recent occasion where you thought you were going to

4   have to bring a sample back from Afghanistan. It

5   turns out you didn't, but can you tell me what the

6   plan was you had in place to bring that sample back?

7   A.   We had a plan in place to move the individual

8   from where they were to the provider to have blood

9   drawn. There was then going to be a move to the

10   facility that I don't know the name of to centrifuge,

11   process the sample, move the sample on a flight that

12   was going to be moving to Germany, and then the flight

13   from Germany, they would have taken the sample and

14   then forwarded it onto the lab, and I could tell you I

15   get samples from Germany almost three times a week.

16   It takes two days for samples to reach the lab. So

17   there was a stepwise plan in place.

18   Q.   Was that sample going to be frozen somewhere?

19   A.   It would have been frozen. I don't know

20   where it was going to be frozen. That had not yet

21   been worked out yet. So...

22   Q.   We talked a little bit about freezing samples

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1   immuno suppressed patients, be they transplant

2   patients or HIV patients. It's a routine test that's

3   done.

4   Q. Does your lab perform CD4 tests?

5   A. Not anymore. Not anymore.

6   Q. Would it require a different sample to

7   perform CD4 testing than what is used to perform viral

8   load testing?

9   A. It takes whole blood, yes. It takes a

10   different sample.

11   Q. Very last subject, are there -- jumping to a

12   related subject. Are there any FDA approved

13   point-of-care tests for viral load?

14   A. No. No, there are not. There are not.

15   MS. CUTRI-KOHART: That's all I have.

16

17   FURTHER EXAMINATION

18   BY MR. SCHOETTES:

19   Q. Just a few follow-up questions. You

20   mentioned Germany in a previous answer. Are there

21   labs in Germany that can conduct HIV viral load

22   testing?

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1   A.   I'm sure Landstuhl could.

2   Q.   What is Landstuhl?

3   A.   Landstuhl Regional Medical Center is -- well,

4   it used to be, I don't know if it still is, the

5   largest forward trauma center for the military.

6   Q.   So that's a military --

7   A.   Yes.

8   Q.   -- facility in Germany?

9   A.   Yes.

10   Q.   Are there private labs in Germany that can

11   conduct HIV viral load testing?

12   A.   I'm sure there are.

13   Q.   Are there private labs in Germany that can

14   conduct HIV genotype testing?

15   A.   I'm sure there are.

16   Q.   Are there, in fact, labs throughout the world

17   that can conduct HIV viral load testing?

18   A.   Certainly.

19   Q.   The U.S. military contracts with labs here in

20   the United States to conduct viral load testing;

21   right?

22   A.   It can if it's needed, yes.

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1   Q.   What would prevent it from contracting with

2   labs in other countries to conduct HIV viral load

3   testing?

4   A.   I don't know.

5   Q.   You don't know of anything?

6   A.   I don't know if they use private commercial

7   labs, for example, in Germany or not. I do not know.

8   As I said, generally the reference lab for Labcorp is

9   for samples -- is for tests not done within the

10   military system.

11   Q.   And I recognize that your lab does very high

12   quality work. Are there other labs in the

13   United States that also do the same quality of work as

14   your lab?

15   A.   Oh, absolutely.

16   Q.   Are there labs in other countries that do the

17   same quality level of work as your lab?

18   A.   In developed countries, yes.

19   Q.   You were asked a question about how many

20   pounds per day of dry ice were necessary to transport

21   a frozen sample, and I think you said it was two

22   pounds per day; correct?

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1   C E R T I F I C A T E

2   I do hereby certify that the aforesaid testimony

3   was taken before me, pursuant to notice, at the time

4   and place indicated; that said deponent was by me duly

5   sworn to tell the truth, the whole truth, and nothing

6   but the truth; that the testimony of said deponent was

7   correctly recorded in machine shorthand by me and

8   thereafter transcribed under my supervision with

9   computer-aided transcription; that the deposition is a

10   true and correct record of the testimony given by the

11   witness; and that I am neither of counsel nor kin to

12   any party in said action, nor interested in the

13   outcome thereof.

14

15   _____

              Nancy J. Martin, RMR, CSR

16

17   Dated: May 19, 2019

18

19   (The foregoing certification of this transcript does

20   not apply to any reproduction of the same by any

21   means, unless under the direct control and/or

22   supervision of the certifying shorthand reporter.)

EXHIBIT 48

A. De, et al., Physical Fitness Characteristics of Active Duty Air Force Members with HIV Infection

Medicine®

Observational Study

Physical fitness characteristics of active duty US Air Force members with HIV infection

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Abstract
Human immunodeficiency virus (HIV) infection is associated with reduced muscle mass and adverse metabolic effects. We evaluated the impact of HIV infection on longitudinal exercise performance in US Air Force (USAF) members with HIV infection.

USAF members perform standardized fitness assessments every 6 to 12 months with a composite score comprised of abdominal circumference, push-ups, sit-ups, and 1.5-mile run. Fitness tests between 2004 and 2014 for male USAF members with HIV infection (n = 172) were compared with male HIV-negative controls (~10 per case; n = 1636) matched by age and rank category at service entry.

Fitness tests for cases (n = 1821) were divided into 2 groups, before (pre-HIV) and after (post-HIV) diagnosis, and compared with control fitness assessments (n = 30,443) by paired t tests. Random-effects regression analyses were also performed to compare fitness components.

