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GUIDELINES



CONSOLIDATED GUIDELINES ON
**THE USE OF
ANTIRETROVIRAL DRUGS
FOR TREATING AND
PREVENTING HIV INFECTION**

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

JUNE 2013

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AZT	zidovudine (also known as ZDV)
BMI	body mass index
CD4	T-lymphocyte cell bearing CD4 receptor
CDC	United States Centers for Disease Control and Prevention
CNS	central nervous system
d4T	stavudine
DALYs	death- and disability-adjusted life-years
DBS	dried blood spot
ddI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	darunavir/ritonavir
EFV	efavirenz
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETV	etravirine
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine
GNP+	Global Network of People Living with HIV
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDR	multidrug-resistant TB, resistant to at least isoniazid and rifampicin
MTCT	mother-to-child transmission (of HIV)
NFV	nelfinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OST	opioid substitution therapy
PCR	polymerase chain reaction
PI	protease inhibitor
PICO	Population, Intervention, Comparison and Outcomes
PCP/PJP	<i>Pneumocystis (jirovecii)</i> pneumonia
PMTCT	prevention of mother-to-child transmission of HIV
PrEP	pre-exposure prophylaxis of HIV
RAL	raltegravir
RBV	ribavirin
RIF	rifampicin
RNA	ribonucleic acid
RTV	ritonavir
sd-NVP	single-dose nevirapine
TAM	thymidine analogue mutation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

DEFINITION OF KEY TERMS

GENERAL

HIV refers to 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. Within these guidelines, **HIV** refers to both HIV-1 and HIV-2 unless otherwise specified.

AGE GROUPS AND POPULATIONS

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these consolidated guidelines, as well as with other WHO guidelines. It is recognized that other agencies may use different definitions.

An adult is a person older than 19 years of age unless national law defines a person as being an adult at an earlier age.

An adolescent is a person aged 10 to 19 years inclusive.

A child is a person 19 years or younger unless national law defines a person to be an adult at an earlier age. However, in these guidelines when a person falls into the 10 to 19 age category they are referred to as an adolescent (see adolescent definition).

An infant is a child younger than one year of age.

These guidelines define **key populations** to include both vulnerable and most-at-risk populations. They are important to the dynamics of HIV transmission in a given setting and are essential partners in an effective response to the epidemic. People living with HIV are considered a key population in all epidemic contexts.

These guidelines define **most-at-risk populations** as men who have sex with men, transgender people, people who inject drugs and sex workers. Most-at-risk populations are disproportionately affected by HIV in most, if not all, epidemic contexts.

Vulnerable populations are groups of people who are particularly vulnerable to HIV infection in certain situations or contexts, such as adolescents (particularly adolescent girls), orphans, street children, people in closed settings (such as prisons or detention centres), people with disabilities and migrant and mobile workers. Each country should define the specific populations that are particularly vulnerable and key to their epidemic and response based on the epidemiological and social context.

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 is referred to as a partner in the relationship. How individuals define their relationships varies considerably according to cultural and social context.

HEALTH CARE SERVICES

Continuum of HIV care refers to a comprehensive package of HIV prevention, diagnostic, treatment and support services provided for people living with HIV and their families ranging across: initial HIV diagnosis and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care.

A **public health approach** addresses the health needs of a population or the collective health status of the people rather than just individuals. A public health approach involves a collaborative effort by all parts of the health sector, working to ensure the well-being of society through comprehensive prevention, treatment, care and support. For HIV, this involves: simplified limited formularies; large-scale use of fixed-dose combinations for first-line treatment for adults and children; care and drugs given free at the point of service delivery, decentralization; and integration of services, including task shifting and simplified clinical and toxicity monitoring.

HIV TESTING AND PREVENTION

Voluntary counselling and testing (also referred to as client-initiated testing and counselling) describes a process initiated by an individual who wants to learn his or her HIV status. Since there are now many different community approaches to providing HIV testing and counselling and people often have mixed motivations for seeking testing (both recommended by a provider and sought by a client), WHO prefers to use the term **HIV testing and counselling**. All forms of HIV testing and counselling should be voluntary and adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services. Quality assurance of both testing and counselling is essential in all approaches to HIV testing and counselling.

Provider-initiated testing and counselling is HIV testing and counselling recommended by a health-care provider in a clinical setting. Provider-initiated testing and counselling, as with all forms of HIV testing and counselling, should be voluntary and adhere to the five C's.

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.

ART (ANTIRETROVIRAL THERAPY)

ARV (antiretroviral) drugs refer to the medicines themselves and not to their use.

ART refers to the use of a combination of three or more ARV drugs to achieve viral suppression. This generally refers to lifelong treatment. Synonyms are combination ART and highly active ART.

ART for prevention is used to describe the HIV prevention benefits of ART.

Eligible for ART refers to people living with HIV for whom ART is indicated according to the definitions of clinical and immunological eligibility in WHO treatment guidelines. The term is often used interchangeably with "needing treatment", although this implies an immediate risk or an obligation to initiate treatment.

Viral suppression refers to the aim of ART to maintain viral load below the level of detection of available assays, generally less than 50 copies per ml. The current WHO virological criterion for treatment failure is 1000 copies per ml or more.

Universal access to ART is defined broadly as a move to a high level of access ($\geq 80\%$ of the eligible population) for the most effective interventions that are equitable, accessible, affordable, comprehensive and sustainable over the long term; this does not necessarily mean 100% coverage.

HEALTH WORKFORCE

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

Midwives are people trained to assist in childbirth, including registered and enrolled 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.

Nurses include professional nurses, enrolled nurses, auxiliary nurses and other nurses such as dental or primary care nurses.

EPIDEMIOLOGY

Concentrated HIV epidemic: HIV has spread rapidly in one or more defined subpopulation but is not well established in the general population. Numerical proxy: HIV prevalence is consistently over 5% in at least one defined subpopulation but is less than 1% among pregnant women in urban areas.

Generalized HIV epidemic: HIV is firmly established in the general population. Numerical proxy: HIV prevalence consistently exceeding 1% among pregnant women. Most generalized HIV epidemics are mixed in nature, in which certain (key) subpopulations are disproportionately affected.

Mixed epidemics: people are acquiring HIV infection in one or more subpopulations and in the general population. Mixed epidemics are therefore one or more concentrated epidemics within a generalized epidemic.

Low-level epidemic: epidemics in which the prevalence of HIV infection has not consistently exceeded 1% in the general population nationally or 5% in any subpopulation.

Low-, moderate- and high-uptake ART settings refer to settings in which the uptake of ART among those eligible for ART is less than 50%, 50–80% and greater than 80%, respectively.

A setting with a high burden of TB and HIV refers to settings with adult HIV prevalence $\geq 1\%$ or HIV prevalence among people with TB $\geq 5\%$.

HIV incidence is the number of new people acquiring HIV infection in a given period in a specified population.

HIV prevalence refers to the number of people living with HIV at a specific point in time and is expressed as a percentage of the population.

PMTCT (PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV)

In these guidelines, WHO is moving away from the previous terms “Options A, B and B+”. Instead, these guidelines recommend two options: (i) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage or (ii) providing ART (ARV drugs) for pregnant and breastfeeding women with HIV during the mother-to-child transmission risk period and then continuing lifelong ART for those women eligible for treatment for their own health. In settings that are not implementing lifelong ART for all pregnant and breastfeeding women living with HIV, the distinction between prophylaxis (ARV drugs given for a limited time during the risk period for transmitting HIV from mother to child to prevent this) and treatment (ART given both for the mother’s health, based on current adult eligibility and to prevent vertical transmission) is still important.

ARV drugs for women living with HIV during pregnancy and breastfeeding refers to a triple-drug ARV drug regimen provided to mothers living with HIV primarily as prophylaxis during pregnancy and throughout breastfeeding (when there is breastfeeding) to prevent mother-to-child transmission of HIV. In this option, the mother’s regimen is continued lifelong after delivery or after the breastfeeding ends only if she meets the ART eligibility criteria for her own health based on CD4 count or clinical stage. Previous WHO guidance referred to this as **option B**.

Lifelong ART for all pregnant and breastfeeding women living with HIV refers to the approach in which all pregnant women living with HIV receive a triple-drug ART regimen regardless of CD4 count or clinical stage, both for their own health and to prevent vertical HIV transmission and for additional HIV prevention benefits. Previous WHO guidance referred to this as **option B+**.

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FOREWORD



With this publication, WHO issues its first consolidated guidelines for the use of antiretroviral drugs to treat and prevent HIV infection. The guidelines are ambitious in their expected impact, yet simplified in their approach, and firmly rooted in evidence. They take advantage of several recent trends, including a preferred treatment regimen that has been simplified to a single fixed-dose combination pill taken once per day, which is safer and affordable.

The guidelines also take advantage of evidence demonstrating the multiple benefits of antiretroviral therapy. With the right therapy, started at the right time, people with HIV can now expect to live long and healthy lives. They are also able to protect their sexual partners and infants as the risk of transmitting the virus is greatly reduced.

The guidelines represent another leap ahead in a trend of ever-higher goals and ever-greater achievements. In Africa, the region that bears the brunt of the HIV epidemic, an estimated 7.5 million people were receiving treatment at the end of 2012, compared with only 50,000 a decade earlier. Worldwide, some 9.7 million people were receiving treatment, indicating that the global target of providing antiretroviral therapy to 15 million people by 2015 is within reach. The present achievement represents the fastest scale-up of a life-saving public health intervention in history.

A key way to accelerate progress is to start treatment earlier, as recommended in the guidelines. As the evidence now shows, earlier treatment brings the dual advantage of keeping people healthier longer and dramatically reducing the risk of virus transmission to others.

Earlier treatment has the further advantage of simplifying the operational demands on programmes. The guidelines recommend that pregnant women and children under the age of five years start treatment immediately after diagnosis. 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.

Additional recommendations in the guidelines aim to help programmes get services closer to people's homes; expedite 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.

Countries asked WHO for simplified guidance on the use of antiretroviral drugs. I believe these consolidated guidelines go a long way towards meeting that request. They offer recommendations for all age groups and populations. They bring clinical recommendations together with operational and programmatic guidance on critical dimensions of treatment and care, from testing through enrollment and retention, and from general HIV care to the management of co-morbidities.

The new guidelines ask programmes to make some significant changes. They also require increased investments. I am personally convinced that the future of the HIV response will follow the pattern of the recent past: that is, a constant willingness to build on success and rise to new challenges.

WHO estimates that doing so will have an unprecedented impact: global implementation of the guidelines could avert an additional 3 million deaths between now and 2025, over and above those averted using 2010 guidelines, and prevent around 3.5 million new infections.

Such prospects – unthinkable just a few years ago – can now fuel the momentum needed to push the HIV epidemic into irreversible decline. I strongly encourage countries and their development partners to seize this unparalleled opportunity that takes us one more leap ahead.



Dr Margaret Chan
Director-General, WHO

EXECUTIVE SUMMARY

These consolidated 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, care and treatment. Behavioural, structural and biomedical interventions that do not involve the use of ARV drugs are not covered in these guidelines.

The 2013 consolidation process combines and harmonizes recommendations from a range of WHO guidelines and other documents, including the following 2010 guidelines on using antiretroviral therapy (ART) for HIV infection in adults and adolescents, in infants and children and for treating pregnant women living with HIV and preventing HIV infection in infants. Comprehensive guidance is now provided on using ARV drugs across age groups and populations of adults, pregnant and breastfeeding women, adolescents, children and key populations. The guidelines also aim to consolidate and update clinical, service delivery and programmatic guidance.

The 2013 guidelines reflect important advances in HIV responses during the past three years. Since 2010, new technologies, including CD4 point-of-care testing, and new service delivery approaches allow HIV testing and treatment monitoring to be diversified and decentralized. Simple, safer, once-daily, single-pill ARV regimens that are suitable for use in most populations and age groups have become more affordable and more widely available in low- and middle-income countries. Countries are moving towards earlier initiation of triple-drug regimens and simplified programming for the prevention of mother-to-child transmission of HIV (PMTCT) that emphasizes the long-term health of pregnant women and mothers living with HIV and preventing HIV infection among their children. The broader HIV prevention benefits of ARV drugs are being recognized: in addition to improving health and prolonging lives, ART prevents the sexual transmission of HIV, while pre-exposure prophylaxis of HIV with ARV drugs expands HIV prevention options and post-exposure prophylaxis of HIV continues to play an important role in managing HIV exposure in certain populations and settings, including for those who have been sexually assaulted. Although countries are at different stages of ART coverage and implementing the 2010 WHO guidelines, there is a consistent global trend towards initiating HIV treatment earlier.

Consistent with previous WHO guidelines, the 2013 guidelines are based on a public health approach to the further scaling up of ARV drugs for treatment and prevention that considers feasibility and effectiveness across a variety of resource-limited settings. The new clinical recommendations in these guidelines promote expanded eligibility for ART with a CD4 threshold for treatment initiation of 500 cells/mm³ or less for adults, adolescents and older children. Priority should be given to individuals with severe or advanced HIV disease and those with CD4 count of 350 cells/mm³ or less. ART is recommended to be initiated regardless of CD4 count for certain populations, including people with active tuberculosis (TB) disease who are living with HIV, people with both HIV and hepatitis B virus (HBV) infection with severe chronic liver disease, HIV-positive partners in serodiscordant couples, pregnant and breastfeeding women and children younger than five years of age. Harmonization of ART regimens for adults and children is recommended whenever possible, with a new, preferred first-line ART regimen. The need to phase out d4T in first-line ART regimens for adults and adolescents is being reinforced.

Viral load testing is now recommended as the preferred approach to monitoring ART success and diagnosing treatment failure, complementing clinical and immunological monitoring of people receiving ART.

The guidelines emphasize that ARV drugs should be used within a broad continuum of HIV care. Additional new recommendations provide guidance on community-based HIV testing and counselling and HIV testing of adolescents. Apart from new recommendations, summaries of and links to existing WHO guidance are provided for HIV testing and counselling, HIV prevention, general care for people living with HIV, the management of common coinfections and other comorbidities and monitoring and managing drug toxicities. Some existing recommendations need to be updated, and new recommendations will need to be reviewed in the next few years, as new evidence emerges.

Expanded eligibility for ART and a wider range of options for using ARV drugs provide new opportunities to save lives, improve clinical outcomes and reduce HIV incidence but also pose challenges to policy-makers and implementers in many countries. New operational guidance in 2013 provides recommendations for strengthening key aspects of the continuum of HIV care and improving linkages across the health system. This guidance focuses on strategies to improve retention in care and adherence to ART and on decentralizing the provision of ART to primary care, maternal and child health clinics, TB clinics and services to treat drug dependence. The operational guidance also addresses the implications of new clinical recommendations for laboratory services and supply systems for ARV drugs and other commodities.

Guidance specifically developed for HIV programme managers addresses decision-making and planning for the strategic use of ARV drugs in the context of national governance processes, HIV epidemiology, health systems capacity, available financial resources and ethical and human rights considerations. Implementation considerations especially relevant to programme managers are provided for major new recommendations. A concluding chapter on monitoring and evaluation provides preliminary guidance on monitoring the implementation of new recommendations.

The revision process for the 2013 guidelines was conducted 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 and decision-making. Modelling, expert consultations and country case studies have informed clinical, operational and programmatic guidance. The process has identified key gaps in knowledge that will guide the future research agenda. In addition to new recommendations based on the GRADE system, the guidelines summarize existing recommendations from other WHO guidelines. Most of these recommendations were developed using the GRADE system or a modification of the GRADE rating of the strength and quality of the evidence.

The primary audience for these guidelines is national HIV programme managers, especially in low- and middle-income countries. The guidelines are anticipated to guide country policy decisions and planning the scaling up of ART. They will also be a valuable resource for clinicians and informing the priorities of development agencies, international organizations, nongovernmental organizations and other implementing partners during the next few years.

The 2013 guidelines represent an important step towards achieving universal access to ARV drugs for treating and preventing HIV, increasing the efficiency, impact and long-term sustainability of ARV programmes and realizing the ultimate goal of ending the HIV epidemic.

SUMMARY OF NEW RECOMMENDATIONS

The following table summarizes the new WHO recommendations formulated for the 2013 guidelines on HIV testing and counselling, antiretroviral therapy (ART) and HIV service delivery. It also summarizes the guidance provided in Chapter 10 for programme managers. Where the recommendations remain unchanged from 2010 ART guidelines, this is clearly stated in the table.

The table is not comprehensive and does not include all WHO recommendations referred to in these guidelines, specifically recommendations that have been drawn from other, already existing WHO guidelines. The existing WHO recommendations referred to can be found in: Chapter 5 on HIV testing and counselling and HIV prevention, Chapter 6 on general care for people living with HIV, Chapter 8 on the management of common coinfections and other comorbidities and in section 7.4 on monitoring and management of drug toxicities.

HIV testing and counselling	
Topic and population	Recommendations
Community-based testing	<ul style="list-style-type: none"> ● In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (<i>strong recommendation, low-quality evidence</i>). ● In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (<i>strong recommendation, low-quality evidence</i>).
HIV testing and counselling of adolescents ^a	<ul style="list-style-type: none"> ● HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) (<i>strong recommendation, very-low-quality evidence</i>). ● HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents in generalized epidemics (<i>strong recommendation, very-low-quality evidence</i>). ● We suggest that HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents in low and concentrated epidemics (<i>conditional recommendation, very-low-quality evidence</i>). ● We suggest that adolescents 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 (<i>conditional recommendation, very-low-quality evidence</i>).

When to start ART in people living with HIV

Topic and population	Recommendations
<p>When to start ART in adults and adolescents^a</p>	<ul style="list-style-type: none"> ● As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm³ (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in all individuals with HIV with CD4 count >350 cells/mm³ and ≤ 500 cells/mm³ regardless of WHO clinical stage (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations: <ul style="list-style-type: none"> ● Individuals with HIV and active TB disease (<i>strong recommendation, low-quality evidence</i>). ● Individuals coinfectd with HIV and HBV with evidence of severe chronic liver disease (<i>strong recommendation, low-quality evidence</i>). ● Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (<i>strong recommendation, high-quality evidence</i>).
<p>When to start ART in pregnant and breastfeeding women</p>	<ul style="list-style-type: none"> ● All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (<i>strong recommendation, moderate-quality evidence</i>). ● For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (<i>conditional recommendation, low-quality evidence</i>). ● In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (<i>conditional recommendation, low-quality evidence</i>).

^aAn adolescent is a person aged 10 to 19 years inclusive.

When to start ART in people living with HIV (continued)

Topic and population	Recommendations
ARVs and duration of breastfeeding	<p>The key principles and recommendations established in 2010 remain, including:</p> <p>National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.</p> <p>In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival:</p> <ul style="list-style-type: none"> ● Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) 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. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided (<i>strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months</i>).
When to start ART in children	<ul style="list-style-type: none"> ● ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count. <ul style="list-style-type: none"> ● Infants diagnosed in the first year of life (<i>strong recommendation, moderate-quality evidence</i>) ● Children infected with HIV one year to less than five years of age (<i>conditional recommendation, very-low-quality evidence</i>). ● ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤ 500 cells/mm³, regardless of WHO clinical stage. <ul style="list-style-type: none"> ● CD4 count ≤ 350 cells/mm³ (<i>strong recommendation, moderate-quality evidence</i>) ● CD4 count between 350 and 500 cells/mm³ (<i>conditional recommendation, very-low-quality evidence</i>). ● ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (<i>strong recommendation, moderate-quality evidence</i>). ● ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection (<i>strong recommendation, low-quality evidence</i>)

What ART regimens to start

Topic and population	Recommendations
<p>First-line ART regimens for adults</p>	<ul style="list-style-type: none"> ● First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). ● TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (<i>strong recommendation, moderate-quality evidence</i>). ● If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following options is recommended: <ul style="list-style-type: none"> ● AZT + 3TC + EFV ● AZT + 3TC + NVP ● TDF + 3TC (or FTC) + NVP (<i>strong recommendation, moderate-quality evidence</i>). ● Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (<i>strong recommendation, moderate-quality evidence</i>).
<p>First-line ART for pregnant and breastfeeding women and their infants</p>	<ul style="list-style-type: none"> ● A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (<i>strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants</i>). ● Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (<i>strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding</i>).

What ART regimens to start (continued)

Topic and population	Recommendations
First-line ART for children younger than 3 years of age	<ul style="list-style-type: none"> ● A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen (<i>strong recommendation, moderate-quality evidence</i>). ● Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (<i>conditional recommendation, low-quality evidence</i>). ● For infants and children infected with HIV younger than three 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 (<i>strong recommendation, moderate-quality evidence</i>). ● For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC + 3TC or AZT + 3TC (<i>strong recommendation, low-quality evidence</i>).
First-line ART for children 3 years of age and older (including adolescents)	<ul style="list-style-type: none"> ● For children infected with HIV three years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (<i>strong recommendation, low-quality evidence</i>). ● For children infected with HIV three years to less than 10 years old (and adolescents weighing less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order: <ul style="list-style-type: none"> ● ABC + 3TC ● AZT or TDF + 3TC (or FTC) <i>(conditional recommendation, low-quality evidence)</i>. ● For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order: <ul style="list-style-type: none"> ● TDF + 3TC (or FTC) ● AZT + 3TC ● ABC + 3TC <i>(strong recommendation, low-quality evidence)</i>.

Monitoring ART response and diagnosis of treatment failure

Topic and population	Recommendations
All populations	<ul style="list-style-type: none"> ● Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (<i>strong recommendation, low-quality evidence</i>). ● If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (<i>strong recommendation, moderate-quality evidence</i>).

Second-line ART: what ARV regimen to switch to

Topic and population	Recommendations
<p>What ARV regimen to switch to in adults and adolescents</p> <p>(includes pregnant and breastfeeding women)</p>	<ul style="list-style-type: none"> ● Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI). ● The following sequence of second-line NRTI options is recommended: <ul style="list-style-type: none"> • 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 (<i>strong recommendation, moderate-quality evidence</i>). ● Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART (<i>strong recommendation, moderate-quality evidence</i>).

Second-line ART: what ARV regimen to switch to (continued)

Topic and population	Recommendations
<p>What ARV regimen to switch to in children (including adolescents)</p>	<ul style="list-style-type: none"> ● After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI (<i>strong recommendation, moderate-quality evidence</i>). ● After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken (<i>conditional recommendation, very-low-quality evidence</i>). ● After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI (<i>conditional recommendation, low-quality evidence</i>). ● 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 (<i>strong recommendation, low-quality evidence</i>). ● 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) (<i>strong recommendation, low-quality evidence</i>).
<h3>Third-line ART</h3>	
Topic and population	Recommendations
All populations	<ul style="list-style-type: none"> ● National programmes should develop policies for third-line ART (<i>conditional recommendation, low-quality evidence</i>). ● Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs (<i>conditional recommendation, low-quality evidence</i>). ● Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (<i>conditional recommendation, very low-quality evidence</i>).
Special considerations for children	<p>Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible. Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.</p>

Operations and service delivery	
Topic	Recommendations
Interventions to optimize adherence to ART	<ul style="list-style-type: none"> ● Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions (<i>strong recommendation, moderate-quality evidence</i>).
Service integration and linkage	<ul style="list-style-type: none"> ● In generalized epidemic settings, ART should be initiated and maintained in eligible 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 (<i>strong recommendation, very-low-quality evidence</i>). ● In settings with a high burden of HIV and TB, ART should be initiated for an individual living with HIV in TB treatment settings, with linkage to ongoing HIV care and ART (<i>strong recommendation, very-low-quality evidence</i>). ● In settings with a high burden of HIV and TB, TB treatment may be provided for an individual living with HIV in HIV care settings where TB diagnosis has also been made (<i>strong recommendation, very-low-quality evidence</i>). ● ART should be initiated and maintained in eligible people living with HIV at care settings where opioid substitution therapy (OST) is provided (<i>strong recommendation, very-low-quality evidence</i>).
Decentralization of treatment and care	<p>The following options should be considered for decentralization of ART initiation and maintenance.</p> <ul style="list-style-type: none"> ● Initiation of ART in hospitals with maintenance of ART in peripheral health facilities (<i>strong recommendation, low-quality evidence</i>). ● Initiation and maintenance of ART in peripheral health facilities (<i>strong recommendation, low-quality evidence</i>). ● Initiation of ART at peripheral health facilities with maintenance at the community level (that is, outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits (<i>strong recommendation, moderate-quality evidence</i>).

Operations and service delivery (continued)

Topic	Recommendations
Task-shifting	<ul style="list-style-type: none"> ● Trained non-physician clinicians, midwives and nurses can initiate first-line ART (<i>strong recommendation, moderate-quality evidence</i>). ● Trained non-physician clinicians, midwives and nurses can maintain ART (<i>strong recommendation, moderate-quality evidence</i>). ● Trained and supervised community health workers can dispense ART between regular clinical visits (<i>strong recommendation, moderate-quality evidence</i>).

Guidance for programme managers

Topic	Guidance
Guidance for programme managers	<p>For deciding on the implementation of the clinical and operational recommendations, it is recommended that:</p> <ul style="list-style-type: none"> ● The national authorities do so using a transparent, open and informed process. This process should have broad stakeholder engagement, including meaningful participation from the affected communities, and take into account the specifics of the recommendations under discussion. ● The decision-making process take into account data on the national and local HIV epidemiology, current ART programme performance and the socioeconomic, policy and legal context, including the budgetary, human resource requirements and other health system implications. The latter would identify which inputs and systems are currently available and which areas require additional investment. ● The decision-making process take into account the ethics, equity and human rights, the impact and cost-effectiveness and the opportunity and risk dimensions of alternative implementation options.

INTRODUCTION

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1. INTRODUCTION

1.1 Background and context

WHO first published guidelines on the use of ART for HIV infection among adults and adolescents in 2002 (1) and on the use of ARV drugs for PMTCT in 2004 (2). The 2006 updates of the guidelines (3–5) introduced the concept of a public health approach, with simplified and harmonized ART regimens (6). These publications and their updates, most recently in 2010 (7–9), have provided important guidance to countries that have scaled up national ARV programmes during the past decade. In 2013, for the first time, WHO has revised and combined these and other ARV-related guidance documents into one set of consolidated guidelines that addresses the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the broad continuum of HIV care.

These guidelines were updated in late 2012 and early 2013. The ARV regimens now available, even in the poorest countries, are safer, simpler, more efficacious and more affordable than ever before. New testing strategies and approaches are enabling earlier diagnosis of HIV in a wider range of settings, and new, more affordable technologies for monitoring people receiving ART are becoming available. Countries are moving towards triple-drug regimens and simplified programming for PMTCT that emphasizes the long-term health of pregnant women and mothers living with HIV as well as their children. Important new evidence has shown that ARV drugs offer significant benefits in preventing HIV transmission (10). Although countries are at different stages of ART coverage and implementation of the 2010 guidelines (7–9) and there are still important gaps in research, there is a consistent global trend towards expanding access and the earlier initiation of treatment.

Expanding the eligibility criteria for ART and the options for using ARV drugs creates opportunities to save lives and reduce HIV transmission but can pose significant technical, operational, programmatic and ethical challenges to policy-makers and implementers in many low- and middle-income countries. These include implementing a strategic mix of approaches to ensure more timely diagnosis of HIV infection in both health facility and community settings. Effective linkage and referrals between care settings, innovative, decentralized approaches to delivering ART services and effective adherence support and interventions are also needed to ensure that people are retained in long-term care. Reliable, quality-assured and affordable laboratory monitoring tools, adequate health workforce capacity and uninterrupted drug supplies are also essential.

At the programmatic level, countries often encounter difficulties in reaching the people who need ARV drugs the most. They may face difficult choices in allocating limited resources and determining programme priorities to make the best use of ARV drugs for treatment and prevention in combination with other HIV prevention methods. National HIV programmes may need to justify increased investment in ARV programmes by assessing the costs and benefits and demonstrating how they impact on HIV morbidity, mortality and incidence.

1.2 Rationale for consolidated guidelines

The consolidated guidelines offer the following anticipated benefits.

Guidance on using ARV drugs is presented within the context of the continuum of HIV-related prevention, treatment and care. In addition to providing recommendations on the clinical use of ARV drugs for treatment, the guidelines address other major aspects of HIV-related care.

The guidelines address the use of ARV drugs for all age groups and populations.

Previously separate WHO guidelines on using ART among adults and adolescents have been combined with those for children and for PMTCT, harmonizing ARV regimens and treatment approaches to the extent possible across age groups and populations.

New and existing guidance is harmonized. Consolidation has allowed for new recommendations to be harmonized with relevant, existing WHO guidance.

Consolidation promotes the consistency of approaches and linkage between settings. Consolidated recommendations help to facilitate linkage and promote consistency of approaches across the various settings in which ARV drugs and related services may be provided, including specialized HIV care, primary care, community-based care, maternal and child health services, TB services and services for people who use drugs.

Updates will be more timely and comprehensive. Consolidated guidelines enable key clinical, operational and programmatic implications of new science and emerging practice in the use of ARV drugs to be comprehensively reviewed every two years across populations, age groups and settings.

1.3 Objectives

The objectives of the consolidated guidelines are:

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

1.4 Target audience

The guidelines are intended primarily 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;
- managers of maternal, newborn and child health and reproductive health programmes;
- clinicians and other health service providers;
- 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 resource-limited settings.

1.5 Scope and components

The guidelines address clinical, operational and programmatic aspects of using ARV drugs for HIV treatment and prevention (Fig. 1.1).

1.5.1 Introductory chapters

The guidelines include several introductory chapters.

Chapter 1: Describes the background, context, rationale and objectives of the guidelines and the target audience.

Chapter 2: Outlines the guiding principles that underpin the guidelines.

Chapter 3: Describes the methods and process for developing the guidelines.

Chapter 4: Presents the format used to present new recommendations.

1.5.2 Clinical guidance

The recommendations in Chapters 5, 6 and 7 address key aspects of using ARV drugs for HIV treatment and prevention for all age groups and populations along the continuum of care from HIV-related diagnosis to care and treatment.

Chapter 5: Summarizes HIV testing and counselling approaches, with links to existing WHO guidance. In addition, it summarizes approaches to using ARV drugs for preventing HIV transmission (pre-exposure prophylaxis and post-exposure prophylaxis of HIV and ARV drugs for prevention in serodiscordant couples) within the context of comprehensive combination HIV prevention, with links to existing WHO guidance. Note that the guidelines do not address behavioural, structural and biomedical prevention interventions that do not involve the use of ARV drugs.

Chapter 6: Summarizes general HIV care for individuals from the time that they are diagnosed with HIV infection to the time that they are initiated on ART, including practices for linking people diagnosed with HIV infection to HIV care and treatment, the components of a general care package and preparing individuals for starting ART.

Chapter 7: Includes recommendations on ART for adults (including pregnant and breastfeeding women), adolescents and children, including updated recommendations applicable to the majority of populations regarding the optimal timing for initiating ART (when to start); updated recommendations on the most effective and feasible first- and second-line treatment regimens (what to start and what to switch to); updated recommendations for monitoring the response to and toxicity of ART; and a discussion of third-line ART.

Chapter 8: Includes a summary of approaches to preventing and managing common HIV-related opportunistic infections, other coinfections and other comorbidities, with links to existing WHO guidance.

1.5.3 Operational and service delivery guidance

Chapter 9: Includes recommendations in six major operational and service delivery areas in which action is essential to further scaling up ARV programmes and ensuring their effectiveness and sustainability across the health system. These areas are: retention in care; adherence to ART; human resources; models of service delivery, focusing on decentralizing ART to primary health care services and integrating ART with TB treatment, antenatal care and maternal and child health programmes and drug dependence services; laboratory services; and drug supply management.

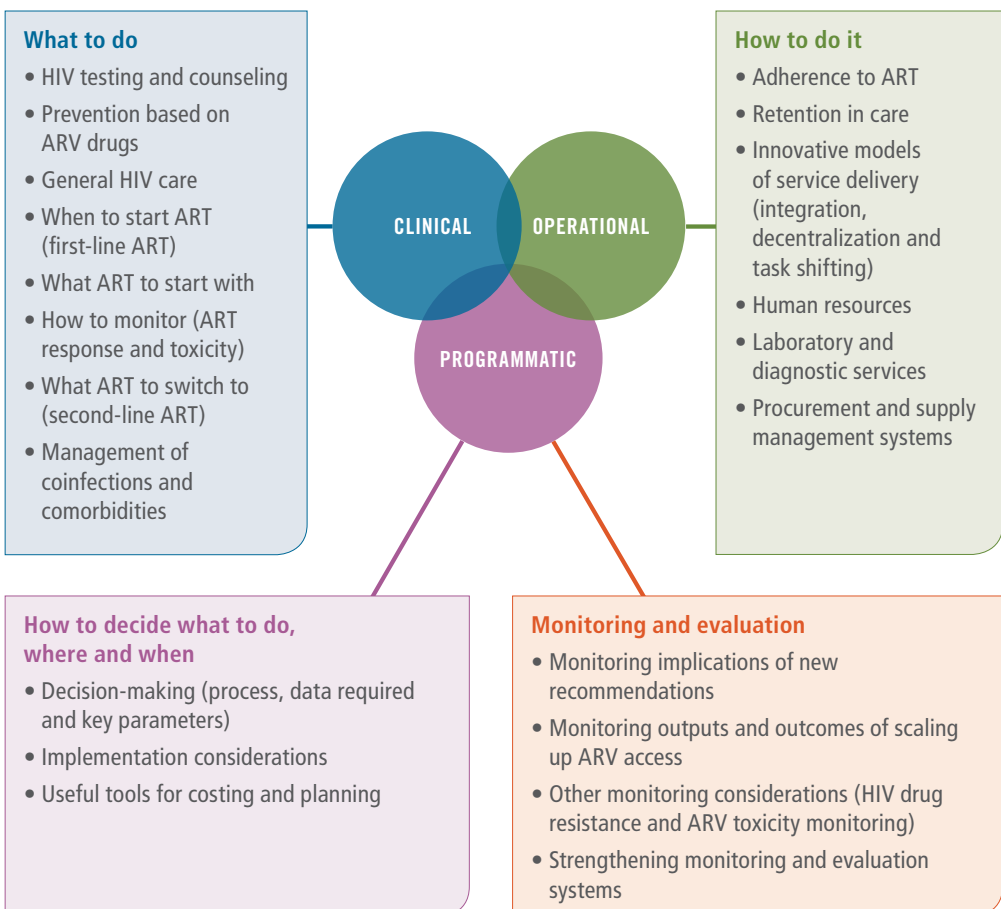
1.5.4 Guidance for programme managers

Chapter 10: Aims to assist countries in decision-making and programme planning. Implementation will involve various policy mixes based on local context, including the prevalence and dynamics of HIV infection; modes of transmission; the organization and capacity of health systems; relative income; and the current coverage of interventions. The chapter proposes steps to ensure fair, inclusive and transparent decision-making processes at the country level; discusses parameters to consider in assessing and adapting the global recommendations in countries; and suggests tools for costing and planning. Considerations for implementation across the health system and for specific, key recommendations in the guidelines are also discussed.

1.5.5 Monitoring and evaluation

Chapter 11: Provides guidance on the implications for monitoring of key new recommendations in these guidelines. It proposes a range of indicators that may be used to track the implementation of new recommendations and indicators to monitor the performance of programmes across the continuum of care. Chapter 11 also highlights opportunities provided by new recommendations to review and strengthen monitoring and evaluation systems.

Fig. 1.1 Components of the consolidated guidelines





GUIDING PRINCIPLES

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2. GUIDING PRINCIPLES

2.1 Contribution to global health goals

Implementing these guidelines will contribute to achieving universal access to HIV prevention, treatment, care and support in accordance with the goals and targets articulated in the 2006 Political Declaration on HIV/AIDS (1) and the 2011 Political Declaration on HIV and AIDS: Intensifying Our Efforts to Eliminate HIV and AIDS (2). These guidelines will also contribute to attaining specific health sector goals in the Global Health Sector Strategy on HIV/AIDS 2011–2015 (3) and the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive (4). Major targets for 2015 include reducing by half the percentage of young people 15–25 years who are infected with HIV compared with 2009; reducing the number of children newly infected with HIV by 90% compared with 2009; reducing the number of people dying from HIV-related causes by 25% compared with 2009; reducing by half the number of HIV-related maternal deaths compared with 2009; reducing by half the number of people dying from TB compared with 2004; and having 15 million people on ART in low- and middle-income countries. In the longer term, the guidelines will contribute to and inform efforts to achieve universal health coverage, a key pillar of the post-2015 development agenda.

2.2 Public health approach

In accordance with WHO guidance on HIV since 2002, these guidelines are based on a public health approach to scaling up the use of ARV drugs for HIV treatment and prevention (5). The public health approach seeks to ensure the widest possible access to high-quality services 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.

2.3 Strengthening health systems through innovation and learning

The recommendations and innovations in service delivery described in these guidelines should be implemented with a view to strengthening the continuum of HIV care and broader health systems, especially primary care and chronic care.

HIV services are already being integrated at lower-level health facilities in many settings with a high burden of HIV infection, while services for PMTCT are increasingly becoming core elements of maternal and child health services. HIV, TB, hepatitis, drug dependence and harm reduction services are being integrated to varying degrees. As people receiving ART begin to age and HIV infection becomes a chronic, manageable condition, improving the integration of HIV services with care for noncommunicable diseases will also become more important. In accordance with these trends, the guidelines promote the adaptation of service delivery models that strengthen the continuum of HIV care and enable the timely initiation of ART in a variety of settings, ensuring that people are appropriately referred to services and are retained in and adhere to lifelong treatment.

National HIV programmes should consider undertaking implementation research to determine how best to adopt and adapt these guidelines to their local context and bringing to scale more efficient and effective services.

2.4 Increasing the effectiveness and efficiency of programmes

In the context of limited financial resources, competing priorities and health system constraints, countries may face difficult choices among an expanding range of options for using ARV drugs to reduce HIV morbidity, mortality and transmission. These guidelines are based on the principle that countries should further scale up and optimize the effectiveness and efficiency of HIV programmes through a strategic approach to using ARV drugs that involves:

- Giving priority to providing ARV drugs to people living with HIV who are eligible for treatment and most in need;
- Exploring opportunities to enhance the impact of ARV drugs on HIV prevention by starting treatment earlier in certain populations;
- Increasing the effectiveness and reach of ARV programmes across the continuum of care through a strategic mix of quality-assured HIV testing approaches, improving adherence and retention, innovative service delivery, integrating ART in a wider range of settings and strengthening links between services; and
- Engaging in both short- and longer-term efforts to optimize and harmonize drug regimens and increase their affordability and to develop and implement simpler and more affordable point-of-care diagnostics and laboratory services.

2.5 Promoting human rights and health equity

Access to HIV prevention, treatment, care and support should be recognized as fundamental to realizing the universal right to health, and these guidelines should be implemented based on core human rights and ethical principles. In general, HIV programmes need to ensure that ARV drugs and related interventions are accessible to the people who need them most, including pregnant women, children and key populations, and that they are provided in an environment that minimizes stigma and discrimination. Informed consent – notably for HIV testing but also for initiating ART – should always be obtained. Adequate safeguards must be in place to ensure confidentiality.

Some countries may face significant ethical challenges as they seek to implement these guidelines in the context of constraints on resources and health systems. A key challenge may involve the need to give priority to ensuring ART for the people who are most ill and those already receiving treatment, while also striving to implement expanded eligibility criteria. Each country will need to plan its own approach to ensuring that current ARV programmes are not disrupted and that expanded access is fair and equitable.

2.6 Implementation based on local context

Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness. A strong recommendation for a specific approach to service delivery should not necessarily be viewed as an endorsement of that model over an effective service delivery model already in place in a country.



METHODS AND PROCESS

FOR DEVELOPING THE GUIDELINES

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3. METHODS AND PROCESS FOR DEVELOPING THE GUIDELINES

3.1 Overview

The 2013 consolidated guidelines compile new recommendations, existing recommendations and other guidance across the continuum of HIV care. This includes guidance on HIV diagnosis, general HIV care and the strategic use of ARV drugs for treating and preventing HIV infection, based on a public health approach. New clinical and operational recommendations were developed in accordance with procedures outlined by the WHO Guidelines Review Committee (1) and are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system (2–11). Most recommendations cited from existing guidance were developed using the GRADE system. In a few cases where GRADE was not used, the text notes this. Chapter 10 did not use the GRADE approach, since the programmatic guidance does not contain any formal recommendations.

3.2 Information sources

The following sources of information were used in developing new recommendations.

- **Systematic reviews** were commissioned on 41 topics framed using Population, Intervention, Comparison and Outcome (PICO) format by the WHO Guideline Steering Group (3) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The 41 topics covered the continuum of HIV care (9 on when to start; 11 on what to start; 4 on monitoring the response to treatment; 6 on monitoring toxicity; 11 on various aspects of service delivery; and 5 on adherence interventions). The WHO Guideline Steering Group established the critical outcomes for the reviews of clinical evidence (mortality, morbidity, transmission and severe adverse reactions) and for the reviews of operational service delivery (mortality, morbidity, transmission, access, retention in care, viral suppression and adherence) in consultation with the Guidelines Development Groups. Systematic reviews were outsourced to researchers who developed search protocols and conducted reviews of the available scientific evidence. Searches of electronic databases (MEDLINE/PubMed, Embase, CENTRAL), conference databases (Aegis, AIDSearch, NLM Gateway and hand searches) and clinical trial registers (<http://clinicaltrials.gov>, www.controlled-trials.com and www.pactr.org) used relevant keywords and search strings. The Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) includes the search protocols, the full list of review questions and the GRADE tables and evidence summaries for each topic.
- **A standardized GRADE evidence table** was used to present quantitative summaries of the evidence and assessment of its quality for each PICO question by outcome. The GRADE system was used to rate the quality of evidence (4–10) and the strength of the recommendations (11) (Box 3.1; Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
- **Community consultations** on values and preferences in priority areas for the guidelines were conducted through an online e-survey and moderated e-forum discussions with civil society networks and coordinated by the International HIV/AIDS Alliance and the Global Network of People Living with HIV (GNP+). Focus group discussions were also held in Uganda and Malawi on the experiences of pregnant women with lifelong ART, and on PMTCT and paediatric ART in South Africa (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

- **Two global community and civil society consultations** on service delivery across the continuum of care in generalized and concentrated epidemic settings.
- **Consultations with health workers** working with adults and with children on the values and preferences related to priority areas in the guidelines were conducted through an e-survey (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
- **The sixth annual survey in 2012 of the WHO AIDS Medicines and Diagnostics Service** on the use of ARV drugs and diagnostics in 80 low- and low-middle-income countries (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
- **Mathematical modelling** on the impact and cost–effectiveness of earlier ART in various populations and settings, based on data from countries with both generalized and concentrated epidemics (India, Kenya, South Africa, Viet Nam and Zambia), together with modelling of various treatment monitoring strategies were undertaken by the HIV Modelling Consortium (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
- **An impact assessment** using the Spectrum model to estimate the increased number of adults and children eligible for ART based on various eligibility criteria (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).
- **Reports on country implementation experiences** were provided on using option B+ for PMTCT in Malawi; introducing TDF in first-line ART regimens in Zambia; phasing out d4T in Zimbabwe; and scaling up viral load monitoring in Médecins Sans Frontières programmes in southern Africa.
- **An electronic e-survey of country-level end-users** was undertaken of WHO guidelines on ARV drugs to identify areas for improvement in format, presentation and dissemination (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

3.3 External participation

3.3.1 Guideline Development Groups and peer review process

The process was supported by four, separate, external Guideline Development Groups (Adult; Maternal and Child Health; Operational and Service Delivery; and Programmatic, comprising 108 individuals) and an external peer review group of over 100 individuals. The acknowledgements list the members of these Groups. The composition of the Groups was in accordance with WHO procedures for developing guidelines (1) and included HIV experts, researchers, programme managers, guideline methodologists, epidemiologists, human rights experts, development agencies, United Nations partners, civil society representatives and representatives from networks of people living with HIV. Appropriate representation by geography and sex was considered. Community group members were selected following an open call for nominations. A full draft of the guidelines was circulated for comment to members of the Guideline Development Groups and the external peer review group.

3.3.2 Conflicts of interest

All members of the Guideline Development Groups and peer review group completed WHO declaration of interest forms (including participation in consulting and advisory panels, research support and financial investment). A total of 21 Guideline Development Group members and 12 peer reviewers declared membership of pharmaceutical industry or other advisory panels or receipt of consulting fees, and 23 Guideline Development Group members and 13 peer reviewers declared pharmaceutical industry financial support through grants for research.