Mean composite scores for cases were higher post-HIV (87.06 ± 9.10) compared with pre-HIV (84.92 ± 8.36; $P = 0.004$) and did not differ from respective controls. Compared with pre-HIV, mean push-up (51.50 ± 9.67 vs 50.35 ± 11.18; $P = 0.018$) and sit-up (51.66 ± 7.81 vs 50.57 ± 9.19; $P < 0.001$) counts improved post-HIV, whereas run times were similar (11:53 ± 1:42 vs 11:51 ± 2:05; $P = 0.056$). Regression analyses demonstrated that cases had significantly lower predicted abdominal circumference and push-up counts over time compared with controls, regardless of pre-HIV or post-HIV status ($P < 0.05$ for all).

Although functional limitations may occur in the setting of HIV infection, vigorous exercise performance can be both preserved and improved in HIV-infected individuals at a level comparable with HIV-uninfected persons.

Abbreviations: AIDS = acquired immune deficiency syndrome, ART = antiretroviral therapy, BMI = body mass index, HIV = human immunodeficiency virus, SAMMC = San Antonio Military Medical Center, USAF = United States Air Force, VL = viral load.

Keywords: AIDS, exercise, fitness, HIV, muscle strength

1. Introduction

Life expectancy for human immunodeficiency virus (HIV) infection has significantly improved in the 3 decades after recognition of the first clinical cases of acquired immune deficiency syndrome (AIDS).[1,2] However, HIV infection

remains associated with increased morbidity and impaired physical performance. Comorbid conditions are also increased in HIV-infected persons compared with those of similar age in the HIV-uninfected population.[3] In particular, HIV infection is associated with increased risk of cardiovascular disease and metabolic disturbances, including diabetes and metabolic syndrome, which can further add to physical dysfunction associated with HIV infection.[4–6]

There are a variety of mechanisms by which HIV infection can lead to impairments in physical function. For example, a reduction in lean muscle mass can be observed in HIV infection, which is associated with faster HIV progression, morbidity, and mortality.[7–9] Fat redistribution is also well-described, with loss of subcutaneous adipose tissue and gain of visceral adipose tissue, the latter which has been associated with increased cardiovascular risk and an increased 5-year, all-cause mortality in HIV-infected persons.[10–13] Advanced HIV disease is often marked by impairments in both muscle strength and aerobic function.[7,14] The development of AIDS or opportunistic infections can result in a decline in physical performance due to factors such as fatigue, anorexia, dysphagia, malabsorption, muscle atrophy, and decreased habitual physical activity.[15,16] Finally, HIV-associated weight loss and wasting remains common in some patients even in the modern era of antiretroviral therapy (ART).[17]

The majority of exercise and physical performance studies in the literature have been conducted in older HIV-infected persons. In these studies, individuals with HIV infection demonstrated impairments in mild to moderate physical activity, such as reduced gait speed and 6-minute walk times, and also greater overall difficulty with other physical activities.[18,19] In contrast, studies evaluating the impact of HIV infection on vigorous

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exercise are limited and typically involved the implementation of short-term, structured exercise programs without longitudinal follow-up.[20–22] There are no published longitudinal studies of physical fitness that include assessments of both aerobic performance and muscle strength in a population with HIV infection. The US Air Force (USAF) conducts standardized fitness assessments for all active duty members every 6 to 12 months, which evaluates body composition, muscle strength, and aerobic performance. To better understand the impact of HIV on physical performance with vigorous exercise, we evaluated longitudinal fitness characteristics for active duty USAF members with and without HIV infection.

2. Methods

USAF members have mandatory HIV testing every 2 years, or more frequently in the setting of deployment or if clinically indicated.[23] All USAF members diagnosed with HIV infection have mandatory clinical evaluations at the San Antonio Military Medical Center (SAMMC) every 6 to 12 months. The USAF manages all healthcare, travel, and lodging costs. Clinical visits include HIV disease staging, laboratory evaluation, immunizations, and HIV education. We conducted a retrospective study using physical fitness tests and data from electronic medical records collected from active duty USAF members diagnosed with HIV infection between January 1, 2004 and August 31, 2014. This retrospective study was approved by the SAMMC Institutional Review Board.

Since 2004, the standardized USAF fitness test is comprised of 4 components. Body composition is determined by measurement of abdominal circumference. Strength is assessed by the number of push-ups and sit-ups performed in 1 minute and aerobic conditioning is evaluated by a timed 1.5-mile run. A composite score (maximum = 100) is calculated by summation of the component scores for abdominal circumference (maximum score = 20), sit-ups (maximum score = 10), push-ups (maximum score = 10), and 1.5-mile run (maximum score = 60). Performance scores for each component are based on decade of age, sex, and amount of repetitions or elapsed time (available at http://www.afpc.af.mil/affitnessprogram/charts.asp). A passing composite score is ≥75 and an excellent score is ≥90. Body mass index (BMI) is also calculated, but not included in the composite score. USAF members take the standardized fitness test upon entry into military service. The frequency of subsequent fitness assessments depends upon the composite score of the most recent fitness test, with passing scores requiring testing at 6 months and excellent scores testing at 12 months. Members with physical injuries, pregnancy, or other conditions that limit the ability to take the fitness assessment are either deferred from testing or take only certain components of the test.