The focus of the 2013 guidelines was on the development of new or updated recommendations on the use of ARV drugs in adults, adolescents, children and pregnant women. The WHO secretariat and co-chairs of each Guideline Development Group considered that important areas for potential conflict of interest would be evidence for exclusive engagement with one pharmaceutical company, or a major role within completed, ongoing or planned trials on either the timing of ART, or evaluation of specific ART regimens. The WHO Guideline Steering Group reviewed all declarations, and found no case where there was exclusive membership of an advisory group panel, receipt of consulting fees or financial support through research grants from only one pharmaceutical company. There was also a further declaration at the Guideline Development Group meeting of the involvement of members as investigators in key trials and studies. Overall, the WHO Guideline Steering Group and co-chairs of each Guideline Development Group were satisfied that there had been a transparent declaration of interests, and that no case necessitated exclusion from the deliberations. The broad range of constituencies represented on the different Guideline Development Group panels was also noted, and that the majority of members had no declared interests. All individuals with declared interests therefore proceeded to participate fully in the Guideline Development Group meetings or to act as peer reviewers.

3.4 Process of formulating recommendations

Four Guideline Development Group meetings were held in Geneva, Switzerland between November 2012 and January 2013 (Operational and Service Delivery Guideline Development Group, November 2012; Adult Guideline Development Group and Maternal and Child Health Guideline Development Group, December 2012; and Programmatic Guideline Development Group, January 2013). The systematic reviews, evidence tables prepared in accordance with GRADE and other relevant information described in section 3.2 were presented and discussed at these meetings and made available through a password-protected web site. The proposed recommendations were then considered, informed by a standardized decision-making table for each topic (Box 3.1) encompassing the following elements: existing and proposed recommendations; summary of the evidence; benefits and risks; community and health care worker values and preferences; costs and resource implications; cost-effectiveness; feasibility and barriers to implementation; equity, ethics and human rights implications; the suggested rating of the strength of recommendations (strong or conditional) and quality of the evidence; research gaps and needs; and the overall rationale for the recommendations.

The Guideline Development Groups discussed both the proposed wording of the recommendations and the rating of its strength (strong or conditional). All decisions were reached by discussion and consensus on the recommendations, including their strength and, where appropriate, the conditions to be attached to the recommendations. Disagreements were resolved through e-mail discussions, teleconferences and redrafting recommendations and rationale. Early drafts of sections of the guidelines were circulated to Guideline Development Group members, and a full draft of the guidelines was circulated to Guideline Development Group members and peer reviewers for comment. The extensive comments from more than 100 reviewers were addressed where possible and incorporated into the revised guidelines.

Box 3.1 Approach to rating the quality of evidence and strength of recommendations using the GRADE system

Since 2008, WHO has followed the GRADE system. GRADE separates the rating of the quality of evidence from the rating of the strength of the recommendation.

The **quality of evidence** is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low (Table 3.1) (4–10). Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including the risk of bias, inconsistency of results across studies, 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 multiple studies show the same effect, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect (10). The higher the quality of evidence, the more likely a strong recommendation can be made.

The **strength of a recommendation** reflects the extent to which the Guideline Development Group was confident that the desirable effects of following a recommendation outweigh the potential undesirable effects. The strength is influenced by the following factors: the quality of the evidence, the balance of benefits and harms, values and preferences, resource use and the feasibility of the intervention (Table 3.2).

The GRADE system classifies the strength of a recommendation in two ways: “strong” and “conditional” (11). A **strong recommendation** is one for which the Guideline Development Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects. A **conditional recommendation** is one for which the Guideline Development Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the Guideline Development Group is not confident about these trade-offs. Table 3.3 summarizes the implications of a strong or conditional recommendation for individuals, clinicians and policy-makers.

The reasons for making a conditional recommendation include the absence of high-quality evidence; imprecision in outcome estimates; variability in the values and preferences of individuals regarding the outcomes of interventions; small benefits; applicability in all settings versus specific settings; and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Table 3.1 GRADE classification of the level of evidence

Level of evidence	Rationale
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the effect
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Table 3.2 Key domains considered in determining the strength of recommendations

Domain	Rationale
Benefits and risks	Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation will be made.
Values and preferences (acceptability)	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation will probably be made. If there are strong reasons that the recommended course of action is unlikely to be accepted, a conditional recommendation is more likely to be made.
Costs and financial implications (resource use)	Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is more probable.

Table 3.3 Implications for strong and conditional recommendations for individuals, clinicians and policy-makers

	Strong recommendation	Conditional recommendation
Individual	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not
Clinician	Most individuals should receive the recommended course of action	Be prepared to help individuals to make a decision that is consistent with their own values
Policy-maker	The recommendation can be adapted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

3.5 Other methods

Recommendations from existing guidelines. In addition to new recommendations based on the GRADE system, the guidelines summarize existing relevant recommendations from other WHO guidelines). Most of these recommendations were developed using the GRADE system or an alternative grading used prior to 2008 (A (strongly recommended) to C (optional)) and I–IV (level of evidence) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). For these existing recommendations, no new evidence reviews were undertaken. Recommendations that require updating are noted, and it is clearly stated where updated guidelines are planned.

Where systematic reviews and GRADE assessment of quality of evidence to support new recommendations were not possible or appropriate, qualitative reviews of the literature were undertaken and presented. This applies to specific topics in Chapter 9, including retention across the continuum of care, but this did not lead to formal recommendations.

Guidance for programme managers on programmatic decision-making. Chapter 10 and Chapter 11 did not involve formulating recommendations or rating of the quality of evidence and therefore did not follow the GRADE system. The process involved a narrative review of literature on both the process and criteria for evidence-based ethical decision-making, a review of relevant WHO policies and World Health Assembly resolutions, and results from mathematical modelling on the impact and cost–effectiveness of earlier ART in various populations and settings. Structured discussions were held among Guideline Development Group members regarding setting priorities for key clinical recommendations in various epidemic scenarios (settings with generalized and concentrated epidemics and with low, moderate and high ART coverage).

3.6 Dissemination

The guidelines will be disseminated as a printed publication and electronically on the WHO web site in the six official United Nations languages. The web version will include all annexes. A short version will summarize key new and existing recommendations for easy reference. A library of all supporting documentation and evidence will also be made available on the web site. WHO headquarters will work closely with regional and country offices and implementing partners to ensure their wide dissemination through regional and subregional meetings. Assistance will be provided to Member States to adapt the guidelines to their national contexts.

An evaluation of how users have implemented the guidelines has been developed to assess the uptake of the recommendations and the barriers to effective implementation. A review of the guidelines is planned for 2015. Interim technical and programmatic updates may be developed if important new evidence becomes available.



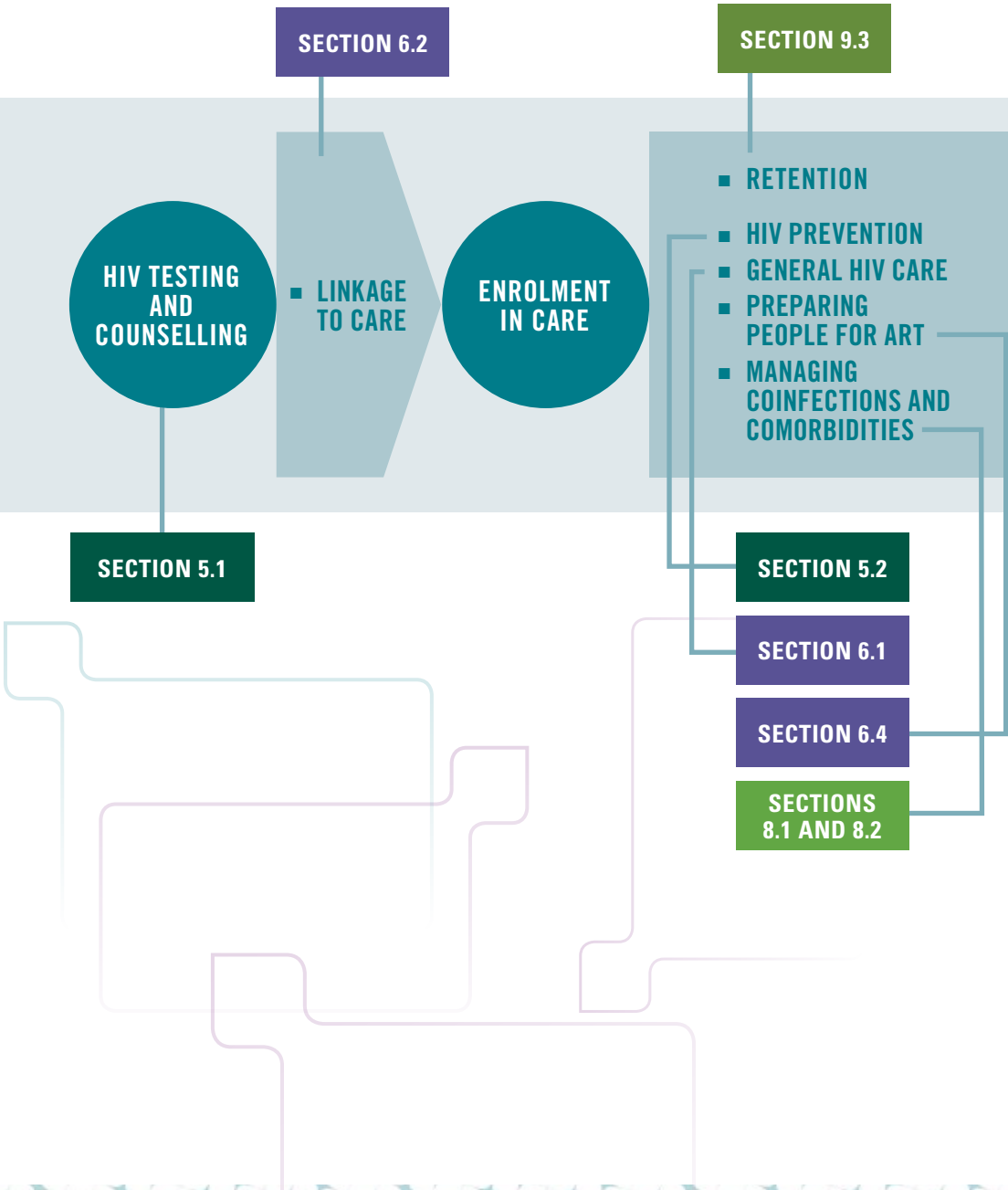
ORGANIZATION OF THE GUIDELINES

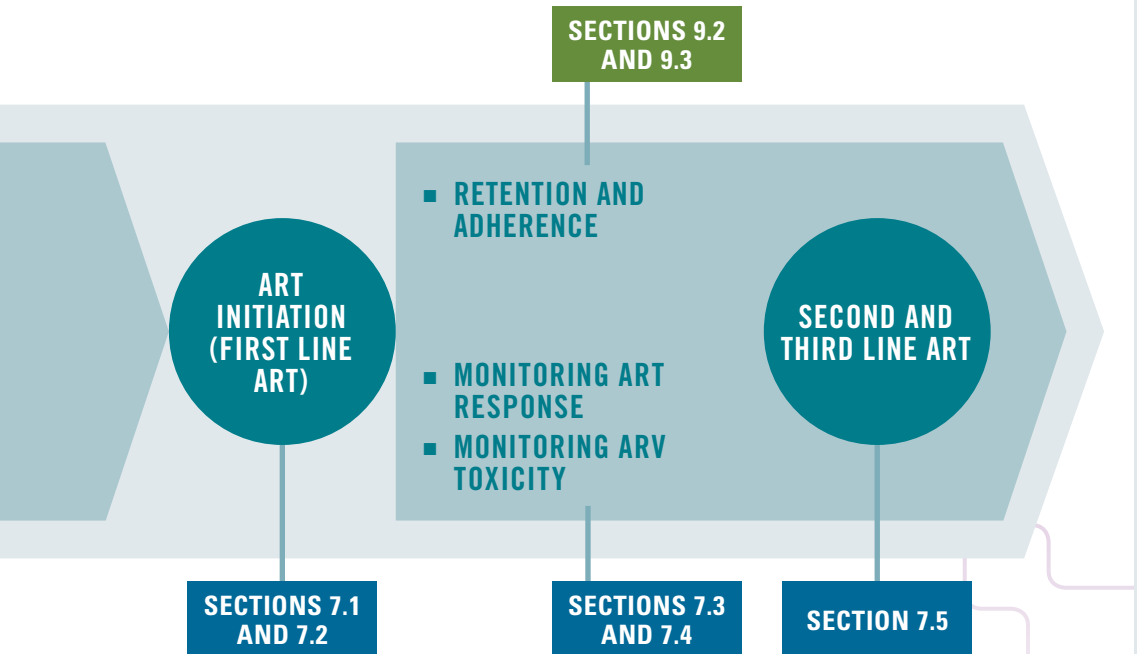
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4. ORGANIZATION OF THE GUIDELINES

Continuum of care





4.1 Structure of presentation for new recommendations

New recommendations in these guidelines are flagged by a symbol . These include existing recommendations that have been updated, where a new evidence review was undertaken as part of this guidelines process. When the original recommendation remained unchanged, this is clearly indicated. They are presented in the following format to reflect the full evidence review and discussion held within the Guideline Development Group for new recommendations.

- **Recommendation.** The new recommendation and the strength and quality of evidence assessed using the GRADE method are stated.
- **Background.** Previous WHO guidance in this area and key developments since recommendations were last published are described. When the recommendation relates to a specific population, the key issues for that population may be briefly summarized.
- **Rationale for recommendation and supporting evidence.** The new evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation are summarized.
- **Clinical or implementation considerations.** In some cases, key clinical implementation issues specific to the recommendation are listed. For several key recommendations, discussion of implementation considerations relevant to programme managers is presented in Chapter 10.
- **Key research gaps.** In some cases, critical issues requiring further research are briefly described or listed, where these are integral to the recommendations.
- The references relating to each section are listed at the end of the guidelines by chapter number.

4.2 Structure of presentation of selected recommendations from existing guidelines

Two chapters summarize recommendations from existing WHO guidelines: Chapter 5 on HIV testing and counselling as well as the use of ARV drugs for prevention; and Chapter 8 on general HIV care, including prevention and management of coinfections and comorbidities. In general, these are presented in the following format:

- **Background;**
- **Source(s) for recommendation(s);**
- **Additional guidance (where appropriate); and**
- **Existing recommendation(s).**

The new recommendations and the strength and quality of the evidence assessed using the GRADE method (or an alternative method) are stated.

4.3 How to use the guidelines for specific populations

These guidelines include recommendations for adults, pregnant and breastfeeding women, adolescents, children, and key populations. The population relevant to each recommendation is clearly specified and also marked by an appropriate symbol for quick reference.



Adults



Children



Pregnant women



Key populations



Adolescents

Tables 4.1–4.4 also summarize the chapter and section number of key recommendations and guidance for specific populations: - pregnant and breastfeeding women, adolescents, children and infants, and key populations. The tables highlight selected topics that are particularly relevant to the respective populations. However, the topics listed are not exhaustive and many of the recommendations and other guidance are relevant across different populations.

4.3.1 Pregnant and breastfeeding women

Table 4.1 summarizes the location of key guidance and recommendations specific to pregnant and breastfeeding women.

Table 4.1. Key recommendations and guidance for pregnant and breastfeeding women

Chapter	Topic	Chapter subsections
Chapter 5: HIV diagnosis and ARV drugs for HIV prevention	HIV testing in health facilities	Section 5.1.2
	Community-based HIV testing and counselling	Section 5.1.3
	HIV testing and counselling in specific populations: couples	Section 5.1.4.1
	HIV testing and counselling in specific populations: pregnant and postpartum women	Section 5.1.4.2
	HIV testing and counselling in specific populations: early infant diagnosis	Section 5.1.4.3
	ART for prevention among serodiscordant couples	Section 5.2.2
Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment	General care for people living with HIV	Section 6.3
	Preparing people living with HIV for ART	Section 6.4
	What to expect in the first months of ART	Section 6.5



Table 4.1 (continued)

Chapter	Topic	Chapter subsections
Chapter 7: Antiretroviral therapy	When to start ART in pregnant and breastfeeding women	Section 7.1.2
	ARV drugs and duration of breastfeeding	Section 7.1.3
	Special considerations for the care and management of pregnant women	Section 7.1.3; Box 7.1
	First-line ART for pregnant and breastfeeding women and ARV drugs for their infants	Section 7.2.2
	Monitoring response to ART and diagnosis of treatment failure (includes pregnant and breastfeeding women)	Section 7.3
	Monitoring and substitutions for ARV drug toxicities (includes pregnant and breastfeeding women)	Section 7.4
	Second-line ART for adults and adolescents (includes pregnant and breastfeeding women)	Section 7.5.1
	Third-line ART (includes pregnant and breastfeeding women)	Section 7.6
Chapter 8: Managing common coinfections and comorbidities	Prevention, screening and management of coinfections	Section 8.1
	Preventing and managing other comorbidities and chronic care for people living with HIV	Section 8.2
Chapter 9: Guidance on operations and service delivery	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Adherence to ART: pregnant and postpartum women	Section 9.2.1
	Delivering ART in antenatal care and maternal and child health settings	Section 9.4.2.1
	Decentralization and task shifting	Sections 9.4.3 and 9.5.2
Chapter 10: Guidance for programme managers	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Implementation considerations for key recommendations: moving to lifelong ART for all pregnant and breastfeeding women	Section 10.6 Box 10.4
Chapter 11: Monitoring and evaluation	Monitoring implications of new recommendations	Section 11.2
Annexes	Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children	Chapter 12
	Annex 3. Algorithms for the 2013 recommendations for pregnant and breastfeeding women	
	Annex 6. Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women	
	Annex 7. Dosages of recommended ARV drugs for adults and adolescents (includes pregnant and breastfeeding women)	

4.3.2 Adolescents

WHO defines adolescence as 10–19 years old. Adolescents with HIV include those surviving perinatal infection and those newly acquiring infection as they become sexually active or are exposed through injecting drug use, other unsafe injections and blood transfusions. Adolescents may access care in a variety of settings, including paediatric and antenatal care clinics, as well as adult clinics. Since few health systems provide adolescent-specific services it can be challenging for adolescents to access health care and maintain adherence to treatment regimens.

In general, in these guidelines, clinical and general care recommendations for adults apply to adolescents. Where guidance for adolescents is addressed in recommendations for children, this is clearly indicated. There are four specific recommendations on testing and counselling taken from additional recent adolescent-specific guidance. The 2013 *Guidance on HIV testing and counselling for adolescents and care for adolescents living with HIV* contains recommendations on HIV testing and counselling and delivery of services for adolescents (Table 4.2).

Table 4.2. Key recommendations and guidance for adolescents

Chapter	Topic	Chapter subsections
Chapter 5: HIV diagnosis and ARV drugs for HIV prevention	HIV testing in health facilities	Section 5.1.2
	Community-based HIV testing and counselling	Section 5.1.3
	HIV testing and counselling in specific populations: adolescents	Section 5.1.4.4
Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment	General care for people living with HIV	Section 6.3
	Preparing people living with HIV for ART	Section 6.4
	What to expect in the first months of ART	Section 6.5
Chapter 7: Antiretroviral therapy	When to start ART in adults and adolescents	Section 7.1.1
	First-line ART for children three years and older (includes adolescents)	Section 7.2.4
	TB co-treatment in children with HIV	Section 7.2.5
	Monitoring response to ART and the diagnosis of treatment failure (includes adolescents)	Section 7.3
	Monitoring and substitutions for ARV drug toxicities (includes adolescents)	Section 7.4
	Key ARV drug interactions (includes adolescents)	Table 7.17
	Second-line ART for adults and adolescents	Section 7.5.1
	Second-line ART for children includes adolescents	Section 7.5.2
Third-line ART (includes adolescents)	Section 7.6	



Table 4.2 (continued)

Chapter	Topic	Chapter subsections
Chapter 8: Managing common coinfections and comorbidities	Prevention, screening and management of coinfections	Section 8.1
	Preventing and managing other comorbidities and chronic care for people living with HIV	Section 8.2
	Nutritional care and support among adolescents and adults living with HIV	Section 8.2.4.1
Chapter 9: Guidance on operations and service delivery	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Adherence to ART: adolescents	Section 9.2
	Decentralization and task shifting	Sections 9.4.3 and 9.5.2
Chapter 10: Guidance for programme managers	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Implementation considerations for key recommendations for programme managers: raising the CD4 threshold for initiating ART in adults and adolescents from 350 to 500 cells/mm ³	Section 10.6; Box 10.2
Chapter 11: Monitoring and evaluation	Monitoring implications of new recommendations	Section 11.2
Annexes	Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children	Chapter 12
	Annex 2. Algorithm for the 2013 recommendations for adults and adolescents	
	Annex 7. Dosages of recommended ARV drugs for adults and adolescents	

4.3.3 Children

The location of the most important guidance and recommendations specific to children (younger than 10 years) is summarized in Table 4.3.

Table 4.3. Key recommendations and guidance for children

Chapter	Topic	Chapter subsections
Chapter 5: HIV diagnosis and ARV drugs for HIV prevention	HIV testing and counselling in health facilities	Section 5.1.2
	Community-based HIV testing and counselling	Section 5.1.3
	HIV testing and counselling in specific populations: infants and children	Section 5.1.4.3
Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment	General care for people living with HIV	Section 6.3
	Preparing people living with HIV for ART	Section 6.4
	What to expect in the first months of ART	Section 6.5
Chapter 7: Antiretroviral therapy	When to start ART in children	Section 7.1.4
	First-line ART for children younger than 3 years of age	Section 7.2.3
	First-line ART for children 3 years of age and older	Section 7.2.4
	TB co-treatment in children with HIV	Section 7.2.5
	Monitoring response to ART and the diagnosis of treatment failure (includes children)	Section 7.3
	Monitoring and substitutions for ARV drug toxicities (includes children)	Section 7.4
	Key ARV drug interactions (includes children)	Table 7.17
Chapter 8: Managing common coinfections and comorbidities	Prevention, screening and management of coinfections (includes children)	Section 8.1
	Immunizations	Section 8.1.8
	Preventing and managing other comorbidities and chronic care for people living with HIV	Section 8.2.4.2
	Nutritional care and support among children living with HIV	
Chapter 9: Guidance on operations and service delivery	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Adherence to ART: infants and children	Section 9.2.1
	Decentralization and task shifting	Sections 9.4.3 and 9.5.2



Table 4.3 (continued)

Chapter	Topic	Chapter subsections
Chapter 10: Guidance for programme managers	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues.	
	Implementation considerations of key recommendations: scaling up treatment for children	Section 10.6; Box 10.6
	Implementation considerations of key recommendations: phasing out d4T	Section 10.7; Box 10.7.
Chapter 11: Monitoring and evaluation	Monitoring implications of new recommendations	Section 11.2
Annexes	Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children	Chapter 12
	Annex 4. Algorithm for the 2013 recommendations for children	
	Annex 5. Algorithm for early infant diagnosis	
	Annex 7. Weight-based dosing for ARV formulations for children	

4.3.4 Key populations

In these guidelines, key populations include both vulnerable and most-at-risk populations. Most-at-risk populations include men who have sex with men, transgender people, people who inject drugs and sex workers.

The use of ART in key populations should follow the same general principles and recommendations as for adults. There is one recommendation on community-based HIV testing, that is specific to key populations.

The location of the most important guidance and recommendations specific to key populations is summarized in Table 4.4.

Table 4.4 Key recommendations and guidance for key populations

Chapter	Topic	Chapter subsections
Chapter 2: Guiding principles	Promoting human rights and health equity	Section 2.5
Chapter 5: HIV diagnosis and ARV drugs for HIV prevention	HIV testing and counselling in health facilities	Section 5.1.2
	Community-based HIV testing and counselling	Section 5.1.3
	HIV testing and counselling in specific populations: key populations	Section 5.1.4.5

Table 4.4 (continued)

Chapter	Topic	Chapter subsections
Chapter 6: Linking people diagnosed with HIV infection to HIV care and treatment	General care for people living with HIV	Section 6.3
	Preparing people living with HIV for ART	Section 6.4
	What to expect in the first months of ART	Section 6.5.1
Chapter 7: Antiretroviral therapy	When to start ART in adults and adolescents (includes key populations)	Section 7.1.1
	First-line ART for adults (includes key populations)	Section 7.2.1
	Monitoring response to ART and the diagnosis of treatment failure (includes key populations)	Section 7.3
	Monitoring and substitutions for ARV drug toxicities (includes key populations)	Section 7.4
	Second-line ART for adults and adolescents (includes key populations)	Section 7.5.1
	Third-line ART (includes key populations)	Section 7.5.3
Chapter 8: Managing common coinfections and comorbidities	Prevention, screening and co-management of coinfections	Section 8.1
	Preventing and managing common coinfections and comorbidities	Section 8.2
	Drug use and drug use disorders	Section 8.2.3
Chapter 9: Guidance on operations and service delivery	Adherence to ART: most-at-risk populations (including sex workers, men who have sex with men, transgender people and people who inject drugs)	Section 9.2.1
	ART in settings providing opioid substitution therapy, integrating and linking services	Section 9.4.2.3
	Decentralization and Task shifting	Sections 9.4.3 and 9.5.2
Chapter 10: Guidance for programme managers	Guidance throughout this chapter is relevant across populations. The topics listed here are indicative of some of the specific issues	
	Socioeconomic, policy and legal context	Section 10.3.4
	Ethics, equity and human rights	Section 10.4.1
	Implementation considerations for key recommendations: raising the CD4 threshold for initiating ART in adults from 350 to 500 cells/mm ³	Section 10.6; Box 10.2



Table 4.4 (continued)

Chapter	Topic	Chapter subsections
Chapter 11: Monitoring and evaluation	Monitoring implications of new recommendations	Section 11.2
Annexes	Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children	Chapter 12
	Annex 7: Dosages of recommended antiretroviral drugs	

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Goal of this chapter

To provide a summary of existing and new evidence-based clinical recommendations outlining a public health approach to diagnosing HIV infection and providing ARV drugs for prevention in the context of the broad continuum of HIV care, with a focus on settings with limited health system capacity and resources.

5. CLINICAL GUIDELINES ACROSS THE CONTINUUM OF CARE: HIV DIAGNOSIS AND ARV DRUGS FOR HIV PREVENTION

5.1 HIV testing and counselling



5.1.1 Introduction

People access HIV treatment, care and prevention through the gateway of HIV testing and counselling. It is currently estimated globally that about half of the people living with HIV do not know their HIV status. The people who do know often test late, and poor linkages from HIV testing and counselling to care – including failure to assess rapidly for ART eligibility – mean that many people start treatment when they are already significantly immunocompromised, resulting in poor health outcomes and ongoing HIV transmission. The overall HIV testing and counselling goal for a national HIV programme should be to identify as many people living with HIV as early as possible after acquiring HIV infection, and link them appropriately and in a timely manner to prevention, care and treatment services. The people tested who are not infected should be linked to appropriate prevention services, such as voluntary male medical circumcision in the priority countries in sub-Saharan Africa, or harm reduction services for those who use drugs, and encouraged to retest at a later time.

Diverse models of HIV testing and counselling services are available to increase access to HIV diagnosis, including testing services in health care facilities, freestanding sites and a wide range of community-based approaches. These are described in detail in the WHO 2012 strategic HIV testing and counselling framework (1). The use of rapid HIV diagnostic tests that can be used at point of care has become an important strategy to expand access, increase the return of same-day results and enable appropriate referral and follow-up. Countries should choose a strategic mix of service delivery models to achieve equitable access to HIV testing and counselling, based on the local context, the nature of the epidemic, cost–effectiveness and available resources. The mix should facilitate diagnosing as many people living with HIV as early as possible to enable timely linkage to ART. Strategies should be able to reach the people who are most vulnerable, most-at-risk and marginalized (Box 5.1).

The use of a single HIV test to diagnose HIV infection is not sufficient; it must be confirmed by following the steps outlined in the updated WHO 2012 HIV testing strategies (algorithms) (1). Quality assurance systems should be put in place to minimize false-positive and false-negative results. Failure to do this will lead to people being given incorrect test results, with potential serious adverse long-term consequences. Quality assurance and quality improvement measures are also important for the counselling process to ensure that HIV testing and counselling is always conducted in an acceptable and effective manner.

Box 5.1 HIV testing and counselling: guiding principles

All forms of HIV testing and counselling should be voluntary and adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services.

Mandatory or coerced testing is never appropriate, whether that coercion comes from a health care provider or from a partner or family member.

The following key principles apply to all models of HIV testing and counselling and in all circumstances.

- People receiving HIV testing and counselling must give informed consent (verbal consent is sufficient and written consent is not required) to be tested and counselled. They should be informed of the process for HIV testing and counselling and their right to decline testing.
- HIV testing and counselling services are confidential, meaning that what the HIV testing and counselling provider and the person discuss will not be disclosed to anyone else without the expressed consent of the person being tested. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Counsellors should raise, among other issues, whom else the person may wish to inform and how they would like this to be done. Shared confidentiality with a partner or family members and trusted others and with health care providers is often highly beneficial.
- HIV testing and counselling services must be accompanied by appropriate and high-quality pre-test information (which can be provided as group pre-test information in some settings) and post-test counselling. Quality assurance mechanisms and supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.
- HIV testing and counselling providers should strive to provide high-quality testing services, and quality assurance mechanisms should be in place to ensure the provision of correct test results. Quality assurance may include both internal and external measures and should include support from the national reference laboratory as needed.
- Connections to prevention, care and treatment services should include the provision of effective referral to appropriate follow-up services as indicated, including long-term prevention and treatment support.

Quality assurance of both testing and counselling is essential in all approaches used.

5.1.2 HIV testing and counselling in health facilities

Background

WHO recommends routinely offering HIV testing and counselling in clinical settings (known as provider-initiated testing and counselling) as an efficient and effective way to identify people with HIV who could benefit from treatment.

Source for recommendations:

- *Guidance on provider-initiated HIV testing and counselling in health facilities.* Geneva, World Health Organization, 2007 (http://whqlibdoc.who.int/publications/2007/9789241595568_eng.pdf) (2).



Existing recommendations (2)

In generalized epidemics, provider-initiated testing and counselling should be recommended to everyone (adults, adolescents and children) attending all health facilities, including medical and surgical services; sexually transmitted infection, hepatitis and TB clinics; public and private facilities; inpatient and outpatient settings; mobile or outreach medical services; services for pregnant women (antenatal care, family planning and maternal and child health settings); services for key populations; services for infants and children; and reproductive health services.

In concentrated and low-level epidemics, provider-initiated testing and counselling should be recommended in all health facilities for:

- adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB; and
- HIV-exposed children, children born to women living with HIV and symptomatic infants and children.

Provider-initiated testing and counselling should be considered in sexually transmitted infection, hepatitis and TB services, antenatal care settings and services for key populations (notably men who have sex with men, transgender people, sex workers and people who inject drugs).

5.1.3 Community-based HIV testing and counselling

In addition to providing HIV testing and counselling in clinical settings, HIV testing and counselling can be offered in a variety of settings in the community.

New recommendations (2013)

NEW

- In generalized HIV epidemics, community-based HIV testing and counselling with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (*strong recommendation, low-quality evidence*).
- In all HIV epidemic settings, community-based HIV testing and counselling for key populations, with linkage to prevention, care and treatment services is recommended, in addition to provider-initiated testing and counselling (*strong recommendation, low-quality evidence*).

Background

These guidelines include expanded criteria for eligibility for ART for children, adolescents, adults and pregnant and breastfeeding women living with HIV. To maximize the individual and public health benefits of these recommendations, people living with HIV must be diagnosed and linked to care early in the course of HIV infection. Although facility-based testing is a key approach, people living with HIV are often identified late in the course of HIV disease in clinical settings, and some populations, including men and adolescents, and especially key populations, have low utilization of health care services. Community-based

testing approaches may reach people with HIV earlier in the course of HIV disease than provider-initiated testing and counselling, as well as reaching populations that may not normally attend health services.

The use of rapid HIV diagnostic tests using blood from a finger-prick sample taken by trained lay counsellors and community health workers has facilitated the expansion of HIV testing and counselling in community settings including homes, transport stations, religious facilities, schools, universities, workplaces and venues frequented by key populations. Continued expansion of community-based testing to complement facility-based testing is an important consideration in achieving universal knowledge of HIV status and earlier diagnosis linked to care and treatment. Community-based HIV testing and counselling includes using mobile, door-to-door, index, campaign, workplace and school-based HIV testing and counselling approaches (1).

Rationale and supporting evidence

The recommendations are based on evidence and on operational and programmatic considerations. The systematic review identified four randomized studies (3,4) and eight observational studies (5–10) comparing community-based testing to facility-based testing in generalized epidemics (Web Annex: www.who.int/hiv/pub/guidelines/arv2013/annexes). Overall, community-based approaches had increased rates of people testing for the first time and adults diagnosed with CD4 counts exceeding 350 cells/mm³. However, the frequency of positive test results was higher in health facility-based testing than in many community settings. The systematic review found that HIV testing and counselling coverage at the district level increased as a result of offering community-based HIV testing and counselling (using either door-to-door or mobile approaches) in combination with facility-based HIV testing and counselling.

An additional review covering key populations identified three studies comparing community-based testing to facility-based testing in key populations (11–13). Although increased uptake was observed in community-based approaches, the rate of participants receiving their first HIV test was comparable in both the community- and facility-based approaches.

Fifteen studies examined potential negative consequences of community-based testing (10,14–25). These studies discussed both the clients' positive testing experiences and their fears. Eight articles reported that a minority of participants refused HIV testing and counselling because of fear of status disclosure or stigma (10,14–17,21,23,25). The studies did not demonstrate that community-based approaches either reduced stigma or fear or increased them or other harms.

The few studies comparing the cost per person tested using facility- and community-based testing found that the cost per person tested was similar in both approaches (Web Annex: www.who.int/hiv/pub/guidelines/arv2013/annexes).

Although the review provided low-quality evidence overall, there was consensus that the critical programmatic advantages of community-based HIV testing and counselling and an assessment of values, preferences, costs and feasibilities provided sufficient basis for the Guideline Development Group to propose strong recommendations.

Community-based testing should be implemented in addition to provider-initiated testing and counselling. Multiple approaches are needed, which may include stand-alone sites, home-based testing, mobile outreach (including in workplaces, schools, universities, special testing campaigns and events) and multi-disease campaigns tailored to epidemiological and social contexts.

5.1.4 HIV testing and counselling in specific populations

5.1.4.1 Couples

Background

Studies in several countries have shown that couples HIV testing and counselling is acceptable, feasible and effective. It can identify seroconcordant positive couples who can be linked to treatment and receive treatment adherence support. It also identifies couples with serodiscordant HIV test results who can benefit from HIV prevention interventions. Services should be offered to married and cohabiting couples, premarital couples, polygamous unions and any other partnerships. As with all HIV testing and counselling approaches, couples HIV testing and counselling should be voluntary. Health providers must be aware of the potential for intimate partner-based violence and should support individuals when they do not want to test with their partners. Couples HIV testing and counselling can be offered in all settings where HIV testing and counselling is provided, including antenatal care and TB services. Support to encourage the testing of the partners of people living with HIV is also an efficient and effective way of identifying additional people living with HIV, who then can benefit from treatment. Further, couples HIV testing and counselling can be an important intervention to increase access to earlier ART and reach more men with treatment. Offering family counselling and testing to couples where one or both are living with HIV can identify children, adolescents and other household members who have not previously been diagnosed.

Source for recommendations:

- *Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples.* Geneva, World Health Organization, 2012 (http://whqlibdoc.who.int/publications/2012/9789241501972_eng.pdf) (26).

Existing recommendations (26)

- Couples and partners should be offered voluntary HIV testing and counselling with support for mutual disclosure (*strong recommendation, low-quality evidence*).
- Couples and partners in antenatal care settings should be offered voluntary HIV testing and counselling with support for mutual disclosure (*strong recommendation, low-quality evidence*).
- Couples and partner voluntary HIV testing and counselling 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*).

5.1.4.2 Pregnant and postpartum women

Background

Provider-initiated testing and counselling for pregnant women and linkage to prevention and care are needed to promote the mother's health and prevent new paediatric infections and can contribute to a strategy for couples testing.

Source for recommendations:

- *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).

Existing recommendations (2)

Generalized epidemics

- Provider-initiated testing and counselling is recommended for women as a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings.
- Re-testing is recommended in the third trimester, or during labour or shortly after delivery, because of the high risk of acquiring HIV infection during pregnancy.

Low-level and concentrated epidemics

- Provider-initiated testing and counselling should be considered for pregnant women. Many countries prioritize provider-initiated testing and counselling in antenatal care as a key component of their effort to eliminate the mother-to-child transmission of HIV and are effectively bundling HIV testing with syphilis screening, hepatitis testing or other key tests relevant to the setting as well as strengthening the underlying maternal and child health system.

5.1.4.3 Infants and children

Background

HIV-exposed infants and children younger than 18 months should be tested within four to six weeks of birth so that those already infected with HIV can start ART. Mortality is very high among untreated infants infected with HIV in the first year of life, making early HIV testing, prompt return of results and rapid initiation of treatment essential. In this population, HIV infection can only be definitively confirmed using virological tests because of the presence of persisting maternal HIV antibody in the child up to 15–18 months of age. Virological tests include assays to detect viral nucleic acid (HIV DNA, RNA or total nucleic acid) or p24 antigen. Currently, virological testing is most commonly performed on dried blood spot (DBS) specimens, with collection at local sites and transport and testing at centralized laboratories. While early testing is increasing, there are ongoing challenges of access, return of results and initiation of early treatment in infants testing positive. Point-of-care virological testing, in development, is expected to greatly improve early diagnosis and treatment. Because some infants are not identified as HIV-exposed or are lost to postpartum follow-up, provider-initiated



testing and counselling should be implemented in infant care settings for additional case-finding. Final diagnosis (or definitive diagnosis) at the end of the risk period for mother-to-child transmission (breastfeeding period) should be ensured. A negative HIV antibody test in a known HIV-exposed infant can be useful to exclude HIV infection if there is no ongoing exposure. (See Annex 5 for the algorithm on HIV diagnosis in children less than 18 months of age.)

For children 18 months of age and older (who are not breastfeeding or who stopped breastfeeding at least six weeks earlier), standard HIV serological tests such as rapid diagnostic tests can be used to reliably determine HIV infection status. WHO recommends provider-initiated testing and counselling for all children who are malnourished, have TB, are admitted to hospital or have other signs or symptoms of HIV infection. Other approaches such as testing all children in childhood vaccination programmes have been implemented in some settings to increase chances of finding HIV-infected children. The recommendations on diagnosis of HIV infection in infants and children will be reviewed in the coming year.

Table 5.1 Summary of recommended testing approaches for infants (27)

Category	Test required	Purpose	Action
Well, HIV-exposed infant	Virological testing at 4–6 weeks of age	To diagnose HIV	Start ART if HIV-infected
Infant – unknown HIV exposure	Maternal HIV serological test or infant HIV serological test	To identify or confirm HIV exposure	Need virological test if HIV-exposed
Well, HIV-exposed infant at 9 months	HIV serological test (at last immunization, usually 9 months)	To identify infants who have persisting HIV antibody or have seroreverted	Those HIV seropositive need virological test and continued follow up; those HIV negative, assume uninfected, repeat testing required if still breastfeeding
Infant or child with signs and symptoms suggestive of HIV infection	HIV serological test	To confirm exposure	Perform virological test if <18 months of age
Well or sick child seropositive >9 months and <18 months	Virological testing	To diagnose HIV	Reactive – start HIV care and ART
Infant or child who has completely discontinued breastfeeding	Repeat testing six weeks or more after breastfeeding cessation – usually initial HIV serological testing followed by virological testing for HIV-positive child and <18 months of age	To exclude HIV infection after exposure ceases	Infected infants and children <5 years of age, need to start HIV care, including ART

Source for recommendations:

- *WHO recommendations on the diagnosis of HIV infection in infants and children*. Geneva, World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241599085_eng.pdf) (27)
- *Guideline on HIV disclosure counselling for children up to 12 years of age*, Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241502863_eng.pdf) (28).

Existing recommendations (27)

- 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 all HIV-exposed infants have HIV virological testing at four to six weeks of age or at the earliest opportunity thereafter (*strong recommendation, high-quality evidence*).
- For 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 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 well, HIV-exposed infants undergo HIV serological testing at around nine months of age (or at the time of the last immunization visit). Infants who have reactive serological assays at nine months should have a virological test to identify HIV-infected infants who need ART (*strong recommendation, low-quality evidence*).
- It is strongly recommended that children 18 months of age 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*).

Existing recommendation (28)

- Children of school age should be told their HIV-positive status and their parents or caregiver's status; younger children should be told their status incrementally to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure (*strong recommendation, low-quality evidence*).

5.1.4.4 Adolescents

Background

Adolescents are often underserved and given insufficient priority in many HIV programmes, with poor access to and uptake of HIV testing and counselling and linkage to prevention and care. Adolescents with HIV include those surviving perinatal infection and those newly acquiring infection as they become sexually active or are exposed through injecting drug use, other unsafe injections and blood transfusions. In generalized epidemic settings, many vertically infected infants are not diagnosed through programmes for PMCT and would benefit from earlier HIV diagnosis and treatment. In many settings, adolescent girls and adolescents from key populations are also vulnerable to HIV infection and would benefit from access to acceptable and effective HIV services, including HIV testing and counselling. Consent issues may pose a barrier to access for adolescents in some settings and are discussed in detail in the WHO 2013 guidelines for adolescents (29).

Source for recommendations:

- *Guidance on HIV testing and counselling for adolescents and care for adolescents living with HIV.* Geneva, World Health Organization, 2013, in press (29).

New recommendations (2013) (29)

NEW

- HIV testing and counselling, with linkages to prevention, treatment and care, is recommended for adolescents from key populations in all settings (generalized, low and concentrated epidemics) (*strong recommendation, very-low-quality evidence*).
- HIV testing and counselling with linkage to prevention, treatment and care is recommended for all adolescents in generalized epidemics (*strong recommendation, very-low-quality evidence*).
- We suggest that HIV testing and counselling with linkage to prevention, treatment and care be accessible to all adolescents in low and concentrated epidemics (*conditional recommendation, very-low-quality evidence*).
- We suggest that adolescents 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*).

Rationale and supporting evidence

These recommendations were developed as part of new HIV guidelines for adolescents from WHO, UNESCO, UNFPA, UNICEF and GNP+ published in 2013 and are based on systematic reviews of the evidence, community consultations to assess values and preferences of adolescents and health providers and consideration by the respective Guideline Development Group. For the most part, published evidence for adolescent-specific recommendations is lacking; for these guidelines, considerable weight is given to expert opinion, values and preferences of adolescents and their health care providers, and to the field experience of practitioners. Further details are provided in the summary of evidence in the full *Guidance on HIV testing and counselling for adolescents and care for adolescents living with HIV* (29).

5.1.4.5 Key populations

Background

HIV testing and counselling has been provided to key populations since HIV tests were first developed. WHO produced guidance for testing people who inject drugs in 2006, for prisoners and refugees in 2009, for men who have sex with men and for transgender people in 2011 and for sex workers in 2012.

For key populations, especially those who are criminalized, HIV testing and counselling services are sometimes used in punitive or coercive ways. Both existing and new recommendations for HIV testing and counselling for these most-at-risk and vulnerable groups therefore emphasize consent and confidentiality as well as ensuring that HIV testing and counselling is part of a comprehensive prevention, care and treatment programme.

The 2012 WHO HIV testing and counselling strategic framework (1) summarizes HIV testing and counselling for all of these groups and populations (Tables 5.2 and 5.3).

Additional guidance:

- *Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach.* Geneva, World Health Organization, 2012 (http://apps.who.int/iris/bitstream/10665/77745/1/9789241504744_eng.pdf) (33).
- *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 (http://whqlibdoc.who.int/publications/2011/9789241501750_eng.pdf) (34).

NEW



Table 5.2 Summary of HIV testing and counselling recommendations for generalized epidemics

Who to test	When to test	Where to test	Relevant WHO guidance
Everyone attending health facilities	Integrate in all health care encounters	All settings, including primary health care, outpatient medical and surgical wards, antenatal care and maternal and child health, TB, family planning and sexually transmitted infection clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Partners and couples	Premarital, pregnancy, after separations, new partnerships and at the start of care and ART For the HIV-negative person in serodiscordant couples, offer re-testing every 6–12 months	Primary health care settings, voluntary counselling and testing sites, ART clinics, antenatal care, family planning clinics, sexually transmitted infection clinics, community and mobile outreach, home	<i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i>
Families of index cases	As soon as possible after the family member is diagnosed	Primary health care settings, ART clinics, maternal and child health and antenatal care settings, homes and community and mobile outreach	<i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Planning, implementing and monitoring home-based HIV testing (31)</i>
Key populations: people who inject drugs, men who have sex with men, transgender people, sex workers, prisoners, and partners of people who inject drugs	Every 6–12 months	Primary health care settings, sexually transmitted infections clinics and outreach services, including harm reduction and other sites providing services to key populations	<i>Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (32)</i> <i>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 (33)</i> <i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i>

Table 5.2 (continued)

Who to test	When to test	Where to test	Relevant WHO guidance
Pregnant women and male partners	At first antenatal care visit Re-test in third trimester or peripartum Offer partner testing	Antenatal care, delivery, postpartum	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i> <i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i>
Infants and children <18 months old	Early infant diagnosis at 4–6 weeks for all infants whose mothers are living with HIV or if maternal HIV status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends	Maternal and child health services Paediatric clinics Immunization clinics	<i>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</i>
Children	Establish HIV status for all health contacts	Child inpatients and outpatients, immunization clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Adolescents	Integrate into all health care encounters Annually if sexually active; with new sexual partners	Primary health care, outpatients, inpatients, voluntary counselling and testing sites, youth-friendly services, family planning and sexually transmitted infections clinics	<i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i> <i>Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29)</i>

Table 5.3 Summary of HIV testing and counselling recommendations for low-level and concentrated epidemics

Who to test	When to test	Where to test	Relevant WHO guidance
People with signs or symptoms of HIV infection	Integrate in health care encounter	Sexually transmitted infection clinics, TB clinics, medical wards, other clinics	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Partners of people with HIV	As soon after partner diagnosis as possible For the negative person in serodiscordant couples, offer re-testing every 6–12 months	Clinical settings including primary health care settings, ART, TB, sexually transmitted infection clinics, voluntary counselling and testing	<i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i>
Families of index cases	As soon as possible after the family member is diagnosed	ART clinics, maternal and child health and antenatal care settings, homes, community outreach	<i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Planning, implementing and monitoring home-based HIV testing (32)</i> <i>Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples (26)</i>
Key populations: people who inject drugs, men who have sex with men, transgender people and sex workers	Every 6–12 months	Sexually transmitted infection clinics, outreach services for key populations and harm-reduction services	<i>Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (32)</i> <i>Service delivery approaches to HIV testing and counselling (HTC): a strategic HTC programme framework (1)</i> <i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i>
Pregnant women	At the first antenatal care visit	Antenatal care	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>

Table 5.3 (continued)

Who to test	When to test	Where to test	Relevant WHO guidance
Infants and children <18 months old	Early infant diagnosis at 4-6 weeks for all infants whose mothers are living with HIV or if maternal HIV status is unknown; determine the final infant HIV infection status after 18 months and/or when breastfeeding ends	Maternal and child health services Paediatric clinics Immunization clinics	<i>WHO recommendations on the diagnosis of HIV infection in infants and children (27)</i>
Children with signs or symptoms of HIV infection or who have a family member living with HIV	Integrate in health care encounter	In all health settings	<i>Guidance on provider-initiated HIV testing and counselling in health facilities (2)</i>
Adolescents from key populations	Every 6–12 months	Youth-friendly services, sexually transmitted infection clinics, outreach	<i>Delivering HIV test results and messages for re-testing and counselling in adults (30)</i> <i>Guidelines on HIV testing and counselling for adolescents and care and treatment for adolescents living with HIV (29)</i>

5.2 HIV prevention based on ARV drugs¹

5.2.1 Oral pre-exposure prophylaxis

Background

Oral pre-exposure prophylaxis of HIV (PrEP) is the daily use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. Clinical trials of daily oral PrEP have shown evidence of effectiveness with serodiscordant heterosexual couples (35), men and transgender women who have sex with men (36), high risk heterosexual couples (37), people who inject drugs (38).

Source for recommendations:

- *Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects.* Geneva, World Health Organization, 2012 (http://apps.who.int/iris/bitstream/10665/75188/1/9789241503884_eng.pdf) (39).

Existing recommendations (39)

Existing WHO recommendations (39) are for the use of oral PrEP in demonstration projects for serodiscordant couples and men and transgender women who have sex with men.

- *Serodiscordant couples.* When serodiscordant couples are identified and where additional HIV prevention choices for them are needed, daily oral pre-exposure prophylaxis (either TDF or the combination of TDF + FTC) may be considered as a possible additional intervention for the uninfected partner (*conditional recommendation, high-quality evidence*).

If oral pre-exposure prophylaxis is to be provided for the HIV-negative partner in same-sex, male serodiscordant couples, the combination of TDF + FTC should be used, as evidence of effectiveness and safety in male-to-male penetrative sex is available for this regimen only.

- *Men and transgender women.* Where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral pre-exposure prophylaxis (specifically the combination of TDF + FTC) may be considered as a possible additional intervention (*conditional recommendation, high-quality evidence*).

¹ Chapter 7 covers other aspects of ARV drugs as prevention, including PMTCT.

5.2.2 ART for prevention among serodiscordant couples



Source for recommendations:

- *Couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples.* Geneva, World Health Organization, 2012 (http://whqlibdoc.who.int/publications/2012/9789241501972_eng.pdf) (26).

Existing recommendations (26)

- People with HIV in serodiscordant couples who start ART for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner (*strong recommendation, high-quality evidence*).
- HIV-positive partners with a CD4 count ≥ 350 cells/mm³ in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*).

5.2.3 Post-exposure prophylaxis for occupational and non-occupational exposure to HIV



Background

Post-exposure prophylaxis is short-term ART to reduce the likelihood of acquiring HIV infection after potential exposure either occupationally or through sexual intercourse. Within the health sector, post-exposure prophylaxis should be provided as part of a comprehensive package of universal precautions that reduces the exposure of personnel to infectious hazards at work. WHO post-exposure prophylaxis guidelines for occupational exposure have not been reviewed since 2006 and will be updated by 2014. The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure. The choice of post-exposure prophylaxis drugs should be based on the country's first-line ART regimen for HIV. A recent recommendation (40) relates specifically to post-exposure prophylaxis in the case of sexual assault.

Source for recommendation:

- *Responding to intimate partner violence and sexual violence against women: clinical and policy guidelines.* Geneva, World Health Organization, in press (40).

Existing recommendation (2013) (40)

- Consider HIV post-exposure prophylaxis for women presenting within 72 hours of a sexual assault. Use shared decision-making with the survivor to determine whether HIV post-exposure prophylaxis is appropriate (*strong recommendation, very-low-quality evidence*).



5.2.4 Combination HIV prevention



Background

People's HIV prevention needs change during their lifetime, and a combination approach helps people to access the types of interventions that best suit their needs at different times. Combining approaches may also result in synergies that have greater impact than single interventions alone. Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of the following.

- **Other biomedical interventions** that reduce HIV risk practices and/or the probability of HIV transmission per contact event, including the following.
 - **Male and female condoms.** Male condoms reduce heterosexual transmission by at least 80% and offer 64% protection in anal sex among men who have sex with men (41), if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect (42).
 - **Needle and syringe programmes** are highly associated with a reduction in HIV transmission through injecting drug use (43).
 - **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 (44-45).
 - **Voluntary medical male circumcision** reduces acquisition of infection and the risk of acquisition for men by up to 66% and offers significant lifelong protection (4).
- **Behavioural interventions** reduce the frequency of potential transmission events, including the following.
 - **Targeted information and education.** Programmes that use various communication approaches – for example, school-based sex education, peer counselling and community-level and interpersonal counselling – to disseminate behavioural messages designed to encourage people to reduce behaviour that increases the risk of HIV and increase the 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 and your partner's HIV status).
- **Structural and supportive interventions** affect 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 reform, measures to reduce stigma and discrimination, the promotion of gender equality and prevention of gender-based violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

LINKING PEOPLE DIAGNOSED WITH HIV INFECTION TO HIV CARE AND TREATMENT

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Goal of this chapter

To provide an overview of issues and interventions related to general HIV care for individuals from the time that they are diagnosed with HIV infection to the time that they are initiated on ART, including practices for linking people diagnosed with HIV infection to HIV care and treatment, the components of a general care package, and preparing individuals for starting ART.

6. THE CONTINUUM OF CARE: LINKING PEOPLE DIAGNOSED WITH HIV INFECTION TO HIV CARE AND TREATMENT

6.1 Introduction



It is critical for people living with HIV to enrol in care as early as possible. This enables both early assessment of their eligibility for ART and timely initiation of ART as well as access to interventions to prevent the further transmission of HIV, prevent other infections and comorbidities and thereby to minimize loss to follow-up. The 2012 WHO strategic HIV testing and counselling programme framework (1) especially emphasizes the importance of ensuring linkage between HIV testing and counselling programmes and prevention, treatment, care and support services.

6.2 Good practices for linkage to care

Interventions to improve linkage to care need to be more rigorously evaluated. However, several systematic reviews and observational studies suggest that several good practices can improve linkage to care (2–4). These include integrating HIV testing and counselling and care services; providing on-site or immediate CD4 testing with same-day results; assisting with transport if the ART site is far from the HIV testing and counselling site; involving community outreach workers to identify the people lost to follow-up; ensuring support from peers or expert patients; and using new technologies, such as mobile phone text messaging.

6.3 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. Not all people living with HIV are eligible for ART and, of those eligible, not all will be able to access ART immediately. Others may choose to defer ART to later. Enrolment in care provides an opportunity for close clinical and laboratory monitoring and early assessment of eligibility for ART and timely initiation, and aims to minimize loss to follow-up. Many care interventions are relevant across the full continuum of care, including HIV-exposed individuals and people living with HIV before initiating, and during ART.

General care includes basic HIV prevention, promoting the health of people living with HIV and the screening, prophylaxis and management of HIV-related coinfections and comorbidities. WHO has produced summary guidance on general care and prevention interventions (5–7), and in 2008, recommended a package of 13 prevention interventions for adults and adolescents living with HIV in resource-limited settings (5). These include (1) psychosocial counselling and support; (2) disclosure and partner notification; (3) co-trimoxazole prophylaxis; (4) TB counselling, screening and preventive therapy; (5) preventing common fungal infections; (6) preventing sexually transmitted infections and supporting reproductive health needs, including prevention of and screening for cervical cancer; (7) malaria (co-trimoxazole, bed-nets and preventing malaria among pregnant women); (8) selected vaccine-preventable diseases; (9) nutrition; (10) family planning; (11) PMTCT; (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 6.1 provides an overview of elements of a general care package for people living with HIV. Section 8.1 summarizes key recommendations from existing WHO guidelines on the screening, prophylaxis and timing of ART with the most common coinfections, comorbid conditions and other health conditions.

Table 6.1 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 ART regimen	Comment and cross-references
General care						
WHO clinical staging	✓	✓	✓			Annex 1
Past and current HIV-related conditions						
Pregnancy status	✓	✓	✓	✓	✓	Section 8.2.6.1
Family planning and Contraception						Sections 7.1.2 and 7.2.2
PMTCT						
Support for disclosure and partner notification	✓	✓	✓	✓	✓	Section 5.1.4
Risk reduction counselling and combination HIV prevention approaches	✓	✓	✓	✓	✓	Section 5.2.4
Screening for, preventing and managing comorbidities and noncommunicable diseases	✓	✓	✓	✓	✓	Section 8.2.1
Screening for and managing mental health problems and substance use	✓	✓	✓	✓	✓	Sections 8.2.2 and 8.2.3
Psychosocial counselling and support						



Table 6.1 (continued)

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching ART regimen	Comment and cross-references
General care						
Managing pain and symptoms	✓	✓	✓	✓	✓	Section 8.2.5
Nutritional assessment and counselling		✓	✓	✓	✓	Section 8.2.4
Nutritional, growth and development assessment in children and adolescents	✓	✓	✓	✓	✓	Sections 7.1.3 and 8.2.4
Infant and child feeding						
Preventing and treating coinfections						
Co-trimoxazole preventive therapy	✓	✓	✓	✓	✓	Section 8.1.1
Intensified TB case-finding	✓	✓	✓	✓	✓	Section 8.1.2
Isoniazid preventive therapy	✓	✓	✓		✓	Section 8.1.2
Screening for cryptococcal infection and fungal prophylaxis		✓	✓			Section 8.1.3
Screening for hepatitis B and C		✓	✓		✓	Section 8.1.4
Malaria prevention (insecticide-treated bed-nets and prophylaxis)	✓	✓	✓	✓	✓	Section 8.1.5
Screening for sexually transmitted infections	✓	✓	✓	✓	✓	Section 8.1.6
Prevention of and screening for cervical cancer		✓	✓	✓	✓	Section 8.1.7

Table 6.1 (continued)

Service	At HIV diagnosis	At enrolment into care	At initiation of ART	Stable while receiving ART	At treatment failure and switching ART regimen	Comment and cross-references
Assessing for vaccine-preventable diseases	✓	✓	✓	✓	✓	Section 8.1.7
Preparing people for ART		✓	✓			Section 6.4
Preparing, assessing and supporting adherence			✓	✓	✓	Sections 6.4 and 9.2
Current medications		✓	✓	✓	✓	See section 7.4.6

6.4 Preparing people living with HIV for ART

Before people start ART, it is important to have a detailed discussion with them about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. For children with HIV, this conversation should directly involve the carer and include discussion about disclosing their HIV status (see Chapter 5). Retesting all people living with HIV before initiating ART is good practice to ensure correct diagnosis of HIV infection. Initiation of ART should always consider nutritional status, any comorbidities and potentially interacting medications for possible contraindications or dose adjustment.

The choice to accept or decline ART ultimately lies with the individual person or his or her caretaker, and if they choose to defer initiation, ART can be offered again at subsequent visits. If there are mental health, substance use or other problems that are major barriers to adherence, appropriate support should be provided, and readiness to initiate ART should be reassessed at regular intervals. A wide range of patient information materials as well as community and peer support can help the person's readiness and decision to start therapy.

People starting treatment and carers should understand that the first ART regimen offers the best opportunity for effective viral suppression and immune recovery, and that successful ART requires them to take the medications exactly as prescribed. They should be advised that many adverse effects are temporary or may be treated, or that substitutions can often be made for problematic ARV drugs. (See section 9.2 for strategies to support adherence to an ART regimen.) People receiving ART and carers should also be asked regularly about any other medications they take, including herbal remedies and nutritional supplements.

People receiving ART should understand that, while the ARV drugs reduce the risk of HIV transmission, they cannot be relied on to prevent other people from acquiring infection. They 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.

6.5 What to expect in the first months of ART

Although taking ART is a lifelong commitment, the first six months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but opportunistic infections 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 ART. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are commonest 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 counts or are severely malnourished (8,9).

CD4 recovery

In most adults and children, CD4 cell counts rise when ART is initiated and immune recovery starts. Generally, this increase occurs during the first year of treatment, plateaus, and then continues to rise further during the second year (10). However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count when initiating ART. Failure to achieve some CD4 recovery should alert the health care provider to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy.

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 is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy (11,12). It may present in two different ways: **paradoxical IRIS**, when an opportunistic infection or tumour diagnosed before ART initially responds to treatment but then deteriorates after ART starts; or **unmasking IRIS**, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity.

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumours and non-infectious conditions (11,12). The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi's sarcoma and herpes zoster. BCG vaccine-associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is routine. A low CD4⁺ cell count (<50 cells/mm³) at ART initiation, disseminated opportunistic infections or tumours and a shorter duration of therapy for opportunistic infections before ART starts are the main risk factors (11,12). IRIS is generally self-limiting, and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of or poor adherence to ART.

The most important steps to reduce the development of IRIS include: earlier HIV diagnosis and initiation of ART before a decline to below 200 CD4 cells/mm³; improved screening for opportunistic infections before ART, especially TB and *Cryptococcus*; and optimal management of opportunistic infections before initiating ART. Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed. Chapter 8 summarizes existing WHO recommendations for the optimal timing of ART among people with TB (see section 8.1.2) and cryptococcal disease (see section 8.1.3) based on evidence from randomized clinical trials.

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Goal of this chapter

To provide updated, evidence-based clinical recommendations outlining a public health approach to ART in the context of the continuum of HIV care, with a focus on resource and capacity limited settings.

7. CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE: ANTIRETROVIRAL THERAPY

7.1 When to start ART

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. The 2013 Guidelines Development Group recommends that national HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm³ or less, giving priority to initiating ART among those with severe/advanced HIV disease (see Annex 1) or a CD4 count of 350 cells/mm³ or less. It is also recommended to initiate ART in people with active TB disease and HBV coinfection with severe liver disease, all pregnant and breastfeeding women with HIV, all children younger than five years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count (Table 7.1).

Table 7.1 Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women and children

Population	Recommendation
Adults and adolescents (≥10 years)	<p>Initiate ART if CD4 cell count ≤500 cells/mm³</p> <ul style="list-style-type: none"> As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³
	<p>Initiate ART regardless of WHO clinical stage and CD4 cell count</p> <ul style="list-style-type: none"> Active TB disease HBV coinfection with severe chronic liver disease Pregnant and breastfeeding women with HIV HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)
Children ≥5 years old	<p>Initiate ART if CD4 cell count ≤500 cells/mm³</p> <ul style="list-style-type: none"> As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤350 cells/mm³
	<p>Initiate ART regardless of CD4 cell count</p> <ul style="list-style-type: none"> WHO clinical stage 3 or 4 Active TB disease
Children 1–5 years old ^a	<p>Initiate ART in all regardless of WHO clinical stage and CD4 cell count</p> <ul style="list-style-type: none"> As a priority, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with CD4 count ≤750 cells/mm³ or <25%, whichever is lower
Infants <1 year old ^a	<p>Initiate ART in all infants regardless of WHO clinical stage and CD4 cell count</p>

^aInitiate ART in all HIV-infected children below 18 months of age with presumptive clinical diagnosis of HIV infection.

7.1.1 When to start ART in adults and adolescents



New recommendations

- As a priority, ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm³ (*strong recommendation, moderate-quality evidence*). NEW
- ART should be initiated in all individuals with HIV with a CD4 count >350 cells and ≤ 500 /mm³ regardless of WHO clinical stage (*strong recommendation, moderate-quality evidence*).^a NEW
- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:
 - Individuals with HIV and active TB disease (*strong recommendation, low-quality evidence*).
 - Individuals coinfectd with HIV and HBV with evidence of severe chronic liver disease^b (*strong recommendation, low-quality evidence*). NEW
 - Partners with HIV in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners (*strong recommendation, high-quality evidence*).
 - Pregnant and breastfeeding women with HIV (see section 7.1.2 for recommendations). NEW

^aThere is insufficient evidence and/or favourable risk–benefit profile to support initiating ART at a CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or coinfectd with HIV-2, individuals with HIV coinfectd with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

^bThere is insufficient evidence and/or favourable risk-benefit profile to support initiating ART in everyone coinfectd with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults.



Table 7.2. Summary of when to initiate ART in adults and adolescents

When to start ART in adults and adolescents	
Target population	Recommendation
Severe/advanced HIV infection (WHO clinical stage 3 or 4)	Initiate ART in all individuals regardless of CD4 cell count
HIV infection (WHO clinical stage 1 or 2)	Initiate ART if CD4 \leq 500 cells/mm ³ (CD4 \leq 350 cells/mm ³ as a priority)
TB disease	Initiate ART in all individuals with active TB disease regardless of CD4 cell count ^a (<i>Unchanged from 2010 recommendations (2)</i>)
Hepatitis B coinfection	Initiate in all individuals with CD4 \leq 500 cells/mm ³ and regardless of CD4 cell count in the presence of severe chronic liver disease ^b
HIV-serodiscordant couples	Provide ART to all partners infected with HIV regardless of CD4 cell count (to reduce the risk of HIV transmission to the negative partner) (<i>Existing 2012 recommendation (49)</i>)

^a TB treatment should be initiated first, followed by ART as soon as possible afterwards (and within the first eight weeks of initiating TB treatment). For those with a CD4 count less than 50 cells/mm³, ART should be provided within two weeks of starting TB treatment (*see section 8.1.2*).

^b 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, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

Background

Since 2002, WHO guidelines on ART have evolved as the body of evidence to support the earlier initiation of ART has progressively increased (1). The 2010 WHO guidelines for adults and adolescents (2) recommended initiating ART for all individuals (including pregnant women) with a CD4 count \leq 350 cells/mm³ regardless of WHO clinical stage and for those with severe or advanced HIV disease (WHO clinical stages 3 or 4) regardless of CD4 count. This strong recommendation was based on moderate-quality evidence from randomized controlled trials (3,4) and observational studies (5–8) showing that initiating ART at or below this CD4 threshold reduced mortality, disease progression (including TB), vertical HIV transmission and serious adverse events. Mathematical modelling simulations also suggested that initiating ART earlier could impact on both sexual and vertical HIV transmission if there is high treatment coverage and full adherence (9). For people with active TB disease or HBV coinfection requiring HBV treatment, the 2010 guidelines (2) recommended initiating ART regardless of CD4 cell count.

Global ART coverage for those eligible according to the 2010 recommendations (CD4 \leq 350 cells/mm³) had reached 54% – or more than 8 million people – by the end of 2011 (10), but coverage varies across regions, ranging from 15% to 68% (11). Only 9 low- and middle-income countries have reported coverage exceeding 80%, and 68 countries have reported coverage of less than 50%. Nevertheless, policy changes in countries have been significant. A recent survey in 92 countries (Web Annex www.who.int/hiv/

pub/guidelines/arv2013/annexes) showed that more than 90% had adopted the CD4 threshold for initiating ART of 350 cells/mm³ or less, and several other countries have moved their CD4 threshold above 350 cells/mm³. The median CD4 count at the time ART is initiated, although increasing, has been far lower than 350 cells/mm³ in almost all settings, including high-income countries (12,13), and late presentation for treatment is associated with high early mortality rates and poor retention in care (6,14). Increasing knowledge of HIV status, strengthening links between testing and care and ensuring optimal long-term retention and adherence remain significant challenges in many settings.

Rationale and supporting evidence

Since 2010, evidence and programmatic experience have continued to shift the risk-benefit ratio towards initiating ART earlier. Increasing evidence also indicates that untreated HIV may be associated with the development of several non-AIDS-defining conditions (including cardiovascular disease, kidney disease, liver disease, several types of cancer and neurocognitive disorders) (15–17) and that initiating ART earlier reduces such events and improves survival. Recent evidence (18) also show that ART substantially reduces sexual transmission in HIV-serodiscordant couples, but not all studies have reported survival benefits. At the same time, more convenient and less toxic regimens have become more widely available, and ARV costs have continued to fall. How early ART should be started is still debated, and the Guidelines Development Group paid close attention to evaluating the potential benefits and harms to the individual and community in developing these new recommendations.

Initiating ART in individuals with symptomatic and asymptomatic HIV disease at a CD4 count ≤ 350 cells/mm³ as a priority

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 counts. The 2013 Guidelines Development Group did not change the strength and quality of evidence for this recommendation established in the 2010 ART guidelines (2). Moderate-quality evidence from two randomized controlled trials and several observational studies shows that initiating ART at CD4 ≤ 350 cells/mm³ significantly reduces mortality, disease progression and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions (2).

Initiating ART at a CD4 count between 350 and 500 cells/mm³

The risk-benefit analysis of the rationale for ART initiation between 350 and 500 CD4 cells/mm³ in these guidelines was debated. The Guidelines Development Group agreed that impact on HIV transmission is strongly supported by the evidence. The quality of evidence for clinical benefit of earlier ART initiation was rated as moderate using the GRADE system, as it mostly relies on observational data mainly from high-income countries. The Guidelines Development Group strongly recommended earlier ART as a public health approach. In settings where feasibility of implementation is a concern, the Guidelines Development Group suggested conducting operational research during implementation to assess context-specific factors such as feasibility, linkage to and retention in care, adherence and resource allocation.

The recommendation for initiating ART at CD4 counts between 350 and 500 cells/mm³ is based on a systematic review with GRADE evidence profiles (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) that assessed the quality and strength of the evidence from 21 observational studies (8,19–39) and three randomized controlled trials (3,18,40) reporting morbidity, mortality and immunological and virological outcomes. They showed that initiating ART at a CD4 count >350 cells/mm³ compared with treatment at a CD4 count ≤350 cells/mm³ reduced the risk of progression to AIDS and/or death, TB, development of a non-AIDS-defining illness and increased the likelihood of immune recovery. Although no studies suggest that earlier ART causes individual harm, these studies were of limited duration.

The pooled analysis of the observational studies found a consistent decreased risk of death with earlier initiation of ART in 13 studies (21–23,26,29–31,34–39) and a decreased risk of progression to AIDS or death in 9 studies (21,23,26,27,30,33,34,36,39) and 3 randomized controlled trials (3,18,40), with a low level of heterogeneity, supporting moderate-quality evidence for earlier treatment. A further subgroup analysis showed a reduced risk of mortality with a CD4 threshold for initiating ART of 500 cell/mm³. The impact on immune recovery was inconsistent and rated as low- to very-low-quality evidence (20,24,28). Two studies found no significant difference in the likelihood of viral suppression (<500 copies/ml), risk of virological failure and viral rebound when treatment is initiated at higher or lower CD4 cell counts (20,36).

In the pooled analysis of two randomized controlled trials (3,18) there was low-quality evidence supporting ART initiation at higher CD4 thresholds for reducing mortality, disease progression or the combined outcome of death and/or progression and, in one trial, the risk of non-AIDS-defining illnesses. The risk of severe adverse events did not differ significantly, but the risk of Grade 3 or 4 laboratory abnormalitiesⁱⁱ was increased in one randomized controlled trial (40). Since treatment in the delayed arm of the SMART trial (3) was initiated when the CD4 count fell below 250 cells/mm³ (rather than 350 cells/mm³), the quality of the evidence for clinical benefit was graded as low because of imprecision and indirectness.

A separate systematic review (41) identified one randomized clinical trial (18) and two observational studies (42,43) reporting a decreased risk of TB when individuals initiated ART with CD4 counts exceeding 350 cells/mm³. ART also reduces recurrent TB by about 50% (44). Dynamic models have suggested ART initiation above 350 cells/mm³ could lead to a more substantial reduction in population tuberculosis incidence (45).

Finally, there is high-quality evidence from one randomized controlled trial (18) indicating that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners. This is supported by the secondary outcomes of a trial that also found a 92% reduction in HIV sexual transmission from partners with HIV taking ART (46).

Cost and cost-effectiveness

The Guidelines Development Group reviewed mathematical simulations of the costs and epidemiological benefits of initiating ART at a CD4 count ≤350 cells/mm³, CD4 count ≤500 cells/mm³ and for all adults with HIV regardless of CD4 cell count. These models suggest that expanding the ART eligibility criteria to ≤500 cells/mm³ could lead to substantial health benefits and be cost-effective in both generalized and concentrated epidemic settings; the increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing

ⁱⁱ Grade 3 and 4 laboratory abnormalities are considered as severe drug adverse reactions and usually requires discontinuation of ARV drugs until the patient is stabilized and substitution for an alternative drug (See Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)

new HIV infections (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, these benefits depend on a high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The models also show that, because the greatest costs are associated with full implementation of the 2010 ART guidelines (2) (initiating ART at CD4 count ≤ 350 cells/mm³), the incremental cost of moving the ART initiation criterion from a CD4 count ≤ 350 cells/mm³ to ≤ 500 cells/mm³ is relatively small, especially if countries already have a substantial number of people with HIV with a CD4 cell count less than 350 cells/mm³ already receiving ART. These modelling findings support the recommendation to initiate ART in adults and adolescents with HIV with a CD4 count ≤ 350 cells/mm³ as a priority. However, the cost implications at the regional and country levels should be explored further, since countries have different levels of treatment coverage and local cost considerations depending on their context and resources.

Potential harms

Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication, and longer follow-up is needed to evaluate potential harms and benefits. The long-term safety profile of ART and the implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.

Feasibility

According to cohort and national programme data, the number of people needing treatment could increase by up to 25% if eligibility is based on CD4 counts increasing from ≤ 350 cells/mm³ to ≤ 500 cells/mm³ (47,48) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). However, 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 numbers of people who actually access treatment in the absence of increased uptake of HIV testing and counselling, stronger linkages to care, adequate treatment monitoring and sustained adherence support.

Implementing the recommendation to initiate ART in individuals with HIV with CD4 counts between 350 and 500 cells/mm³ may involve additional human, infrastructure and financial resources. Chapter 10 discusses these issues in further detail.

Initiating ART regardless of CD4 cell count

*HIV-positive partners in HIV-serodiscordant couples*ⁱⁱⁱ

The results of the HPTN052 study (18) strongly support the use of ART to prevent HIV transmission among HIV-serodiscordant couples. The Guidelines Development Group therefore endorsed the recommendations established in the 2012 WHO guidance on HIV testing and counselling including ART for treatment and prevention in serodiscordant couples (49) that the sexual partner with HIV in such a couple should be offered ART regardless of CD4 count.

ⁱⁱⁱ An HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.

Treating active TB disease^{iv}

In 2010, WHO recommended starting ART in all people with HIV and active TB regardless of CD4 cell count, and that TB treatment should be started first, followed by ART, as soon as possible afterwards (and within the first eight weeks). The Guidelines Development Group reviewed evidence from three randomized clinical trials that showed for people with TB and severe immunodeficiency (CD4 count ≤ 50 cells/mm³), starting ART before eight weeks has a clinical benefit compared with deferring treatment to later than eight weeks (50–52), and endorsed the 2010 recommendations. Implementation of the recommendations on HIV and TB management may be facilitated by integration of services (Chapter 9).

HIV and HBV coinfection with evidence of severe chronic liver disease^v

HIV coinfection affects almost every aspect of the natural history of HBV infection. The consequences include higher rates of chronicity; less spontaneous HBV clearance; accelerated liver fibrosis progression with increased risk of cirrhosis and hepatocellular carcinoma; higher liver-related mortality and decreased ARV response (53–56). Liver disease has emerged as a leading cause of death in people coinfecting with HIV and HBV (57,58).

The 2010 WHO ART guidelines (2) recommended initiating ART among all individuals coinfecting with HIV and HBV who require treatment for their HBV infection (defined as chronic active hepatitis), regardless of CD4 cell count or WHO clinical stage. However, in the absence of routine screening for HBV, most people are unaware of their HBV status. In addition, there is limited access to costly diagnostic tools for staging liver disease (liver biopsy, transient elastography, HBV-DNA and serum biomarkers) needed to establish the presence of chronic active liver disease and eligibility for HBV treatment.

A meta-analysis (59) and a subgroup analysis of a randomized controlled trial (60) provide low-quality evidence of the overall impact of ART on liver-related morbidity and mortality among individuals coinfecting with HIV and HBV, but these studies did not examine the benefit of initiating ART at higher CD4 counts.

Overall, the Guidelines Development Group considered that there was not sufficient evidence and/or a favourable risk–benefit profile to support initiating ART among all people coinfecting with HIV and HBV with a CD4 count >500 cells/mm³ or regardless of CD4 count or stage of liver disease. There are also risks associated with initiating ART earlier (hepatotoxicity, immune reconstitution inflammatory syndrome and hepatic flares).

However, the Guidelines Development Group does recommend providing ART to all people coinfecting with HIV and HBV regardless of CD4 count in people with evidence of severe chronic liver disease, who are at greatest risk of liver disease progression and mortality. The term severe chronic liver disease was used instead of chronic active hepatitis (as in the 2010 guidelines), as this is a term that is more widely understood and applicable using clinical criteria alone. In settings where ART cannot be provided to all individuals with HIV with CD4 counts ≤ 500 cells/mm³, giving priority to diagnosing and treating individuals coinfecting with HIV and HBV should be considered.

As reported in the 2010 WHO ART guidelines (2), data from one randomized controlled trial support the use of at least two agents with activity against HBV (TDF + 3TC or FTC) in terms of improved viral load response and reduced development of HBV drug resistance (61,62).

^{iv} Active TB disease refers to TB infection where the person has symptoms and clinical disease. Latent TB infection refers to TB infection where the person does not have symptoms or clinical disease. Not all persons with latent TB infection will develop TB disease, but the risk of progressing to disease is very high in people with HIV.

^v 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, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

Critical research gaps in this area include the need for more data on the impact of ART on liver-related outcomes in HBV-coinfected people in resource-limited settings and on the relative impact of ART in people with CD4 cell counts >500 cells/mm³ and early-stage liver disease.

Populations for which no specific new recommendation is made

The Guidelines Development Group did not find evidence and/or favourable risk–benefit profiles to support recommendations for initiating ART at CD4 cell count >500 cells/mm³ or regardless of CD4 cell count or WHO clinical stage in the following populations.

Individuals with HIV who are 50 years of age and older

A pooled analysis of data from 13 cohorts from Europe and North America showed increased risk of death and disease progression in people with HIV older than 50 years of age (26). However, these data were not stratified by CD4 cell count and do not support initiating ART at CD4 counts > 500 cells/mm³ for this group.

Individuals with HIV-2

The lack of randomized treatment studies in individuals with HIV-2 makes it difficult to determine the optimal timing of ART initiation in this population. A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) evaluated observational data from 15 studies and showed no significant differences between initiating ART at a CD4 count ≤ 350 cells/mm³ and >350 cells/mm³, considering the outcomes of mortality, disease progression, increase in CD4 cell count, virological response and risk of drug resistance. The quality of evidence was rated as low to very low, with serious risk of bias and imprecision (few events) for all these outcomes.

Individuals coinfecting with HIV and HCV

Observational studies have shown that coinfection with HIV and HCV accelerates HCV-related progression of liver fibrosis and leads to a higher rate of end-stage liver disease (63) and mortality (63–65).

There is consistent but low-quality observational data about the overall benefit of ART on mortality and progression of liver disease in individuals coinfecting with HIV and HCV based on evidence from a meta-analysis (66), and a review of nine cohort studies that examined the relationship between ART and hepatic fibrosis showing that ART was associated with a decreased rate of liver fibrosis progression, although this was not evaluated by the level of CD4 count (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The Guidelines Development Group endorsed the special note in the 2010 guidelines (2) that initiating ART among people coinfecting with HCV should follow the same principles as in HIV mono-infection. Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence.

There are challenges in diagnosing and treating active HCV infection in settings with limited access to HCV antibody and RNA assays, diagnostic tools for staging of liver disease (such as biopsy) and HCV therapy and in certain populations such as people who inject drugs. However, limited access to HCV testing or treatment and/or high rates of HCV infection should not be barriers to initiating ART.

WHO hepatitis guidelines forthcoming in 2014 will provide detailed guidance on HCV screening, treatment and care. People coinfecting with HIV and HCV receiving ART and HCV drugs require close monitoring because of potential drug interactions and increased risk for drug toxicity between HCV drugs (such as interferon, ribavirin and newer directly acting agents) and ARV drugs.

Key populations

The scale-up of ARV drugs for preventing HIV infection or reducing HIV incidence in key populations has been evaluated in community-wide and ecological studies and mathematical models (67–79). Some of these studies showed a reduction in the community viral load, with and without an associated decline in HIV incidence, invariably where ART coverage is high or access to ART is expanding rapidly. However, the Guidelines Development Group concluded that there is insufficient evidence to recommend earlier initiation of ART in key populations regardless of CD4 cell count. The initiation of ART in key populations should follow the same general principles and recommendations as in other adults and adolescents with HIV.

Clinical considerations

Section 10.6 (Checklist 10.3) discusses implementation considerations for moving the CD4 threshold from 350 cells/mm³ to 500 cells/mm³ of relevance to programme managers.

Key research gaps

Further research is required to determine more fully the clinical benefits and disadvantages of earlier ART initiation. Two large randomized trials are examining the optimal timing for initiating ART, with results expected in 2014 to 2015. The Strategic Timing of Antiretroviral Therapy (START) trial in ARV-naïve adults aged 18 years and older is comparing immediate ART in those with CD4 cell counts above 500 cells/mm³ to ART deferred until the CD4 count falls below 350 cells/mm³ or an AIDS event develops (80). The TEMPRANO trial (Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis against Tuberculosis in HIV-infected Adults – ANRS 12136) is comparing the benefits and risks of initiating ART according to the 2010 WHO guidelines (≤ 350 cells/mm³) (2) to the benefits and risks of initiating ART immediately among adults with CD4 counts >350 cells/mm³ in Côte d'Ivoire (81). These studies will inform future WHO recommendations.

Other research priorities include assessing the incidence of severe adverse events as a result of increased exposure to ART and assessing ART acceptability, uptake, adherence and long-term retention in care for people who initiate ART at higher CD4 counts, and the magnitude of the prevention benefit of immediately initiating ART in key populations.

7.1.2 When to start ART in pregnant and breastfeeding women

New recommendations



- All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART (*strong recommendation, moderate-quality evidence*).
- For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment (*conditional recommendation, low-quality evidence*).
- In some countries, for women who are not eligible for ART for their own health, consideration can be given to stopping the ARV regimen after the period of mother-to-child transmission risk has ceased (*conditional recommendation, low-quality evidence*).

Table 7.3 Programme options for ART for PMTCT

National PMTCT programme option	Pregnant and breastfeeding women with HIV		HIV-exposed infant	
	Regardless of WHO clinical stage or CD4 cell count		Breastfeeding	Replacement feeding
Use lifelong ART for all pregnant and breastfeeding women ("Option B+")	Initiate ART and maintain after delivery and cessation of breastfeeding		6 weeks of infant prophylaxis with once-daily NVP	4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)
Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")	Eligible for treatment ^a	Not eligible for treatment ^a		
	Initiate ART and maintain after delivery and cessation of breastfeeding ^b	Initiate ART and stop after delivery and cessation of breastfeeding ^{b,c}		

^a CD4 count ≤ 500 cells/mm³ or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.

^b Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.

^c In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.

Background

ARV drugs are used for pregnant and breastfeeding women with HIV primarily for the mother's health and to prevent the exposed child from becoming infected. It may also offer benefits for preventing the sexual transmission of HIV. The 2010 WHO PMTCT guidelines (82) recommended lifelong ART for women eligible for treatment (based on the 2010 eligibility criteria of CD4 counts ≤ 350 cells/mm³ or presence of WHO clinical stage 3 or 4 disease) and ARV prophylaxis for PMTCT for women with HIV not eligible for treatment. For those not eligible for treatment, two prophylaxis regimens were recommended: "Option A", AZT for the mother during pregnancy, single-dose NVP (sd-NVP) plus AZT and 3TC for the mother at delivery and continued for a week postpartum; and "Option B", triple ARV drugs for the mother during pregnancy and throughout breastfeeding. Prophylaxis was recommended to start as early as 14 weeks of gestation, and both prophylaxis options included four to six weeks of peripartum NVP or AZT for the infant, regardless of whether the mother was breastfeeding. Countries were advised to choose a national approach for their ARV option for PMTCT based on operational considerations.

To accelerate the rapid global scaling up of ART and PMTCT in resource-limited settings, ensure equitable access to ART for pregnant women and achieve the global goal of eliminating new paediatric infections and keeping mothers alive (83), recommendations need to be further simplified, standardized and harmonized. In 2011, Malawi implemented a new approach of lifelong ART for all pregnant and breastfeeding women with HIV regardless of CD4 count or clinical status, commonly referred to as "Option B+" (84–86). WHO issued a programmatic update in April 2012 (87) outlining some of the operational advantages of Option B and the emerging strategy of Option B+.



These 2013 guidelines recommend ART (one simplified triple regimen) for all pregnant and breastfeeding women with HIV during the period of risk of mother-to-child HIV transmission and continuing lifelong ART either for all women or for the women meeting eligibility criteria for their own health. Option A is no longer recommended.

Rationale and supporting evidence

Advantages of a standardized ART regimen for all pregnant and breastfeeding women with HIV

Although available data continue to show that the Option A and B prophylaxis regimens have similar efficacy in clinical trial settings (88–92), the complexities of Option A have been an impediment to scaling up PMTCT in many countries. These complexities include different treatment and prophylaxis regimens; the requirement for CD4 measurement to determine treatment eligibility and type of regimen; changing antepartum-intrapartum-postpartum regimens; the need for an additional postpartum ARV “tail” in mothers; and extended NVP prophylaxis in infants.

By contrast, providing an optimized, fixed-dose combination first-line ART regimen of TDF + 3TC (or FTC) + EFV (see section 7.2.2) to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits, including the following.

- **Ease of implementation.** The same simplified ART regimen is administered to all pregnant women (regardless of “eligibility” for treatment) and continued during pregnancy and labour and postpartum.
- **Harmonized regimens.** The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults.
- **Increased coverage of ART.** This ensures that immunocompromised women who do not have access to CD4 testing receive appropriate ART without delay.
 - **Vertical transmission benefit.** Provides coverage with ART to maximize the prevention of infant infections.
 - **Maternal health benefit.** Will delay disease progression over the course of treatment (93).
- **Acceptability.** Reviews conducted for these guidelines generally indicated strong community preference and acceptability for this approach.
- **Sexual prevention benefit.** ART will reduce sexual transmission of HIV to sexual partners (18).

The Guidelines Development Group also considered the overall evidence from the systematic review of 21 observational studies (19–39) and three randomized controlled trials (3,18,40) used in the evaluation of when to start ART in adults (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes; see section 7.1.1). The recommendation to increase the use of ART in pregnant and breastfeeding women is made with the understanding that there are limited ARV drug options in resource-limited countries. It also recognizes the need to balance the benefits of starting ART in pregnant and breastfeeding women with the possible risks of ARV drug toxicity to the mother and fetus and infant during pregnancy and breastfeeding. Other issues the Guidelines Development Group considered included costs; cost–effectiveness and health system burden (94,95); issues related to adherence and retention (96), HIV drug resistance, ART failure and the availability of future treatment options; and ensuring treatment access for all people who meet current guidelines on eligibility for treatment.

Lifelong ART versus stopping ART after the risk of mother-to-child HIV transmission ends

The recommendation to provide lifelong ART to all pregnant and breastfeeding women with HIV or to continue ART only for those meeting treatment eligibility criteria for the woman's health is conditional, based on the epidemic setting and country programme, and because of the lack of conclusive evidence on the impact and efficacy of fully implementing lifelong ART.

In generalized epidemic settings and in settings with limited access to CD4 testing, limited partner testing, long duration of breastfeeding or high rates of fertility, the benefits of lifelong ART for all pregnant and breastfeeding women with HIV are clear. It will assure maximum coverage for those needing treatment for their own health, avoid stopping and starting drugs with repeat pregnancies, provide early protection against mother-to-child transmission in future pregnancies, reduce the risk of HIV transmission to HIV-serodiscordant partners and improve maternal health. With the new treatment eligibility threshold of CD4 ≤ 500 cells/mm³, approximately 60% of HIV-infected pregnant women will meet treatment eligibility criteria for their own health (97). Although not well quantified, it is likely that at least an additional 10–20% of women would become eligible for treatment over the subsequent two years after birth.

In countries with concentrated epidemics that have high access to CD4 testing, adequate capacity to provide ART to the pregnant and breastfeeding women eligible for treatment, low fertility rates and/or where breastfeeding for mothers with HIV is not recommended, consideration can be given to stopping the ARV drugs in women not eligible for ART after the period of mother-to-child transmission risk has ended. Regardless of the approach, special effort and supportive initiatives are needed to optimize adherence, especially during breastfeeding, where many programmes currently have poor follow-up, and to assure effective linkages to long-term treatment. Chapter 10 provides additional guidance for national programmes on making the decision between lifelong ART and stopping ART (Box 10.4).

Enhanced ARV toxicity surveillance for exposure throughout pregnancy and the breastfeeding period is critical to evaluate the safety of this approach for women, the fetus and the child. This is especially true as an increasing number of women already receiving ART become pregnant, resulting in much higher levels of ARV drug exposure during early gestation (see Sections 7.2.2 on "What ART regimen to start with" and 7.4 on "Monitoring and substitutions for ARV drug toxicities"). In addition, implementation research is important to ensure that the many gaps in knowledge associated with lifelong ART are addressed.

Transition from the 2010 guidelines to the 2013 guidelines

The new 2013 guidelines recommend that countries currently implementing Option A based on the 2010 guidelines (82) should transition, with appropriate planning, to initiating ART for all pregnant and breastfeeding women with HIV; the 2013 guidelines no longer recommend Option A. Countries moving towards Option B and those currently implementing Option B should consider the advantages and disadvantages of implementing lifelong ART for all pregnant and breastfeeding women in their setting.

Clinical considerations

Section 10.6 (Implementation considerations for key recommendations, Box 10.4) discusses clinical and implementation considerations relevant to programme managers for moving towards lifelong ART for all pregnant and breastfeeding women. A toolkit for managing the transition to lifelong ART for pregnant and breastfeeding women has been developed (98), including a readiness assessment checklist (Annex 6).

Key research gaps

The Guidelines Development Group emphasized the need for more research to support the new recommendations, to inform programmatic decisions and to promote optimal implementation. Key research gaps include the following.

ARV toxicity surveillance. Additional research is needed on the safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in low-resource settings, where malnutrition and comorbidities are more common than in resource-rich countries and monitoring capacity is limited. Better data are needed on mothers' health outcomes, pregnancy outcomes (such as stillbirth, low birth weight and prematurity) birth defects and health outcomes for infants and young children (see Box 7.2).

Maternal and child health outcomes. Research is needed to better define the long-term outcomes in terms of both mother-to-child transmission at the end of breastfeeding and maternal health. In addition to short-term outcomes (such as impact on early mother-to-child transmission rates, which are now commonly measured at six weeks), assessments of long-term outcomes with maternal ART are critical to measure final transmission rates at the end of breastfeeding and HIV-free survival; the health of the mother and children infected or uninfected with HIV; retention in care (for those with both low and high CD4 counts); the long-term success of first-line ART; and HIV drug resistance.