2.1. Study population

Inclusion criteria were male active duty USAF members with HIV infection and fitness tests between January 1, 2004 and August 31, 2014 (n = 172). Exclusion criteria were USAF members with HIV infection not on continuous active duty and females (due to small numbers). The control group was comprised of HIV-uninfected active duty USAF males matched by age and rank status (officer or enlisted) with approximately 10 controls assigned for each case (n = 1636). Composite fitness test scores, and also component scores for abdominal circumference, push-ups, sit-ups, and 1.5-mile run, were assessed. BMI was also

analyzed. Tests that did not include all components of the fitness assessment were excluded for both cases and controls.

2.2. Data management

Fitness tests over time for HIV-infected cases were divided into 2 categories according to the date of HIV diagnosis. The pre-HIV time period includes all fitness tests available until the date of last known HIV-negative screening test. The post-HIV period includes all fitness assessments that occurred after the date of first positive HIV test. Fitness tests for the control group were also divided into 2 categories based on the corresponding test dates matched to the pre-HIV and post-HIV periods for cases. To evaluate the potential impact of HIV infection on physical performance, fitness assessments for cases were compared pre-HIV and post-HIV. Post-HIV cases were also analyzed by categories of CD4 cell count and viral load (VL) at or before the time of fitness tests. Cases were also compared with matched controls of the same age at the time of testing.

2.3. Statistical analysis

Characteristics were compared using simple bivariate tests. Based on Hausman test results, random-effects regression models were used to compare body composition and fitness performance with robust standard errors utilized to control for heteroscedasticity. Cross-sectional regression models were also used to compare the most recent test pre-HIV diagnosis and first test post-HIV diagnosis for cases. Analyses were performed using Stata 13, and P values <0.05 were considered statistically significant.

3. Results

A total of 172 cases with HIV infection and 1636 HIV-uninfected controls were included and contributed 1821 and 30,443 fitness tests, respectively (Table 1). For cases, the mean age at entry into military service entry was 21.2 (±3.6) years and the majority were enlisted members. The mean time from the last documented HIV-negative test to first positive test was 17.8 (±12.4) months, and the mean age at HIV diagnosis was 28.1 (±6.2) years. Among cases, the mean CD4 count and VL at HIV diagnosis was 575 (±269) cells/μL and 3.68 (±1.30) log₁₀copies/mL, respectively.

Cases had a mean of 3.59 (±2.33) tests before HIV diagnosis and 7.44 (±3.71) tests after HIV diagnosis ($P < 0.001$). A total of 47 (27.3%) cases did not have fitness tests available before HIV diagnosis because these fitness assessments occurred before the current testing format was implemented in 2004. The largest proportion of pre-HIV tests occurred in those 18–29 years of age (75.4%), whereas post-HIV tests were similarly distributed between the 18 to 29 (46.8%) and 30 to 39 (42.9%) age categories.

3.1. Pre-HIV versus post-HIV cases

Evaluation of fitness tests for cases before and after HIV infection showed higher mean composite scores post-HIV (87.06 ± 9.10) compared with pre-HIV (84.92 ± 8.36; $P = 0.004$). Mean post-HIV scores were also better than pre-HIV for the components of push-up count (51.50 ± 9.67 vs 50.35 ± 11.18; $P = 0.018$) and sit-up count (51.66 ± 7.81 vs 50.57 ± 9.19; $P < 0.001$), whereas 1.5-mile run times were similar (11:53 ± 1:42 vs 11:51 ± 2:05; $P = 0.056$). Abdominal circumference was no different pre-HIV (32.52 ± 3.30 inches) compared with post-HIV (32.41 ± 3.15

2

Fitness test results for pre-HIV and post-HIV cases compared with controls.

Characteristic	Pre-HIV cases	Post-HIV cases	Pre-HIV vs post-HIV (*P* value)/effect size	Pre-HIV controls	Pre-HIV cases vs controls (*P* value)/effect size	Post-HIV controls	Post-HIV cases vs controls (*P* value)/effect size
Number of persons	125	172	—	1631	—	1636	—
Total number of fitness tests	574	1247	—	14,001	—	16,442	—
Fitness tests per person	3.59 (2.33)	7.44 (3.71)	<0.001/1.15	28.62 (6.18)	<0.001/4.12	6.10 (3.70)	<0.001/0.36
Age at tests, y	26.62 (6.50)	30.79 (6.68)	<0.001/0.62	29.06 (6.35)	<0.001/0.38	29.06 (6.35)	<0.001/0.27
18–29 (reference)	433 (75.40)	584 (46.80)	—	8368 (59.80)	—	9406 (57.21)	—
30–39	116 (20.20)	535 (42.90)	—	4892 (34.90)	—	5984 (36.39)	—
40+	25 (4.40)	128 (10.30)	—	741 (5.30)	—	1052 (6.40)	—
Military rank							
Enlisted (reference)	524 (91.30)	1124 (90.10)	—	12,135 (86.70)	—	14,239 (86.60)	—
Officer	50 (8.7)	123 (9.9)	—	1866 (13.30)	—	2203 (13.40)	—
Body composition							
Body mass index	24.95 (3.41)	25.21 (3.33)	<0.001/0.08	26.18 (3.36)	<0.001/0.37	26.27 (3.35)	<0.001/0.32
Underweight	1 (0.20)	24 (1.90)	—	56 (0.40)	—	69 (0.42)	—
Normal (reference)	335 (58.40)	610 (48.90)	—	5207 (37.20)	—	5912 (35.96)	—
Overweight	186 (32.40)	511 (41.00)	—	6999 (49.90)	—	8343 (50.74)	—
Obese	52 (9.10)	102 (8.20)	—	1739 (12.40)	—	2118 (12.98)	—
Abdominal circumference (inches)	32.52 (3.30)	32.41 (3.15)	0.608/0.03	33.27 (3.03)	0.004/0.25	33.27 (3.00)	<0.001/0.29
Fitness performance							
Composite Score	84.92 (8.36)	87.06 (9.10)	0.004/0.24	85.43 (9.18)	0.468/0.06	85.73 (9.55)	0.050/0.14
≥90 (excellent)	163 (28.40)	527 (42.26)	<0.001	4574 (32.67)	0.011	5735 (34.88)	<0.001
75–89 (pass)	360 (62.72)	651 (52.21)	—	8544 (61.02)	—	9720 (59.12)	—
<75 (fail)	51 (8.89)	69 (5.53)	—	883 (6.31)	—	987 (6.00)	—
Sit-up count	50.57 (9.19)	51.66 (7.81)	<0.001/0.13	52.32 (7.98)	0.037/0.22	52.60 (7.80)	0.116/0.12
Push-up count	50.35 (11.18)	51.50 (9.67)	0.018/0.11	53.04 (10.50)	0.001/0.26	53.30 (10.36)	0.002/0.17
1.5-mile run, min:s	11:51 (2:05)	11:53 (1:42)	0.056/0.01	11:59 (1:56)	0.323/0.05	12:01 (2:11)	0.336/0.23

Data expressed as mean (standard deviation) number of tests or number (%).
HIV = human immunodeficiency virus.

inches; $P = 0.608$). There was a small increase in BMI post-HIV (25.21 ± 3.33) compared with pre-HIV (24.95 ± 3.41; $P < 0.001$), and the largest proportion of assessments had normal BMI (48.9% vs 58.4%, respectively).

3.2. Cases versus controls

Mean composite scores were similar for pre-HIV cases (84.92 ± 8.36) and controls (85.43 ± 9.18; $P = 0.468$). For mean component scores, push-up (53.04 ± 10.50 vs 50.35 ± 11.18; $P = 0.001$) and sit-up (52.32 ± 7.98 vs 50.57 ± 9.19; $P = 0.037$) counts were higher in the control group compared with the pre-HIV group, respectively, whereas run times were no different. Post-HIV mean composite scores were higher than controls (87.06 ± 9.10 vs 85.73 ± 9.55; $P = 0.05$), with a greater proportion achieving "excellent" scores (42.3% vs 34.9%). The post-HIV group had significantly lower mean push-up counts compared with controls (51.5 ± 9.67 vs 53.3 ± 10.36; $P = 0.002$). Both pre-HIV and post-HIV groups had significantly lower mean BMI and abdominal circumference values compared with their respective controls. Predicted scores by age for body composition (Fig. 1), and also the composite scores and individual components for muscle strength and aerobic performance (Fig. 2) are presented for cases and controls.

3.3. Regression modeling

Regression analyses of the most recent test at or before the last HIV-negative date and the first test after HIV diagnosis showed that USAF members with HIV infection had lower BMI and

scored significantly lower on push-up counts than controls (Table 2). Furthermore, cases were 0.48 units lower post-HIV in the predicted abdominal circumference than controls ($P < 0.01$). Longitudinal fitness outcome variables evaluated by random-effects regression models (Table 3) showed no significant differences in outcomes between cases pre-HIV and post-HIV, with the exception of abdominal circumference which was 0.33 units lower post-HIV ($P < 0.05$) as indicated by the negative regression coefficient. Comparisons of cases and controls had several notable findings. Cases had a significantly lower predicted BMI and lower push-up counts over time than controls regardless of pre-HIV or post-HIV status, as the regression coefficients were uniformly negative and statistically significant at or below the $P < 0.05$ level. The predicted abdominal circumference was also 0.55 units lower over time post-HIV compared with controls ($P < 0.001$). Moreover, the odds of achieving an "excellent" composite score in fitness tests over time was 75.1% [(exp $(0.56) = 1.75 - 1) \times 100$] higher for USAF members post-HIV than for uninfected controls.