Adherence and retention. Research is needed to determine how to optimize acceptability, adherence and retention on ART in pregnant and breastfeeding women, including among the women initiating lifelong ART who do not meet current eligibility criteria for their own health. Research is also needed on health systems and community interventions to optimize lifelong ART for pregnant and breastfeeding women with HIV, and the potential impact of different ART initiation strategies in different populations.

7.1.3 ARV drugs and duration of breastfeeding

Recommendations

The key principles and recommendations established in 2010 remain, including:

National or subnational health authorities should decide whether health services will mainly counsel and support mothers known to be infected with HIV to either breastfeed and receive ARV interventions or avoid all breastfeeding given their particular context.

In settings where national authorities have decided that maternal and child health services will mainly promote and support breastfeeding and ARV interventions as the strategy that will most likely give infants born to mothers known to be infected with HIV the greatest chance of HIV-free survival.

- Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) 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. Breastfeeding should then only stop 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*).

Background

The primary aim of WHO recommendations regarding HIV and infant feeding is to improve the HIV-free survival of HIV-exposed infants. This includes reducing the risk of HIV transmission through breast-milk, primarily by providing ARV drugs, while avoiding malnutrition and the increased risk of serious infections in infants and children through unsafe feeding practices.

In 2010, WHO recommended that ARV drugs be provided either to the mother or the infant throughout breastfeeding to reduce the risk of postnatal HIV transmission (82, 99). In countries that recommended breastfeeding with ARV drugs, it was recommended that women with HIV should “continue breastfeeding for the first 12 months of life” and “only stop once a nutritionally adequate and safe diet without breast-milk can be provided” (99). This recommendation was 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 in the presence of ARV drugs (100,101). At that time, there was uncertainty about the mothers’ adherence to ARV drugs as prophylaxis and their ability to give ARV drugs to their breastfeeding infants over longer periods of time up to 18 or 24 months of age. Consequently, there was uncertainty about the level of protection against HIV transmission for children breastfeeding beyond 12 months. Finally, there were limited data on potential adverse events among infants exposed to prolonged – though low-dose – ARV drugs through breast-milk (102–104).

Since 2010, country-level recommendations on the appropriate duration of breastfeeding for women with HIV and their infants (where breastfeeding is recommended) have varied from 12 to 24 months; in some cases, the duration is not specified. Data on ARV drug coverage and adherence during breastfeeding and effective postpartum follow-up of mother–infant pairs remain limited. With increasing antenatal coverage of ARV drugs in PMTCT programmes, the relative proportion of infants infected during breastfeeding may be increasing because of inadequate ARV drug coverage during breastfeeding, emphasizing the importance of an effective postpartum prevention strategy.

The option of providing lifelong ART to all pregnant women with HIV, regardless of CD4 count or clinical stage (section 7.1.2), raises the question of whether these mothers need to limit the duration of breastfeeding.

The Guidelines Development Group therefore considered whether, in the context of pregnant women with HIV receiving lifelong ART regardless of CD4 count or clinical stage, to maintain the recommendation on the duration of breastfeeding as continued breastfeeding for the first 12 months of life or whether to recommend unrestricted duration of breastfeeding. The Guidelines Development Group considered a revision because of the potential operational advantages of extending the breastfeeding period, including:

- harmonizing and simplifying recommendations for mothers with HIV and their infants with those for mothers without HIV would likely simplify public health messaging and improve infant-feeding practices in the entire community; and
- decreasing stigma and possibly increasing acceptability by mothers and communities.

Ultimately, the Guidelines Development Group decided not to change the 2010 recommendations on HIV and infant feeding.



Rationale for not changing the 2010 WHO recommendations on HIV and infant feeding

Overall, there is no new evidence to support changing the 2010 recommendation.

The main concern about promoting unrestricted breastfeeding among mothers with HIV is that mothers may not adhere to ART throughout breastfeeding, placing their infants at risk of HIV transmission. Although this is important at any time when the infant is breastfeeding, it is of particular concern after the infant reaches 12 months of age. Before 12 months of age, breastfeeding provides major protection to the infant against death from diarrhoea, pneumonia and malnutrition. Although breastfeeding continues to provide a range of benefits to the child after 12 months of age, reductions in mortality from these conditions become less significant.

WHO recommendations acknowledge that some mothers may not be able to provide a safe and adequate diet to children beyond 12 months of age without breastfeeding and, in these situations, suggest that breastfeeding should continue. However, evidence to support this as a general approach, including the additional risk of HIV transmission and ARV toxicity surveillance data to exclude possible ARV-related adverse health outcomes for the infant, is not currently available.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for using ARV drugs during breastfeeding include:

- postnatal prophylaxis for infants remains critical: infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP (section 7.2.2);
- specific interventions (such as integrated follow-up with immunization and other well-child services) should be considered to improve postpartum follow-up of mother–infant pairs, which is often weak in most programmes; and
- communicating clearly and effectively with the community and users the value of breastfeeding with ARV drugs and local considerations regarding the duration of breastfeeding.

In addition, the Guidelines Development Group emphasized the need to support enhanced monitoring for potential toxicities from prolonged exposure to ARV drugs (such as sentinel site monitoring of infant cohorts during the first two years of life), for the next three to five years, and to continue monitoring as new drugs are introduced, to assess the effects of ARVs especially on neurodevelopmental outcomes and renal and bone health.

Key research gaps

- the risk of postpartum transmission in the context of ART, with variable duration of breastfeeding and different programme settings;
- 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; and
- interventions to improve adherence to postnatal ARV drugs and breastfeeding and whether initiating lifelong ART in all pregnant and postpartum women enhances adherence to ARV drugs during breastfeeding, which would enable women with HIV to breastfeed without any time restriction.

Box 7.1. Special considerations for the care and management of pregnant women

(See also Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes)

Sources of guidance:

- *Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice*. Geneva, World Health Organization, 2006 (www.who.int/reproductivehealth/publications/maternal_perinatal_health/924159084X/en/index.html).
- *Guidance on global scale-up of the prevention of mother-to-child transmission of HIV*. Geneva, World Health Organization, 2007 (www.who.int/hiv/pub/mtct/pmtct_scaleup2007/en/index.html).
- *IMAI/IMPAC clinical training for integrated PMTCT services*. Geneva, World Health Organization, 2013 (www.who.int/hiv/topics/mtct/training/en).

General guidance

- Pregnant women with HIV should receive at least the minimum package of recommended antenatal visits and pregnancy care, and additional interventions such as screening for sexually transmitted infections, nutritional support and infant feeding and family planning counselling should be considered.
- There is a high risk of HIV transmission during labour and delivery. This risk can be minimized by following several key principles and practices, including reinforcing recommended antenatal clinic visits, especially high-risk management in the late third trimester; promoting facility-based delivery by trained skilled birth attendants; avoiding unnecessary instrumentation and premature rupture of membranes by using a partograph to monitor stages of labour; and non-invasive suction of nasogastric secretions and washing away blood in the newborn.

Additional measures to reduce HIV transmission include the following:

- The early identification of mothers with HIV and providing ARV drugs to both the mother and the newborn baby are essential.
- For mothers presenting at labour with unknown HIV status, rapid HIV testing should be done during labour or immediately postpartum.
- For women testing positive, ARV drugs should be provided to both the mother and child in accordance with current treatment recommendations and with consideration of extended prophylaxis to the infant (see section 7.2.2).
- Health care workers should follow universal precautions for all deliveries, including those involving mothers with HIV.
- Special efforts should be made to ensure that delivery care is provided in a non-stigmatizing and supportive manner.
- Although Caesarean section has been shown to protect against HIV transmission, especially in the absence of ARV drugs or in the case of 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.

Box 7.1 (continued)

Women with HIV and women of unknown HIV status who deliver outside health facilities should be encouraged to be medically assessed at a maternal and child health facility as soon as possible after delivery and to begin or continue appropriate HIV interventions.

Providing follow-up, linkages to care and treatment and postpartum care are especially important for women with HIV and their HIV-exposed infants. Initial care of the child is usually scheduled at the first immunization visit at four to six weeks, including reinforcement of safe feeding practices, review of ARV coverage and early infant diagnosis testing. Follow-up care for the mother should ideally be scheduled at the same time and should include a postpartum check, family planning counselling, review of ARV regimen and adherence support.

7.1.4 When to start ART in children

New recommendations

NEW

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count
 - Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
 - Children infected with HIV one year to less than five years of age (*conditional recommendation^a, very low-quality evidence*).
- ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count ≤ 500 cells/mm³, regardless of WHO clinical stage
 - CD4 count ≤ 350 cells/mm³ (*strong recommendation, moderate-quality evidence*)
 - CD4 count between 350 and 500 cells/mm³ (*conditional recommendation^b, very-low-quality evidence*).
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count (*strong recommendation, moderate-quality evidence*).
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection (*strong recommendation, low-quality evidence*).

^a This recommendation is conditional because of the lack of evidence supporting earlier initiation in this age group, but this approach is expected to provide significant programmatic advantages in settings with limited access to immunological testing, high burden of paediatric HIV disease and low ART coverage among children, since simplifying eligibility criteria for initiating ART is likely to increase ART coverage in children infected with HIV and improve their health outcomes. Priority for ART initiation should be given to children younger than two years of age, because of higher mortality risk, and to children between two and five years of age with advanced disease (WHO HIV clinical stages 3 and 4 or with CD4 count ≤ 750 cells/mm³ or $<25\%$, whichever is lower), regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*) (105).

^b This recommendation is conditional because of the lack of evidence in this population for individual benefit as a result of initiating ART earlier; however, this approach is expected to provide significant programmatic advantages in settings with high coverage of paediatric ART and a programmatic need to align with ARV drug recommendations for adults. If this recommendation is not adopted, ART should be initiated at WHO HIV clinical stages 3 and 4 or with CD4 count ≤ 350 cells/mm³ regardless of WHO clinical stage (*strong recommendation, very-low-quality evidence*) (105).

Table 7.4. Summary of recommendations on when to start ART in children

Age	When you start
Infants (<1 year)	Treat all individuals
1 year to less than 5 years	Treat all individuals (children ≤ 2 years or with WHO stage 3 or 4 or CD4 count ≤ 750 cells/mm ³ or <25% as a priority)
5 years and above	WHO stage 3 or 4 Or CD4 ≤ 500 cells/mm ³ (CD4 ≤ 350 cells/mm ³ as a priority)

Background

Infants and young children have an exceptionally high risk of poor outcomes from HIV infection. Up to 52% of children die before the age of two years in the absence of any intervention (106). By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults (107,108).

The scaling up of early infant diagnosis programmes has increased the identification of infants infected with HIV, but initiating ART early for those who have been found to be infected remains poor. Most HIV-infected children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults (28% versus 57% globally in 2011) (11).

Diagnosing and retaining children exposed to HIV and children infected with HIV in care also presents unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high along the continuum of care (109), with retention especially challenging for children who are in HIV care but not yet eligible for ART.

Some countries are already introducing immediate ART for children younger than five years based on operational and programmatic grounds (110,111).

The 2010 WHO guidelines aligned clinical and immunological criteria for ART eligibility for children older than five years with those for adults (that is, treat for WHO clinical stage 3 or 4 disease or CD4 ≤ 350 cells/mm³) (105). They also recommended treating all children infected with HIV younger than two years of age regardless of clinical or immunological status. For children between two and five years of age, it was recommended that those with WHO stage 3 or 4, clinical disease or CD4 <25% or ≤ 750 cells/mm³ be treated (105).

The review of evidence in 2013, together with operational considerations and values and preferences expressed by care providers, has led to revised recommendations to simplify and expand treatment in children, including initiating ART in all children up to five years and to increase the CD4 count threshold for ART initiation to ≤ 500 cells/mm³ in children 5 years and older, aligning with the new threshold in adults.



Rationale and supporting evidence

These recommendations are based on strong operational and programmatic advantages resulting from simplification of criteria for initiating ART, despite the lack of clinical benefits to support treatment regardless of CD4 or clinical stage beyond infancy. Similarly, for programmatic purposes and given that disease progression in children five years and older is comparable to that of young adults, alignment with ART initiation criteria for adults was considered of high value.

Evidence for increasing the age threshold for early ART to five years

CD4 count and WHO clinical stage can identify children at increased risk of disease progression and death. Previous recommendations were based on observational studies demonstrating that untreated children in the second year of life continue to experience high rates of death and illness compared with children without HIV (106). Child-survival curves suggest that the mortality for children older than two years of age and with CD4 exceeding 25% is about 1–2% per year (107,108).

A systematic review identified only one randomized clinical trial, PREDICT (112), informing this issue (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 counts above 15% and without CDC clinical stage C disease, randomizing them to either immediate treatment or deferred treatment until the CD4 count fell below 15%. AIDS-free survival, neurodevelopmental outcomes and growth parameters did not differ between groups (113).

A causal modelling study was also undertaken using prospective data collected by the leDEA-Southern Africa network on 5732 ART-naïve children 24–59 months old (median age 3.3 years) who had CD4 counts above the existing eligibility thresholds of 25% or 750 cells/mm³ (114) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). The study did not show any survival benefit from early treatment in this population, but a large proportion of children in this age range would rapidly become eligible under the existing criteria, since most children with CD4 count of 750 cells/mm³ or higher at enrolment into care reached the CD4 treatment threshold within three years. More specifically, 32% of this subset of the cohort fell below the thresholds for eligibility after one year and 60% after two years.

Operational and programmatic advantages

Despite the lower risk of progression in children 2–5 years old compared with children younger than two years and the low quality of evidence, the Guidelines Development Group emphasized the operational and programmatic advantages of removing the CD4 barrier to treatment for children under 5 years of age. Treating all children younger than five years of age is expected to simplify paediatric treatment and facilitate a significant expansion of ART coverage for young children. Although this has not been assessed as an outcome, programmatic data suggest that retention is better among children on ART than among those in care but not started on ART (109). Increasing ART coverage and targeting these children for HIV care may also facilitate the treatment of other preventable causes of under-five mortality. This approach will likely represent a small increased burden on current systems (115). Note that late diagnosis is still occurring, and a large proportion of the children identified as infected with HIV would already be eligible for ART based on the 2010 recommendations.

Community values and preferences

Expanding ART to every child younger than five years of age is expected to be well accepted. Assessment of the values and preferences of people living with HIV, caregivers and health care providers of children with HIV showed that earlier initiation is preferable because it is believed to facilitate family-based care, prevent loss to follow-up and improve adherence (116). Nevertheless, there is a risk of resistance if treatment is initiated early in young children and

adherence is poor or drug supplies are suboptimal; this is particularly the case for the youngest children, among whom harmonizing the formulations for children and adults is most difficult. However, the benefits of treatment are likely to outweigh these risks.

Where access to immunological testing is limited, the burden of paediatric HIV disease is high and paediatric ART coverage is low, simplifying the eligibility criteria for initiating ART may significantly improve the overall health outcomes for children with HIV (117). National programmes need to determine how best to implement this recommendation and whether to recommend universal treatment for all children younger than five years or to focus on universal treatment for infants younger than one year and apply clinical and immunological criteria for children one to five years old. When ART initiation is expanded regardless of clinical and immunological status beyond infancy to all children younger than five years, treatment of children younger than two years should be given priority because of their higher risk of death and rapid disease progression. In addition, expanding ART services will require ensuring retention in care and should be matched with concomitant expansion of interventions to support adherence.

Evidence for increasing the CD4 threshold to 500 cells/mm³

The criteria for initiating ART in children five years of age and older are the same as for adults. Although there are limited data to assess the clinical impact of treating children with a CD4 count between 350 and 500 cells/mm³ and the benefits of ARV drugs in preventing sexual transmission are not a factor for this population, this approach has programmatic advantages resulting from harmonizing the criteria with those for adults. It may be most feasible in settings with high ART coverage. As in the case of adults, treating children with CD4 counts ≤ 350 cells/mm³ should be a high priority since they have the highest risk of disease progression.

Coinfection with HIV and HBV

Small cohort studies in which both HIV and HBV are endemic report rates of chronic HBV among children with HIV between 1% and 49% (118). HBV is often acquired in infancy or early childhood and, unlike among adults, may have an immunotolerant phase that lasts throughout childhood and adolescence. Unfortunately, the natural history of the disease among children with HIV is still poorly known, and the benefits from initiating ART earlier in these children remain to be assessed.

Clinical considerations for scaling up ART among children

Section 10.6 discusses implementation considerations relevant to programme managers (see Box 10.6). An additional important implementation consideration for clinicians and other health care providers is that expanding the initiation of ART regardless of clinical and immunological status to children younger than five years eliminates the need for determining the CD4 count to initiate treatment in this age group and avoids delaying ART in settings without access to CD4 testing. However, the availability of CD4 testing, including determining the baseline CD4 count and percentage, remains important to ensure appropriate treatment monitoring in the absence of viral load monitoring.

Key research gaps

More data are needed to define potential clinical benefits and the impact of initiating ART early on morbidity for children younger than five years as well as immunological response and virological response over time. The impact of initiating ART earlier on retention, adherence and potential HIV drug resistance among children with less advanced disease needs to be investigated further. Data are also needed to inform the optimal approach to initiating ART in children coinfecting with HBV.

7.2 What ART regimen to start with (first-line ART)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + FTC or TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years. For children younger than three years, a PI-based regimen is the preferred approach (Table 7.5).

Table 7.5 Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens ^{a, b}
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥ 35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents <35 kg	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC or AZT + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

^a For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

^b ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

7.2.1 First-line ART for adults



New recommendations

NEW

- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI)
 - 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 options is recommended:
 - AZT + 3TC + EFV
 - AZT + 3TC + NVP
 - TDF + 3TC (or FTC) + NVP (*strong 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*).

Table 7.6 Summary of first-line ART regimens for adults^a

First-line ART for adults (including pregnant and breastfeeding women and people with TB and HBV coinfection)	
Preferred regimens	TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Special circumstances ^c	Regimens containing ABC, d4T ^b and boosted PIs

^a For adolescents, see section 7.2.4 on first-line ART for children three years and older which includes adolescents infected with HIV (10 years and older).

^b Using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used. The duration of therapy with this drug should be limited to the shortest time possible and include close monitoring.

^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.

Background

The 2010 WHO ART guidelines (2) recommended that ART in treatment-naïve adults should initially consist of an NNRTI (either NVP or EFV) plus two NRTIs, one of which should be 3TC (or FTC) and the other AZT or TDF. The guidelines emphasized the importance of avoiding d4T as a preferred option in first-line regimens because of its well-known mitochondrial toxicity, using regimens that are potentially less toxic and more suitable for most people, preferably as fixed-dose combinations given the clinical, operational and programmatic benefits. The recommended regimens had better toxicity profiles than d4T but were considered comparable in terms of efficacy, since there was no evidence that AZT is virologically superior to d4T, AZT superior to TDF, TDF superior to d4T or ABC, or EFV superior to NVP.

NEW


The phasing out of d4T as a preferred option in first-line ART has been variable. Some countries have made rapid and substantial progress, whereas others have taken a gradual approach, such as avoiding d4T only for people starting ART or not using d4T in pregnant women (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO (119,120) promotes a more affordable and efficient approach to treatment, including simpler, single-pill, once-daily ART regimens. The 2013 guidelines promote further simplification of ART delivery by reducing the number of preferred first-line regimens and focusing on regimens that may be used across a range of populations.

Rationale and supporting evidence

The move to TDF + 3TC (or FTC) + EFV as the preferred first-line option

A systematic review comparing six regimens showed moderate-quality evidence indicating that a 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 compared with other once- or twice-daily regimens (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). An additional systematic review showed people receiving NVP are twice as likely as those receiving EFV to discontinue treatment because of adverse events (121).

The Guideline Development Group also reviewed a published meta-analysis and a further updated analysis (122, 123) that showed no increased risk of birth defects with EFV compared with other ARV drugs used during the first trimester of pregnancy (122). 3TC and FTC are pharmacologically comparable (123). TDF + 3TC (or FTC) + EFV offers good potential for harmonizing treatment across different populations: TDF/FTC or TDF/3TC are the preferred NRTI backbone for people coinfecting with HIV and HBV and can be used among people coinfecting with TB and among pregnant women. EFV is the preferred NNRTI for people with HIV and TB (pharmacological compatibility with TB drugs) and HIV and HBV coinfection (less risk of hepatic toxicity) and can be used among pregnant women, including those in the first trimester.

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-naïve people. Despite being considered equivalent options, they have potential disadvantages compared with preferred regimens. Use of other drugs such as ABC and boosted PIs are acceptable as potential backup options in special situations but are not recommended as preferred alternatives, considering the principles of optimizing ARV drugs.

NVP in pregnant women

There are continued concerns about the higher risk of adverse events with NVP compared with EFV, and about the use of NVP in women with HIV with CD4 cell counts above 250 cells/mm³, with some studies showing an increased relative risk for severe hepatic and skin reactions in pregnant women using NVP at higher CD4 cell counts (124–126). A systematic review (127), updated in 2013 (134) of the risk of NVP-associated toxicity in pregnant women suggests that the frequency of adverse events is elevated but no higher than that observed in the general adult population. The evidence supporting the theory that pregnant women with HIV who have high CD4 counts are at increased risk of adverse events compared with the general population with HIV is weak. The need for lead-in dosing for initial use of NVP and the fact that it is not available as a fixed-dose combination with TDF + 3TC (or FTC) are important considerations. NVP should therefore be used with caution in pregnant women and women who might be pregnant and only after considering the risk and benefits and available alternatives (see section 7.3.2).

Alternatives to NVP, such as ABC and boosted PIs, are acceptable but should only be used when NVP is not available.

Using alternative regimens and phasing out d4T

The currently recommended alternative regimens (such as AZT instead of TDF or NVP instead of EFV (Table 7.7) are comparable in therapeutic efficacy but have potential clinical and programmatic disadvantages compared with the preferred options. Individuals who are already clinically stable on an alternative regimen with no contraindications can consider continuing that regimen based on national guidance or switch to the preferred options to simplify treatment management, reduce cost, improve tolerability, enhance adherence and promote better regimen sequencing. In special circumstances, ABC and boosted PIs are acceptable but should only be used when other options are not available.

Use of d4T-containing regimens should be discontinued and restricted to cases in which other ARV drugs cannot be used, and the duration of therapy with this drug should be limited to the shortest time possible and include close monitoring. In settings in which d4T regimens are still used as a preferred option for initiating ART, a plan for phasing out d4T should be implemented, preferably towards using TDF-based first-line regimens (2,128,129). Section 10.6 (Box 10.7) further discusses the issue of phasing out d4T.

TDF toxicity

A systematic review on TDF toxicity (Web Annex www.who.int/hiv/pub/guidelines/arv2013annexes) indicates that TDF has a low rate of renal toxicity in the short to medium term, especially among people with pre-existing, or risk factors for, renal disease. Prospective cohort data show that TDF is associated with modest reduction in renal function (measured by the decrease in the estimated glomerular filtration rate) (130,131) and reduction in bone mineral density, but the clinical significance and magnitude of these side effects, especially with prolonged therapy, need to be investigated further. Further research is also needed to determine whether laboratory screening and monitoring of TDF toxicity should be routine or undertaken only in high-risk populations, such as people with hypertension or diabetes or those using boosted PIs. Since TDF renal toxicity is usually tubular, glomerular function tests do not provide a direct measure, and no other simple test can detect renal tubular toxicity. Section 7.4 discusses this issue further.

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.

HIV-2 infection

A systematic review of treatment options for individuals with HIV-2 (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) rated the evidence in all observational studies as being of very low quality, with serious risk of bias, inconsistency and imprecision. Since HIV-2 is naturally resistant to NNRTIs, treatment-naive people coinfecting with HIV-1 and HIV-2 should be treated with a regimen containing three NRTIs (TDF + 3TC (or FTC) + AZT or AZT + 3TC + ABC or a ritonavir-boosted PI plus two NRTIs. If a PI-based regimen is used, the preferred option for first-line therapy should be LPV/r, since this will be procured in low-income settings for both second-line treatment for adults and for first-line treatment for children. SQV/r and DRV/r are alternative boosted-PI options, but they are not available as heat-stable fixed-dose combinations.

7.2.2 First-line ART for pregnant and breastfeeding women and ARV drugs for their infants



New recommendations

NEW

- A once-daily fixed-dose combination of TDF + 3TC (or FTC) + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped (*strong recommendation, low- to moderate-quality evidence: moderate-quality evidence for adults in general but low-quality evidence for the specific population of pregnant and breastfeeding women and infants*).
- Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (*strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding*).

Note: For the recommendations on infant prophylaxis, the GRADE ratings and recommendations shown are from the 2010 guidelines and were not reviewed by the Guidelines Development Group for the current guidelines.

Background

The 2010 WHO guidelines on PMTCT (82) recommended a choice of four different regimens for pregnant and breastfeeding women with HIV who required ART for their own health: AZT + 3TC or TDF + 3TC (or FTC) plus either NVP or EFV. Because of concerns about the increased risk of toxicity of NVP among pregnant women with higher CD4 counts (132–134), the recommended regimens for pregnant women who did not require treatment for their own health and who were receiving triple ARV regimens for PMTCT were AZT + 3TC or TDF + 3TC (or FTC) + EFV as the preferred NNRTI regimens. Alternative regimens were AZT + 3TC plus either LPV/r or ABC, rather than NVP. Although TDF and EFV were recommended, there were limited safety data on their use during pregnancy and breastfeeding.

The 2010 WHO guidelines (82) also recommended four to six weeks of infant NVP (or AZT) as post-exposure prophylaxis for all infants born to mothers who were receiving triple ARV regimens for treatment or prevention. Daily NVP infant prophylaxis throughout breastfeeding was recommended if the mother was not receiving a triple ARV regimen.

In clinical trials, infant prophylaxis has been shown to be especially important for PMTCT when the mother has received limited or no antepartum ARV drugs and when viral suppression has not yet been achieved (135–137). This continues to be a recommended component of PMTCT regimens in resource-rich countries as added protection against exposure to HIV during labour, even when mothers receive ART during pregnancy and when the mother is not breastfeeding (138). The data informing this recommendation have not changed since 2010.

Rationale and supporting evidence

The 2013 guidelines emphasize simplifying and harmonizing first-line therapy. A once-daily fixed-dose combination regimen is recommended, with TDF as the preferred NRTI and EFV as the preferred NNRTI, in combination with 3TC or FTC for all adults – including pregnant and breastfeeding women – as the preferred regimen to improve health outcomes and facilitate adherence and drug procurement (see section 7.2.1 and Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

The ideal first-line regimen for pregnant and breastfeeding women with HIV has low cost; is available as a fixed-dose combination; is safe for both pregnant and breastfeeding women and their infants; is well tolerated; has low monitoring requirements and a low drug-resistance profile; is compatible with other drugs used in clinical care; and is harmonized with the recommendations for non-pregnant adults. The regimen of TDF + 3TC (or FTC) + EFV is available as a once-daily fixed-dose combination and is the recommended first-line regimen for adults because of simplicity, affordability (the cost has declined significantly since 2010) and efficacy against HBV.

Safety is a critical issue for pregnant and breastfeeding women and their infants as well as women who might become pregnant. Although data on EFV and TDF use in pregnant women remain limited, more data have become available since 2010 and provide increased reassurance for recommending TDF + 3TC (or FTC) + EFV as the first-line ARV regimen for pregnant and breastfeeding women (122,139,140). Sections 7.3.1 and 7.5.2 provide more detail on the overall rationale for the recommended first-line regimen, including toxicity and monitoring issues.

Safety of EFV in pregnancy

Early data suggesting birth defects, including anencephaly, microphthalmia and cleft palate among primates with EFV exposure *in utero* (141) and some isolated case reports and retrospective clinical data on neural tube defects among humans (142) have led to concern about using EFV in the first trimester of pregnancy or in non-pregnant women with childbearing potential. The United States Food and Drug Administration and European Medicines Agency advise against using EFV in the first trimester and in women of childbearing potential unless the potential benefits outweigh the potential risks; however, the British HIV Association recently changed its recommendation to allow EFV to be used in the first trimester (143).

Because the risk of neural tube defects is limited to the first five to six weeks of pregnancy and because pregnancy is rarely recognized this early, especially in resource-limited settings, any potential risk of neural tube defects with the use of EFV would be primarily in women who become pregnant while already receiving EFV. Evaluation of prospectively collected data in humans is reassuring; an updated systematic review and meta-analysis, including the Antiretroviral Pregnancy Registry (47,134), reported outcomes for 1502 live births to women receiving EFV in the first trimester and found no increase in overall birth defects and no elevated signal for EFV compared with other ARV exposure in pregnancy (140). With one identified neural tube defect, the estimated prevalence from the systematic review continues to be about 7 per 10 000 population (0.07%), which is comparable to the estimates of 0.02–0.2% in the general population in the USA (138). Because neural tube defects are relatively rare events and there are limited exposures in the Antiretroviral Pregnancy Registry and in the meta-analyses, current available data are sufficient to rule out a potential increased risk greater than three-fold or up to 0.21% (the more limited data available for the 2010 guidelines were sufficient to rule out a 10-fold increased risk). Although the Guidelines Development Group emphasized that better data on birth defects are needed, it felt confident that this potential low risk should be balanced against the programmatic advantages and the clinical benefit of EFV in preventing HIV infection in infants and for the mother's health.

NEW



Safety of NVP in pregnancy: (see section 7.2.1)

Safety of TDF in pregnancy and during breastfeeding

Potential concerns about the safety of TDF include renal toxicity (see section 7.4.3), adverse birth outcomes and effects on bone density. A systematic review assessed the toxicity of fetal exposure to TDF in pregnancy (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In the Antiretroviral Pregnancy Registry, the prevalence of overall birth defects with exposure to TDF in the first trimester was 2.4% of 1612 live births and did not differ from the background rate in the USA. A limited number of studies showed no difference in fetal growth between infants exposed or not exposed to TDF (144,145). TDF has limited penetration into breast-milk, which would limit potential toxicity for the breastfeeding infant. However, there have been no studies of TDF among lactating women, who normally have bone loss during breastfeeding that stabilizes after lactation. More extensive studies are ongoing of TDF bone and renal safety in pregnancy and breastfeeding for both the mother and child.

The once-daily TDF + 3TC (or FTC) + EFV fixed-dose regimen is simple and convenient, and harmonizing the recommendations for pregnant and non-pregnant women simplifies supply chain management. Based on available data and experience, the Guidelines Development Group felt that the clear benefits of this regimen for pregnant and breastfeeding women (and women of childbearing potential) outweigh the potential risks (see section 7.5.2).

Infant prophylaxis

Table 7.8 Simplified infant prophylaxis dosing recommendations (adapted from (82))

Simplified infant prophylaxis dosing recommendations: NVP

Infant age	Daily dosing
Birth ^a to 6 weeks ^b	
• Birthweight 2000–2499 g	10 mg once daily
• Birthweight ≥2500 g	15 mg once daily
> 6 weeks to 6 months ^c	20 mg once daily
> 6 months to 9 months	30 mg once daily
> 9 months until breastfeeding ends	40 mg once daily

^a Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

^b Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.

^c Dosing beyond 6 weeks of age in special situations in which prolonged dosing of up to 12 weeks should be considered (such as the mother having had limited ART and not being likely to be virally suppressed; the infant is identified as HIV exposed after birth and is breastfeeding (Table 7.9)). This is based on the dosing required to sustain exposure among infants of >100 ng/ml with the least dose changes.

Simplified infant prophylaxis dosing recommendations: AZT (only recommended in settings with replacement feeding)

Infant age	Daily dosing
Birth ^a to 6 weeks <ul style="list-style-type: none"> • Birthweight 2000–2499 g^a • Birthweight ≥2500 g 	10 mg twice daily 15 mg twice daily

^a Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

No new data inform any change in the recommendations on infant prophylaxis. For breastfeeding infants, six weeks of infant NVP is recommended; for infants receiving replacement feeding, four to six weeks of infant NVP or AZT continues to be recommended. If toxicity from infant NVP requires discontinuing the drug or if infant NVP is not available, infant 3TC can be substituted. Several studies (146,147) have safely used infant prophylaxis during breastfeeding with 3TC.

Although the Guidelines Development Group did not formally review this, it considered several scenarios in which longer infant prophylaxis might be appropriate. Because several weeks or months are required for maternal ART to achieve viral suppression and a breastfeeding infant may not be protected against postnatal transmission during that period, or when a breastfeeding mother initiates ART very late in pregnancy (such as less than four weeks prior to delivery) during labour or postpartum, increasing the duration of infant NVP prophylaxis to 12 weeks can be considered.

Infant prophylaxis is also important when a breastfeeding mother interrupts ART during breastfeeding, as this places her infant at increased risk of postnatal transmission. In such situations, providing daily infant NVP during the period of maternal ART interruption should be considered, and this could be stopped six weeks after maternal ART is restarted (or one week after breastfeeding ends, whichever comes first). Table 7.9 summarizes the range of scenarios for maternal and infant prophylaxis.

Table 7.9 Summary of maternal and infant ARV prophylaxis for different clinical scenarios

Scenario	Maternal ARV prophylaxis ^a	Infant ARV prophylaxis ^b	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy ^{c,d}	Initiate maternal ART	NVP ^c	6 weeks ^c
Mother diagnosed with HIV during labour or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP	6 weeks; consider extending this to 12 weeks
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	NVP ^c	6 weeks ^c
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP – strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding	Refer mother for HIV care and evaluation for treatment	No drug	Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

^aIdeally, obtain the mother's CD4 cell count at the time of initiating or soon after initiating ART; country guidelines should be used to determine whether ART is lifelong or is stopped after the risk for transmission has ended.

^bIf infant NVP causes toxicity or NVP is not available, 3TC can be substituted.

^cIf the mother is using replacement feeding, infant AZT can be substituted for infant NVP; if there is documented maternal viral suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.

^dIf it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.

Alternative regimens: for toxicity, intolerance or lack of availability of recommended regimens

AZT is recommended as the alternative NRTI for non-pregnant women who cannot tolerate or receive TDF. Given the extensive safety and efficacy data on AZT in pregnant and breastfeeding women, AZT is also the recommended alternative NRTI for pregnant and breastfeeding women.

For non-pregnant women who cannot tolerate or receive EFV, the recommended alternative NNRTI is NVP. However, because ART (triple ARV drugs) is now recommended for pregnant and breastfeeding women regardless of CD4 cell count, concerns remain regarding the use of NVP in women with higher CD4 counts. Although the 2010 guidelines (2,82) stated that the benefit of NVP outweighed the risk for women with CD4 counts of 250 to 350 cells/mm³, data on safety in women with CD4 counts ≥ 350 cells/mm³ are limited, and the finding of life-threatening hepatic toxicity when NVP was used for occupational post-exposure prophylaxis in individuals without HIV infection raises concerns regarding its use for individuals with higher CD4 count. However, a recent systematic review of the risk of NVP-associated toxicity in pregnant women (134) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) suggests that the frequency of adverse events is no higher than that in the general adult population. Further, data on the association between NVP toxicity and elevated CD4 cell counts are conflicting, and the risk of significant hepatic toxicity in most studies is about 3% (121). Data suggest that switching to NVP for individuals who have been treated and had viral suppression is not associated with elevated toxicity even where the immune system has reconstituted. Finally, the alternative to substituting NVP for EFV toxicity would be a PI, which is the recommended second-line therapy and is more expensive than NNRTI drugs. On balance, the Guidelines Development Group held that the overall benefit of substituting NVP for pregnant or breastfeeding women in the rare circumstances that EFV is not tolerated outweighs the potential risks.

Clinical considerations

Maintaining the drug supply chain and ensuring uninterrupted delivery of maternal ART and infant ARV drugs during pregnancy and breastfeeding are critical for PMTCT. All antenatal care and maternal and child health sites providing PMTCT services should have the capacity to initiate, support and monitor ongoing maternal ART and infant ARV drugs.

Key research gaps

Surveillance of ARV drug toxicity. Research is needed to continue to evaluate both the short- and long-term effects of EFV, TDF and other ARV drugs on pregnant and breastfeeding women, fetuses and children, including monitoring for birth defects and other adverse pregnancy outcomes and evaluating the renal and bone effects of TDF on both the woman and HIV-exposed infant.

Acceptability of EFV as first-line ART. The level of intolerance to EFV and whether switching to an alternative first-line regimen is necessary needs to be studied further, as do ways to support alternative first-line regimens in programme settings for pregnant and breastfeeding women.

Infant prophylaxis. Better data are needed on the optimal duration of infant prophylaxis when mothers receive ART, especially if the mother starts ART late in pregnancy or during the postpartum period and hence is not virally suppressed at the time of delivery or when breastfeeding begins. NVP formulations that are improved and easier to administer are needed to facilitate drug administration to neonates and infants.

Optimal management of infants identified as HIV exposed during breastfeeding.

It is important to determine the extent to which perinatal HIV exposure is missed antenatally

and the extent of maternal seroconversion, appropriate strategies for postpartum screening of infants for HIV exposure and optimal testing and prophylaxis strategies.

Stopping NNRTI-based ART (use of a “tail”). Because of the prolonged half-life of EFV (and NVP), suddenly stopping an NNRTI-based regimen risks developing NNRTI resistance. For women who choose to or must stop EFV-based ART because of toxicity or other conditions, more data are needed to determine whether an NRTI “tail” coverage is needed to reduce this risk. Pharmacokinetic modelling reviewed for the guidelines suggests that, if the NRTI backbone included TDF, such a tail may not be needed, but if the NRTI backbone included AZT, a two-week tail is advisable (EFV has a longer half-life than NVP).

7.2.3 First-line ART for children younger than three years of age

New recommendations



- A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen (*strong recommendation, moderate-quality evidence*).
- Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained (*conditional recommendation, low-quality evidence*).

Special note: The randomized control trial supporting the use of this approach (148,161) defined virological suppression as a viral load ≤ 400 copies/mm³, with the goal of identifying the children who are more likely to be able to safely substitute LPV/r with NVP. The use of a higher viral load cut-off for determining virological suppression has not been studied in the context of this strategy.

- For infants and children infected with HIV younger than three 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*).
- For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC (*strong recommendation, low-quality evidence*).

Table 7.10 Summary of first-line ART regimens for children younger than three years

Preferred regimens	ABC ^a or AZT + 3TC + LPV/r ^b
Alternative regimens	ABC ^a or AZT + 3TC + NVP ^c
Special circumstances ^e	d4T ^d + 3TC + LPV/r d4T ^d + 3TC + NVP

^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. The CHAIN working group developed this recommendation. Availability and cost should be carefully considered.

^b As recommended by the United States Food and Drug Administration, using LPV/r oral liquid should be avoided in premature babies (born one 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. Dosing for children younger than 6 weeks should be calculated based on body surface area (Annex 3).

^c During the finalization of these guidelines, the United States Food and Drug Administration approved the use of EFV in children 3 months to 3 years old weighing more than 3.5 kg. Due to the limited data to inform the best use of this drug in the use of this drug in this age group, the Guidelines Development Group agreed to maintain NVP as the recommended NNRTI for children under 3 years. WHO will provide further guidance as soon as the additional data become available.

^d Because of the limited options available for children younger than three years, d4T is still included among the recommended NRTIs, but its use should be restricted to the situations in which toxicity to AZT is suspected or confirmed and ABC cannot be used. The duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

^e 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.

Background

Optimizing first-line ART in children younger than three 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 require alternative therapeutic approaches 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 ARV drug exposure for PMTCT.

Young children with HIV who are exposed to NNRTIs used for PMTCT have demonstrable viral resistance (150), which compromises the response to NVP-containing first-line ART (151,152). For this reason, the 2010 WHO guidelines (105) recommended the use of LPV/r-based treatment in children younger than 24 months of age previously exposed to NNRTIs. For young children not exposed to NNRTIs or whose status was unknown, an NVP-based regimen was recommended (105).

New evidence has become available for this age group suggesting the superiority of a LPV/r-based regimen regardless of PMTCT exposure (153,154). Several strategies have also been tested 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. (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

Rationale and supporting evidence

This recommendation is based on evidence of the superiority of a LPV/r-based regimen for young children balanced against feasibility considerations.

Efficacy of a LPV/r-based regimen for infants and young children

A systematic review of two randomized trials (153,154) shows that children younger than 36 months have a reduced risk of discontinuing treatment and virological failure or death if they are started on a LPV/r-based regimen instead of a NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In addition, surveillance of drug resistance among children younger than 18 months (149,155) provides further evidence of detectable NNRTI resistance even among children without any history of exposure to ARV drugs for PMTCT or whose exposure status is unknown, suggesting that a history of exposure for PMTCT may not be an accurate marker for identifying children at higher risk of HIV resistance to NNRTI.

LPV/r is known to have a better resistance profile that protects against the selection of NRTI resistance without compromising the use of other PIs in second-line regimens (156,157–159). In addition, a potential advantage is offered by the considerable reduction in the incidence of malaria among children receiving LPV/r-based, as recently demonstrated in a randomized trial comparing the use of LPV/r versus NVP or EFV among children in Uganda receiving an artemether + lumefantrine combination for treating malaria episodes (160).



Feasibility of LPV/r in resource-limited settings

Providing an LPV/r-based regimen to infants and children younger than three years in some resource-limited settings may be challenging. The current LPV/r syrup formulation has cold-chain requirements until the point of dispensing. The syrup is unpalatable, with the potential for suboptimal adherence, as highlighted in the values and preferences survey among health workers, and the risk of metabolic complications among children who initiate LPV/r early in life is unknown. Further, LPV/r is costly and administering this with TB treatment is complex. Alternative approaches are proposed to overcome these challenges.

A recent randomized clinical trial (148,161) and an ongoing randomized clinical trial (162) have evaluated a strategy in which LPV/r is started and later substituted with an NNRTI (NVP or EFV). 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. This approach has been shown to be safe and effective in the trial setting for children with sustained virological suppression achieved after receiving LPV/r-based first-line therapy, especially in the absence of HIV resistance to NNRTI before initiating ART (148,161). However, this approach may also add complexity to treatment programmes and may require access to virological monitoring. This strategy may therefore only be viable in settings in which viral load and/or genotype testing are available.

In settings in which none of these approaches is feasible or affordable, an NVP-based regimen provides an effective alternative, especially given the availability of two- and three-drug fixed-dose combinations. As observed in a recent randomized controlled trial, good virological outcomes (83% had a viral load less than 400 copies per ml for 3.7 years irrespective of age) can be achieved by starting children on ABC, 3TC and an NNRTI (163). EFV has not been used in this age group, however during the finalization of these guidelines the United States Food and Drug Administration approved this drug for children 3 months to 3 years old weighing more than 3.5 kg. Dosing for this population is provided in Annex 7 and further guidance on how best to use this drug as an alternative to LPV/r or NVP will be provided when additional data are available.

Choice of NRTIs

The choice of NRTIs should aim to construct a robust and durable backbone that balances minimizing toxicity, minimizing cost and maximizing feasibility. Only limited evidence (164) from head-to-head comparisons informs the selection of NRTIs (AZT or ABC) combined with 3TC in a triple ART regimen. However, the choice of first-line NRTIs affects second-line ART, and failure of AZT is known to result 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). 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 not be as critical. By contrast, HIV resistance to ABC does not lead to resistance to thymidine analogues and preserves or even increases the susceptibility of HIV to AZT and d4T for second-line use (159).

Although ABC may be preferable in the interest of ART sequencing (159,165) and harmonizing with the regimens for older children, availability is limited in resource-limited settings. In addition, the cost of ABC may be a significant barrier to adopting it in many countries, especially when combined with LPV/r. Definitive data on the comparative efficacy of ABC and AZT are expected from ongoing studies (166).

Since 2010, WHO has recommended that d4T be phased out because of its known long-term toxicity. However, in settings in which using AZT may not be advisable because of the high risk of anaemia (such as malaria-endemic settings) and in which ABC is not available, d4T remains an option within the limited treatment options for this specific age group. d4T also remains important in the situation in which toxicity to AZT is suspected or confirmed and ABC cannot

be used. However, the duration of therapy with this drug should be limited to the shortest time possible. Box 10.7 provides guidance on phasing out d4T.

In developing these recommendations, the Guidelines Development Group emphasized:

- the importance of potent, first-line regimens for which there is evidence of better virological response as indicated by randomized controlled trials in this age group;
- the need to address the increasing evidence of HIV resistance to NNRTI among children younger than 18 months, especially in the context of the recommendation to treat pregnant women with EFV-based regimens for PMTCT;
- the desirability of having one preferred regimen for children younger than three years while providing alternative strategies that remain less costly, preserve second-line options and address feasibility concerns;
- anticipating the availability of new formulations during the next few years (sprinkles or sachets containing LPV/r);
- using 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;
- identifying a subset of children who can benefit from alternative strategies to preserve PIs for use in second-line ART as indicated by a randomized trial; and
- identifying a manageable regimen, such as ABC + 3TC + AZT, for use in the context of TB co-treatment that can maintain good clinical and immunological response after virological suppression on standard ART.

Clinical considerations

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important consideration for clinicians and other health care providers relates to the challenges of providing LPV/r for young children. When clinicians anticipate significant difficulties in dealing with storing or administering LPV/r, using NVP (especially an NVP-based fixed-dose combination) can be considered. In addition, using LPV/r oral liquid should be avoided in premature babies or in full-term babies younger than 14 days (167). Dosing for children younger than six weeks should be calculated based on body surface area (Annex 3).