The majority of post-HIV cases had relatively preserved CD4 counts at or before fitness tests, with 90.7% having CD4 counts ≥ 350 cells/μL. Although data for timing of ART initiation were not available, VL suppression (<50 copies/mL) was assessed as a surrogate for effective treatment, with 56.4% of cases having VL suppression at the time of fitness testing. Regression analyses of post-HIV cases with CD4 count ≥ 350 vs <350 cells/μL showed no difference in composite results, individual fitness test components, or BMI. However, analyses of VL ≥ 50 vs <50 copies/mL showed a reduction of 2.71 units and 1.14 units for composite ($P < 0.001$) and "excellent" scores ($P < 0.01$), respectively.
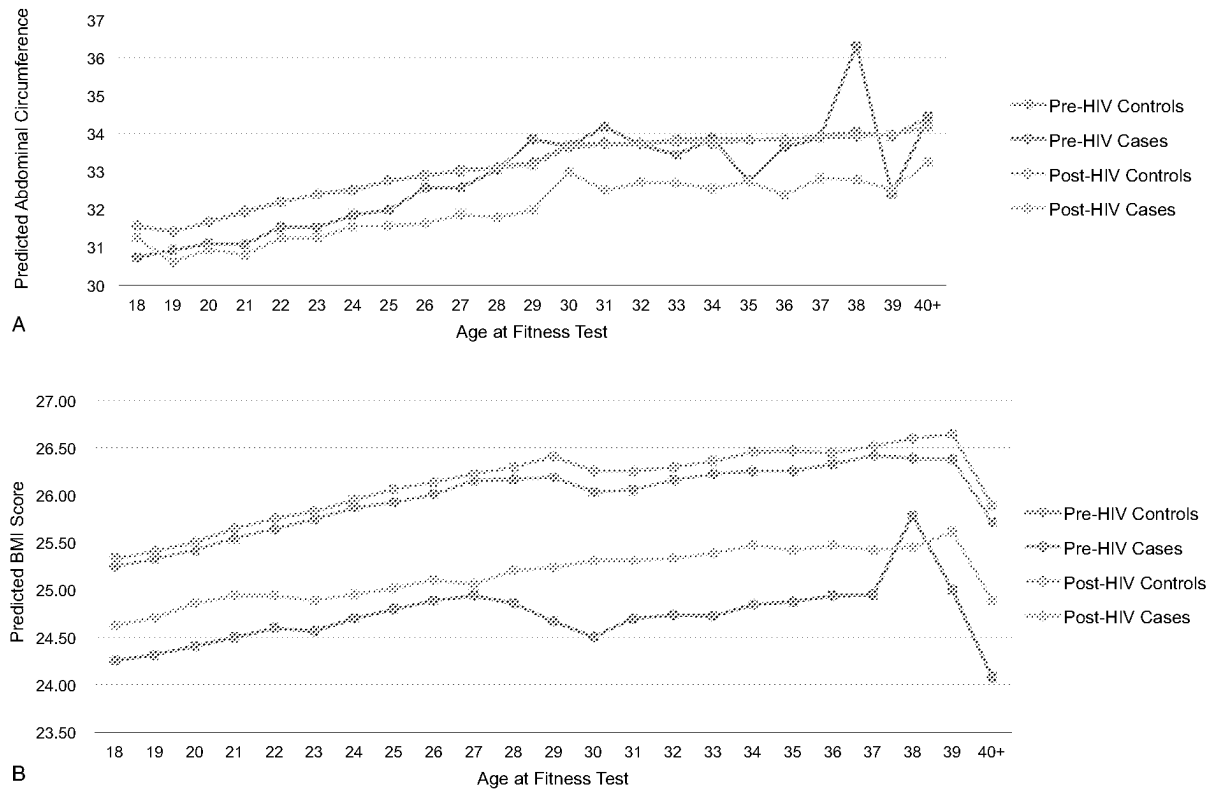
3

Figure 1. Adjusted body composition values by age and HIV status.

4. Discussion

This study analyzed service-mandated fitness tests to assess vigorous physical exercise performance in HIV-infected USAF members. Both the longitudinal and cross-sectional results demonstrate that during a 10-year span from 2004 to 2014, USAF members with HIV had similar composite test scores compared with HIV-uninfected controls. These results suggest that impaired physical fitness is not a barrier to continuing military service for USAF members with HIV infection. Interestingly, we observed improved performance in several test components after HIV diagnosis, which suggests that members may have increased their physical conditioning as part of improved health-seeking behaviors.

Despite advances in medical therapy, physical and functional limitations are commonly observed in HIV-infected populations. For example, HIV infection can be complicated by skeletal muscle wasting, particularly metabolically active lean tissue, which has been associated with increased all-cause mortality and accelerated disease progression.[24–26] In a study of over 900 patients with skeletal muscle and adipose tissue assessments by magnetic resonance imaging, lower muscle mass was independently associated with an increased risk of mortality.[12] USAF fitness tests assessed muscle strength by timed push-ups and sit-ups. Although muscle strength was statistically lower post-HIV compared with controls, both push-up and sit-up counts were also statistically lower pre-HIV compared with controls. The availability of preinfection fitness test data was essential because analyses demonstrated that these characteristics were present before HIV infection and thus eliminated HIV as the explanation for lower muscle strength compared with controls. In addition,

cases improved muscle strength after HIV infection as demonstrated by statistically higher push-up and sit-up counts compared with pre-HIV values. These results suggest that HIV-associated reduction in muscle strength is either not present in a population or can be mitigated by improved physical conditioning.

HIV infection is also associated with decreased exercise and activity tolerance. For example, 1 study observed a decrease in peak aerobic capacity with 6-minute walk test results below the age-specific threshold in 24% of HIV-infected individuals.[27] While not as commonly noted in activities of daily living, limitations are particularly evident in vigorous activities ranging from 8% of asymptomatic individuals to 58% of persons with AIDS.[19,28] Even in those on ART, limitations in oxygen delivery to muscles during exercise have been noted with an approximate decrease of 70% of maximum predicted maximal oxygen uptake and significantly lower lactic acid thresholds.[29] Although functional data, such as oxygen delivery and uptake, were not specifically measured in our study, performance on the 1.5-mile run component of the fitness test can serve as a surrogate for these assessments. USAF members performed the 1.5-mile run in approximately 12 minutes, and these values did not differ pre-HIV or post-HIV, or when compared with controls. It is possible that functional limitations may be minor or unapparent in HIV-infected persons who perform regular vigorous exercise and maintain a high level of physical conditioning before HIV infection.