Key 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 for PMTCT still needs to be fully explored outside trial settings. In addition, more evidence is needed to inform the optimal choice of NRTIs and to confirm the safety of EFV-containing regimens, as a first-line option or within PI-sparing strategies in the absence of viral load or genotyping. Studies to fully address the long-term metabolic implications of using LPV/r-based regimens for infants and young children are also needed.

7.2.4 First-line ART for children three years and older (including adolescents)


NEW

New recommendations

- For children infected with HIV three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (*strong recommendation, low-quality evidence*).

Special note: In determining the choice of NNRTI for first-line therapy, national programmes should consider the dosing characteristics of EFV (once-daily) and NVP (twice-daily) and how this aligns with the NRTI backbone. For example, NVP may be a better choice if the recommended regimen is a twice-daily option using a fixed-dose combination.

- For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order:

- ABC + 3TC
- AZT or TDF + 3TC (or FTC)

(*Conditional recommendation, low-quality evidence*).

Special note: Consideration should be given to the relative merits of ABC versus TDF versus AZT for this population. There is no definitive evidence to make a preferred recommendation, and each option has its respective risks and benefits. ABC can be used once daily, is available across age groups as a fixed-dose combination with 3TC and harmonizes with TDF from a resistance perspective (168). AZT has been widely used and is available as dual and triple fixed-dose combinations with NVP but is dosed twice daily and can cause severe anaemia. TDF has recently been approved for use in children (169), and the advantages include once-daily dosing. However, paediatric TDF formulations are not widely available, experience with TDF in children is limited and there are concerns about the long-term effects of bone toxicity (170,171). Considerations that support the adoption of TDF as the national recommendation include: the national programme uses TDF for adults and pregnant women and a suitable TDF fixed-dose combination formulation for children is available.

- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:

- TDF + 3TC (or FTC)
- AZT + 3TC
- ABC + 3TC

(*Strong recommendation, low-quality evidence*).

Special note: TDF-containing fixed-dose combinations are currently only available in adult, unscored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents.

ABC or boosted PIs can be used in special circumstances.

Table 7.11 Summary of recommended first-line ART regimens for children and adolescents

	Children 3 years to less than 10 years and adolescents <35 kg	Adolescents (10 to 19 years) ≥35 kg
Preferred	ABC ^a + 3TC + EFV	TDF + 3TC (or FTC) + EFV ^a
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances^c	d4T ^b + 3TC + EFV d4T ^b + 3TC + NVP	ABC + 3TC + EFV ABC + 3TC + NVP

^a These recommendations apply to children and adolescents who are initiating first-line ART. Children and adolescents who are already taking ABC-containing regimens can safely substitute TDF for ABC, if this is needed for programmatic reasons. Children and adolescents who are on d4T-containing regimens without evidence of treatment failure can safely substitute ABC or TDF for d4T. Despite a lack of direct evidence, consideration can also be given to substituting ABC or TDF for AZT with the goal of simplifying and harmonizing treatment regimens across age groups. Including TDF in initial ART regimens for children with HBV coinfection offers the potential advantage of reducing the selection of HIV resistance to 3TC that may compromise future options for HBV treatment.

^b d4T use should be restricted to situations in which toxicity to AZT is suspected or confirmed and access to ABC or TDF is lacking. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

^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.

Background

Despite increased access to early infant diagnosis and the widespread availability of several child-friendly fixed-dose combinations, ART coverage among children lags significantly behind that of adults. Treatment recommendations for children should be easy to implement at all levels of the health system, including the primary care level, and by all ART service providers, rather than paediatric specialists alone.

The 2010 WHO ART guidelines for children three years and older (105) recommended starting with an NVP- or EFV-containing regimen combined with an NRTI backbone. The recommended NRTI backbones, in preferential order, were 3TC + AZT or 3TC + ABC or 3TC + d4T. For adolescents with HBV, the preferred backbone was TDF + FTC or 3TC. The new recommendations in the 2013 guidelines are based on new evidence on the preferred NRTIs and NNRTIs to use in this group of children.

Rationale and supporting evidence

The United States Food and Drug Administration (172) and European Medicines Agency (173) approved using TDF for children older than two years of age, 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 (169). In addition, the fact that HIV resistance to TDF – specifically K65R – can enhance the antiviral effect of AZT may make TDF a good choice for first-line therapy in terms of sequencing NRTIs from first- to second-line regimens (165,174–176). However, experience with TDF in young children is limited, and although TDF is known to reduce bone mineral density, it is not clear whether this is permanent



and how it might affect future patterns of growth and fracture risk, as highlighted in the values and preferences survey among health workers. In addition, TDF formulations for younger children are not widely available and to date there are no TDF-containing paediatric fixed-dose combinations. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been more thoroughly studied in children and is generally well tolerated. ABC is also available in paediatric fixed-dose combination formulations but is significantly more costly. Further, among people with HLA-B*5701, it can cause potentially fatal hypersensitivity; although this is very rare among African children, it can affect up to 3–4% of Caucasian and Asian children (177).

A systematic review based on observational data indicates that EFV has a better short-term toxicity profile and is associated with better virological response than NVP (121,178). Most children currently receiving ART are treated with regimens that contain NVP, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. The primary reason for this discrepancy relates to the relative availability of NVP or EFV in fixed-dose combinations for children or adults. 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.

In developing these recommendations, the Guidelines Development Group emphasized:

- using potent first-line regimens;
- the convenience of once-daily dosing and the use of fixed-dose combinations whenever possible;
- using non-thymidine analogues – either ABC or TDF – in first-line regimens to maximize the response to AZT in second-line ART; and
- providing treatment recommendations for older children and adolescents that are aligned with those for adults.

Clinical considerations for scaling up ART for children

Section 10.6 (Implementations considerations for key recommendations, Box 10.6) discusses implementation considerations relevant to programme managers. An important 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 fixed-dose combinations become available and programmes transition into different first-line regimens. Modifying the ART regimens of clinically stable people can be considered to simplify treatment management and harmonize the ART regimens in use. Table 7.12 summarizes considerations for simplifying and harmonizing ART for children with no history of treatment failure.

Table 7.12 Considerations for simplifying and harmonizing ART for children with no history of treatment failure^a on any regimen

Regimen containing:	Guidance	Individual advantages	Programmatic advantages
d4T	Change d4T to age-appropriate NRTI in accordance with the regimen recommended by the national programme	<ul style="list-style-type: none"> • Reduced risk of d4T-related toxicity • May improve adherence as a result of once-daily dosing (if ABC or TDF are chosen) 	<ul style="list-style-type: none"> • Aligned with adult regimens
LPV/r	No need to change, but consider substituting NVP or EFV for LPV/r if there is sustained virological response on LPV/r	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • May improve adherence as a result of once-daily dosing (if on EFV) • May reduce the risk of exacerbating anaemia 	<ul style="list-style-type: none"> • Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	<ul style="list-style-type: none"> • Fixed-dose combinations can be used (if also on EFV) 	<ul style="list-style-type: none"> • Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV particularly from age 3 years	<ul style="list-style-type: none"> • May improve adherence as a result of once-daily dosing (if combined with ABC or TDF) 	<ul style="list-style-type: none"> • Aligned with adult regimens

^aDefined based on the criteria for treatment failure adopted nationally.

Key research gaps

The long-term efficacy and safety of TDF, ABC and EFV and the recommended combination need further investigation. More data are needed on the bone, growth and renal toxicity profiles of TDF in children and adolescents, especially in the context of malnutrition and stunting. Similarly, adverse events associated with EFV during adolescence, such as central nervous system 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.

7.2.5 TB co-treatment in children with HIV



TB is one of the most common opportunistic infections affecting children with HIV. Selecting regimens that are compatible with TB therapy is therefore essential. Interactions between rifampicin and LPV/r or NVP mean that co-treatment in children under three years is challenging, but a recent large randomized controlled trial (163) of ART in children has generated preliminary evidence on the efficacy of triple nucleoside therapy which, despite limited data in the context of TB co-treatment, offers a suitable option for children who require TB treatment while already receiving ART (Table 7.13).

The recommended regimens for children diagnosed with TB and starting ART are consistent with the 2010 recommendations and are summarized in Table 7.13, together with broader guidance on choosing regimens for co-treatment of HIV and TB.

Table 7.13 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		Two NRTIs + NVP, ensuring that dose is 200 mg/m ² or 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 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

Table 7.13 (continued)

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 Substitute NVP for LPV/r, ensuring that dose is 200 mg/m ² or Continue LPV/r; consider 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; consider 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 consider 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 new dosing guidelines (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

^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 (163), this regimen should be considered as the preferred option for children younger than three years who are receiving a LPV/r-based regimen when starting TB treatment. The United States Food and Drug Administration 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. An EFV-based regimen in children under 3 years is still not recommended as pharmacokinetics 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 a 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 (179), and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.



7.3 Monitoring response to ART and the diagnosis of treatment failure



7.3.1 Laboratory monitoring before and after initiating ART

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ARV drugs. Table 7.14 summarizes recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for coinfections and noncommunicable diseases.

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology ^a HCV serology <i>Cryptococcus</i> antigen if CD4 count ≤ 100 cells/mm ³ ^b Screening for sexually transmitted infections Assessment for major noncommunicable chronic diseases and comorbidities ^c
Follow-up before ART	CD4 cell count (every 6–12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT ^d Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF ^e Alanine aminotransferase for NVP ^f
Receiving ART	CD4 cell count (every 6 months) HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF ^e
Treatment failure	CD4 cell count HIV viral load	HBV (HBsAg) serology ^a (before switching ART regimen if this testing was not done or if the result was negative at baseline)

^a If feasible, HBsAg testing should be performed to identify people with HIV and HBV coinfection and who therefore should initiate TDF-containing ART.

^b Can be considered only in settings with a high prevalence of cryptococcal antigenaemia (>3%) (180).

^c Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

^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 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/mm³ and HCV coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

7.3.2 Monitoring the response to ART and the diagnosis of treatment failure

New recommendations



- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure (*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*).

Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs. Viral load testing is usually performed in plasma; however, certain technologies that use whole blood as a sample type, such as laboratory-based tests using dried blood spots and point-of-care tests, are unreliable at this lower threshold, and where these are used a higher threshold should be adopted.

Viral load should be tested early after initiating ART (at 6 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 virological failure where possible.

Background

Monitoring individuals receiving ART is important to ensure successful treatment, identify adherence problems and determine whether and which ART regimens should be switched in case of treatment failure. Before 2010, WHO guidelines on ART recommended using clinical outcomes and CD4 count for routinely monitoring the response to ARV drugs. However, the value of viral load testing as a more sensitive and early indicator of treatment failure is increasingly recognized and is the gold standard for monitoring the response to ARV drugs in high-income settings.

The 2010 WHO guidelines recommended that countries consider phasing in viral load testing to monitor the response to ART and use a viral load threshold above 5000 copies/ml in an adherent person with no other reasons for an elevated viral load (such as drug interactions, poor absorption and intercurrent illness). However, most ART programmes in resource-limited settings still do not have access to viral load testing and continue to rely on clinical and immunological monitoring. This limited use of viral load monitoring has been identified as a key reason for the lower than expected rates for switching ART regimens in resource-limited settings.

Rationale and supporting evidence

Although evidence from clinical trials for a survival benefit of viral load testing is limited, it can provide an early indication of treatment failure, and the 2013 guidelines strongly recommend using it for detecting virological failure and/or confirming treatment failure among people with evidence of clinical and/or immunological failure (Table 7.15). Since several clinical and epidemiological studies show that the risk of HIV transmission is very low when the viral load is lower than 1000 copies/ml (181), the Guidelines Development Group also recommended reducing the viral load threshold for treatment failure from 5000 copies/ml to 1000 copies/ml.




Table 7.15 WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	<p>Adults and adolescents</p> <p>New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)^a after 6 months of effective treatment</p>	<p>The condition must be differentiated from immune reconstitution inflammatory syndrome^b occurring after initiating ART</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure^a</p>
	<p>Children</p> <p>New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment</p>	
Immunological failure	<p>Adults and adolescents</p> <p>CD4 count falls to the baseline (or below)</p> <p>or</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</p> <p>A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure (182). The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure</p>
	<p>Children</p> <p>Younger than 5 years</p> <p>Persistent CD4 levels below 200 cells/mm³ or <10%</p> <p>Older than 5 years</p> <p>Persistent CD4 levels below 100 cells/mm³</p>	
Virological failure	<p>Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support</p>	<p>The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined</p> <p>An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed</p> <p>Assessment of viral load using DBS and point-of-care technologies should use a higher threshold</p>

^a See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 1.

^b Section 6.1 discusses immune reconstitution inflammatory syndrome.

Virological monitoring (viral load) versus immunological (CD4) and clinical monitoring (WHO clinical staging)

The main rationale for recommending viral load monitoring as the preferred approach compared with immunological and clinical monitoring is to provide an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation of drug-resistance mutations and improving clinical outcomes. Measuring viral load can also help to discriminate between treatment failure and non-adherence (183) and can serve as a proxy for the risk of transmission at the population level (76).

There is still limited evidence to support any additional survival benefit of viral load monitoring over CD4 and/or clinical monitoring among individuals with HIV receiving ART. A systematic review identified three randomized clinical trials on virological versus immunological and clinical monitoring (184–186) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Compared with immunological and/or clinical monitoring, adding viral load monitoring has not been associated with reduced mortality. In one of these trials (185), no significant difference in the incidence of clinical failure, switching to second-line regimens and resistance mutations was found. One cohort modelling study among adults also found that adding virological monitoring to clinical and/or immunological criteria made no difference in mortality or new AIDS-defining illnesses (187). Although randomized controlled trials have not yet shown that viral load monitoring translates into survival gains, follow-up has been limited (less than five years) and longer follow-up is required to examine the longer-term impact on survival, resistance profile and HIV transmission.

A systematic review provided moderate-quality evidence that current WHO guidelines on immunological and clinical monitoring for treatment failure have poor sensitivity and lower positive predictive value for identifying virological failure in adults (187–200) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). This means that many of the people who are identified with immunological failure in fact have adequate virological suppression and risk being misclassified as having treatment failure and switched unnecessarily to second-line therapy. A further systematic review using data in children also provided moderate-quality evidence that immunological criteria (201–204) have low sensitivity and positive predictive value for identifying children with virological failure.

Immunological monitoring versus clinical monitoring

Where viral load monitoring is unavailable, clinical monitoring and CD4 monitoring are recommended (205). Although a systematic review of two randomized controlled trials (184,206) provide moderate-quality evidence of mortality and morbidity benefits with CD4 and clinical monitoring compared with routine clinical monitoring in adults receiving ART, these trials largely focused on CD4 and clinical monitoring in people who initiated ART at CD4 counts below 200 cells/mm³ (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Existing immunological and clinical criteria may have decreased sensitivity and specificity to detect treatment failure in people who initiate ART at higher CD4 counts, and more accurate immunological criteria for these people remain to be identified.

Routine versus targeted viral load monitoring to detect treatment failure

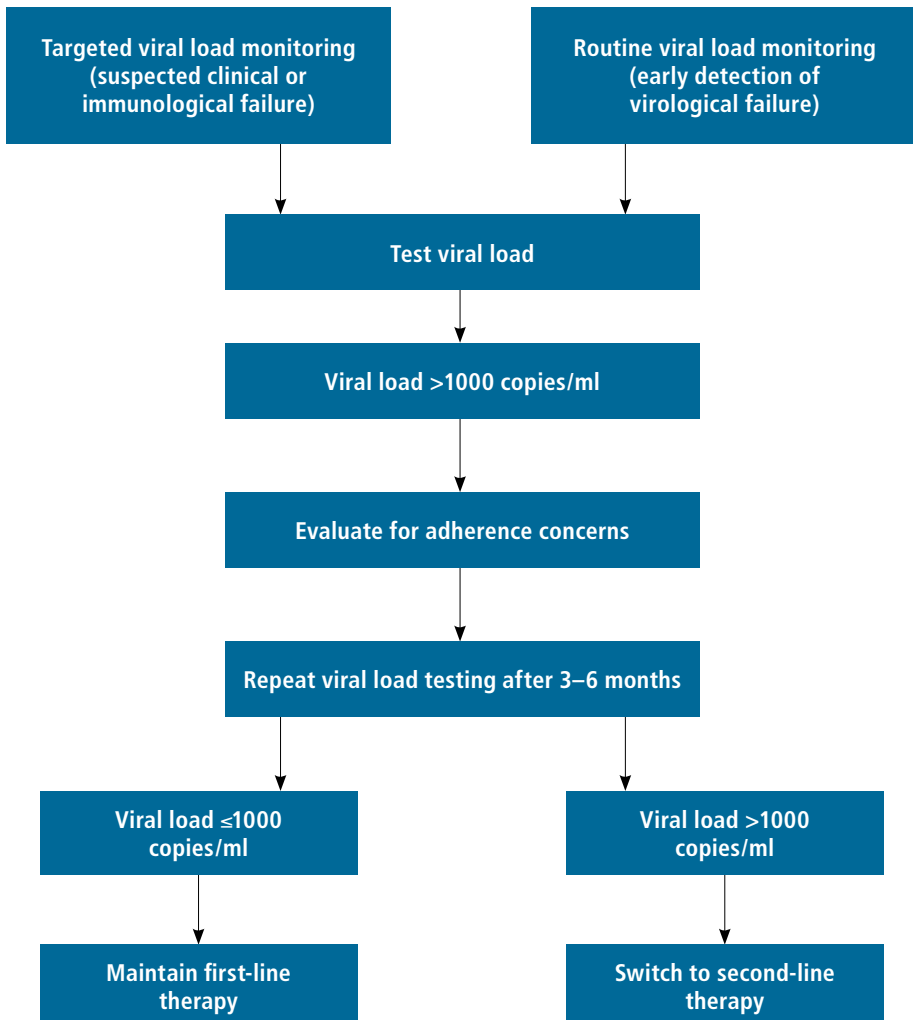
Viral load should be monitored routinely (every 6–12 months) to enable treatment failure to be detected earlier and more accurately. In settings with limited access to viral load testing, a targeted viral load strategy to confirm failure suspected based on immunological or clinical criteria (Table 7.15) should be used to avoid unnecessary switching to second-line ART. Targeted viral load monitoring is less costly than routine viral load testing, but as with clinical and immunological monitoring, 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 virological failure

The optimal threshold for defining virological failure and for switching ART regimens has not been established. The rationale for the threshold of 1000 copies/ml was based on two main sources of evidence. First, 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 unless low-level viraemia is sustained (207). Second, clinical and epidemiological studies show that the risk of HIV transmission and disease progression is very low when the viral load is lower than 1000 copies/ml (181,208,209).

Most standard blood and plasma viral load platforms available and being developed have good diagnostic accuracy at this lower threshold. However, the sensitivity of dried blood spots for viral load determination at this threshold may be reduced (210,211). Programmes relying on dried blood spot technology for viral load assessment may therefore consider retaining the higher threshold (3000–5000 copies/ml) until sensitivity at lower thresholds is established (212–214).

Fig. 7.1 Viral load testing strategies to detect or confirm treatment failure and switch ART regimen in adults, adolescents and children



Special considerations for children

These guidelines aim to harmonize monitoring approaches for children with those recommended for adults. As more children start ART earlier and at higher CD4 counts, viral load monitoring to detect treatment failure and lack of adherence will be increasingly beneficial. In addition, viral load may be instrumental for implementing treatment strategies to preserve second-line options as children age (such as switching from LPV/r to an NNRTI once virological suppression is sustained) (see section 7.3.3).

Evidence from one randomized controlled trial conducted in several countries (including the United States of America, European countries, Brazil and Thailand, PENPACT1 (158), suggests that switching treatment at lower viral load thresholds does not lead to better clinical and virological outcomes but does minimize the development of HIV drug resistance, especially for NRTIs when an NNRTI-based regimen is used. In this context, alignment with the viral load thresholds recommended for adults is advisable. However, viral load results in the first six months after initiating ART should be interpreted carefully, as infants and young children may require longer to achieve virological suppression because of high baseline viral load.

The recommendation to initiate ART for all children younger than five years of age regardless of clinical and immunological criteria means that CD4 cell count testing at baseline is not required for initiating ART. However, where viral load monitoring capacity is limited or unavailable, CD4 monitoring – including baseline measurement and CD4 percentage for children younger than five years of age – will still be important for monitoring treatment response.

As in the case of adults, lack of viral load or CD4 capacity should not prevent children from starting ART. The results from a recently completed trial show that mortality and disease progression are comparable between clinical monitoring and laboratory monitoring, especially in the first year of treatment (163).

Clinical considerations for scaling up viral load testing

Section 10.6 (see section on implementation considerations for key recommendations, Box 10.3) discusses clinical and implementation considerations relevant to programme managers. Additional implementation considerations for clinicians and health workers include the following.

- **Access to ART should be the first priority.** Lack of laboratory tests for monitoring treatment response should not be a barrier to initiating ART.
- **Setting priorities.** If viral load testing is limited, it should be phased in using a targeted approach to confirm treatment failure. This may be especially relevant in populations receiving ARVs to reduce HIV transmission, such as pregnant and breastfeeding women and among serodiscordant couples, for whom sustained viral load suppression is critical to the efficacy of the strategy.

7.4 Monitoring and substitutions for ARV drug toxicities



7.4.1 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.

7.4.2 Major types of ARV toxicities

The 2010 WHO ART guidelines recommended 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 were advised (but not required) for specific high-risk people using certain drugs. Table 7.16 lists key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment. More data are needed on whether routine or periodic laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all individuals or only people at higher risk.

Table 7.16 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 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T If ABC is being used in second-line ART, substitute with TDF
	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider integrase inhibitors
ATV/r	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Nephrolithiasis and risk of prematurity	Risk factors unknown	
AZT	Anaemia, neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count ≤ 200 cells/mm ³	If AZT is being used in first-line ART, substitute with TDF or ABC If AZT is being used in second-line ART, substitute with d4T
	Lactic acidosis or severe hepatomegaly with steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	

Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
d4T	Peripheral neuropathy, lipatrophy or lipodystrophy	Older age CD4 count ≤ 200 cells/mm ³ Concomitant use of isoniazid or ddl	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If DRV/r is being used in second-line ART, substituting with ATV/r or LPV/r can be considered. When it is used in third-line ART, limited options are available
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	NVP. If the person cannot tolerate either NNRTI, use boosted PIs
	Hepatotoxicity	Underlying hepatic disease – HBV and HCV coinfection Concomitant use of hepatotoxic drug	
	Convulsions	History of seizure	
	Hypersensitivity reaction, Stevens-Johnson syndrome	Risk factors unknown	
	Potential risk of neural tube birth defects (very low risk in humans) (122,140) Male gynaecomastia		
ETV	Severe skin and hypersensitivity reactions	Unknown	Limited options are available



Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	If LPV/r is used in first-line ART for children, use an age-appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT interval	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea	Risk factors unknown	
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 >250 cells/mm ³ in women CD4 >400 cells/mm ³ for men First month of therapy (if lead-in dose is not used)	EFV. If the person cannot tolerate either NNRTI, use boosted PIs
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome)	Risk factors unknown	
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available

Table 7.16 (continued)

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF (169)	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease Older age BMI <18.5 (or body weight <50 kg) Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC If TDF is being used in second-line ART (after d4T + AZT use in first-line ART), substitute with ABC or ddl
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir)

7.4.3 Monitoring TDF toxicity

TDF nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease (130).

According to a systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes), no studies have properly compared monitoring strategies for people receiving TDF, such as routine toxicity monitoring versus care with no monitoring or incidental monitoring in case of perceived clinical need. One clinical trial (the DART trial) comparing laboratory with clinical monitoring showed that individuals receiving TDF have an increased risk of reduced estimated glomerular filtration rate but no increased risk of renal failure over a median five years of follow-up (low-quality evidence). A few observational cohort studies reported that using TDF was associated with an increased risk of chronic kidney disease. However, the exposure time to TDF in all these studies was considered too short to indicate a long-term increased risk for renal failure, the occurrence of bone fractures or changes in fat distribution.

The best parameter for TDF-related renal toxicity monitoring needs to be evaluated; meanwhile, laboratory monitoring using a creatinine test is not mandatory to initiate treatment with TDF. However, it is advisable for high-risk people (those who are older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) to detect and limit further progression of renal impairment. High frequency of glycosuria has also been found in people without diabetes biopsied for TDF nephrotoxicity with increased serum creatinine compared with TDF-treated people with a normal glomerular filtration rate, suggesting that dipstick glycosuria may be a cost-effective screening test for serious TDF-induced kidney injury (215).

TDF-related decreases in bone mineral density have been observed in children, although it is unclear how reducing bone mineral density might impact future growth patterns or the risk of bone fracture. In addition, an accurate and feasible method to measure bone mineral density still needs to be identified, and significant uncertainty remains around how best to monitor TDF-related bone toxicity among children. Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while children are receiving treatment with TDF (169).

Clinical considerations

- Laboratory monitoring is not mandatory to initiate treatment with TDF.
- Routine blood pressure monitoring may be used to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine test is routinely available, use the estimated glomerular filtration rate^a at baseline before initiating TDF regimens.
- Do not initiate TDF when the estimated glomerular filtration rate is <50 ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Monitor growth in children using TDF.

^aUsing the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) formulas for estimation. An online calculator is available at <http://nephron.com/cgi-bin/CGSI.cgi>.

CG formula: $eGFR = (140 - \text{age}) \times (\text{Wt in kg}) \times 0.85 \text{ (if female)} / (72 \times \text{Cr in mg\%})$.

MDRD formula: $eGFR = 175 \times \text{SerumCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if patient is black)} \times 0.742 \text{ (if female)}$.

Key research gaps

More data are needed on how to best monitor renal function in people using TDF-containing regimens (whether toxicity monitoring should be routine or targeted in high-risk groups, with alternative drugs for high-risk people). In addition, more data are needed to understand the frequency and clinical relevance of reduced bone mineral density in children. More accurate and affordable methods to monitor bone toxicity should be identified for this specific population.

7.4.4 Toxicity monitoring for other ARV drugs

AZT

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin is recommended before initiating ART, mainly among adults and children with low body weight, low CD4 counts and advanced HIV disease. People with HIV with severe anaemia at baseline (haemoglobin <7.0 g/dl) should avoid AZT as first-line therapy.

NVP

The laboratory measurement of liver enzymes has very low predictive value for NVP-containing regimens. However, monitoring hepatic enzymes is recommended if feasible, especially for women with HIV who have CD4 cell counts >250 cells/mm³ and individuals with HIV who are coinfecting with HBV or HCV. Section 7.2.1 provides more information on the safety of NVP among individuals with high CD4 cell counts.

EFV

The main type of toxicity of EFV is central nervous system side effects, which typically resolve after a few weeks. However, in some cases, they can persist for months or not resolve at all. Despite concerns about the potential risk of teratogenicity associated with using EFV during pregnancy, a recent meta-analysis found no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV drugs (122). Section 7.3.2 provides more information on the safety of EFV among pregnant women.

7.4.5 Drug substitutions for ARV drug toxicity

Drug regimen or single agent substitutions may be required for drug toxicity and to avoid drug interactions. Section 7.4.3 provides guidance on managing specific types of ARV drug toxicity.

Clinical considerations

- Delaying substitutions or switches when there are severe adverse drug effects may cause harm and may affect adherence, leading to drug resistance and treatment failure.
- When drug interruptions are required, such as for severe and life-threatening adverse events related to toxicity, it is important to consider the various half-lives of ARV drugs. For example, when a NNRTI needs to be discontinued, a staggered approach should be used by prolonging the use of the NRTI backbone for two to three weeks. Alternatively, the NNRTI could be temporarily substituted with a boosted PI.

7.4.6 Drug substitutions for ARV drug toxicity

Providers should be aware of all drugs that people with HIV are taking when ART is initiated and new drugs that are added during treatment maintenance. There are several key drug interactions (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes).

WHO TB treatment guidelines review key considerations for managing coinfection with TB and HIV (216). A key contraindicated drug combination includes rifampicin and PIs. When people coinfecting with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment, if the boosting dose of RTV is increased or double the standard dose of LPV/r is used (see section 7.6.1). For children, using a triple NRTI regimen (such as AZT + 3TC + ABC) should also be considered.

Ribavirin and peginterferon alpha-2a are often used for treating HCV. Administration of these agents with AZT has been associated with an increased risk of anaemia and hepatic decompensation. People coinfecting with HCV and HIV and receiving AZT may need to be switched to TDF.

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 fluconazole) could be used to ensure adequate treatment of fungal infections among people with HIV.

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria (217). One recommended artemisinin-based combination therapy is artesunate and amodiaquine. EFV increases the concentrations of amodiaquine and has been associated with significant elevations of liver transaminases. Alternative artemisinin-based combination therapies (such as artemether plus lumefantrine, artestunate plus mefloquine or artesunate plus sulfadoxine-pyrimethamine) could be used to prevent severe toxicity in people with HIV.

WHO recommends methadone and buprenorphine for treating opioid dependence (218). Co-administering EFV decreases methadone concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People receiving methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose.

ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives (219). Limited data suggest potential drug interactions between many ARV drugs (especially some NNRTIs and RTV-boosted PIs) and estrogen-based hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the ARV drug. 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 to compensate for any possible reduction in the effectiveness of the hormonal contraception.

Concomitant use of boosted PIs and NNRTI 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.

WHO recommends using statins for people with a 10-year cardiovascular risk exceeding 30% (220). Boosted PIs may lead to increased concentrations of lovastatin and simvastatin. Increased concentrations may increase the risk of developing serious adverse events such as myopathy (including rhabdomyolysis). Alternative dyslipidaemia agents should be used to prevent severe toxicity among people with HIV.

Table 7.14 Key ARV drug interactions and suggested management^a

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and peg-interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T
Boosted PI (ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)
	Estrogen-based hormonal contraception	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
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
NVP	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

^a This table was developed using the University of Liverpool's drug interaction charts, a resource which can be found online at www.hiv-druginteractions.org. A more comprehensive table of ARV drug interactions is available on the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).

Box 7.2 Surveillance of ARV drug toxicity

WHO commissioned systematic reviews on specific types of toxicities associated with key ARV drugs and laboratory monitoring strategies to consolidate and update technical guidance (140,169). The reviews highlighted remaining evidence gaps in the potential increased risk of toxicity associated with the long-term use of ARV drugs, the use of ARV drugs during pregnancy and in breastfeeding mothers, children and adolescents and populations with associated risk factors and in laboratory monitoring for toxicity.

The available evidence is limited to studies with limited sample size or short duration. It is essential to monitor the use of ARV drugs in resource-limited countries where toxicities may present a different pattern in association with environmental or behavioural factors, the prevalence of other conditions and where ARV drugs are used in association with other medicines. Implementing toxicity surveillance will provide the opportunity to produce evidence on specific types of toxicity, increase confidence in the use of the drugs, identify populations with risk factors and plan preventive strategies.

The Guidelines Development Group encouraged WHO to strengthen toxicity surveillance activities to increase evidence on toxicity in key areas. These areas cover a potential increased risk of toxicity associated with the long-term use of ARV drugs, renal and bone toxicity associated with using TDF among adults and children, the safety of using EFV- and TDF-containing regimens during pregnancy and in breastfeeding mothers and using TDF among children, adolescents and populations with associated risk factors. Developing laboratory markers to monitor renal function among people using TDF is another important area for research.

Several toxicity surveillance activities have already started with WHO support, using standardized approaches at sentinel sites in resource-limited settings. Targeted and systematic surveillance is being conducted in Côte d'Ivoire to monitor renal toxicity associated with TDF in first- and second-line regimens, with an assessment of laboratory monitoring needs in three sentinel sites. A similar approach is being implemented in Viet Nam to assess renal toxicity associated with TDF and central nervous system toxicity associated with EFV in people who use ARV drugs to prevent HIV infection, such as in serodiscordant couples. In the Lao People's Democratic Republic, anaemia associated with AZT and hypersensitivity associated with NVP are monitored using a targeted and systematic surveillance approach. In Malawi, a surveillance programme will monitor infant growth, following mothers who are breastfeeding and receiving TDF.

The implementation of a pregnancy registry, including a surveillance programme for birth defects, is recommended where feasible to assess the safety of ARV drugs and any other medicines during pregnancy and risk factors for adverse pregnancy outcomes, including maternal health outcomes, premature births, stillbirths, low birth weight and congenital abnormalities. WHO, the United States President's Emergency Plan for AIDS Relief, the United States Centers for Disease Control and Prevention and the United States National Institutes of Health support the establishment of ARV pregnancy registries and birth defect surveillance in sentinel sites in Malawi, South Africa and Uganda to assess the use of EFV-containing regimens at large scale among pregnant women.

Surveillance of ARV drug toxicity will help to better understand the long-term risk of ART toxicity and optimize the management of ARV drugs for HIV treatment and prevention in all populations.

7.5 What ART regimen to switch to (second-line ART)

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART. In children using a PI-based regimen for first-line ART, switching to NNRTI or maintaining the PI regimen is recommended according with age (Table 7.18).

Table 7.18 Summary of preferred second-line ART regimens for adults, adolescents, pregnant women and children

Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC + LPV/r ^a AZT + 3TC + ATV/r ^a	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	If a NNRTI-based first-line regimen was used		ABC + 3TC + LPV/r ^b	ABC + 3TC + LPV/r ^b TDF + 3TC (or FTC) + LPV/r ^b
	If a PI-based first-line regimen was used	<3 years	No change from first-line regimen in use ^c	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

^a DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

^b ATV/r can be used as an alternative to LPV/r for children older than six years.

^c Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

7.5.1 Second-line ART for adults and adolescents



New recommendations

NEW

- Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + 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*).

Table 7.19 Summary of preferred second-line ART regimens for adults and adolescents

Target population	Preferred second-line regimen ^a	
Adults and adolescents (≥10 years)	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
Pregnant women	Same regimens 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) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)	

^aABC and ddI can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

Background

The 2010 WHO ART guidelines recommended that second-line adult regimens include a boosted-PI plus two NRTIs (determined by the drug used in first-line therapy). Those guidelines placed a high value on using simpler second-line regimens, ideally heat-stable formulations and fixed-dose combinations (once-daily formulations when possible).

Except for the recommendation for people with HIV and TB, the recommendations in 2013 remain unchanged from the 2010 recommendations.

Rationale and supporting evidence

Protease Inhibitor (PI) options for second-line ART

Since 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 is an alternative but is currently not available as a fixed-dose combination, although one is in development. The other PIs (FPV/r, IDV/r and SQV/r) are not available as heat-stable fixed-dose combinations and/or are associated with high pill burden and higher frequency of side effects.

The Guidelines Development Group emphasized the importance of simplifying second-line ART by reducing the pill burden and limiting the number of preferred second-line regimens that could be used across populations (adults, adolescents, children, pregnant women and people coinfecting with TB, HBV and HCV). The use of less toxic, more convenient and more efficacious heat-stable fixed-dose combinations was also considered critical.

A systematic review (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes) of data from six clinical trials comparing drugs used for second-line ART (ATV/r, LPV/r and DRV/r) concluded that there was no evidence to support changing the recommendation in the 2010

NEW



guidelines (221–226). These studies showed low- to very-low-quality evidence (downgraded in the GRADE evaluation primarily for indirectness and imprecision) for using ATV/r or DRV/r (once-daily) over LPV/r (twice-daily) or vice versa as preferred boosted PI options. ATV/r was considered to be comparable to LPV/r in one trial among ART-experienced individuals (221). In a trial among ART-naive individuals, ATV/r showed a better virological response and better retention in care when compared with LPV/r (224). In two studies, people receiving DRV/r-containing regimens also showed better virological response and retention in care than people receiving LPV/r, both in treatment-naive and experienced people (222,226). This evidence was downgraded to low or very low quality, primarily for indirectness and imprecision. DRV/r has been used for second-line therapy in high-income settings. However, two key factors currently preclude DRV/r as a preferred option in these guidelines. These include the high cost and it not being available as a heat-stable fixed-dose combination. Additional research is required to better understand sequencing strategies for PIs in second- and third-line therapy. The different drug toxicity profiles of ATV/r and LPV/r, the contraindication of ATV/r and rifampicin and the lack of WHO approval for its use in children younger than six years provide additional grounds for maintaining both PIs as equal options (Table 7.20). The Guidelines Development Group recommended that DRV/r should be maintained as a preferred third-line drug. However, using it as an alternative option to LPV/r or ATV/r for second-line therapy can be considered, especially when competitively priced fixed-dose combinations are available.

NRTI backbone

The Guidelines Development Group maintained the rationale adopted in 2010, recommending drug sequencing consistent with ART-optimizing principles (in particular, availability as fixed-dose combinations and tolerability) and resistance mutation risk, based on the NRTIs used in the first-line regimen. 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 (that is, TDF), AZT should be used in second-line ART. 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, since they have no specific advantage and add complexity and cost.

For individuals coinfecting 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.

For people with active TB disease receiving rifampicin, all boosted PIs in standard doses are contraindicated because of drug interactions and significant reductions in PI plasma concentrations (227–230). In this situation, LPV/r and SQV/r may be used with an adjusted, super-boosted dose of RTV (LPV/r 400 mg/400 mg twice daily or SQV/r 400 mg/400 mg twice daily) or doubling the LPV/r daily dose (LPV/r 800 mg/200 mg twice daily), but this is associated with high levels of toxicity and requires close clinical and laboratory monitoring. The recommendation to use LPV/r 800 mg/200 mg twice daily is based on evidence graded as low-quality, and it is associated with a similar level of toxicity as LPV/r 400 mg/400 mg twice daily (230,231). However, this option may be less complex and more feasible, since LPV/r is widely available as a single formulation, whereas RTV is not. However, when rifabutin is used in place of rifampicin, all boosted PIs can be concomitantly administered in their standard doses (Table 7.20).

Clinical 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 for boosted PI and NRTI components (such as TDF + 3TC (or FTC) + ATV/r) should

be adopted. If a TDF-based regimen is failing, twice-daily dosing for boosted PI and NRTI components (such as AZT + 3TC + LPV/r) should be adopted.

Key research gaps

Several ongoing studies comparing various drugs and ARV classes (232–236) will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches (the results are expected after 2014). Further investigation is needed of the role of DRV in second- and third-line regimens (optimal dosing in adults and children, once versus twice daily, fixed-dose combinations with other boosting agents and integrase inhibitors and sequencing strategies). Several trials are underway that are examining induction and maintenance using PI/r monotherapy in maintenance. The potential of including rifabutin as part of fixed-dose combinations for TB treatment also needs to be explored.

Table 7.20 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 to 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	±	+	±
Potential for future reduction in cost	Low	Low	High
Accessibility in countries (registration status)	Low	High	Low
Availability of generic formulations	Yes	Yes	No

^a Approved only for children >6 years old.

^b Approved only for children >3 years old.

^c Only if used in higher doses.

^d A heat stable FDC is currently under development.

7.5.2 Second-line ART for children (including adolescents)



New recommendations

NEW

- After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI. *(Strong recommendation, moderate-quality evidence)*
- After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken. *(Conditional recommendation, very-low-quality evidence)*
- After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI. *(Conditional recommendation, 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)*

Table 7.21 Summary of recommended first- and second-line ART regimens for children (including adolescents)

	Children	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	No change ^a
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV
		AZT + 3TC + LPV/r	ABC or TDF ^b + 3TC + EFV
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r ^c
		TDF ^b + 3TC (or FTC) + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC ^c (or FTC) + LPV/r ^c

^a 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 the recent 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 only be given to children >2 years.

^c ATV/r can be used as an alternative to LPV/r in children older than 6 years.

Background

Recommending potent and effective second-line regimens for infants and children is especially difficult because of the current lack of experience in resource-limited settings and the limited formulations available. This highlights the importance of choosing potent and effective first-line regimens and ensuring their durability and effectiveness by optimizing adherence.

The 2010 WHO guidelines recommended a regimen based on a PI boosted with RTV and combined with two NRTIs as the second-line treatment for children who fail a regimen of two NRTIs plus an NNRTI (105). For infants and young children exposed to an NNRTI as part of PMTCT interventions and starting a PI-based regimen in first-line ART, the recommendation for second-line was to use two new NRTIs and an NNRTI, as this was the only new drug class available.

The recommendations are now better informed by paediatric clinical trial data (156,158,237) and observational data (157). The Guidelines Development Group also considered operational and programmatic issues including the availability of heat-stable formulations and fixed-dose combinations for children.

Rationale and supporting evidence

After reviewing data for adults and children and considering factors such as the availability of a heat-stable fixed-dose combination, optimal daily dose, regimen harmonization with adults, high cost and availability of alternatives, the main recommendations established in the 2010 guidelines were maintained.

For children for whom a LPV/r-based first-line regimen has failed, NNRTIs remain the only new drug class that can be introduced. Randomized data among older children (158) provide 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 (and the limited data available to inform the use of EFV) in children younger than three years (153,154) and the potential rapid re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group (238).

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 (156,237,239,240). In this context and in the absence of robust second-line alternatives such as DRV/r-containing regimens, the Guidelines Development Group recommended that children younger than three years of age should be maintained on LPV/r until the age of three years, despite treatment failure. However, a more rapid switch should be considered in situations in which failure results from poor adherence because of the poor palatability of LPV/r or in cases of advanced HIV disease. In such cases, children younger than three years should be switched to a NVP-based regimen, and close monitoring should be provided to ensure adequate adherence.

For children starting first-line ART with an NNRTI-based regimen, PI-based regimens remain the recommended choice for second-line therapy. LPV/r is the preferred option, but ATV/r and DRV/r may be considered if more appropriate formulations become available.

Despite its toxicity profile and limited role in TB and HIV coinfection, ATV/r is a promising alternative to LPV/r for children older than six years of age. ATV/r has some advantages over LPV/r, including lower cost and the potential for once-daily dosing. DRV/r is the PI of choice following LPV/r or ATV/r treatment failure and would be valuable as a third-line drug or as second-line therapy in young children for whom first-line ART with LPV/r has

NEW



failed. However, ATV/r is currently only licensed for use among children older than six years and DRV/r in children older than three years. Neither ATV/r nor DRV/r is currently available as a co-formulated fixed-dose combination for children. The Paediatric ARVs Working Group identified appropriate doses of both drugs using current WHO weight bands and simply scaling down from the current adult fixed-dose combination tablets. Validation studies are urgently needed to develop adequate paediatric formulations.

Unboosted PIs (such as fosamprenavir (FPV), DRV and ATV) and other PIs (such as IDV/r, SQV/r, FPV/r and TPV/r) are associated with reduced virological suppression, high pill burden and/or a higher frequency of side effects and are therefore discouraged (241).

Notably, liquid RTV requires cold storage, is unpalatable, has significant gastrointestinal intolerance and is poorly tolerated by infants and children. The heat-stable 100-mg fixed-dose combination tablet formulation of LPV/r for children is better tolerated but cannot be cut or crushed; many children have difficulty in swallowing this tablet whole. Data on whether LPV/r can be given once daily are expected soon from an ongoing randomized trial (242). New heat-stable paediatric sprinkle formulations appear to be a suitable alternative and will be available in the near future (243).

The sequencing of NRTI was determined based on optimizing principles for ARV drugs and the need to maximize antiviral activity despite the 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 drug (ABC or TDF) was used in the first-line regimen, AZT should be used in the second-line regimen. The added value of ddI in second-line regimens is unclear; continuing 3TC despite the likely presence of 3TC resistance is the preferred option. HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication and may also induce some degree of resensitization to AZT or TDF, although this is based on *in vitro* data (165,244).

Key research gaps

More evidence is needed to inform the choice of second-line regimens for young children for whom an LPV/r-based first-line regimen has failed. Validation studies to assess simplified dosing for ATV/r and DRV/r fixed-dose combinations are critical to ensure future effective alternatives. Innovative second-line strategies such as PI + integrase inhibitors or induction and maintenance using PI/r monotherapy among children should also be investigated.

7.6 Third-line ART



New recommendations

NEW

- 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 integrase inhibitors 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*).

Background

In 2010, WHO made recommendations on third-line ART in the context of limited evidence to guide third-line strategies. Although there were few studies of newer agents, cohort data showed high mortality among people for whom second-line ART had failed (245).

Rationale and supporting evidence

The Guidelines Development Group maintained the recommendations established in the 2010 WHO guidelines. In so doing, the Guidelines Development Group emphasized balancing the need to develop policies for third-line ART with the need to expand access to first-line and second-line ART. It also recognized that many countries have financial constraints that limit the adoption of third-line regimens.

Data from randomized controlled trials are available for DRV/r, etravirine (ETV) and raltegravir (RAL), but most studies have been conducted in well-resourced or middle- to high-income countries. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. In a published pooled subgroup analysis, DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping was shown to be superior to the control group (boosted PI + OBR plus the optimized background regimen, where the investigator selected the boosted PI) among highly treatment-experienced individuals (222). DRV/r was also shown to be non-inferior to LPV/r among treatment-experienced people after 96 weeks (223). Among individuals with limited treatment options, RAL + OBR provided better viral suppression than the OBR alone for at least 96 weeks (246,247). Similarly, ETV + OBR provided better viral suppression and improved immunological response than the optimized background regimen alone after 96 weeks (248). In people with multidrug-resistant HIV who have few remaining treatment options, the combination of RAL, ETV and DRV/r was well tolerated and was associated with a rate of virological suppression similar to that expected among treatment-naïve people (249,250).

Evidence from post-marketing reports indicates higher rates of hypersensitivity to ETV than previously reported (251). ETV + RAL is not approved for use in individuals younger than 16 years of age. There are limited data on the use of these newer drugs in infants, children and pregnancy, including very limited pharmacokinetic and safety data.

NEW


Special considerations for children

Strategies that balance the benefits and risks for children need to be explored when second-line treatment fails. For older children and adolescents who have more therapeutic options available to them, constructing third-line ARV regimens with novel drugs used in treating adults such as ETV, DRV and RAL may be possible (for details on using these drugs in children, see Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). Children on a second-line regimen that is failing with no new ARV drug options should continue with a tolerated regimen. If ART is stopped, opportunistic infections still need to be prevented, symptoms relieved and pain managed.

Clinical considerations

The criteria for diagnosing the failure of second-line ART are the same as those used for diagnosing the failure of first-line ART. The demand for second- and third-line regimens will increase as access to viral load monitoring improves and first-line ART continues to be scaled up. Although developing a policy on access to third-line ART is desirable, it should not compromise access to initiation of first-line ART. The costs of potential third-line drugs, such as DRV, ETV and RAL, are not well established in resource-limited settings but are expected to be higher than those of first- and second-line regimens.

Key research gaps

Many areas require more information to guide second- and third-line ART for resource-limited settings, including monitoring critical outcomes for people receiving second-line ART, studying once-daily dosing for DRV/r and RAL as an alternative to NRTI-based regimens in second-line ART, and developing heat-stable formulations of DRV/r. Pharmacovigilance research is needed, including studies on the long-term safety and potential drug–drug interactions with TB, malaria, hepatitis and opioid substitution therapy drugs. As the epidemic matures in low- and middle-income countries, pilot studies are urgently needed on implementing third-line ART in settings with limited capacity and resources in the health system.

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Goal of this chapter

To provide a summary of selected existing clinical recommendations and relevant resource documents on preventing and managing common coinfections and comorbidities in the context of the broad continuum of HIV care, with a focus on resource and capacity limited settings.

8 CLINICAL GUIDANCE ACROSS THE CONTINUUM OF CARE: MANAGING COMMON COINFECTIONS AND COMORBIDITIES

Introduction

Various coinfections, comorbidities and other 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 already existing WHO guidelines and related materials, focusing on the screening, prophylaxis and timing of ART for these conditions; it does not cover their broader management. Sources and links are provided for relevant guidelines, including the evidence base and rationale supporting different recommendations. The strength of recommendations and quality of evidence is rated using either the GRADE system (strong or conditional recommendations and high, moderate, low and very low quality of evidence) or an alternative grading used prior to 2008 (A (strongly recommended) to C (optional)) and I–IV (level of evidence). In some cases, the sources and web links only are provided. These recommendations were not reviewed or discussed during the 2013 guideline development process, but are included as part of the consolidation of guidance related to HIV care and ARV drugs.

8.1 Prevention, screening and management of common coinfections

8.1.1 Co-trimoxazole preventive therapy



Background

Co-trimoxazole preventive therapy (CPT) should be implemented as an integral component of a package of HIV-related services. Existing recommendations cover initiation of co-trimoxazole preventive therapy among adults, adolescents, pregnant women and children for prevention of *Pneumocystis* pneumonia, toxoplasmosis and bacterial infections, as well as benefits for malaria prophylaxis and discontinuation of co-trimoxazole preventive therapy.

Source for recommendations

Guidelines on co-trimoxazole prophylaxis for HIV-related infection among children, adolescents and adults: recommendations for a public health approach. Geneva, World Health Organization, 2006 (www.who.int/hiv/pub/plhiv/ctx/en) (1).

These recommendations will be updated in 2014.

Key selected existing recommendations

Table 8.1 shows the recommendations. Refer to the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) for methodology used in rating the quality of evidence.

Table 8.1 Criteria for initiating, discontinuing and monitoring co-trimoxazole preventive therapy according to the 2006 WHO guidelines

Age	Criteria for initiation	Criteria for discontinuation ^a	Dose of co-trimoxazole	Monitoring approach
HIV-exposed infants	In all, starting at 4–6 weeks after birth (A-III)	Until the risk of HIV transmission ends or HIV infection is excluded (A-I)	See Annex 7	Clinical at 3-monthly intervals (A-III)
<1 year	In all ^b (A-II)	Until 5 years of age regardless of CD4% or clinical symptoms ^c (A-IV) or Never (A-IV)		
1–5 years	WHO clinical stages 2, 3 and 4 regardless of CD4 % or Any WHO stage and CD4 <25% (A-I) or In all ^b (C-IV)	Never (A-IV)	See Annex 7	Clinical at 3-monthly intervals (A-III)
≥5 years, including adults	Any WHO stage and CD4 count <350 cells/mm ³ (A-III) ^d or WHO 3 or 4 irrespective of CD4 level (A-I) or In all ^b (C-III)	Never (A-IV) or when CD4 ≥350 cells/mm ³ after 6 months of ART ^e (C-IV) or CD4 ≥200 cells/mm ³ after 6 months of ART ^c (B-I)	See Annex 7: for <30 kg, 960 mg daily	Clinical at 3-monthly intervals (A-III)

^a Discontinue also if the person has Stevens-Johnson syndrome, severe liver disease, severe anaemia, severe pancytopenia or negative HIV status.

Contraindications to co-trimoxazole preventive therapy: severe allergy to sulfa drugs; severe liver disease, severe renal disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

^b In all regardless of CD4 percentage or clinical stage in settings with high HIV prevalence, high infant mortality due to infectious diseases and limited health infrastructure.

^c If initiated primarily for *Pneumocystis pneumonia* or toxoplasmosis prophylaxis.

^d Some countries may choose to adopt a CD4 threshold of <200 cells/mm³.

^e In settings with high prevalence of bacterial infections or malaria.



8.1.2 Tuberculosis



Background

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should be provided to all people with HIV with active TB disease. HIV care settings should implement the WHO *Three I's* strategy: intensified TB case-finding, isoniazid preventive therapy (IPT) and infection control at all clinical encounters.

Source for recommendations

- *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, World Health Organization, 2012 (www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en) (2).

Additional 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).
- *WHO policy on TB infection control in health-care facilities, congregate settings and households*. Geneva, World Health Organization, 2009 (www.who.int/tb/publications/2009/9789241598323/en).
- *Treatment of tuberculosis: guidelines for national programmes*. 4th ed. 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 extrapulmonary TB among adults and adolescents: recommendations for HIV prevalent and resource-constrained settings*. Geneva, World Health Organization, 2007 (<http://wholibdoc.who.int/2007/HTM>).
- *Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational "how-to". Practical considerations*. Geneva, World Health Organization, 2011 (whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf).
- *Recommendations for investigating contact 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).
- *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf).
- *Childhood tuberculosis guidelines*. Geneva, World Health Organization, forthcoming (expected 2013).

Key selected existing recommendations

TB case-finding and antituberculosis treatment (2)

- Adults and adolescents living with HIV should be screened for TB with a clinical algorithm; those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases (Fig. 8.1) (*strong recommendation, moderate-quality evidence*).
- Children living with HIV who have any of the following symptoms of 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, children should be offered isoniazid preventive therapy regardless of their age (Fig. 8.2) (*strong recommendation, low-quality evidence*).
- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of rifampicin treatment regimen (*strong recommendation, high-quality evidence*).

The optimal dosing frequency is daily during the intensive and continuation phases (*strong recommendation, high-quality evidence*).

- Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB (*strong recommendation*).

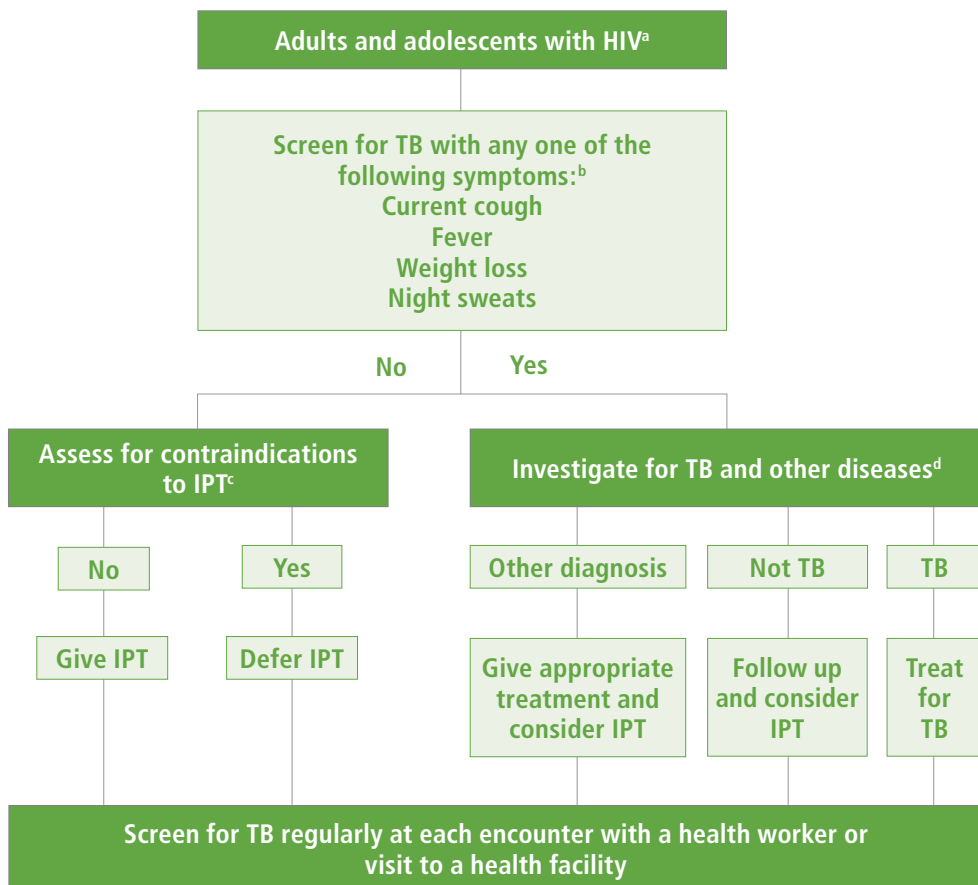


Key selected existing recommendations

Isoniazid preventive therapy (IPT) (2)

- 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*).
- **Duration of IPT**
 - Adults and adolescents who are living with HIV, have 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 irrespective 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 TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also those on ART, those who have previously been treated for TB and pregnant women
(*conditional recommendation, moderate-quality evidence*).
- A TST is not a requirement for initiating IPT in people living with HIV
(*strong recommendation, moderate-quality evidence*).
People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals
(*strong recommendation, high-quality evidence*).
- Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT
(*strong 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
(*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 services
(*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 disease, should receive isoniazid for an additional six months
(*conditional recommendation, low-quality evidence*).

Fig. 8.1 Algorithm for TB screening among adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



IPT: isoniazid preventive therapy

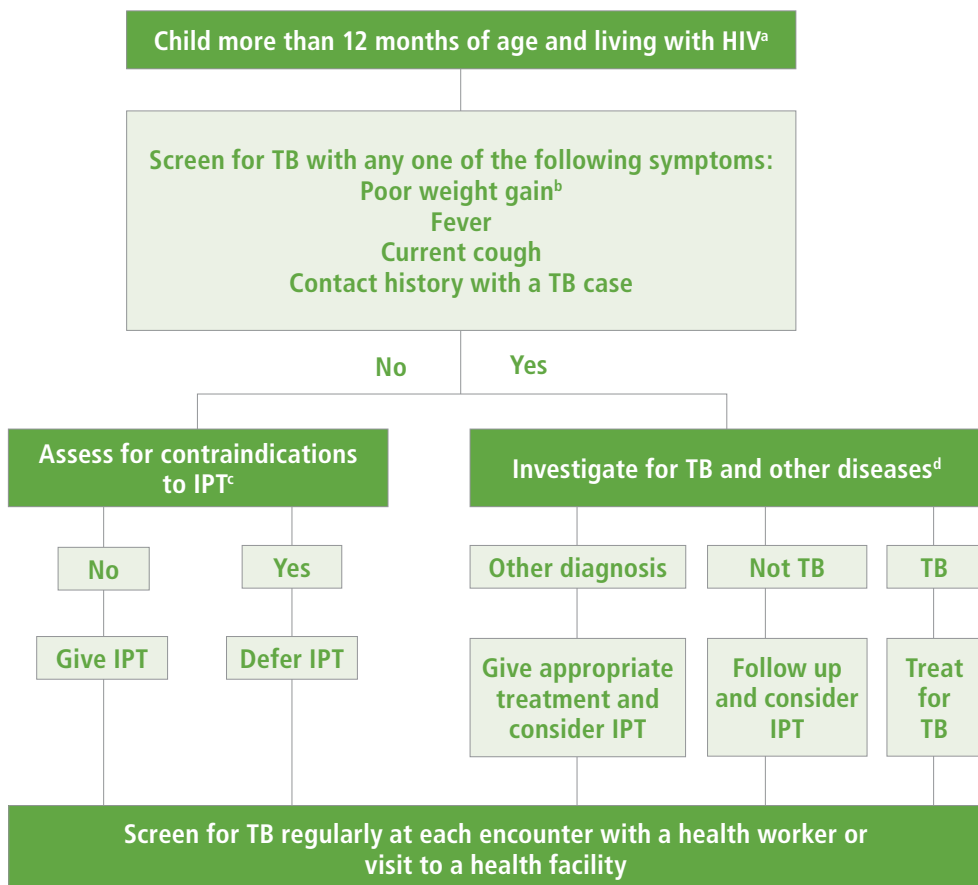
^a Every adult and adolescent should be evaluated for eligibility to receive antiretroviral therapy. Infection control measures should be given priority to reduce *Mycobacterium tuberculosis* transmission in all settings that provide care.

^b Chest radiography can be done if available but is not required to classify people into TB and non-TB groups. In settings with high HIV prevalence and a high TB prevalence among people living with HIV (such as exceeding 10%), strong consideration must be given to adding other sensitive investigations.

^c Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting isoniazid preventive therapy. Although not a requirement for initiating isoniazid preventive therapy, tuberculin skin testing may be performed as a part of eligibility screening in some settings.

^d Investigations for TB should be performed in accordance with existing national guidelines.

Fig. 8.2 Algorithm for TB screening among children older than one year of age and living with HIV



IPT: isoniazid preventive therapy

^a All infants younger than one year should be provided with isoniazid preventive therapy if they have a history of household contact with a person with TB.

^b Poor weight gain is defined as (1) reported weight loss or very low weight (weight for age less than -3 z-score), (2) underweight (weight for age less than -2 z-score), (3) confirmed weight loss ($>5\%$) since the last visit or (4) growth curve flattening.

^c Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. A past history of TB should not be a contraindication to starting isoniazid preventive therapy. Although not a requirement for initiating isoniazid preventive therapy, tuberculin skin testing may be performed as part of eligibility screening in some settings.

^d Investigations for TB must be performed in accordance with existing national guidelines.

Infection control

Background

People living with HIV are at high risk of acquiring TB in health care facilities and congregate settings. National TB programmes and national HIV programmes should provide managerial direction for implementing TB infection control programmes. Each health care facility should have a TB infection control plan for the facility that includes administrative, environmental and personal protection measures to reduce the transmission of TB in health care and congregate settings and surveillance of TB disease among workers (Box 8.1). Health care workers with HIV should be provided with ART and isoniazid preventive therapy if they are eligible.

Sources for recommendations

- *WHO policy on TB infection control in health-care facilities, congregate settings and households*. Geneva, World Health Organization, 2009 (www.who.int/tb/publications/2009/9789241598323/en) (3).
- *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) (4).
- *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, World Health Organization, 2012 (www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en) (2).
- *Childhood tuberculosis guidelines*. Geneva, World Health Organization, forthcoming (expected 2013) (5).

Box 8.1. Summary of recommendations for key actions for infection control (3)

Administrative (facility-level infection control committee and protocols)

- A triage system to identify people suspected of having TB
- Separate people with suspected or confirmed TB
- Cough etiquette and respiratory hygiene
- Rapid diagnosis with Xpert MTB/RIF (with prompt treatment of active TB) (*strong recommendation, low-quality evidence*).

Health workers and carers

- Surveillance and information
- Package of care for HIV-positive workers (ART and isoniazid preventive therapy)
- Protective equipment (particulate respirator masks that meet or exceed N95 standards)
- Relocation for health care workers living with HIV to a lower-risk area (*strong recommendation, high-quality evidence*).

Environmental

- Ventilation (mechanical)
- Ventilation (natural)
- Upper-room ultraviolet germicidal irradiation (*strong recommendation, low-quality evidence*).

Personal

- Spend as much time as possible outside
- Cough etiquette
- Sleep alone while smear-positive
- Avoid congregate settings and public transport while smear-positive (*strong recommendation, low-quality evidence*).

Key selected existing recommendations

Timing of ART for adults and children with TB

- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of the CD4 count (*strong recommendation, low-quality evidence*) (4).
- Antituberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (*strong recommendation, moderate-quality evidence*). The HIV-positive TB patients with profound immunosuppression (such as CD4 counts less than 50 cells/mm³) should receive ART immediately within the first two weeks of initiating TB treatment (2).
- ART should be started in any child with active TB disease as soon as possible and within eight weeks following the initiation of antituberculosis treatment irrespective of the CD4 count and clinical stage (*strong recommendation, low-quality evidence*) (5).
- Efavirenz should be used as the preferred NNRTI in patients starting ART while on antituberculosis treatment (*strong recommendation, high-quality evidence*) (2).

- Section 7.2 provides more detailed information and recommendations on the co-treatment of TB and HIV.
- More detailed information and recommendations on drug interactions between ARV drugs and TB drugs are available in the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes).

Multidrug-resistant TB and HIV

Background

Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant to at least isoniazid and rifampicin. Patients with both HIV and MDR-TB face complicated clinical management, fewer treatment options and poorer treatment outcomes. Limited information is available about the association between HIV and MDR-TB at the population level, especially because only 40% of the people with active TB are tested for HIV (6). 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 (7).

People with HIV with suspected drug-resistant TB should be tested using Xpert MTB/RIF where possible, since this test is more sensitive for detecting TB among people with HIV and rapidly detects rifampicin resistance, thus greatly shortening the time to diagnosing and treating MDR-TB.

The burden of MDR-TB should be reduced by strengthening HIV prevention, improving infection control and improving collaboration between HIV and TB control activities, with special attention to the groups at the highest risk of MDR-TB and HIV infection, such as people who inject drugs and those exposed in congregate settings.

Source for recommendation

- *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) (4)

Additional guidance

- *Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational "how-to". Practical considerations*. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf).

Key selected existing recommendation (4)

- WHO recommends ART for all patients with HIV and drug-resistant TB, requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of anti-tuberculosis treatment (*strong recommendation, very-low-quality evidence*).

8.1.3 Cryptococcal infection



Background

Cryptococcal meningitis is one of the most important opportunistic infections and a major contributor to high mortality before and after ART is initiated. WHO 2011 Rapid Advice covers diagnosis, screening and prevention of cryptococcal infection, induction, consolidation and maintenance regimens, monitoring and managing toxicities, timing of ART and discontinuing maintenance regimens. Full guidelines will be published at the end of 2013.

Source for recommendations

- *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) (8).

Key selected existing recommendations

Screening and prophylaxis (8)

- Use of routine serum or plasma *Cryptococcus neoformans* antigen (CrAg) screening in ART-naïve adults, followed by pre-emptive antifungal therapy if CrAg-positive and asymptomatic, to reduce the development of cryptococcal disease, may be considered prior to ART initiation in patients with a CD4 count of less than 100 cells/mm³ and where this population also has a high prevalence of cryptococcal antigenaemia (*conditional recommendation, low-quality evidence*).
- Routine use of antifungal primary prophylaxis for cryptococcal disease in people living with HIV with a CD4 count of less than 100 cells/mm³ and who are CrAg-negative or where CrAg status is unknown is not recommended prior to ART initiation (*strong recommendation, high-quality evidence*).
- The use of routine CrAg screening and pre-emptive antifungal therapy in ART-naïve adolescents and children with a CD4 count of less than 100 cells/mm³ prior to ART initiation is not recommended (*conditional recommendation, low-quality evidence*).



Timing of ART (8)

- Immediate ART initiation is not recommended in patients with cryptococcal meningitis due to the high risk of immune reconstitution inflammatory syndrome with central nervous system disease, which may be life-threatening (*conditional recommendation, low-quality evidence*).
 - Among people living with HIV 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 two to four weeks of induction and consolidation treatment with amphotericin containing regimens combined with flucytosine or fluconazole; or
 - after four to six weeks of induction and consolidation treatment with a high-dose oral fluconazole regimen (*conditional recommendation, low-quality evidence*).
- See the source above for recommendations on discontinuing secondary prophylaxis.

8.1.4 Hepatitis B and C



Background

Chronic hepatitis B virus infection affects 5–20% of the 33 million people living with HIV worldwide, and hepatitis C affects 5–15%, although this may be up to 90% among people who inject drugs (9,10). The burden of coinfection is greatest in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa for hepatitis B. Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, including those on ART. A comprehensive approach includes prevention, hepatitis B and hepatitis C screening, hepatitis B vaccination and treatment and care for people with HIV coinfecting with hepatitis B and/or hepatitis C.

Additional guidance

- *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).

Guidance on timing of ART in hepatitis B and C

- **Hepatitis B: when to start and what to start.** See sections 7.1.1, 7.1.4 and 7.2.7.
- **Hepatitis C: when to start and what to start.** Initiating ART among people with HIV and hepatitis C should follow the same general principles as for the general population of people living with HIV (section 7.1).

The WHO guidelines for the management of hepatitis C are scheduled to be published in 2014. They will provide detailed guidance on hepatitis C screening, hepatitis C-specific treatment and general hepatitis C care.

8.1.5 Malaria



Background

People with HIV with immunosuppression living in malaria-endemic areas are at high risk of complications of malaria, and all infants and children under five years of age and pregnant women are at particular risk of severe malaria and its complications.

Key interventions to control malaria include prompt and effective treatment with artemisinin-based combination therapies and using insecticide-treated nets and indoor residual spraying with insecticide to control the vector mosquitoes. An additional intervention recommended in areas of high transmission for specific high-risk groups is intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis.

People living with HIV who develop malaria should receive prompt, effective antimalarial treatment regimens. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test.

The drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have clinically important pharmacokinetic interactions (especially artemesinins, lumefantrine, NNRTIs and protease inhibitors). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for adverse drug reactions, and people with HIV receiving zidovudine, or efavirenz should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of increased risk of neutropaenia in combination with zidovudine, and hepatotoxicity in combination with efavirenz.

Source for recommendations

- *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) (11).

Additional guidance

- *Guidelines for the treatment of malaria*. 2nd ed. Geneva, World Health Organization, 2010 (www.who.int/malaria/publications/atoz/9789241547925/en/index.html).
- *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).
- *Technical Expert Group meeting on intermittent preventive treatment in pregnancy (IPTp)*. Geneva, World Health Organization, 2007 (www.who.int/malaria/publications/9789241596640/en).
- *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).
- *Test, treat and track. Scaling up diagnostic testing, treatment and surveillance for malaria*. Geneva, World Health Organization, 2012 (www.who.int/malaria/publications/atoz/test_treat_track_brochure.pdf).
- Additional information: malaria [web site]. Geneva, World Health Organization, 2013 (www.who.int/topics/malaria/en).



Key selected existing recommendations (11)^a

- In areas of stable malaria transmission, people living 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 infection. (A-I)
- Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to patients with HIV receiving co-trimoxazole prophylaxis. (A-III)

^aSee the Web Annex (www.who.int/hiv/pub/guidelines/arv2013/annexes) for methodology used in rating quality of evidence.

8.1.6 Sexually transmitted infections and cervical cancer



Background

HIV, other sexually transmitted infections and non-sexually transmitted infections of the reproductive tract frequently coexist. Most of these infections are asymptomatic, especially among women. However, even asymptomatic sexually transmitted infections can cause complications, be transmitted to sexual partners and enhance HIV transmission. Further, HIV infection alters the natural history of sexually transmitted infections. The objectives of diagnosing and managing sexually transmitted infections include identifying the infection and providing appropriate treatment and preventing transmission. Screening, diagnosis and treatment of sexually transmitted infections should be offered routinely as part of comprehensive HIV care among adults and adolescents.

WHO guidelines on treating and managing sexually transmitted infections are scheduled to be updated in 2014. Other recent guidelines cover recommendations on periodic screening and periodic presumptive treatment for asymptomatic sexually transmitted infections in sex workers, and periodic testing for asymptomatic urethral and rectal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections and asymptomatic syphilis infection among female sex workers, men who have sex with men and transgender people.

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. The risk and persistence of human papillomavirus infection increases with decreasing CD4 count and increasing HIV viral load. Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women living with HIV should be followed closely for evidence of pre-cancerous changes in the cervix, regardless of ART status or CD4 count and viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions that will prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management for pre-cancerous and cancerous lesions should be provided. WHO guidance covers human papillomavirus vaccination and prevention, screening and treatment and palliative care of cervical cancer. To date, concerns about safety or reduced efficacy among females 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 guidance

Sexually transmitted infections

- *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).
- *Guidelines for the management of sexually transmitted infections*. Geneva, World Health Organization, 2004 (www.who.int/hiv/pub/sti/pub6/en).
- *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).
- *WHO meeting report. Report of the Expert Consultation and review of the latest evidence to update guidelines for the management of sexually transmitted infections*. Geneva, World Health Organization, 2011 (www.who.int/reproductivehealth/publications/rtis/rhr_11_37/en).
- WHO guidelines on the syndromic approach to managing people with symptoms of sexually transmitted infections and treating specific sexually transmitted infections are scheduled to be updated in 2014.
- *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).

Cervical cancer

- Human papillomavirus vaccines: WHO position paper. *Weekly Epidemiological Record*, 2009, 84:118–131 (www.who.int/wer/2009/wer8415.pdf).
- *Comprehensive cervical cancer prevention and control: a healthier future for girls and women*. Geneva, World Health Organization, 2013 (www.who.int/reproductivehealth/topics/cancers/en/index.html).
- *WHO guidelines on use of cryotherapy for cervical intraepithelial neoplasia*. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241502856_eng.pdf).

8.1.7 Vaccines for people living with HIV



Background

People living with HIV should be assessed for eligibility for vaccination at all stages of care. HIV-exposed infants and children and young adults with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules. Those with more severe immunosuppression may be at higher risk of complications from live vaccines. Inactivated vaccines are more effective among people receiving ART and those without immunosuppression, but they are safe and can be used with some efficacy in all groups.



Additional guidance

- For complete vaccination schedules and detailed guidance: *WHO recommendations for routine immunization – summary tables* [web site]. Geneva, World Health Organization, 2012 (www.who.int/immunization/policy/immunization_tables/en/index.html).
- For position papers on each vaccine, and statement about use in people living with HIV: (www.who.int/immunization/documents/positionpapers/en/index.html).

8.2 Preventing and managing other comorbidities and chronic care for people living with HIV

8.2.1 Screening for and care of noncommunicable diseases



Background

People living with HIV are at increased risk of developing a range of noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung disease and some types of cancer (12,13). With effective ART, people living with HIV are also living longer and experiencing NCDs associated with ageing. 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 screening, monitoring and managing NCDs, especially through primary care. Integrating interventions such as nutrition assessment, dietary counselling and support, smoking cessation, promoting exercise, monitoring blood pressure and where available cholesterol as part of HIV care provide opportunities for reducing the risks of NCDs among people living with HIV. WHO has defined a package of essential NCDs (WHO PEN) interventions along with recommendations on screening for and treating NCDs. Additional guidance on diagnosis and management of NCDs in people living with HIV is planned for 2014.

Additional guidance

- *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).

8.2.2 Mental health



Background

People living with HIV and their carers may have a wide range of mental health needs. The most common mental health comorbidities among people living with HIV include depression, anxiety, dementia and other cognitive disorders and substance use disorders. HIV care settings provide an opportunity to ensure the detection and management of mental disorders among people living with HIV. Treatment or lack of treatment for these conditions can affect adherence to ARV drugs, retention in care and may involve potential side effects and drug interactions.

WHO has no specific recommendations on screening and treatment for mental disorders among people living with HIV. The Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders in non-specialized health settings makes recommendations related to general mental health that can be relevant to people living with HIV. Additional guidance on management of mental health conditions in people living with HIV is planned for 2014.

Additional guidance

- *mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings*. Geneva, World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241548069_eng.pdf).

8.2.3 Drug use and drug use disorders



Background

People living with HIV who use drugs may experience a range of disorders related to their drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated with a range of bloodborne and local infections, including viral hepatitis, septicæmia and bacterial endocarditis, in addition to HIV.

WHO has developed guidance for the treatment of opioid dependence and prevention of hepatitis B and C among people who inject drugs.

WHO, UNODC and UNAIDS recommend a comprehensive package of nine interventions for HIV prevention, treatment and care for people who inject drugs, including needle and syringe programmes, opioid substitution therapy, HIV testing and counselling, ART, preventing and treating sexually transmitted infections, condom programmes, targeted behaviour change communication, preventing and treating viral hepatitis and preventing and treating TB.

Additional guidance

- WHO, UNODC and UNAIDS. *Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users*. Geneva, World Health Organization, 2012 (www.who.int/hiv/pub/idu/targets_universal_access/en/index.html).
- *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).



8.2.4 Nutritional care and support

8.2.4.1 Among adolescents and adults living with HIV



Background

Low energy intake combined with increased energy demands because of HIV infection (14–17) and related infections may lead to HIV-related weight loss and wasting. In addition, an altered metabolism, reduced appetite and higher incidence of diarrhoea may lower nutrient intake and absorption and also lead to nutrient losses. These effects may all be compounded in low income, food insecure contexts. Low body mass in adults (body mass index^{vi} less than 18.5kg/m²), weight loss and wasting in children are all independent risk factors for HIV disease progression and mortality (18,19). 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 during all HIV care and treatment. Malnourished HIV patients, especially in food insecure contexts, may require food supplements, in addition to ART, to ensure appropriate foods are consumed to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection or ART should trigger further assessment and appropriate interventions.

WHO is currently revising recommendations for nutritional care and support of adolescents and adults living with HIV, including pregnant and lactating women.

8.2.4.2 Among children living with HIV



Background

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 (20). If poor growth is identified, then further assessment should be performed to determine the cause, and plan 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

- *Guidance on Nutrition assessment, education, counselling and support for adolescents and adults living with HIV.* Geneva, World Food Programme and World Health Organization, 2013.
- *Guidelines on HIV and infant feeding.* 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 and FAO. *Nutritional care and support for people living with HIV/AIDS: a training course.* Geneva, World Health Organization, 2009 (www.who.int/nutrition/publications/hiv aids/9789241591898/en/index.html).

^{vi}Body mass index: indicates adequacy of weight in relation to height for older children, adolescents and adults. It is calculated as the weight in kg divided by the height in metres squared. The acceptable range for adults is 18.5 to 24.9, and for children this varies with age.

8.2.5 Palliative care: symptom management and end-of-life care



Background

Throughout 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 when possible, while controlling the pain. Further, effectively managing the side effects of ART is important to support adherence.

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).

8.2.6 Other relevant general guidance on care

8.2.6.1 Family planning, counselling and contraception



Additional guidance

- *Medical eligibility criteria for contraceptive use.* 4th ed. Geneva, World Health Organization, 2009 (www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html).
- *Hormonal contraception and HIV. Technical statement 16 February 2012.* Geneva, World Health Organization, 2012 (www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html).



8.2.6.2 Providing safe water, sanitation and hygiene



Additional guidance

- *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/pubprev_care/OMS_EPP_AFF_en.pdf).
- *Evaluating household water treatment options: health-based targets and microbiological performance specifications*. Geneva, World Health Organization, 2011 (www.who.int/water_sanitation_health/publications/2011/evaluating_water_treatment.pdf).
- *Guidelines for drinking-water quality*. 4th ed. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf).

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Goal of this chapter

To provide guidance on key issues related to operations and service delivery that need to be addressed to strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems.

9 GUIDANCE ON OPERATIONS AND SERVICE DELIVERY

9.1 Introduction



ARV drugs and related services need to be delivered as effectively, equitably and efficiently as possible by optimizing available human and financial resources, ensuring appropriate links between care settings and services, supporting adherence to lifelong treatment and maximizing retention of patients across the continuum of care. This chapter provides broad guidance in six operational and service delivery areas in which action is essential to ensure the long-term effectiveness and sustainability of ARV programmes. These areas are:

- adherence to ART;
- retention across the continuum of care;
- service delivery, comprising service integration and linkage and decentralization of HIV care and treatment;
- human resources, including task shifting;
- laboratory and diagnostic services; and
- procurement and supply management systems.

New recommendations, developed through the GRADE process, are found in the sections on adherence and service delivery and human resources and include: text messages to promote adherence; ART integration into and linkage with maternal and child health, TB and opioid substitution therapy services; decentralization of ART; and task shifting.

9.2 Adherence to ART

9.2.1 Barriers to adherence

WHO defines treatment adherence as “the extent to which a person’s behaviour – taking medications, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” (1). For ART, a high level of sustained adherence is necessary to (1) suppress viral replication and improve immunological and clinical outcomes; (2) decrease the risk of developing ARV drug resistance; and (3) reduce the risk of transmitting HIV.

Multiple factors related to health care delivery systems, the medication and the person taking ARV drugs may affect adherence to ART. The individual factors may include forgetting doses; being away from home; changes in daily routines; depression or other illness; a lack of interest or desire to take the medicines; and substance or alcohol use. Medication-related factors may include adverse events; the complexity of dosing regimens; the pill burden; and dietary restrictions. Health system factors may include requiring people with HIV to visit health services frequently to receive care and obtain refills; travelling long distances to reach health services; and bearing the direct and indirect costs of care. Lack of clear information or instruction on medication, limited knowledge on the course of HIV infection and treatment

and adverse effects can all be barriers to adherence to ART. Moreover, uninterrupted ARV drug supply and continuity of care are essential for people to adhere to their medication. Lack of continuity of care is a strong predictor of non-adherence in the longer term. Adherence to ART may also be challenging in the absence of supportive environments for people living with HIV and due to HIV-related stigma and discrimination (2,3).

Pregnant and postpartum women



The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other challenges during this period may include dealing with the diagnosis of HIV infection (many women learn about their HIV infection during routine screening during pregnancy); concerns about how ART affects the health of the fetus; pill burden; the number of clinic visits during pregnancy; fear of disclosure of HIV status to partners; long waiting times at clinics; and lack of follow-up and transfer to other clinics after delivery (4,5).

Adolescents



Adherence challenges faced by adolescents include a potentially large pill burden if they are treatment-experienced; stigma and fear of disclosure; concerns about safety of medications; adverse effects; peer pressure and perceived need to conform; not remembering to take medications; and inconsistent daily routine. The transition from paediatric to adolescent care presents several challenges that may affect treatment adherence in adolescents. These include assuming increased responsibility for their own care (which may lead to treatment interruptions because of forgetfulness); an inability to navigate the health care system; lack of links between adult and paediatric services; lack of health insurance; and inadequately skilled health care providers (6,7). Depression and substance use have also been shown to present challenges in adolescents.

Infants and children



Adherence among children is a special challenge. The limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence (3,8,9). 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; suboptimal HIV care and treatment for family members could result in suboptimal care for the child.

Mental health disorders

Adherence to ART is known to be complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Studies have linked uncontrolled depressive symptoms with low levels of adherence to ART and poor treatment outcomes. As a result, several treatment strategies target depression and psychosocial stress to improve adherence to ART, ranging from co-counselling for HIV and depression to appropriate medical therapies for individuals with mental disorders (10–13).

Substance use disorders

Individuals with substance use disorders may have poor adherence to ART. Alcohol and other drug use could be associated with forgetfulness, poor organization and diversion of monetary and time priorities (10,14–16).



Most-at-risk populations (including sex workers, men who have sex with men, transgender people and people who inject drugs)



In several settings, most-at-risk populations face multiple challenges to accessing health services. Service delivery approaches to improve longitudinal care and maintain adherence for most-at-risk populations remains a critical gap in many settings. Experience indicates encouraging results with peer-based interventions that include strong social support such as outreach teams, peer educators and health workers providing multidisciplinary, non-judgemental and respectful care.

Incarceration

Incarceration may negatively affect continuity of care, diminish trust and predispose individuals to poor financial and social support both during and after incarceration. Substance use disorders may also be an additional challenge for this population. People who are incarcerated have the additional risk of acquiring TB, resulting in high morbidity and mortality rates in the absence of efficacious HIV and TB treatment (17). However, excellent outcomes can be achieved with adequate support and structured treatment programmes within the prison setting.

9.2.2 Interventions to optimize adherence to ART

No single adherence intervention or package of interventions is effective for all populations and all settings. People's needs and circumstances may also change over time, and programmes and care providers therefore need to tailor a combination of feasible interventions to maximize adherence to ART based on individual barriers and opportunities.

Programme-level interventions for improving adherence to ART include: (1) avoiding imposing out-of-pocket payments at the point of care, (2) using fixed-dose combination regimens for ART and (3) strengthening drug supply management systems to reliably forecast, procure, and deliver ARV drugs and prevent stock-outs.

The individual-level adherence intervention recommendation in this section relates to the use of mobile phone text messages. There have been simple and robust trials to demonstrate its importance as one of many adherence tools. Adherence interventions, such as text messaging, should clearly be provided as part of a total package of several interventions. Many individual-level adherence interventions are indicated for reasons in addition to improving adherence to ART. For example, nutritional support, peer support, management of depression and substance use disorders and patient education are vital components of routine health and HIV care.

Efforts to support and maximize adherence should begin before ART is initiated. Developing an adherence plan and education are important first steps. Initial patient education should cover basic information about HIV, the ARV drugs themselves, expected adverse effects, preparing for treatment and adherence to ART. Adherence preparation should not delay treatment initiation, when prompt action is necessary.

Patient education and counselling and peer support

Patient education and counselling are essential both when ART is initiated and throughout the course of treatment. Informing and encouraging people receiving ART and their families and peers are essential components of chronic HIV care. Studies show that counselling improves adherence to ART, and in some settings there is an association between peer support and high rates of adherence and retention (18–23).

Substance use and mental health interventions

Studies indicate that improving well-being by treating depression and managing substance use disorders improves HIV treatment outcomes. The systematic review identified very-low-quality evidence from one observational study evaluating opioid substitution therapy for improving adherence. After 12 months, the rates of unsuppressed viral loads were comparable among people who inject drugs using opioid substitution therapy and people who inject drugs without opioid substitution therapy (24). The systematic review also identified very-low-quality evidence from one randomized trial evaluating the treatment of depression for improving adherence. After 12 months, the risk of non-adherence was similar among those who received depression treatment and those who did not (25). WHO recommends co-treatment of depression and substance use disorders irrespective of HIV status, and concurrent treatment should be evaluated in relation to adherence to ART. Other services for people living with HIV who use drugs, such as needle and syringe programmes, drug dependence treatment and peer outreach, provide opportunities for supporting treatment adherence.

Nutritional support

Nutrition assessment, care and support are essential components of HIV care. HIV programmes should ensure that existing national policies on nutritional support are observed when it is necessary and feasible to maximize adherence to ART and achieve optimal health outcomes in food-insecure settings.

Nutritional support could include nutritional counselling, cash transfers and subsidizing food costs and/or food vouchers. ART in conjunction with nutritional support could accelerate recovery. The systematic review identified one study from low- and middle-income countries with low-quality evidence showing that nutritional support provided by community health workers to people receiving ART reduces the risk of non-adherence after one year among food-insecure individuals relative to the standard of care (26).

Financial support

Financial support may include reimbursement for the costs of receiving HIV care (including drugs, diagnostics, clinical services and transport vouchers) and may potentially mitigate the burden of HIV in disadvantaged settings. The systematic review identified very-low-quality evidence that financial support reduces the risk of non-adherence one year post-intervention relative to the standard of care (27). Programmes and care providers should consider a broader programmatic approach for reducing the costs of care for people living with HIV that would include avoiding out-of-pocket payments at the point of care, decentralizing and coordinating care and exploring opportunities to minimize health facility visits. Programmes need to consider ethical implications and equity in providing food and financial support or other similar interventions for people living with HIV and not others. Standardized criteria for supporting people receiving ART may need to be developed based on national poverty levels.

Reminder and engagement tools

New recommendation



- Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions (*strong recommendation, moderate-quality evidence*).



Background

Forgetfulness and changes in daily routines are often cited as the main reason for poor adherence to ART in most settings, although the specific reasons for forgetting to take medication could vary. Reminders and communication that engage people in taking ARV drugs could be an important intervention to improve adherence through behavioural change.

The use of mobile text messages for supporting adherence and in health care delivery in general has increased as access to phone technology expands (28). Using this, however, requires adequate national regulations to protect the privacy of the people receiving text messages (29,30). Programmes may explore public-private partnerships to accelerate the scaling up of mobile phone-based interventions.

Rationale and supporting evidence

Mobile phone technology may be a convenient reminder mechanism to engage people living with HIV in care. Moreover, since mobile phones are widely used globally, using them may not require major changes to people's daily routines. Mobile phone text messaging is also relatively inexpensive or without marginal cost, is a succinct way of sending a message without the need to talk and offers a record of messages.

The systematic review identified five randomized trials and two observational studies on mobile phone text messaging for improving adherence to ART. High-quality evidence from two randomized trials found that text messages contributed to reduced unsuppressed viral loads after one year (31,32). This finding was consistent with high-quality evidence from three randomized trials that found reduced non-adherence levels after one year (31,33,34).

Four observational studies evaluated the use of text messaging for less than one year. Very-low-quality evidence from one observational study found reduced unsuppressed viral loads after nine months (35). Although moderate-quality evidence from two randomized trials showed similar non-adherence levels after 4–6 months (36,37), very-low-quality evidence from two observational studies suggests reduced non-adherence levels after 6–9 months (35,38). Overall, the systematic review supports the use of text message reminders, although the quality of the data was variable and duration of follow-up short (up to one year).

Other patient reminders

Other patient reminder tools include alarms, phone calls, diaries and calendars and are used to send brief reminders about the timing of ARV drugs, drug dosage and appointments. The evidence does not demonstrate that these interventions support treatment adherence better than the standard of care.

The systematic review identified four randomized trials. Moderate-quality evidence from one randomized trial found that the risk of unsuppressed viral loads was similar after 18 months of follow-up using alarms versus the standard of care (19). Low-quality evidence from one randomized trial also found that rates of non-adherence and unsuppressed viral loads were similar after three months using phone calls compared with the standard of care (39). Very-low-quality evidence from one randomized trial further found that the risk of unsuppressed viral load and non-adherence was similar after 15 months using diaries relative to the standard of care (40). Finally, low-quality evidence from one randomized trial found that non-adherence was similar using calendars relative to the standard of care after one year of follow-up (41). Using these interventions requires further exploration among different populations and settings.

9.2.3 Monitoring adherence to ART in routine programme and care settings

Objective monitoring of adherence to ARV drugs is necessary for effective and efficient treatment planning and ongoing support. Each facility visit brings opportunity for assessing and supporting treatment adherence. Effectively monitoring adherence requires a combination of approaches based on human and financial resource capacity, acceptability to people living with HIV and to health workers and the local context.

Viral load monitoring

These guidelines recommend viral load monitoring to diagnose and confirm treatment response and failure. Although treatment failure is often caused by lapses in adherence to ART, it may also result from other factors (such as drug stock-outs, drug interactions or malabsorption). However, viral load monitoring does not provide an opportunity for care providers to monitor non-adherence in real time and prevent progression to treatment failure. Viral load monitoring must therefore be combined with other approaches to monitoring adherence.

Pharmacy refill records

Pharmacy refill records provide information on when people living with HIV pick up their ARV drugs (42,43). When people obtain pharmacy refills at irregular intervals, this may indicate non-adherence to ART; however, in many routine care settings, people may pick up their medications when receiving care irrespective of their adherence level. This behaviour could lead health care providers to overestimate adherence by solely using pharmacy refill records. A recent validation study to assess the usefulness of various adherence monitoring approaches found pharmacy records to be more reliable than self-report (44). In many settings, pharmacy refill records are already a part of national monitoring and evaluation frameworks and can also provide additional information on adherence to ART when used in combination with other tools.

Self-report

Asking people living with HIV or their caregivers how many doses of medication they have missed since the last visit (or within a specified number of days in the past) can help to estimate non-adherence. However, although this method is commonly used, people may not remember missed doses accurately or may not report missed doses because they want to be perceived as being adherent and to avoid criticism. Counselling on the importance of remembering and/or documenting ARV drug 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 (45).