There are several possible explanations as to why HIV infection did not seem to substantially impact exercise performance in our study in contrast to other studies. For example, most published studies are not directly comparable since mild to
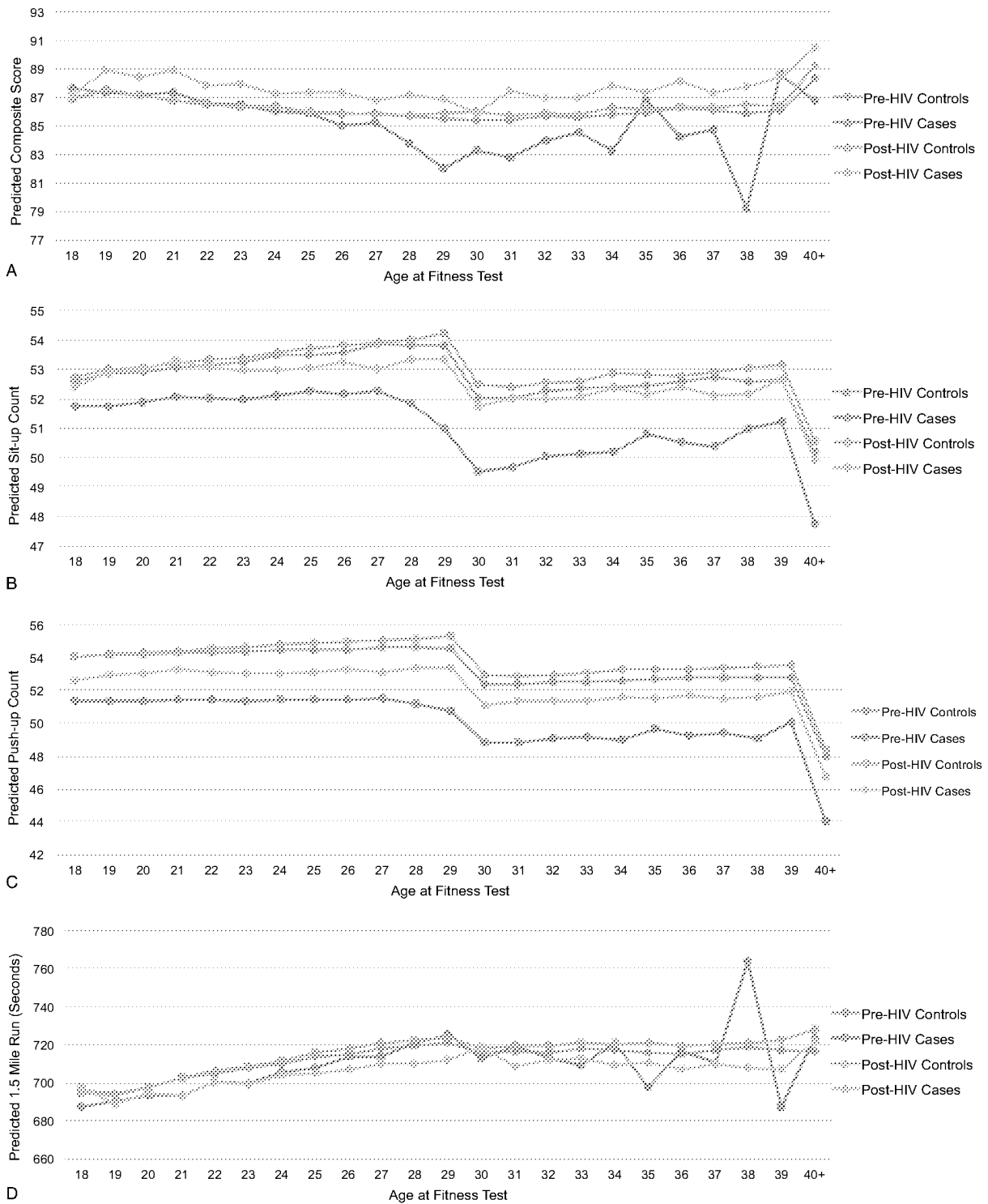
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Figure 2. Adjusted fitness test performance by age and HIV status.

moderate physical activity endpoints, such as 6-minute walk, chair rise time, and gait speed, were evaluated.[18,19] Studies involving vigorous activities are limited, and usually involved structured exercise programs in persons without a high level of physical conditioning before study entry.[14,20,22] This is in contrast to the USAF population who were required to continually maintain fitness standards. Patient characteristics such as advanced HIV disease with AIDS and/or low CD4 counts

have been associated with impairments in both muscle strength and aerobic function.[7,14,30] However, USAF members are typically diagnosed early due to mandated HIV testing with relatively preserved CD4 counts, and we did not observe differences in exercise performance for those with CD4 counts below 350 cells/µL. Lower composite and "excellent" scores were observed for persons with nonsuppressed VLs ($\geq$50 copies/mL). This most likely represents the subgroup which had not

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Cross-sectional regression models predicting body composition and performance for last fitness test pre-HIV and first fitness test post-HIV for cases compared with controls.