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 may throw away tablets prior to health care visits, leading to overestimated adherence (45,46). Although unannounced visits at people's homes could lead to more accurate estimates, this approach poses financial, logistical and ethical challenges. Counting pills also requires health care personnel to invest significant time and may not be feasible in routine care settings.

9.3 Retention across the continuum of care

9.3.1 Background

Retaining people living with HIV across the continuum of care is essential for optimal health outcomes. Among those who do not have immediate indications for ART, care visits provide opportunities for screening, prevention and treatment of other conditions and comorbid illnesses, including providing co-trimoxazole prophylaxis, PMTCT, isoniazid preventive therapy and regular screening for TB and clinical and laboratory monitoring to allow timely initiation of ART once the indications arise. For people who are eligible for ART at the time they test HIV-positive, rapid linkage to care is critical; delays of days or weeks with people already being ill with TB or other opportunistic infections increases the risk of mortality (47,48). For people living with HIV who are receiving treatment, uninterrupted ART and continual monitoring are essential for sustained viral suppression and optimal treatment outcomes.

Retaining people living with HIV in care, especially people who are not yet eligible for ART and those who are eligible but have not yet initiated treatment, poses a great challenge. Synthesis of available literature from sub-Saharan Africa showed that 54% of those who are not yet eligible for ART were lost to follow-up before becoming eligible, while 32% of the people living with HIV who were eligible for ART were lost before initiating treatment (49,50). Outcomes among those lost to follow-up may vary, as loss to follow-up reported at the health facility level can include people who have self-transferred to another facility, unascertained deaths and true losses to follow-up. People who discontinue care – especially those who are not eligible for ART at initial assessment – frequently return to care only after they become ill with advanced HIV disease, when early mortality after initiating ART is significant (51,52). Data on the proportion of people who remain on ART over time in low- and middle-income countries show that most discontinued care occurs within the first year of starting therapy. In some settings, many people living with HIV who are lost to follow-up in the first months after initiating ART have died (53). In 2011, the average retention rate at 12 months after initiating ART was 81% (92 reporting countries), 75% at 24 months (73 reporting countries) and 67% at 60 months (46 reporting countries) (53).

Multiple factors relating to the health care delivery systems and patients could facilitate or hinder retention in HIV care. Interventions to improve linkage to and retention in HIV care, from diagnosis and across the continuum of care, need to address issues reported by the people receiving care and related to the health system and require a more targeted evaluation in different settings and populations (54–57).

9.3.2 Good practices for retention across the continuum of care

NEW

Optimizing retention in HIV care requires interventions at multiple levels of the health care system as well as implementation research. Given the broad array of challenges and heterogeneity of barriers across settings, no single approach is likely to work for everyone in all settings. Improving the understanding of barriers and innovative strategies to address them are important priorities in implementation research and public health.

Studies show that the direct and indirect costs of care affect the ability of people living with HIV to remain in care. They consistently report that the distance from health care facilities is a barrier to retention in diverse settings and along the continuum of HIV care. Related transport costs and loss of income while seeking care serve as disincentives when health facilities are located far from the person's home. Bringing services closer to

communities, where feasible, reduces the indirect costs of care for the people living with HIV and their families and improves retention.

Waiting times at the facility during consultation are frequently high, especially in settings with a high burden of HIV infection (58,59). Reorganizing services, such as systems for appointment, triage, separating clinical consultation visits from visits to pick up medicine, integrating and linking services and family-focused care may reduce waiting times at the health facility (59,60).

Many people living with HIV who are not yet eligible for ART may not attend clinic appointments and may not return to care until they are symptomatic. Regularly following up these individuals is important to ensure continual monitoring and timely initiation of ART. Countries have used approaches and achieved positive outcomes, including providing co-trimoxazole prophylaxis free of user charges, on-site or immediate CD4 testing with same-day results and peer support to improve retention in care (22,61,62).

Key populations generally experience more barriers to accessing health services. Interventions harnessing social support have emerged as a promising approach to counteract the structural, economic, service delivery and psychosocial constraints that affect retention in care.

Table 9.1 summarizes the factors related to the health system and people receiving ART influencing retention and adherence and potential interventions.

Table 9.1 Factors related to the health system and people receiving ART affecting retention and adherence with possible interventions

Factors related to the health system	Possible interventions
High direct and indirect costs of receiving care	<ul style="list-style-type: none"> ● ART and related diagnostics and services free of charge at the point of care ● Decentralize ART where feasible ● Scheduled facility visits ● Reduce waiting time at the facility level: <ul style="list-style-type: none"> • Appointment system • Separate clinical consultation visits from appointments for picking up medicines • Link, integrate and coordinate care • Family-focused care (organizing services around the needs of the family) when appropriate
Stock-outs of ARV drugs	Optimize pharmaceutical supply management systems to forecast, procure and deliver ARV drugs. Use fixed-dose combinations to simplify forecasting and supply management systems
Lack of a system for monitoring retention in care	Implement systems for patient monitoring across the continuum of care, including cohort analysis and patient tracking systems

Table 9.1 (continued)

Factors related to the health system	Possible interventions
Lack of a system for transferring people across different points of care	Interlinked patient monitoring system across services for HIV, TB, maternal and child health and PMTCT; system for transitioning from paediatric to adolescent and adult services and from maternal and child health and TB services to chronic HIV care
Pill burden and complex ARV drug regimens	Use fixed-dose combinations to reduce the pill burden and simplify the regimens
Lack of accurate information for patients and their families and peer support	Engage and integrate community health workers, volunteers and people living with HIV in peer support, patient education and counselling, and community-level support
Adherence support	Task shifting for involving community health workers Linking with community-level interventions and resources such as peer adherence support Using known effect reminder methods (such as text messaging) Peer support also provides opportunities for in-person reminders
Poor relationship between patient and care provider	Train health workers on how to: reduce stigma; improve treatment preparedness, adherence and retention; provide adherence support and care for key populations; and provide simplified approaches for educating patients and their families
Lack of time for educating people in HIV care	Task shifting and sharing among clinic team members People living with HIV as patient experts and peer supporters A team approach to care
Adverse drug effects	Preparedness and knowledge of how and when to self-manage adverse effects and when to return to the clinic
Factors related to the people receiving HIV care	Possible interventions
Forgetfulness, life stress, stigma and discrimination	Using text messaging to keep patients engaged Peer and family support Link to community support group
Comorbidity, substance and alcohol use disorders and mental health disorders	Manage HIV with mental health disorders, alcohol and other substance use disorders and link with community and social support
Patient knowledge and beliefs related to HIV infection, its course and treatment	Integrate the education of patients and their families and counselling, broader community literacy and education and community engagement

9.4 Service delivery

9.4.1 Good practices in providing chronic care (63)

In many countries, health services are organized primarily to provide episodic acute care. As HIV begins to become a manageable, chronic condition, programme managers and care providers need to consider how current health delivery systems can be reorganized to provide chronic care.

Once people are diagnosed and enrolled in chronic care, follow-up visits should be scheduled and planned. Waiting until people present with symptoms or preventable complications is costly and inefficient. People living with HIV require care that anticipates their needs at different stages of the care continuum. Compared with the acute care model, planned chronic care models provide opportunities for prevention, early identification of issues and timely intervention.

Chronic care requires broad support for people living with HIV from their communities and health care teams to stay in care, adhere to treatment and cope with stigma. People living with HIV and their families need to be informed about HIV infection and the anticipated side effects of medicines and supported to adhere to treatment. Health care teams play an important role in linking people living with HIV with community-level interventions, resources and support.

A system to keep information on the people receiving care at health facilities is critical for ensuring the continuity of chronic care. A patient registry serves a reminder function for follow-up services. Health care teams can use it to identify people's needs, to follow-up and plan care, to monitor responses to treatment and to assess outcomes for both individuals and for the overall treatment cohort. Information systems can be paper-based or based on an electronic registry, depending on local context. Programmes should develop a systematic strategy for collecting and aggregating key information that supports better management of the patient and ensures high-quality care. A robust patient information system is also critical for high-quality monitoring and evaluation of programmes and for supply management systems.

When effective operational solutions such as successful service delivery models and processes of care are identified in existing systems, programmes need to consider scaling up such models of care.

9.4.2 Integrating and linking services

Chronic care requires integrating and linking related services to ensure comprehensive and consistent patient management over time, including providing related services in single 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 long-term adherence support and optimize patient retention in care. Programmes for HIV, sexual and reproductive health, maternal and child health, TB and drug dependence need to collaborate to successfully implement ART and related services at different levels of the health system. Issues to be considered include mobilizing and allocating resources; training, mentoring and supervising health workers; procuring and managing drugs and other medical supplies; and monitoring and evaluation.

9.4.2.1 Delivering ART in antenatal care and maternal and child health settings



New recommendation

NEW

- In generalized epidemic settings, ART should be initiated and maintained in eligible 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*).

Background

In 2011, coverage of effective ARV drug regimens for PMTCT reached 57% in low- and middle-income countries. However, in the same year, only 30% of pregnant women who needed ART for their own health received it, compared with 54% ART coverage for all eligible adults in low- and middle-income countries (53). Ensuring access to ART for pregnant women with HIV who are eligible for treatment continues to be a challenge, as does provision of ARVs for PMTCT among pregnant adolescent girls living with HIV, female sex workers and women who inject drugs.

Because many women living with HIV only access health services at the time of pregnancy, maternal and child health settings provide a key opportunity to expand access to ART for those who need treatment (56,57). In most generalized epidemic settings, maternal and child health services are provided at the primary care level, where pregnant women and children predominantly access health services. Existing WHO guidance recommends that provider-initiated HIV testing and counselling be implemented in all antenatal and maternal and child health care settings in generalized epidemics and that it should be considered in antenatal and maternal and child health settings for key populations in concentrated and low-level epidemics (64).

These 2013 guidelines recommend that triple-drug ART or ARV prophylaxis be initiated among all pregnant and breastfeeding women living with HIV, regardless of CD4 count, and that countries decide whether to continue this for all pregnant and breastfeeding women or just those who are eligible for treatment for their own health. Therefore, ART should be available in maternal and child health clinics or easily accessible in a linked clinic approach. Countries with generalized epidemics may consider a phased approach to providing ART in maternal and child health settings and effectively transforming such settings into ART sites, giving priority to facilities with the largest burden of HIV and building health systems to ensure uninterrupted ART, adherence and retention.

A challenge is to continue ART beyond the mother-to-child transmission risk period. Not all maternal and child health settings will have capacity to provide long-term HIV care and treatment for women, their partners and infants. These settings will need to assess the best time for referring and linking mothers and their infants to chronic HIV care. This assessment may include the women's progress in treatment and the capacity and quality of HIV care in the maternal and child health setting as well as the acceptability and proximity of alternative HIV care settings.

Rationale and supporting evidence

The systematic review evaluated the effect of delivering HIV care and treatment in antenatal care and maternal and child health settings on access to ART, mortality, morbidity and retention on ART in generalized epidemic settings. One cluster-randomized trial and three observational studies assessed the impact of delivering ART in antenatal care and maternal and child health settings compared with referring people to HIV care clinics for ART. This positively influenced adherence to ART during pregnancy, enrolment in care and the uptake of ART among women living with HIV. Comparable outcomes were observed for maternal mortality, morbidity, immune response, infant HIV testing uptake, mother-to-child transmission and satisfaction with care. The quality of some of these studies was downgraded because of relatively few events (65–70).

The alternative to providing ART in antenatal care and maternal and child health settings is to refer eligible women and infants to HIV facilities to receive HIV treatment. Referral systems may contribute to the low ART coverage among pregnant and breastfeeding women and infants (57). Referral-based models may further require women and infants to receive care at separate service delivery points that may require pregnant women to travel and wait in queues to receive HIV care and treatment. Studies from Malawi (55), Uganda (56) and Zimbabwe (57) have found that long queues at HIV clinics and the cost of transport from homes to clinics were among the main reasons for loss to follow-up for pregnant and breastfeeding women.

Although HIV programmes may invest to expand access and reduce health facility waiting times, delivering ART in settings where pregnant and breastfeeding women are already receiving care could improve access and provide opportunities for a continuum of care from providing HIV testing to ART at a single site that is also providing antenatal and postnatal care.

In a recent study, women had positive experiences in antenatal care clinics providing ART. They reported that the personnel had “treated them” well and “given them helpful counselling” and that their babies had received “good care” and were free from HIV infection because of this. Other research has explored the operational feasibility of providing ART in maternal and child health care settings and its acceptability to health care personnel in antenatal care clinics. Providers felt that integration increased efficiency, decreased the time people spent in clinics, improved relationships with providers and adherence to ART because of decreased stigma and increased confidentiality. All these factors increased the satisfaction of the people receiving care and may have contributed to improving the quality of care (66,71).



9.4.2.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings



New recommendations

- In settings with a high burden of HIV and TB, ART should be initiated for an individual 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 an individual living with HIV in HIV care settings where TB diagnosis has also been made (*strong recommendation, very-low-quality evidence*).

Background

In 2011, 79% and 48% of the people with TB who were known to be living with HIV received co-trimoxazole prophylaxis and ART, respectively (72). The percentage of people with TB with a documented HIV-positive test result who received ART exceeded 75% in only 6 of the 41 countries with the highest burden of HIV and TB, globally.

Since 2010, WHO has recommended ART for everyone with TB who is living with HIV, regardless of their CD4 count. TB treatment should be initiated first, followed by ART as soon as possible within the first eight weeks of starting TB treatment. Co-trimoxazole prophylaxis is also recommended for all TB patients with HIV. These service delivery recommendations are intended to facilitate expanded ART coverage for people with HIV and TB and to support the early diagnosis and treatment of TB among people living with HIV.

Although the treatment of TB has been decentralized to the community level in most settings, HIV treatment remains difficult to access in many places. Data from a WHO survey indicate that the ratios of the number of health facilities providing TB treatment to the number of health facilities providing ART ranged from 1.3 to 30.2 (72). Moreover, despite a high burden of HIV and TB coinfection, services for HIV and TB treatment may be offered at geographically different sites. Although HIV and TB programmes may invest financial and human resources to improve access and reduce the time associated with receiving care, offering ART and TB treatment at a single point could improve access and adherence to HIV and TB treatment by providing a continuum from HIV testing to HIV and TB co-treatment at a single site.

Implementing TB infection control measures is crucial in HIV care settings to minimize the risk of nosocomial (occurring in a health care setting) transmission of TB. See section 8.1.2 for WHO recommendations on TB infection control in health care settings.

Rationale and supporting evidence

Since people with HIV and TB who do not initiate ART and co-trimoxazole prophylaxis have high mortality and since the combination of ART and co-trimoxazole improves survival (73–75), increasing ART and co-trimoxazole coverage is probably paramount in reducing the large number of people who die from having HIV and TB globally. The systematic review evaluating the effectiveness of delivering ART in TB treatment settings identified 19 observational studies, many of which showed increased ART uptake and timeliness of ART initiation. However, data on mortality and TB treatment success were inconsistent. The systematic review evaluating the effect 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. The quality of evidence was weighed along with programmatic risks and benefits; acceptability; values; preferences; cost implications; feasibility; critical contextual constraints; and contextual relevance. There was consensus that, although the quality of evidence was not high using the GRADE method, there was sufficient rationale to proceed with strong recommendations (76–96).

9.4.2.3 ART in settings providing opioid substitution therapy

New recommendation

NEW

- ART should be initiated and maintained in eligible people living with HIV at care settings where opioid substitution therapy (OST) is provided (*strong recommendation, very-low-quality evidence*).

Background

Data from 49 countries indicate that injecting drug use increases the risk of acquiring HIV infection 22-fold relative to the general population, and in countries in eastern Europe up to 40% of the people acquiring HIV infection are people who inject drugs and their sexual partners (97). Existing WHO guidance states that consideration should be given to recommending HIV testing and counselling to all people attending drug dependence treatment services in generalized, concentrated and low-level epidemics when this is socially acceptable and epidemiologically appropriate. Plans for provider-initiated testing and counselling in such settings should emphasize supportive social, policy and legal frameworks (64).

These guidelines recommend the same criteria for eligibility for ART for all adults regardless of drug use behaviour. Limited global data are available on ART coverage among key populations; however, where data are available, there are often gaps between the coverage among people who inject drugs relative to that of the general population. In 2010, a report including 19 low- and middle-income countries in Europe and central Asia indicated that only 22% of people living with HIV who inject drugs and are eligible for ART received it (53).

For treating opioid dependence, WHO recommends opioid substitution therapy (with methadone or buprenorphine) combined with psychosocial assistance (98). Where there are many opioid-dependent people living with HIV, treatment of opioid dependence should be integrated with and administered in conjunction with HIV treatment. Although ART outcomes improve among people living with HIV who inject drugs and are also accessing opioid substitution therapy, enrolment in settings providing opioid substitution therapy should not be a prerequisite for initiating or maintaining ART for people who use opioids. Nevertheless, providing ART in settings providing opioid substitution therapy may expand access to ART for people who inject drugs.

Common comorbidities such as alcohol use disorders, mental health disorders, TB and viral hepatitis also need to be addressed as part of a comprehensive package of harm reduction interventions, requiring a multi-skilled workforce and close collaboration within the health sector.

NEW



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 and continuity of HIV care and ART when people transition from incarceration to the community.

Rationale and supporting evidence

In many countries, people who inject drugs are a marginalized population with limited access to and utilization of health care services. Drug overdose and AIDS are leading causes of death in this population (99). Randomized trials found that opioid substitution therapy decreases illicit drug use and increases retention in care relative to placebo (98). Observational studies found that opioid substitution therapy decreases mortality relative to not being in care (100). ART outcomes also improved among people with HIV who inject drugs and are accessing opioid substitution therapy (16). The systematic review found one randomized trial and three observational studies evaluating the effect of delivering ART in settings providing opioid substitution therapy. Most of these studies had small sample sizes that limited the statistical power. Some studies observed trends for improved viral suppression and reduced mortality, whereas others found comparable rates of viral suppression and mortality (101–103).

This recommendation focuses on expanding access to ART by delivering the service in settings providing opioid substitution therapy. Coverage of opioid substitution therapy also remains low in many settings, and policy-makers should evaluate whether providing opioid substitution therapy in settings providing HIV care and treatment is feasible. Where health authorities or the health sector do not manage drug-dependence services, HIV programmes need to collaborate closely with social welfare departments and community and nongovernmental organizations that provide these services.

9.4.3 Decentralizing HIV treatment and care



New recommendations

NEW

The following options should be considered for decentralization of ART initiation and maintenance.

- 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 (that is outside health facilities in settings such as outreach sites, health posts, home-based services or community-based organizations) between regular clinical visits (*strong recommendation, moderate-quality evidence*).

Background

Although rapidly scaling up HIV programmes has significantly improved access to ART and increased the health and survival of people living with HIV, it also poses significant challenges to health systems. Decentralizing ART to primary care settings may ease the burden of routine management on other parts of the health system and may improve equity by promoting access to ART in rural areas. In several settings, transport cost is a significant barrier to access and retention in care. In many settings with a high burden of HIV infection, hospitals have long waiting times because of a large flow of patients needing care. Decentralizing HIV care and treatment could reduce the workload for health care personnel, thereby reducing waiting times for people with HIV and people receiving care at hospitals for other conditions and bring HIV services closer to people's homes. HIV-related services such as TB care and maternal and child health services are decentralized to primary care in several settings. People living with HIV, affected communities and community-based interventions play a pivotal role in providing HIV testing, care and treatment and social support. Decentralizing HIV care and treatment can further strengthen community engagement, linking community-based interventions with health facilities, and may optimize access to services, care-seeking behaviour and retention in care.

Rationale and supporting evidence

The systematic review identified two observational studies evaluating how decentralization of initiating and maintaining ART in peripheral health facilities affects patient attrition (patient death and losses to follow-up). Attrition declined after 12 months, resulting largely from significantly reduced losses to follow-up. The systematic review identified four observational studies evaluating how maintaining ART at peripheral health facilities affected patient attrition. Attrition declined after 12 months, due to losses to follow-up and death. The systematic review also identified two cluster-randomized trials evaluating how community-based maintenance of ART affects attrition. Comparable rates of attrition were observed after 12 months (104–115).

When deciding which decentralization option to implement, programme managers may consider (1) the number of people living with HIV likely to attend decentralized settings; (2) whether decentralization brings services closer to people who would otherwise travel long distances to receive ART; and (3) whether decentralizing ART reduces the workload at centralized facilities. This recommendation calls for links to the supply of diagnostics and medicines, services, training and supervision of health workers to maintain the quality of care. In addition, in several settings, decentralizing ART will involve task shifting to ensure an appropriate mix of health care personnel at peripheral facilities.

A WHO operations manual for delivering HIV care and treatment at primary health centres in high-prevalence, resource-limited settings (116) provides additional guidance.

Implementation considerations for decentralizing ART

Box 10.5 discusses implementation considerations relevant to programme managers.



9.5 Human resources

9.5.1 Building human resource capacity

Within the past decade, in the context of the rapid scaling up of HIV care and treatment, in-service training has assumed a key role in rapidly upgrading the competencies of health practitioners.

All health workers, including community health workers, need to be regularly trained, mentored and supervised to ensure high-quality care and the implementation of updated national recommendations. Given the rapidly evolving knowledge on HIV care and treatment, countries need to consider a system for supporting health workers' continuing education, including clinical mentoring and regular supportive supervision. 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 support the efficient use of health workers' time and other resources (116,117).

It is, however, equally important to fully embrace and strengthen HIV care and treatment in existing pre-service courses leading to health workers graduating and being certified in various disciplines. Health workers also need to be equipped to manage HIV as a chronic condition, and to work in a team and need to be familiar with the national guidelines and care protocol. In several countries, people living with HIV, other community workers and volunteers are already involved in delivering HIV testing, counselling, care, treatment and social support services. In addition, people living with HIV are 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.

Countries should consider long-term reform that could support human resource strategies related to task shifting and introducing new types of health workers (such as for HIV testing or peer counsellors) on a sustainable basis within a comprehensive and nationally endorsed regulatory framework (laws and proclamations, rules and regulations, policies and guidelines). Although volunteers can make a valuable contribution on a short-term or part-time basis, all trained health workers who are providing essential health services, including community health workers, should receive adequate wages and/or other appropriate and commensurate incentives (116).

9.5.2 Task shifting for HIV treatment and care

New recommendations



- 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*).

Background

Reorganizing, integrating and decentralizing HIV treatment and care will require re-examining the roles and tasks of teams of health care providers involved in delivering chronic HIV care. Task shifting involves the rational redistribution of tasks among health workforce teams. With this approach, specific tasks are reassigned, where appropriate, from highly qualified health workers to health workers with shorter training and fewer complementary qualifications to more efficiently and effectively use the available human resources. Task shifting should be implemented alongside other strategies designed to increase the total numbers and capacity of all types of health workers.

Health care personnel remain insufficient in many settings with a high burden of HIV. Although increasing the capacity of countries to train more health care personnel is crucial, clinical tasks need to be shared and shifted to ensure that enough health workers are available to care for people with HIV. Task shifting improves access to ART at sites without physicians (such as rural health facilities, TB services and maternal and child health services). Task shifting also allows physicians to spend more time managing more complex clinical conditions such as coinfection and other comorbidities, toxicity of ART or treatment failure.

WHO guidance in 2008 (118) recommended that nurses and non-physician clinicians may initiate and maintain first-line ART and that community health workers may monitor people receiving ART during long-term follow-up. Since these recommendations were largely based on programme review and good practices, the evidence related to task shifting for ART was reviewed when developing these consolidated guidelines.

In this guideline, **initiation of ART** includes assessment for ART eligibility (based on clinical and/or immunological criteria); assessment for opportunistic infections; adherence counselling; and the prescribing of first-line ART. **Maintenance of ART** includes ongoing clinical assessment; monitoring for toxicity, treatment failure (clinical, immunological and virological) and opportunistic and other coinfections; adherence counselling; and the further prescribing of ART. **Dispensing ART** includes assessment for any new signs and symptoms, adherence monitoring and support and dispensing medication to patients who are already on ART between regular clinic visits.

Rationale and supporting evidence

The systematic review identified three randomized trials and six observational studies addressing task shifting. Overall, the data showed no difference in mortality and losses to care when nurses or non-physician clinicians initiate or maintain people on ART or when community health workers maintain people on ART, relative to physicians providing this care. The quality of care in these studies was ensured by (1) providing training, mentoring, supervision and support for nurses, non-physician clinicians and community health workers; (2) ensuring clear indications for patient referral; (3) implementing referral systems and (4) implementing monitoring and evaluation systems. Patient education could help people and their families understand that care provided by nurses and community health workers is not of lower quality than that provided by physicians (106–108,111,113,114,119–121).

Shifting the initiation and maintenance of ART to adequately trained and supervised nurses and community health workers may enable substantial cost savings through (1) the ability to decentralize care to primary care facilities; (2) lower overhead costs for delivering quality care (with comparable or better outcomes) by nurses, non-physician clinicians and community health workers compared with physicians; and (3) decreased facility and utility costs (if care is being delivered in health facilities complemented with community-level services).

9.6 Laboratory and diagnostic services

9.6.1 Overview

These guideline recommendations support increased access to HIV care and treatment, which will also require increased access to laboratory and diagnostic services. To ensure that testing services are accurate and reliable, relevant quality assurance systems need to be developed and strengthened.

Within a country, a multiplicity of testing settings may exist, such as laboratories, maternal and child health clinics, HIV testing and counselling sites, community-based testing and thus a multipronged and networked approach to selecting diagnostics and laboratory systems should be planned and adopted. Since an increasing number of new diagnostic tests and point-of-care systems is entering the market, the use of only high-quality diagnostics and equipment needs to be ensured. Strategic planning for properly placing and harmonizing testing platforms should be carried out to ensure appropriate use and cost-effectiveness.

9.6.2 Implementation considerations and good practices

This guidance to strengthen laboratory and diagnostic services emphasizes the importance of leadership and governance, high-quality laboratory services, expanding testing services and developing the health workforce:

- to strengthen and expand laboratory and diagnostic services;
- to support a dedicated specimen referral system;
- to increase access to HIV viral load testing;
- to support the expansion of diagnostic services to include testing at the point of care;
- to train and certify health workers who perform the testing; and
- to ensure high-quality diagnostics and plans for implementation, including quality assurance.

9.6.3 Strengthening and expanding laboratory and diagnostic services

The following areas are important to strengthen the network of laboratory and diagnostic services for implementing the guideline recommendations:

- standardizing testing methods to streamline procurement, quality assurance and training;
- incorporating new testing approaches and systems into national laboratory strategic plans and policies;
- evaluating diagnostics for their performance and operational characteristics to validate testing algorithms (with back-up options) before introduction;
- carrying out strategic planning for properly placing and harmonizing testing platforms to ensure appropriate use and cost-effectiveness;
- expanding current laboratory networks to support and monitor the decentralization and integration of testing services or to provide access to testing when diagnostic services are unavailable at service delivery sites; and
- allocating appropriate resources to ensure the availability of testing services, including human and financial resources.

9.6.4 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 testing and other testing (for example, CD4 and early infant diagnosis). 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 and rapidly and dependably reporting test results back to the referring site with linkage to care. Rapidly reporting results is essential for timely care.

9.6.5 Increasing access to HIV viral load testing

The guidelines call for monitoring the response to treatment and diagnosing and confirming treatment failure with viral load testing. This will require strengthening the existing laboratory services and phased expansion of monitoring services into peripheral facilities and can include:

- strengthening and leveraging existing CD4 and early infant diagnosis networks;
- ensuring that laboratories have adequate infrastructure, technical testing expertise and quality assurance and quality improvement programmes;
- ensuring an appropriate mix of high-volume centralized laboratory testing and testing at the point of care for facilities in remote locations; and
- the use of dried blood spots as a tool to increase access to viral load testing.

9.6.6 Expanding diagnostic services to point-of-care settings

Decentralizing laboratory and diagnostic services requires that all aspects of testing be in place before implementing services, including:

- 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 supply chain and equipment service; and
- establishing data management systems for timely identification of quality issues and regional and national data reporting.

Table 9.2 provides guidance on organizing testing services at various levels of the health care delivery system.

Table 9.2 Tiered laboratory network at various levels of the health care delivery system

Health care delivery level	Laboratory service	Human resources
National	Enzyme immunoassays for diagnosis Higher throughput CD4 HIV molecular technologies including HIV viral load testing and quantitative and qualitative early infant diagnosis HIV resistance testing	Senior laboratory specialists
Regional or provincial	Enzyme immunoassays for diagnosis Higher throughput CD4 HIV molecular technologies including HIV viral load testing and quantitative and qualitative early infant diagnosis	Laboratory specialists and senior technicians
District	Enzyme immunoassays for diagnosis Low-throughput CD4 Chemistry, haematology and microbiology	Laboratory technicians and assistants
Primary care	HIV rapid diagnostic tests and other point-of-care tests Collecting DBS	First-level trained health workers such as nurses and clinical officers
Community-based	HIV rapid diagnostic tests	Community health workers

Source: adapted from: *WHO expert meeting report on short, medium, longer term product development priorities for HIV-related diagnostics*, 6–7 June 2012, Geneva, Switzerland (122).

9.6.7 Providing guidance for developing health workers' capacity, including staff training and certification

Countries require guidelines for the qualification of personnel who will perform the laboratory tests. The guidelines should include training requirements for specific tests and the process for certification and recertification. All health workers assigned to perform point-of-care testing must be trained and proficient on the testing procedure, specimen collection and quality assurance before implementing these services.

9.6.8 Implementing comprehensive quality management systems

Developing a comprehensive quality management system including external quality assessment and quality control is essential. The quality management system should:

- be implemented within the laboratory network and all remote testing sites;
- be incorporated into the routine testing procedures and monitored;
- ensure that testing sites undertake quality control, as appropriate;
- ensure that testing sites are enrolled in an external quality assessment scheme (proficiency testing programme);
- ensure the use of standard operating procedures for all processes, including specimen collection and processing, test methods, interpreting results and reporting;
- ensure the use of standardized logbooks or electronic data management and reporting, including identifying errors and potential misclassification; and
- ensure that equipment and facilities are maintained, both preventive and corrective.

9.7 Procurement and supply management systems

9.7.1 Overview

Ensuring adequate and continuous availability of quality and affordable essential medicines, diagnostics and other consumables at service delivery sites is a critical role of procurement and supply management systems. The increasing number of people who need chronic HIV care, especially in settings with a high burden of HIV infection, necessitates an uninterrupted supply of HIV-related health products. This can be achieved only if the procurement and supply management system is strengthened at all levels of the health system. Moreover, ARV drug regimens and formulations and HIV treatment recommendations need to be regularly updated in response to new developments and emerging evidence. This requires a more efficient and dynamic supply management system to prevent waste and shortages.

9.7.2 Rationale and supporting evidence

Successful HIV programmes are only possible if all services providing ART are equipped with an uninterrupted and sustained supply of high-quality ARV drugs, preferably WHO-prequalified products. Other pharmaceuticals that are needed to support ART services include medicines to prevent or treat opportunistic infections, and laboratory reagents, supplies and equipment to diagnose HIV and opportunistic infections, monitor the progression of HIV infection and treatment response and detect adverse drug reactions. Since a single health facility may not carry out the dispensing of all needed pharmaceuticals, in some settings clients would need to be able to access services through a referral system.

9.7.3 Implementation considerations and good practices

Management support is integral to each component of the procurement and supply management cycle: selection, procurement, storage and distribution, use and monitoring. It includes a variety of activities at all levels of the health care delivery system: from the national programme level down to where medicines are dispensed and diagnostics are used. The main activities include managing the information system, ensuring timely information flow between stakeholders at different levels and securing financial and other resources, including the medicines and diagnostics needed for the programme. The following provides broad guidance on key activities at each stages of the supply management cycle.

9.7.3.1 Selecting pharmaceuticals and diagnostics

Countries adapting these guidelines may need to update national medicine lists to include newly recommended ARV drug regimens and formulations and diagnostics. The advantage of using the essential list concept is to enable a health system to limit other more expensive or WHO-delistated medicines and diagnostics from being purchased and accelerating the registration of WHO-prequalified products to facilitate quality-assured procurement (123). If a selected fixed-dose combination or other ARV drug regimen is not on the national list or not registered in the country, HIV programme managers need to coordinate with the national drug regulatory authority and request that these drugs be put on the list and registered.

Detailed national ART guidelines, for example, that provide recommendations for managing toxicity or treatment failure and recommended formulations for weight and age can help to standardize prescribing and dispensing practices and facilitate forecasting for ARV drugs.

Synchronized introduction of new guidelines with forecasting, procurement and distribution planning during the phasing in and phasing out of new and old ARV drug products will minimize the waste of products that are being phased out and shortages of newly recommended products.

In several settings, paediatric formulations are not widely available. The national medicine list should be optimized for paediatric ARV drug formulations, to include fixed-dose combinations, scored or dispersible products that facilitate adherence and supply management. Countries may consider removing less preferred products and aligning paediatric formulations with those of adults, where possible.

Health workers need to be trained at different levels in managing pharmaceuticals and diagnostics, including forecasting, procurement and distribution and ensuring adequate supervision throughout the supply system.

9.7.3.2 Procurement

A uniform and harmonized national procurement system is required for efficiently procuring quality-assured affordable ARV drugs and diagnostics (124,125). Procurement should be based on appropriate selection of products and need-based forecasting, considering consumption, expanding services, phasing in and phasing out formulations and implementing new recommendations. Transparent procedures should be adopted to achieve best-value procurement and a quality assurance system implemented to procure, store and distribute high-quality pharmaceuticals, diagnostics and other health products (124,126).

Procurement systems should:

- procure the most effective, heat-stable, fixed-dose quality-assured ARV drug formulations in the right quantities, at the lowest possible cost and in a timely manner;
- request that the partners supporting the national HIV programme consolidate and harmonize ARV drugs and diagnostics procurement and supply management systems and pool demands for ARV drugs and diagnostics, exploring options for pooling under a common tender system;
- use a publicly accessible database to facilitate access to information about prices and support competition (127–130); and
- follow the principles described in the United Nations interagency guidelines for donated drugs (131).

9.7.3.3 Storage and distribution

Appropriate storage and distribution of HIV medicines, diagnostics and other commodities are important components of the supply management system (Table 8.3). Product integrity and quality need to be maintained during storage and distribution (125,132), and waste from spoilage and expired products should be minimized. Integrated supply systems should be promoted when planning for decentralization, building on what exists and strengthening capacity where required. For example, existing immunization programme infrastructure, including cold chains, could be used to expand the supply of paediatric formulations, such as LPV/r liquid formulations. Facilities should have adequate storage space, trained personnel and the tools to manage supplies effectively. The number of storage levels should be rationalized to reduce the supply pipeline.

Accurate inventory records should be maintained and a system created to track products that enter and leave the supply system. A routine consumption-based reordering cycle at service delivery sites should be established. Flexibility should be introduced in the supply system such as procedures for reporting and redistribution of excess ARV drug supplies, more frequent ordering and filling of non-routine orders to minimize expiry and stock-outs. Pharmaceutical and diagnostic products need to be adequately stored, especially if ART delivery is further decentralized and is dispensed from an increasing number of peripheral health facilities. Measures are required during transport and storage to prevent theft and fraud such as vehicle tracking systems, secured storage areas, audits and labelling of ARV drug products procured by HIV programmes.

9.7.3.4 Use and monitoring

Robust information systems ensure the availability of accurate and timely consumption data on ARV drugs and other information required for effectively monitoring the performance of the entire supply system and for forecasting the ARV drugs and diagnostics needed. Monitoring procurement and supply management through the effective use of early warning indicators prevents stock-outs and overstocks leading to expiry (126).

Table 9.3 Summary checklist of pharmaceutical supply management issues

Phase	Activity	Determination
Planning	Selecting products	Updated national HIV guidelines Updated national lists to include newly recommended ARV drug regimens and formulations and diagnostics
	Estimating and quantifying ARV drug requirements	
Procurement	Selecting and locating suppliers	Open and transparent communication with industry Prequalified suppliers Implementing review mechanisms
	Assuring the quality of products and sources	Criteria for manufacturer prequalification Implementing a prequalification system Using the WHO certification scheme, inspecting and testing the quality of samples Pre-shipment physical inspection with random sampling for laboratory testing Systems for records and supply monitoring
	Arranging for purchasing	Ongoing assessment of purchasing options Need for special labelling and packing Need for reserve or buffer stocks Managing purchasing arrangements
Distribution, rational use and monitoring	Receiving supplies in the country	Port clearance, including availability of funds for paying duties and taxes Securing appropriate warehousing at all levels needed Physical inspection on arrival of each consignment with random sampling for laboratory testing
	Distributing in the country	A logistics system for timely distribution to end-users
	Rationally using and monitoring pharmaceuticals	Providers adequately trained Systems for monitoring and reporting, including monitoring adverse effects feeding into the selection; rational prescription; and forecasting in place At the central level, any problem such as theft, recall by the supplier, poor quality and adverse drug reactions should be recorded and reported at different levels to all relevant bodies. This would involve developing problem-reporting forms, indicating to whom they should be sent, and what action should be taken

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Goal of this chapter

To provide programmatic guidance for decision-makers and planners at the national level as they work to adopt and implement the clinical and operational recommendations in these guidelines.

10. GUIDANCE FOR PROGRAMME MANAGERS

10.1 Introduction

The recommendations in these guidelines increase the number of people eligible for ART, promote new first- and second-line regimens and propose changes in approaches and strategies to laboratory monitoring to maximize treatment effectiveness.

National stakeholders face several important choices on how to optimally translate these recommendations into national practice. For example, although evidence of clinical efficacy supports the uptake of interventions, issues such as cost and cost-effectiveness, ethical and human rights considerations, the perceptions of various stakeholders and the legal and regulatory environment must also be taken into account (1).

National HIV programme managers play a unique role in managing the process for adapting and implementing the HIV guideline recommendations in their respective countries. First, convening a broad, inclusive and transparent consultative process can help to define what programme changes are relevant and necessary, such as revising national protocols, guidelines and regulations. Second, in parallel, it is necessary to secure the financial resources and political support required to implement the proposed changes. Third, systems are required to ensure broad accountability for implementation from all partners at all levels and adequately document performance to inform programming decisions and maintain political support. Lastly, implementation and operations research should be supported so that innovative approaches can be assessed and taken to scale.

Human rights and ethical principles should guide the revision of national treatment policies to ensure that they are equitable and meet the specific needs of all beneficiaries. New recommendations should inform the HIV programme's overarching vision, goals and objectives, and existing strategic plans should be adapted accordingly to assure consistency, avoid duplication and leverage potential economies of scale (2).

As HIV programmes mature and increasingly focus on the challenges of long-term prevention, treatment, care and support, national responses need to be considered within the broader health and development contexts. The sustainability and effectiveness of HIV programmes can be greatly enhanced by creating and strengthening linkages with other health and non-health programmes (3).

10.2 Decision-making process

Decisions regarding the implementation of global recommendations should be made through a transparent, open and informed process that recognizes the multisectoral nature of the HIV response. National HIV programmes should consider convening a multidisciplinary working group, if one is not already in place, to advise on the choices and decisions necessary for updating and implementing national guidelines. The role of the guideline group may include (1) reviewing the current context of national HIV and TB epidemics, including the health sector response and the broader policy environment; (2) assessing global and local evidence related to the new recommendations and advising on how to adequately interpret them within the local context; and (3) identifying implementation issues such as estimated costs, human resource and infrastructure requirements and how these should be addressed (4). Sections 10.3 and 10.5 address these topics in greater detail.

Although national programme managers should oversee the decision-making process, it should also be broadly representative. Broad stakeholder engagement in policy design, implementation, monitoring and evaluation will help to ensure that the national adaptation of global guidelines results in HIV programmes that are legitimate, acceptable, effective and equitable and address community needs (1,5).

The composition of the working group may vary over time and depend on the specific recommendations under discussion. For example, when considering how to improve programmes for preventing the mother-to-child transmission of HIV (PMTCT), joint planning with those responsible for maternal and child health should be undertaken. Checklist 10.1 provides a checklist of key elements to consider in implementing a transparent and inclusive decision-making process.

10.3 Data to support decision-making (5)

10.3.1 Overview

Decisions on how to adapt and implement these guidelines should be based on a careful assessment of epidemiological dynamics and programme performance to identify programme strengths and weaknesses and necessary policy changes, consistent with the principles of “know your epidemic, know your response” (Checklist 10.1) (6,7). In some countries, these data may be available from regular monitoring and evaluation activities or from recent programme assessments. Elsewhere, new analyses may be warranted, such as studies of the modes of HIV transmission, to shed light on key epidemiological or response elements. Quantitative and qualitative data should, whenever possible, be disaggregated by gender, age, subnational administrative categories (such as regions and districts) and other relevant stratifications, including key populations, to ensure that new policies address inequities in access and increase the coverage of interventions. The consolidation of health information systems, including patient record registries, into electronic databases is critical to facilitate the management of increasing amounts of data and improve their robustness and availability for programme decision-making (see section 11.5).

10.3.2 National and local HIV epidemiology

An epidemiological analysis should describe the prevalence levels among the general population and in specific key populations, the rate at which HIV infection is acquired and among whom, including infants, young children, pregnant women and serodiscordant couples. Both prevalence and incidence measurements should aim to identify populations at higher risk for HIV infection, including in generalized epidemic settings,⁹ and adequate population size estimates for these populations should be available so that results can be interpreted appropriately (9). Data on the prevalence and incidence of key coinfections (such as TB and hepatitis B and C) and other comorbidities should also be gathered to inform decision-making.

10.3.3 Programme performance and response analysis

Determining whether current ARV programmes are adequate to address the needs that have been identified requires understanding who is currently accessing these services. Programmes should assess present ARV coverage levels among the general population as well as key populations, the disease stage at which they access care, how well these groups are retained in care and treatment, the ARV regimens used and the impact of ART on viral load suppression, morbidity and mortality. Programmes that are considering raising the CD4 cell count threshold for ART eligibility should ideally have data on the median CD4 cell counts and the stage of HIV disease of people at the time of their HIV diagnosis and at the time of initiating treatment. Disaggregated data for various groups enable assessment of ARV needs and establishment of priorities for delivering services. Data on adherence, retention and viral load suppression are key to assess the quality of the services provided. Surveillance of transmitted and acquired HIV drug resistance can also be instrumental in informing decisions on optimal regimen choices (Box 11.1). Whenever possible, indicators of impact, such as changes in HIV-related incidence, prevalence, morbidity and mortality, should also be reviewed.

10.3.4 Socioeconomic, policy and legal context

A review of epidemiological and programmatic data is incomplete without a deeper understanding of what drives HIV vulnerability and how various political, social, economic and legal factors affect the ability and willingness of various groups – such as men, women, adolescents, sex workers, men who have sex with men, transgender people and people who inject drugs – to seek and access health services. Stigma, discrimination, poverty, gender inequality, education and migration status are key elements that should be taken into account to inform effective HIV programming. The legal context can also affect access to interventions, such as laws related to intellectual property rights and those that criminalize homosexuality, HIV exposure and/or transmission, drug use and sex work. Such laws should be reviewed and reformed to eliminate discriminatory practices, decrease HIV vulnerability, improve access to health services and protect human rights.

⁹ Incidence estimates by modes of transmission have already been developed for some countries and are available from UNAIDS (8).

Checklist 10.1 Process and evidence for decision-making

Process for decision-making (10,11)

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 light of new evidence and arguments?
- Enforcement:** Are all stakeholders aware of the means to ensure that these conditions (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)?

Evidence for decision-making

1. HIV incidence and prevalence

- In what population groups are HIV incidence and prevalence highest? Relevant criteria include gender, 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 % 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?

10.4 Key parameters for decision-making

10.4.1 Ethics, equity and human rights

Multiple legal, social and normative obstacles have resulted in inequitable access to HIV treatment and care. For example, data from 19 countries in Europe and central Asia showed that, although people who inject drugs accounted for 62% of cumulative reported HIV cases with a known transmission route in 2010, they represented only 22% of the people receiving ART in countries surveyed (12,13).

Global and national commitments require providing HIV treatment and prevention to everyone in need, following the human rights principles of non-discrimination, accountability and participation (14–16). National HIV strategies should be planned and implemented from the outset with the ultimate goal of delivering the full package of services and interventions recommended in these guidelines as soon as possible.

Key ethical principles of fairness, equity and urgency should also be observed in the process of reviewing and adapting guidelines. The design of effective and equitable policies implies that strategies should focus comprehensively on addressing barriers to access testing, prevention and treatment services, particularly those faced by key populations. Facility- and community-level reviews may be useful to understand the extent to which services are acceptable and adapted to the specific needs of key populations.

10.4.2 Impact and cost–effectiveness

Realizing positive impact for a population is an important goal of public health programmes and policies. Examples of the impact of HIV programmes include reduced HIV incidence, prevalence, morbidity and mortality and improved quality of life (17). Impact is often a result of a complex set of factors and a combination of diverse inputs and activities or processes, and it is often not attributable to a single intervention or programme (5).