Regression model	HIV-positive	Age at test 30–39	Age at test 40+	Rank, Officer	Normal weight	Overweight	Obese	Constant	F/X^2	R^2
Pre-HIV[†] cases vs pre-HIV controls										
Body mass index	−0.79**	2.14***	2.40***	0.15	–	–	–	24.48***	35.4***	0.078
Abdominal circumference	0.17	1.23***	2.18***	0.38	1.50	4.35***	7.24***	29.20***	169.5***	0.419
Composite score	−1.14	−3.12***	−0.84	2.47***	−1.05	−7.49***	−15.24***	90.90***	69.7***	0.259
Excellent vs not excellent[‡]	−0.21	−1.04***	−0.32	0.53**	0.55	−0.77	−2.40*	−0.41***	274.5***	0.119
Sit-up count	−1.18	−5.78***	−8.80***	1.03	−2.09	−3.96	−6.05*	56.20***	30.3***	0.099
Push-up count	−2.78**	−4.91***	−10.49***	2.60***	−2.47	−2.67	−4.36	56.20***	14.3***	0.048
1.5-mile run, s	−1.87	17.08	−52.55	−17.58	3.43	39.50	113.6**	663.0***	6.6***	0.043
Post-HIV[§] cases vs post-HIV controls										
Body mass index	−0.49*	2.19***	2.26***	0.03	–	–	–	24.47***	34.6***	0.074
Abdominal circumference	−0.48**	1.44***	2.22***	0.34	2.69***	5.40***	8.14***	28.04***	176.5***	0.419
Composite score	0.63	−3.31***	−0.91	2.51***	0.37	−5.79***	−12.51***	89.43***	64.3***	0.239
Excellent vs not excellent[‡]	0.28	−1.06***	−0.51	0.54***	0.71	−0.60	−1.68*	−0.55	271.5***	0.116
Sit-up count	0.22	−5.86***	−8.07***	0.88	1.02	−0.72	−1.90	53.09***	28.2***	0.095
Push-up count	−1.63*	−4.93***	−9.83***	2.66***	1.97	1.81	0.74	51.71***	13.6***	0.046
1.5-mile run, s	14.37	10.02	−21.61	−18.71	−7.29	27.77	99.22*	673.4***	7.0***	0.039

HIV = human immunodeficiency virus.
[†] Most recent fitness test before last negative HIV test date.
[‡] Logistic regression.
[§] First fitness test after HIV diagnosis.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

initiated ART since VL suppression is high (>90%) for those on ART in our population.[31] This presumed lack of ART use may be a marker for reduced interest in personal health or health-seeking behaviors in this subgroup compared with our overall population, which may account for these findings. Other studies evaluating the impact of effective ART on fitness performance have been variable, with several studies showing no impact on aerobic performance or cardiac function.[32,33] In addition, we did not observe any differences in fitness outcomes when comparing fitness tests directly before and after HIV infection, when members were either ART-naïve or recently started on ART, which suggests that other nonmeasured factors may be involved.

Since exercise performance can diminish with age, the younger age of our USAF population is an important feature of our study compared with the predominance of older individuals in other studies. For example, 1 study showed greater loss of physical function in those with HIV infection compared with uninfected persons; however, the median age was 50 years.[34] This is in contrast to our USAF population who had a mean age of 28 years at HIV diagnosis. Interestingly, the younger age group (age ≤44 years) of HIV-infected individuals in this study reported higher physical function than those without HIV infection, and this was the only age group to report similar frequency of exercise compared with HIV-uninfected persons. This raises the question of whether physical inactivity may play a larger role in study outcomes than physical limitations attributed to HIV infection. Physical inactivity may be a significant confounder as 1 study observed that fewer HIV-infected persons met US Department of Health and Human Services Healthy People 2010 physical activity recommendations than persons in the general population.[35] Since our USAF population is required to maintain fitness, it is possible that HIV infection minimally impacts physical function in persons with

higher levels of physical conditioning at the time of HIV acquisition.

This study is the first to evaluate longitudinal physical fitness assessments in HIV-infected persons. Study strengths include the availability of preinfection data and the evaluation of multicomponent standardized fitness tests that assessed both muscle strength and aerobic function in both cases and controls spanning an entire decade. Limitations include the retrospective study design and inability to assess additional aspects of ART use including potential differences in fitness by use of specific treatment regimens and timing of ART initiation. Data for comorbid conditions were also unavailable. Behaviors that may have impacted physical performance, such as routine exercise habits, smoking, and diet, were not captured as part of the standardized fitness assessment.

The benefits of physical activity in the HIV-infected population have been well-documented. Progressive resistive exercise in HIV-infected individuals resulted in improvement in weight, body composition, and lean muscle mass, and a 6-month aerobic and resistance exercise program resulted in decreased heart rate in participants.[10,22,36] Exercise has also been associated with improved cognition with reduced impairments of working memory and speed of information processing.[22,37] Participation in a regular exercise program has also been shown to improve self-efficacy, mood, and fatigue resulting in higher life-satisfaction scores in HIV-infected individuals.[22,38–40] The results of our study show that a high level of exercise performance can be both preserved and improved in individuals with HIV, allowing them to gain the benefits of continued physical exercise despite potential limitations of the disease process. Providers should continue to encourage participation in regular physical activity due to the physical, mental, and emotional benefits of exercise observed in HIV-infected patients.

Random-effects regression models predicting body composition and fitness performance with robust standard errors.

	HIV-positive	Number of tests	Age at test 30–39	Age at test 40+	Rank, Officer	Normal weight	Overweight	Obese	Constant	Wald X²
Pre-HIV vs post-HIV cases										
Body mass index	−0.10	0.13***	0.10	0.44	−0.69				24.22***	68.0***
Abdominal circumference	−0.33*	0.01	0.27*	1.05*	0.39	1.42***	3.41***	4.75***	29.81***	313.1***
Composite score	0.08	0.34***	1.43*	3.15**	1.96	1.02	−4.13***	−6.72***	85.40***	159.6***
Excellent vs not excellent†	0.13	0.22***	0.16	0.72	1.21	0.26	−1.31	−2.24*	−1.74*	139.6***
Sit-up count	0.56	0.31***	−1.21	−3.93***	−0.86	4.36**	3.18*	2.94	46.54***	39.0***
Push-up count	0.15	0.36***	−0.35	−5.52***	−0.93	2.09	1.41	0.66	47.97***	34.3***
1.5-mile run, s	8.37	0.05	−11.95	21.87	−16.12	−21.57	12.04	46.54**	706.7***	44.8
Pre-HIV cases vs pre-HIV controls										
Body mass index	−1.01***	0.18***	−0.08	−0.54***	0.04				25.06***	563.1***
Abdominal circumference	−0.25	−0.01	0.49***	0.84***	0.66***	1.43***	3.26***	5.06***	30.04***	2352***
Composite score	−0.76	0.47***	−0.11	1.87***	2.34***	2.60*	−2.21	−7.93***	84.42***	1153***
Excellent vs not excellent†	−0.38	0.24***	−0.07	0.72***	0.92***	1.04*	−0.70	−2.40*	−2.14*	927.2***
Sit-up count	−1.28	0.41***	−1.63***	−3.66***	−0.33	2.84**	1.73	0.46	49.51***	385.6***
Push-up count	−3.01***	0.22***	−2.13***	−6.81***	0.65***	0.25	−0.47	−1.77	53.69***	227.3***
1.5-mile run, s	0.69	0.65	−3.21	2.17	−24.22***	−26.84**	3.56	33.65	717.7***	342.2
Post-HIV cases vs post-HIV controls										
Body mass index	−0.76**	0.17***	−0.06	−0.52***	−0.17				25.15***	773.8***
Abdominal circumference	−0.55***	−0.01	0.41***	0.64***	0.60***	1.43***	3.24***	4.99***	30.08***	2809
Composite score	0.81	0.41***	0.16	2.44***	2.53***	2.05*	−2.39***	−8.24***	84.90***	1145***
Excellent vs not excellent†	0.56*	0.23***	0.05	0.99***	0.97***	1.05***	−0.59*	−2.25*	−2.20*	1235***
Sit-up count	−0.28	0.38***	−1.56***	−3.67***	−0.50	2.97***	1.90*	0.65	49.55***	470.2***
Push-up count	−1.42**	0.29***	−2.24	−7.21***	0.55	0.73	0.16	−1.15	53.04***	331.3***
1.5-mile run, s	−1.10	1.08*	−3.93	10.58	−28.44***	−20.22**	9.23	47.53***	710.7***	370.3
Post-HIV cases: CD4 count at fitness test ≥350 vs <350 cells/µL	CD4 ≥350	Number of tests	Age at test 30–39	Age at test 40+	Rank, Officer	Normal weight	Overweight	Obese	Constant	Wald X²
Body mass index	−0.32	0.23***	0.07	0.36	−0.91				24.72***	43.92***
Abdominal circumference	0.51	0.02	0.20	0.62	0.36	−0.79	1.24	3.06**	31.29***	89.11***
Composite score	1.21	0.37	2.53	6.67***	2.79	3.43	−0.73	−3.91	81.49***	82.41***
Excellent vs not excellent†	0.74	0.19	1.25*	3.39***	1.13	−0.81	−2.06*	−4.45***	−1.16	27.96***
Sit-up count	−0.99	0.24	−1.22	−3.29*	−0.69	0.12	0.06	0.79	52.49***	7.91
Push-up count	1.04	0.42	−0.01	−4.51*	−0.86	−3.51	−1.18	−1.74	52.97***	24.87**
1.5-mile run, s	0.35	−5.80***	−28.53	25.08	−31.77	−17.35	6.63	55.56*	740.27***	40.93***
Post-HIV cases: viral load at fitness test ≥50 vs <50 copies/mL	VL ≥50	Number of tests	Age at test 30–39	Age at test 40+	Rank, Officer	Normal weight	Overweight	Obese	Constant	Wald X²
Body mass index	0.32	0.27***	0.09	0.44	−0.99				24.22***	43.23***
Abdominal circumference	0.19	0.06	0.23	0.68	0.37*	−0.74	1.25	3.01**	31.54***	88.81***
Composite score	−2.71***	0.04	2.43	6.33***	3.19*	2.99	−0.84	−3.64	84.72***	94.19***
Excellent vs not excellent†	−1.14**	0.06	1.20*	3.20	1.28	−1.09	−2.18*	−4.41***	0.51	33.56***
Sit-up count	−1.24	0.07	−1.35	−3.57	−0.59	−0.13	−0.03	0.93	52.74***	9.30
Push-up count	−0.72	0.34	−0.02	−4.57*	−0.69	−3.55	−1.17	−1.67	54.38***	22.92**
1.5-mile run, s	1.11	−5.69***	−28.34	25.53	−31.94	−17.38	6.43	55.25	739.84	40.85***

HIV = human immunodeficiency virus.
† Logit models.
* P < 0.05.
** P < 0.01.
*** P < 0.001.

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