Cost–effectiveness analysis is one of several economic evaluation tools used to measure the value of delivering particular services. Economic evaluation measures the costs and consequences of alternative programmes, which are then compared to assess how the greatest health benefits can be generated. In cost–effectiveness analysis, impact is often measured using indicators related to a change in health status, such as disability-adjusted life-years (DALYs) gained, which includes the estimated number of deaths and infections averted. As the experience of scaling up ART in low- and middle-income countries demonstrates, the cost–effectiveness of health interventions also changes over time, as costs fall because of gains in scale, improvements in technology or the design of more efficient delivery systems.

During the development of these guidelines, a consortium of research groups independently developed and then compared mathematical models to assess the epidemiological and clinical impact as well as cost–effectiveness ratios of various interventions, notably those related to earlier initiation of ART (Box 10.1).

Although evaluating cost–effectiveness and health impact may be useful in systematically comparing various programme interventions, they should be considered in the light of the ethical, equity and human rights implications associated with different courses of action, especially in settings in which not all eligible individuals currently have access to ART.

Investments in critical enabler programmes (such as integrated treatment and rights literacy programmes, legal services, stigma and discrimination reduction programmes, training for health care workers and law enforcement) can play a role in overcoming barriers to accessing treatment and other HIV-related services and keeping people connected to care. As such, these programmes can contribute to overall cost–effectiveness, in addition to achieving other important objectives, such as reducing discrimination (18).

Box 10.1 Estimating the impact and cost–effectiveness of selected recommendations using mathematical models: results from the independent HIV Modelling Consortium

As HIV programme managers work to implement these guidelines, they may face complex choices on how to optimally allocate resources for HIV treatment: for example, determining the relative allocation of resources for scaling up HIV testing and linkage to care and for increasing access to ART based on expanded eligibility criteria.

The HIV Modelling Consortium, an independent group of research institutions (www.hivmodelling.org), used multiple independent mathematical models based on data sets from four countries with different types of epidemics and current ART coverage – India, South Africa, Viet Nam and Zambia – to examine the health benefits, costs and cost–effectiveness of various strategies for expanding eligibility for ART as well as testing and access to HIV care (19) (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes). In each case, a range of potential options was investigated, including various thresholds for ART eligibility (CD4 cell count less than 500 cells/mm³, all people with HIV and specific key populations), assuming current as well as expanded patterns of HIV testing and linkage to care. The costs and both individual and preventive health benefits associated with each intervention were estimated, including changes in HIV incidence, reductions in the loss of healthy life-years and costs over time. These models also considered the relative cost–effectiveness of strategies, highlighting which of them, for a given budget, would be expected to maximize health gains.

Expanding the criterion for ART eligibility to CD4 cell count ≤ 500 cells/mm³ was found to be highly cost-effective in low- and middle-income settings. However, combining expanded eligibility with a large increase in HIV testing and linkage to care produced the greatest benefits, especially in settings with low ART coverage. Expanding ART eligibility to all adults with HIV (irrespective of CD4 count) was less cost-effective than expanding the criterion to ≤ 500 cells/mm³ because of less immediate improvements in health as the CD4 threshold for initiating ART is increased.

The modelling results should be interpreted in light of some important limitations. Many of these conclusions could change substantially depending on cost assumptions, especially those related to testing and counselling and to retaining people in pre-ART care. Moreover, the models did not consider how the estimated impact and cost–effectiveness of the various interventions would change if they were combined or only partly implemented. Models also did not address potential trade-offs with non-antiretroviral interventions, and several important issues were not covered, such as treatment of children (section 6.2.4 discusses the relative cost-effectiveness of various treatment options for children).

10.4.3 Opportunities and risks

The recommendations in these guidelines have the potential to further reduce HIV-related mortality, improve the quality of life, reduce the number of people acquiring HIV infection and enhance treatment effectiveness. The benefits accrued from implementing them are likely to considerably outweigh the upfront investment needed and have the potential to fundamentally change the course of the epidemic. Nevertheless, domestic factors (such as budget cuts, theft of ARV drugs, attrition of trained health workers and emergence of drug resistance) and external contingencies (such as withdrawal of external financial support, political instability and natural disasters) could negatively affect their implementation. It is essential to design strategies to mitigate such events so that continued service delivery can be assured, especially for those most in need (20).

10.5 Implementation considerations across the health system

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 which areas require additional investment. The six building blocks for health systems identified by WHO provide a useful analytical framework (21). Checklist 10.2 provides a checklist of key critical issues in these areas. Such considerations should not determine whether a particular recommendation is included or excluded from national guidelines but can be used as a tool to understand the impact of a recommendation and how best to adapt it and mobilize resources for its implementation. When the relative budget implications of specific recommendations are considered, it is also important to take into account the costs of inaction in terms of increased mortality, morbidity and HIV transmission. An implementation plan should clearly define the set of activities required in a specified period of time to achieve targeted outcomes, with a clear division of labour among all stakeholders involved in implementing programmes.

Robust procurement and supply management systems are needed to ensure the continued availability of all necessary drugs, diagnostics and other commodities across the various levels of the health system. Pooled or joint procurement can be used to secure lower costs through economies of scale, and careful demand forecasting is key to minimizing waste. Fixed-dose combinations and once-daily therapy should be used whenever possible to support adherence and make treatment as convenient as possible for the people receiving therapy and their caregivers. Laboratory capacity must also be reviewed and services should be strengthened to cope with higher demand, and nationally standardized health information systems and patient monitoring tools should be used in all settings. Stronger interventions are also needed to maximize treatment adherence and retention across the continuum of care. Specific interventions may be needed in particular settings, such as postpartum follow-up of mother–infant pairs.

The quality of health care is a critical dimension to consider in the planning and adaptation process. The rapid scale-up observed during the past decade has left gaps in the quality of service delivery at times that have negatively affected, for example, adherence rates, timely enrolment in care or retention on ART. The implementation of new guidelines provides an opportunity to comprehensively review and address such gaps. Critically, this requires effective monitoring and evaluation systems (see Chapter 11). A key component of sound quality assurance mechanisms is a clear delineation of roles and responsibilities for the delivery of the various functions and inputs (such as leadership, financing, supply chain management, human resources, monitoring and evaluation needed for effectively providing services at the national, regional, district, facility and individual clinician levels). A quality assurance and improvement framework developed for HIV testing and counselling may inform broader quality assurance and quality improvement interventions across the continuum of care (22).

Effective HIV programming is multisectoral in nature and goes beyond biomedical interventions. It is essential to assess how HIV interventions can be optimally linked with other health programmes and non-health services to increase coverage and optimize resources. Planning should also take into account the variety of providers involved in health service delivery, including public, private and not-for-profit organizations. Community involvement and peer outreach strategies are key to improve programme design, promote its sustainability and maximize coverage.

Checklist 10.2 Implementation checklist of key health system issues

The successful implementation of new recommendations depends on several critical decisions in key programme areas.

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 stakeholders such 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, midwives, community health workers and laboratory assistants) are needed and how they can be recruited?
- Can task shifting and sharing be employed to optimize available human resources and expand service delivery? (see section 9.5.2)

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 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 linkages and referrals 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 investments from the ARV programme?
- Is additional communication infrastructure needed, including between health facilities, health workers, laboratories and clients?

Checklist 10.2 (continued)

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 only, or lifelong ART?);
 - testing and counselling;
 - general HIV care;
 - clinical monitoring;
 - mentoring, quality assurance and monitoring; and
 - community-level services.

7. Funding

- Have the sources of funds, such as government budget, social security or health insurance, Global Fund, United States Presidents' Emergency Plan for AIDS Relief, UNITAID and private foundations, been identified? (It is important to consider that out-of-pocket expenditure may limit 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 synergies 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?

10.6 Implementation considerations for key recommendations

Boxes 10.2 to 10.7 discuss implementation considerations for programme managers for six key recommendation areas in these guidelines: (1) changing the CD4 cell count threshold for initiating ART for adults and adolescents from 350 to 500 cells/mm³; (2) scaling up viral load testing; (3) moving to lifelong ART for all pregnant and breastfeeding women; (4) decentralizing ARV services; (5) expanding treatment for children; and (6) phasing out d4T.

Box 10.2 Key implementation considerations for programme managers: raising the CD4 threshold for initiating ART in adults and adolescents from 350 to 500 cells/mm³ (section 7.1.1)



- 1. Treat the sickest people first.** Individuals with CD4 cell counts of less than 350 cells/mm³ have a different mortality profile than those with higher CD4 cell counts. What systems will be in place to ensure that the sickest people are adequately given priority, especially in settings with low ART coverage?
- 2. Phase out d4T.** Given the long-term toxicity and side effects of d4T, programmes raising the ART initiation threshold to 500 CD4 cells/mm³ should have significantly progressed in phasing out d4T in adult and adolescent regimens to optimize treatment outcomes.
- 3. Consider task shifting and decentralization.** Human resource plans should be developed or adjusted to support the policy decision to increase the CD4 eligibility threshold, including through task shifting and training new cadres of health workers (see section 9.5.2).
- 4. Reinforce adherence support.** A higher threshold for initiating ART means that more people who feel healthy will become eligible for treatment. What interventions to promote and reinforce adherence will be implemented for these people?
- 5. Provide treatment monitoring.** As more people initiate ART earlier and stay on it for longer, monitoring viral suppression becomes increasingly important, as keeping people on failing regimens may lead to higher levels of drug resistance, which might compromise the efficacy of treatment, especially of NNRTIs. How will access to viral load monitoring be scaled up?

Box 10.3 Key implementation considerations for programme managers: scaling up viral load testing (section 7.3.2)



- 1. Consider the various diagnostic options.** Several strategies exist to increase access to viral load testing, including the use of dried blood spots (DBS) and, in the near future, point-of-care technologies. Programme managers need to consider the optimal choice in light of multiple factors, such as the availability of existing infrastructure and the number of people receiving services at different levels of care (such as centralized versus peripheral sites).
- 2. Review the use of viral load monitoring in the context of alternative patient monitoring strategies.** The relative benefit of CD4 monitoring in a context of greater viral load availability may need to be reassessed considering the different specificity profiles of these technologies as markers of treatment failure, their cost and technical requirements for implementation. For example, programmes may consider reducing the number of CD4 tests done for people whose viral load is being routinely measured. CD4 testing is still required to determine ART eligibility.
- 3. Provide adherence support.** An important proportion of people receiving ARV drugs develop detectable viral load because of inadequate adherence to treatment and can return to undetectable levels if adequate counselling is in place, avoiding unnecessary switching to second-line regimens.
- 4. Develop treatment literacy on the use of viral load.** As most programmes in low- and middle-income countries have historically relied on CD4 monitoring, people receiving ARV drugs and health care providers may not be familiar with the concept and importance of viral load. Counselling should be provided so that people receiving ARV drugs and health care providers understand the meaning and implications of having a detectable or undetectable viral load and its relation to adherence.

Box 10.3 (continued)

5. **Ensure an adequate supply of second-line ARV drugs.** People whose viral load remains detectable following adherence support have probably developed drug resistance and may need to switch regimens. Programme managers should be prepared to offer alternative regimens, including second-line ARV combinations, to address these situations.
6. **Implement quality assurance strategies.** As viral load testing is scaled up, its quality must be assured. Centralized systems should be enrolled in external quality assurance programmes, while new quality assurance approaches are needed for decentralized and point-of-care systems.

Box 10.4 Key implementation considerations: moving to lifelong ART for all pregnant and breastfeeding women (option B+) (section 7.1.2 and Annex 6)


1. **Consider the appropriate approach to scaling up.** The infrastructure and operational implications of providing lifelong ART to all pregnant and breastfeeding women living with HIV must be carefully reviewed. Countries may consider a phased approach with an early learning phase before full scale-up.
2. **Assure linkages to care and patient transfer.** The location in which ARV drugs are provided to pregnant and breastfeeding women and the provision of long-term ART should be considered and decided before the programme is implemented. Will women continue to receive ART at the site providing ARV drugs for PMTCT or will they be transferred to an existing ART site? What strategies will be put in place to minimize the risk of women being lost to care as they are transferred to various ART service locations?
3. **Review human resource requirements.** Many staff at PMTCT sites have had limited training in and experience with providing ART, especially in settings in which Option A has been implemented for PMTCT. Capacity-building, task shifting and potential expansion of health personnel may be needed to allow PMTCT sites to successfully take on the additional responsibility of providing lifelong ART.
4. **Promote adherence and retention.** Adherence to therapy and retention in care of mother–baby pairs may be especially difficult in the postpartum breastfeeding period. What strategies will be put in place to monitor and support adherence and retention and re-engage in care those lost to follow-up, including both the mother and the HIV-exposed children?
5. **Consider ethical issues.** Initiating lifelong ART for all pregnant and breastfeeding women regardless of CD4 count may result in temporary disparities in access to treatment. For example, a pregnant woman with a high CD4 count may continue to receive ART after delivery, whereas her husband, other family members, neighbours or other women intending to get pregnant with a lower CD4 count may not yet be eligible for treatment. What process and strategies will be put in place at the policy and service delivery levels to address such possible disparities? How can the enrolment of all pregnant and breastfeeding women into lifelong treatment be leveraged to enhance a family approach, including getting partners and other household members tested for HIV and treatment?
6. **Assure the quality of HIV testing.** Developing quality-assurance programmes, including for HIV rapid testing (which in some settings may be the only test used to determine the initiation of lifelong ART) and appropriate use of testing algorithms, will be important to ensure optimal implementation in all areas of the country.



Box 10.4 (continued)

7. **Assess laboratory monitoring needs.** Although CD4 testing may not be required to initiate ART among pregnant women, toxicity and ART response monitoring, including viral load (which is key for assessing viral suppression), should be available, similar to all people receiving ART. Infant diagnosis is also essential to identify infants infected with HIV and to link them to the necessary treatment and care. Surveillance systems (which can be sentinel sites) should be established to evaluate the impact of ART on birth defects, pregnancy outcomes, safety among infants and young children exposed to breastfeeding as well as transmission outcomes and tolerance of first-line ART.
8. **Implement adequate monitoring and evaluation frameworks.** New strategies are needed to ensure high quality and longitudinal cohort data on the mothers and their HIV-exposed infants across a range of service delivery entry points and across the continuum of care. For breastfeeding mothers and infants, the true effectiveness of a PMTCT programme depends on infant infection status and HIV-free survival at the end of the breastfeeding period and not on early infection status at age six weeks.
9. **Provide infant prophylaxis.** Infant prophylaxis is particularly critical for PMTCT in situations of late HIV diagnosis in the mother, limited or no antepartum maternal ART or if maternal ART is interrupted due to toxicity, intolerance or lack of adherence.
10. **Assure continuous drug supply.** An uninterrupted supply of maternal ART during pregnancy and breastfeeding is critical for PMTCT as well as maternal health. Adequate drug forecasting and drug supply chain is essential.

Contextual issues to consider for PMTCT options

Although country programmes will define the choice between (1) providing ART to pregnant or breastfeeding women living with HIV for the duration of the risk of mother-to-child transmission or (2) lifelong ART regardless of CD4 cell count based on local circumstances, preferences and values, several contextual features are especially relevant for decision-making.

1. Providing lifelong ART ("Option B+") to all pregnant and breastfeeding women is particularly relevant in settings with the following characteristics:
 - generalized epidemics;
 - high repeat pregnancy rates¹¹ and low family planning coverage;
 - low partner testing rates;
 - limited access to CD4 testing;
 - low existing coverage of ART for pregnant women who meet the treatment eligibility criteria for non-pregnant individuals; and
 - long duration of breastfeeding by women living with HIV.
2. Providing ART only during the period of risk of mother-to-child transmission (Option B) with continuing lifelong ART only for those women meeting standard eligibility criteria for the treatment of non-pregnant adults is especially relevant in settings with the following characteristics:
 - concentrated epidemics;
 - lower repeat pregnancy rates and higher family planning coverage;
 - high access to CD4 testing;
 - high existing coverage of ART for pregnant women who meet the treatment eligibility criteria for non-pregnant individuals; and
 - formula feeding is recommended, available and safe.

Box 10.5 Key implementation considerations for programme managers: decentralizing ART services (section 9.4.3)



- 1. Examine the models and options.** Programmes should determine which clinical and laboratory services will be available at what level of the health care delivery system. The optimal model for ART decentralization (partial or full) depends on the local context.
- 2. Consider human resources policies and task shifting.** All health workers, including community health workers, need to be trained regularly, mentored and supervised to ensure high-quality care and implementation of updated national recommendations. 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, in addition to nationally standardized training, mentoring and supervision for all health workers involved in HIV care.
- 3. Implement strategies for retaining staff.** Programme managers should support the development and implementation of policies to create a suitable environment for recruiting, retaining and motivating personnel in rural or remote areas, where health worker turnover and attrition may be considerably higher than in urban settings.
- 4. Strengthen linkages and referral systems.** Although community-based treatment programmes provide an important option for decentralizing ART, they should always be linked with regular care at health facilities and with adequate laboratory, diagnostics, monitoring and evaluation and drug and supply management systems.
- 5. Agree on a division of labour.** An efficient division of responsibilities among levels of the health system (national, provincial or regional and district) is crucial to minimize duplication and to optimize the use of resources. The role of each level should match its capacity, and the lines of authority and accountability should be clear and well understood by all.
- 6. Build partnerships.** National regulatory bodies, professional associations and other stakeholders need to be involved when addressing the scope of practice, roles and responsibilities of health workers.

Box 10.6 Key implementation considerations for programme managers: scaling up treatment for children – treating all children under 5 years and raising the CD4 threshold in older children from 350 to 500 cells/mm³ (sections 7.1.4 and 7.2.3)



- 1. Expanding ART coverage should be the first priority.** Since all treatment regimen options have been shown to reduce morbidity and mortality, the use of less preferred options is better than leaving children untreated.
- 2. Younger children are at greater risk of poor outcomes.** Children younger than two years living with HIV have higher mortality rates and more rapid disease progression than older children. Early diagnosis and prompt initiation of ART are especially critical for infants and young children.
- 3. Strengthen links between diagnosis and treatment.** Diagnosis and treatment for children are often performed at different facilities, increasing the risk of their being lost to follow-up. Improving links between early infant diagnosis and ART sites is essential to minimize such losses and improve uptake of ART among children. Family-based approaches to HIV testing and provider-initiated testing and counselling are important approaches to increase HIV diagnosis and treatment among children.
- 4. Optimize and improve the choice of ARV formulations available.** It is critical to accelerate regulatory approval of preferred formulations. Scored dispersible fixed-dose combinations for children with dosage based on weight bands can support the scaling up of ART for children in remote areas.



Box 10.6 (continued)

5. **Leverage existing infrastructure and channels.** Making ART available for children wherever adult ART and PMTCT interventions are provided is key to improving access and uptake, especially as service delivery is decentralized to lower-level health facilities.
6. **Promote retention and adherence.** Children depend on adults for their treatment. It is important to design and implement family-based care strategies that can support and facilitate retention and adherence among children. Interventions must also take into account the special adherence challenges of children who move between households.

**Box 10.7 Key implementation considerations
for programme managers:
phasing out d4T (section 7.2)**


1. **Choose a suitable alternative.** WHO recommends TDF as the preferred alternative to d4T in first-line regimens. TDF is also more likely to be effective than AZT among people who have developed resistance while on d4T.
2. **Design a costed phase-out plan.** The overall operational plan for phasing out d4T should be fully costed and should consider any additional investment in laboratory strengthening and capacity-building that may be required to support implementation.
3. **Identify priorities for implementation.** Because of programme constraints, not all countries may be able to promptly switch everyone receiving d4T to new regimens. Priorities should be clearly defined and agreed with all relevant stakeholders.
4. **Avoid treatment disruption.** Although new d4T orders should be discontinued, adequate and timely forecasting and procurement of the preferred alternative drug are critical to avoid stock-outs and treatment interruption.
5. **Review and compare prices.** Substantial reductions in the price of both TDF and its preferred companion drug EFV have been observed in recent years. Countries are encouraged to ensure they are procuring these drugs at the best possible price. WHO's Global Price Reporting Mechanism may be a useful source of price information (23).
6. **Manage stockpiles.** Options include reserving stocks for back-up situations for individuals who may require d4T in the absence of alternative choices.
7. **Train and educate both clinic staff and people receiving ART.** Clinic staff should be trained and prepared to carry out the transition and to educate ART patients about their new regimens.
8. **Phase out d4T among children when alternatives are available.** WHO's recommendation to phase out the use of d4T applies equally to both adults and children. However, considering the limited availability of age-appropriate NRTI formulations, d4T may be used in special circumstances, especially in settings where formulations of abacavir for children are not available (see sections 7.2.3. and 7.2.4).

10.7 Implementing recommendations in different contexts

10.7.1 Overview

Although all countries have agreed to provide universal access to HIV prevention, treatment, care and support by 2015, the local context – including epidemiology and current coverage of interventions – will determine their trajectory towards this goal. This section provides a broad outline of possible sequencing approaches to phasing in key recommendations, considering the available scientific evidence, results from mathematical models (Box 10.2) and ethical and human rights issues. It draws on views expressed in the Guidelines Development Group on Programmatic Issues and therefore does not constitute formal recommendations. National stakeholders are responsible for the process of revising and adapting the guidelines, and different approaches may be necessary and equally valid.

10.7.2 Implementing recommendations in different epidemic settings

The guidelines recommend that, in all settings, everyone (adults, adolescents and children) presenting with CD4 cell counts less than 500 cells/mm³ should be offered ART. People with CD4 cell counts of 350 cells/mm³ or less should receive ART as a priority. This is a highly cost-effective intervention that can dramatically reduce HIV-related mortality and morbidity, in addition to HIV incidence. ART should also be initiated in all pregnant and breastfeeding women with HIV, regardless of CD4 count, and be provided to all individuals with active TB and HBV coinfection with severe chronic liver disease and for HIV-positive partners in a serodiscordant couple, irrespective of CD4 count. Coverage of ART among children is also often low, and targeted investment is needed to ensure that all eligible children, including all children younger than five years, have timely access. In addition, the guidelines recommend phasing out d4T and increasing the use of fixed-dose combinations of ARV drugs.

In concentrated epidemic settings with low ART coverage, it is critical to identify opportunities to expand access to HIV treatment and care, including testing and counselling, to most-at-risk populations, such as men who have sex with men, transgender people, sex workers, people who inject drugs and prisoners. This requires addressing any structural barriers that may prevent these populations from seeking and accessing care. Integrating HIV services into drug dependence treatment and harm reduction services and TB clinics can be a highly effective approach to reaching these populations (see section 9.4.2). In these settings, given the relatively limited number of pregnant women living with HIV, phasing out option A for PMTCT and providing ART during pregnancy and breastfeeding to reduce the risk of mother-to-child transmission of HIV (option B) are highly effective and relatively low-cost strategies.

In generalized epidemic settings with low ART coverage, ensuring that all individuals with CD4 counts of less than 350 cells/mm³ are identified and enrolled in care and treatment is a priority and requires greatly increasing HIV testing and counselling rates among the general population. This can be accomplished by scaling up an appropriate mix of approaches to HIV testing and counselling, including provider-initiated HIV testing and counselling for everyone seeking care as well as all pregnant or breastfeeding women, with effective referral systems and links to care and treatment (section 5.1). Identifying individuals with CD4 counts between 350 and 500 cells/mm³ provides an important opportunity to link them into care and initiate ART early. Other strategies to improve the overall levels of access to and uptake of ART include decentralizing HIV services to the primary health care level and integrating HIV services with TB and antenatal care and maternal and child health services (see section 9.4.2), and offering pregnant and breastfeeding women living with HIV the option of receiving lifelong ART, based on national programme decisions. In addition, as in concentrated epidemics, it is important to identify and reach key populations and those with poor access to clinical and community-based services. These may include sex workers, people who inject drugs, men who have sex with



men, transgender people or other groups such as adolescent girls, migrants and other mobile populations, older women and certain high-risk occupational groups.

As coverage of ART increases and programmes mature, expanding access to second-line regimens increasingly becomes a programmatic priority. Scaling up viral load monitoring will be important to adequately identify treatment failure and to avoid switching unnecessarily to second-line regimens. Viral load monitoring is also likely to play a central monitoring role in places in which ART is being broadly expanded to reduce HIV incidence.

As people initiate treatment earlier and stay on it for longer, monitoring the quality of service delivery and strengthening service linkages to improve retention throughout the cascade of care are essential to optimize treatment outcomes and long-term programme performance.

10.8 Useful tools for costing and 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 costing and budgeting of HIV and related interventions and services.

Spectrum 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 number of deaths averted by ART, the number of infant infections averted by PMTCT and adult, PMTCT and paediatric treatment needs and costs. The key data needed to generate these estimates are demographic projections, HIV incidence trends, historical data on the numbers of people receiving ART, the numbers of pregnant women receiving PMTCT interventions and the unit costs for ART for adults and for PMTCT. All countries already have AIM files prepared as part of their national epidemiological estimates, so both modules can be rapidly applied.

The Goals module can be used to estimate the number of adult HIV infections averted by ART under different eligibility criteria and rates of scale-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 (numbers 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. OneHealth can also be downloaded free of charge (24).

WHO and collaborating organizations have recently developed a variety of tools to assist with drug quantification and supply management. Several are available for download, with a description of their main purposes and programmatic focus (25). Guidance on the costing of different PMTCT options has also been developed (26). 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 (27,28).

MONITORING AND EVALUATION

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Goal of this chapter

To provide programmatic guidance for decision-makers and planners at the national level in tracking the implementation of these guidelines and monitoring their impact on HIV programmes and people receiving ART.

11. MONITORING AND EVALUATION

11.1 Introduction

As countries adapt and implement these guidelines, monitoring and evaluation frameworks and systems need to be adapted to collect and analyse information to track the implementation and impact of new recommendations. Monitoring and evaluation will help programme managers to assess the effectiveness of interventions and linkages between services along the cascade of treatment and care for HIV and associated conditions (Fig. 11.1). Such information is essential to detect and respond to bottlenecks or gaps in programme performance and to adequately characterize and respond to patient attrition. As programmes mature, monitoring individual- and population-level outcomes, including toxicity and adverse events, drug resistance, viral suppression, mortality, survival and incidence, is also essential to assess the impact of programmes.

Fig. 11.1 The HIV treatment and care cascade



Data can be collected in many ways, including routinely reported data from all facilities or sentinel sites; population-based surveys; surveillance data; observations on cohorts of people living with HIV; and periodic evaluation. Programme input 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 inappropriate. In considering how best to collect critical data, efforts should also be made to review monitoring systems, such as better linking the monitoring of services for PMTCT, TB and ART and integrating HIV drug resistance monitoring into routine health information systems. Involving civil society in monitoring and evaluation activities is also critical to better understand successes and failures, especially in assessing the perceptions, values and experiences of people living with HIV, key populations and the broader community in accessing and using services. The community can also play a key role in designing and implementing data collection tools and analysing and interpreting findings.

WHO is developing a consolidated guide on monitoring and evaluation of HIV in the health sector that brings together the various elements of monitoring and evaluation systems for HIV programmes. The guide will consolidate and align existing monitoring and evaluation approaches in relevant programmatic areas (such as HIV testing and counselling, ART, PMTCT and HIV drug resistance) with the recommendations in these guidelines and will also include new guidance in emerging areas for HIV monitoring and evaluation. The publication on three interlinked patient monitoring systems (1) will also be updated to reflect this new monitoring and evaluation guidance.

11.2 Monitoring implications of new recommendations

The monitoring and evaluation strategy should monitor service delivery, including inputs and processes as well as outputs and outcomes, such as the number of people receiving interventions and the impact at the individual and population levels (see section 11.3). The monitoring and evaluation plan should include a framework to track progress in implementing the guidelines to verify whether new policies on ART eligibility and recommendations on and plans for treatment or service delivery are actually implemented. This will enable national programmes to document the effect of the shift in guidelines and can contribute to evaluating the impact of the guidelines.

Table 11.1 lists key areas to review when implementing major new recommendations in these guidelines. For each key area, potential topics to monitor and possible implications for revising monitoring systems are provided. Not all information needs to be captured routinely; data needs and the timing of data collection depend on the local context.

Table 11.1 Implications for monitoring of the key recommendations in these guidelines

Summary of new recommendation areas	Implications for monitoring
HIV testing and counselling	Monitor the uptake of community-based HIV testing strategies and testing services for adolescents, including systems for linkages to care
When to start ART	<p>Monitor the number and percentage of different populations (such as adults, adolescents, children and pregnant and breastfeeding women) who have initiated ART based on the new eligibility criteria</p> <p>Review the monitoring system to assess what disaggregation is needed for what purpose (such as CD4 counts ≤ 200 cells/mm³ to routinely monitor late diagnosis or CD4 counts ≤ 350 cells/mm³ and 350–500 cells/mm³ to periodically assess the distribution of CD4 when ART is initiated) and how to best collect the relevant data, and age disaggregation of children (such as <2 years and <5 years).</p>
Which ART regimen to start	<p>Monitor the first- and second-line ART regimens people are receiving</p> <p>Monitor the phasing out and/or introduction of specific drugs (such as d4T and TDF)</p> <p>Monitoring tools may need to be adjusted to reflect new regimen options</p>
Response to ART and diagnosing treatment failure	<p>Monitor the percentage of people receiving ART who had a viral load test and received the results</p> <p>Monitor the reasons for switching ART regimen</p>

Table 11.1 (continued)

Summary of new recommendation areas	Implications for monitoring
Service delivery	<p>Monitor retention and adherence among various populations</p> <p>Monitor the integration of ART into facilities providing maternal and child health services, TB services and drug dependence services if planned by documenting the facilities providing ART</p> <p>Monitor whether the initiation and maintenance of ART has been decentralized as planned at various facilities by documenting the expansion of ART facilities</p> <p>Monitor the functionality of linkages from maternal and child health services, TB services and drug dependence services to HIV care and ART and linkages between communities, peripheral facilities and hospitals by documenting transfers</p>
Task shifting	<p>Monitor the number of non-physician clinicians, midwives and nurses who are trained in ART</p> <p>Monitor the number of non-physician clinicians, midwives and nurses who are initiating first-line ART and maintaining ART and the number of people they have initiated or maintained on ART</p> <p>Monitor the number of community health workers who are trained and are dispensing ART between regular clinical visits, and capture the number of people to whom they dispense ART</p>

11.3 Monitoring the outputs and outcomes of scaling up access to ARV drugs

In addition to monitoring the implementation of new recommendations, health information systems need to be reviewed and adapted to appropriately monitor the outputs and outcomes associated with the new recommendations. Table 11.2 lists areas for gathering data for assessing whether scaling up programmes leads to the anticipated outputs and outcomes at various points along the cascade of HIV treatment and care. Most of the areas have associated indicators in existing WHO guidance (Web Annex www.who.int/hiv/pub/guidelines/arv2013/annexes provides additional details on indicators and references) and/or form part of internationally agreed core indicators that all countries should track within the framework of the Global AIDS Response Progress Reporting process (2). In some evolving areas (such as links between HIV diagnosis and ART, retention of pregnant women in using ARV drugs and viral load monitoring), indicators are still being reviewed and evaluated. The forthcoming consolidated monitoring and evaluation guide for HIV in the health sector will provide more detailed guidance.

Table 11.2 Overview of data areas for monitoring and evaluating the HIV treatment cascade

Step in the cascade	Indicator areas	Relevance
People living with HIV	Estimated number of people living with HIV in various categories	Estimates the distribution of people living with HIV among the population Estimates the size of relevant populations and need for HIV interventions, to help focus planning
HIV diagnosis	Percentage of the general population with known HIV test status and within specific populations as well	The level of testing coverage of relevant populations indicates efforts to scale-up HIV testing and counselling, including provider-initiated testing and counselling Measuring the proportion of population groups aware of their HIV status identifies where more effort may be needed
	Number of people newly diagnosed with HIV infection	Number of people living with HIV newly diagnosed with HIV infection in a given period Indicates the pool of people who should be linked to care
Linkage and enrolment in HIV care	Percentage of people newly diagnosed with HIV infection enrolled in HIV care	Measures strength of link between diagnosis and enrolment in care Indicates access to and uptake of HIV care following a positive HIV test
	Profile of people living with HIV initiating HIV care	Identifies who is enrolled in care and whether key populations and priority groups are linked to care
	Retention in care of people living with HIV not yet initiating ART, including HIV-exposed infants	Acts as a proxy measure for maintained linkage to the care of adults and children who may start ART in the future
Antiretroviral drugs: coverage	Number of people receiving ART (and coverage)	Coverage of ART among eligible people living with HIV, by population groups of interest and regimen Indicates trends in the number of people receiving ART, to be used to review programme expansion and plan drug supply Helps estimate unmet need for ART and equity in access to ART
	Number of people receiving ARV drugs for PMTCT (and coverage)	Coverage of ARV drugs for PMTCT among pregnant women with HIV Estimates unmet need for ARV drugs for PMTCT Input to model the impact of services for PMTCT

Table 11.2 (continued)

Step in the cascade	Indicator areas	Relevance
Antiretroviral drugs: drug supply	Percentage of ART facilities with ARV drug stock-outs in a given period	Indicates stock-outs, which could directly affect treatment adherence and clinical outcomes, and may contribute to HIV drug resistance
Antiretroviral drugs: adherence and retention	Adherence	Indicates the quality of care and the likelihood of viral suppression Adherence acts as an early warning indicator of drug resistance
	Percentage retained on ART and PMTCT	Indicates retention over time and the success of ART programmes Helps to monitor losses and identify where to strengthen engagement in care Low retention acts as an early warning indicator for HIV drug resistance
Viral suppression	Percentage of viral suppression	Effectiveness of ART programmes in achieving viral suppression
Impact	Mortality	Decline in HIV-related deaths and even overall mortality in countries with a high burden of HIV indicates successful HIV programmes
	Incidence and the number of adults and children acquiring HIV infection	Decline in incidence indicates how successful HIV prevention and treatment programmes are in limiting the number of people acquiring HIV infection Identifying who is acquiring HIV infection and where the infection was acquired helps to focus planning Elimination of new HIV infections among children is a measure of the success of PMTCT programmes
	Mother-to-child transmission rate	The mother-to-child transmission rate indicates how much vertical transmission occurs
	Survival	Increased survival and extended life-years of people living with HIV receiving ART is a measure of the impact of ART Survival, including HIV-exposed children and children living with HIV, indicates the levels of access to and the quality of health care

11.4 Other monitoring considerations

Programmes are increasingly moving beyond coverage indicators to focus on critical outcomes, such as viral load suppression and immune reconstitution, and on the broader impact of HIV treatment, including HIV-related mortality and HIV incidence. However, programmes also need to measure potential unintended outcomes, such as HIV drug resistance and ARV-related toxicities. Periodic evaluations and implementation research are also central to reviewing programmes.

11.4.1 HIV drug resistance

WHO recommends the use of early warning indicators to help identify deficits in programme performance that favour the emergence of HIV drug resistance (Box 11.1). WHO also recommends that countries undertake surveillance of HIV drug resistance and provides specific guidance on how to do the surveys required.

11.4.2 Sentinel surveillance for ARV toxicity monitoring

Surveillance of the toxicity of ARV drugs is essential to identify and address preventable adverse events. Various approaches have been developed to monitor the toxicity of ARV drugs, including targeted and systematic surveillance reporting on specific types of toxicity and serious adverse events caused by a specific drug in targeted populations, and the pregnancy exposure registry following a cohort of pregnant women exposed to ART, including birth defect surveillance. WHO technical guidance on implementing toxicity monitoring at sentinel sites will become available in 2013.

11.4.3 Evaluation, including impact and programme performance, and implementation research

Routine monitoring should 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 important to assess perceptions and values of service recipients and communities along with barriers, facilitators and experiences in delivering and receiving services.

Impact indicators, such as incidence, morbidity and mortality, are often difficult to measure. Guidance on the use of assays for recent infection to estimate HIV incidence at the population level has been recently developed (3), and guidance on monitoring mortality, including the cause of death, will be available in 2013. A short guide summarizing five methods to measure the impact of programmes for PMTCT (4) is already available, and detailed guidance that can be adapted to implement each method will become available in 2013.

Mathematical modelling is often undertaken to project various scenarios for programme planning and evaluating impact. Ensuring the availability of robust data is especially important when estimating the prevention impact of ARV drugs at the population level, as multiple sources of information and uncertainty come into play. Specific data collection efforts and models for particular contexts may provide more accurate estimates.

Box 11.1 Monitoring HIV drug resistance

HIV drug resistance poses a significant threat to the success of national HIV programmes. Drug resistance results in more rapid virological failure among people receiving first-line regimens and increases the need for second-line regimens, which may be associated with greater toxicity, adverse events, poorer adherence and higher costs. Drug resistance may also affect the ability to prevent HIV transmission using ARV-based pre- or post-exposure prophylaxis or topical microbicides.

Surveillance of drug resistance should be an integral component of national HIV programmes. Surveillance data should inform the selection of first- and second-line regimens for ART, as well as ARV drugs for PMTCT, to optimize treatment outcomes within a public health approach.

WHO and its partners have developed a standardized and complementary assessment strategy to be implemented by countries, for both adult and paediatric populations, with the following components.

Monitoring early warning indicators for HIV drug resistance. Early warning indicators use existing clinic and pharmacy records to assess the factors associated with the emergence of HIV drug resistance at the level of ART programmes and clinics. These factors include ART prescribing practices; drug supply continuity; adherence to ARV drug regimens measured by on-time pick-up of ARV drugs; retention in care; and viral load suppression, when available. The monitoring of early warning indicators should be integrated into a country's monitoring and evaluation system and provides the information needed to address practices that may lead to poor outcomes and HIV drug resistance.

Surveys to monitor acquired HIV drug resistance and associated factors in populations receiving ART. The WHO generic protocol for monitoring acquired HIV drug resistance uses a standardized survey methodology to assess population-level virological suppression at the national level and the emergence of HIV drug resistance among populations receiving treatment. Performed regularly at representative sites, these surveys provide evidence for action at the programme and clinic level to minimize HIV drug resistance. They also provide evidence to optimize the selection of first- and second-line ART regimens.

Surveys to monitor pre-treatment HIV drug resistance. The WHO generic protocol for surveillance of pre-treatment HIV drug resistance provides a nationally representative estimate of HIV drug resistance in populations initiating therapy. Performed regularly at representative ART clinics, these surveys support national, regional and global decision-making regarding the choice of first-line regimens.

Surveillance of transmitted HIV drug resistance among individuals recently infected with HIV. The WHO generic protocol for surveillance of transmitted HIV drug resistance provides estimates of transmitted HIV drug resistance in recently infected populations, and the results should contribute to ART policy decisions, including guidelines on ART regimens and HIV prophylaxis.

Surveillance of HIV drug resistance among infants under 18 months of age. The WHO generic protocol for surveillance of HIV drug resistance among children under 18 months of age can provide estimates of national prevalence of HIV drug resistance among infants diagnosed with HIV infection through early infant diagnosis testing. The results assess differences in HIV drug resistance prevalence between populations exposed to ARV drugs for PMTCT and those with unknown exposure to support the selection of optimal first-line ART for this population.

National strategies for assessing HIV drug resistance should be developed and routinely implemented as part of comprehensive HIV treatment programmes.

11.5 Reviewing and strengthening monitoring and evaluation systems

The recommendations in these guidelines may require certain adaptations to the monitoring and evaluation system. Guidance is available on the 12 components of a monitoring and evaluation system and tools to review and strengthen national HIV monitoring and evaluation systems (5). Table 11.3 highlights some specific areas to review to ensure that monitoring and evaluation systems are aligned to the new ARV guidelines.

Table 11.3 Critical aspects of monitoring and evaluation systems and implications of the new recommendations

Selected elements of monitoring and evaluation systems	Key considerations to review with new guidelines
Patient monitoring system	<ul style="list-style-type: none"> Improving the monitoring of enrolment and retention in HIV care Accurate accounting for transfers and losses Updating data elements required for patient monitoring in line with new guidelines, such as changes in regimen and including viral load (where available) Revisit disaggregation categories and links and synergy for systems for monitoring ARV drugs for PMTCT, TB and ART Move to electronic systems where feasible
Data flow and integration	<ul style="list-style-type: none"> One standardized monitoring and evaluation system, agreed on by all partners and stakeholders, including necessary updates based on evolving ARV drug policies and practices Common country standards and data flow, based on any changes in service delivery Clarify integration of programmes for PMTCT, TB programmes and ART programmes and transfer to ART programmes Consider a unique patient identifier Use of mobile phones where proven opportunities exist Functional links between HIV and health management information systems
Data generation and quality assurance approach	<ul style="list-style-type: none"> Clear protocols for data generation, standard operating procedures for aggregation, where they do not exist, for any new indicators and for new service delivery scenarios Review available laboratory data as a source of key information Regular assessment of the data quality in facilities and at the subnational level Supportive supervision, including new elements of ARV drug policy and implementation plans Update national reporting forms to capture any new national-level data, including identifying the frequency of data collection necessary for various indicators
Data use at various levels and programme reviews	<ul style="list-style-type: none"> Regular review of standardized data at the facility, regional and national levels to identify issues and improve programmes, including a review of early warning indicators for HIV drug resistance Review and update the strategy for using data based on new ARV drug policies and a corresponding monitoring and evaluation framework and plan

Table 11.3 (continued)

Selected elements of monitoring and evaluation systems	Key considerations to review with new guidelines
Periodic reporting and data accessibility	<p>Maintaining national and subnational databases, to include new data elements</p> <p>Regular data dissemination and public accessibility of data related to the evolving HIV programme</p> <p>Periodic (sub-) national and international reports to reflect and document the roll-out of new ARV drug policies and their impact</p>
Monitoring and evaluation system capacity	<p>Human and institutional capacity for data generation and analysis at the facility, subnational and national levels, for monitoring and evaluation that is relevant to updated ARV drug guidance and policies</p> <p>Appropriate investment in monitoring and evaluation and reflection in grants (including those from the Global Fund to Fight AIDS, Tuberculosis and Malaria) of the monitoring and evaluation adjustments required to strengthen existing capacity and capture new guidance on ARV drugs</p>
Monitoring and evaluation plan	<p>A costed national plan with a list of core indicators and planned evaluations, with focus on results and accountability, revisited in light of new guidelines on ARV drugs</p> <p>Regular assessment of the implementation of the monitoring and evaluation plan, based on the updated plan</p>
Evaluation and operational and implementation research	<p>Plan and strategy for evaluating impact, considering the rollout of the new guidelines on ARV drugs</p> <p>Agenda and plan for implementation research, considering the rollout of the new guidelines on ARV drugs</p> <p>Review of research results for improving programmes</p>
Monitoring and evaluation partnerships and coordination	<p>Coordinating programme monitoring and reporting activities among key stakeholders and partners</p> <p>Alignment with national health strategy, link with other programme strategies (maternal and child health services, TB and key populations) and international initiatives (Commission for Information and Accountability for Women's and Children's Health, ending mother-to-child transmission of HIV (eMTCT) and Global AIDS Response Progress Reporting (2))</p>

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12. ANNEXES

Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children

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).

Adults and adolescents ^a	Children
Clinical stage 1	
Asymptomatic	Asymptomatic
Persistent generalized lymphadenopathy	Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight)	Unexplained persistent hepatosplenomegaly
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)	Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Herpes zoster	Herpes zoster
Angular cheilitis	Lineal gingival erythema
Recurrent oral ulceration	Recurrent oral ulceration
Papular pruritic eruption	Papular pruritic eruption
Fungal nail infections	Fungal nail infections
Seborrhoeic dermatitis	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 moderate malnutrition ^b not adequately responding to standard therapy
Unexplained chronic diarrhoea for longer than 1 month	Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (intermittent or constant for longer than 1 month)	Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)
Persistent oral candidiasis	Persistent oral candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia	Oral hairy leukoplakia
Pulmonary tuberculosis	Lymph node tuberculosis
	Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)	Severe recurrent bacterial pneumonia
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Acute necrotizing ulcerative gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10 ⁹ /l) and/or chronic thrombocytopaenia (<50 x 10 ⁹ /l)	Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10 ⁹ /l) or chronic thrombocytopaenia (<50 x 10 ⁹ /l)

Adults and adolescents ^a	Children
Clinical stage 3	
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis
Clinical stage 4^c	
HIV wasting syndrome <i>Pneumocystis (jirovecii) pneumonia</i> Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or ano-rectal of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin) Symptomatic HIV-associated nephropathy or cardiomyopathy Recurrent septicaemia (including nontyphoidal <i>Salmonella</i>) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition ^d not responding to standard therapy <i>Pneumocystis (jirovecii) pneumonia</i> Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) Central nervous system toxoplasmosis (after the neonatal period) HIV encephalopathy Extrapulmonary cryptococcosis, including meningitis Disseminated nontuberculous mycobacterial infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis (with diarrhoea) Chronic isosporiasis Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) Cerebral or B-cell non-Hodgkin lymphoma HIV-associated nephropathy or cardiomyopathy

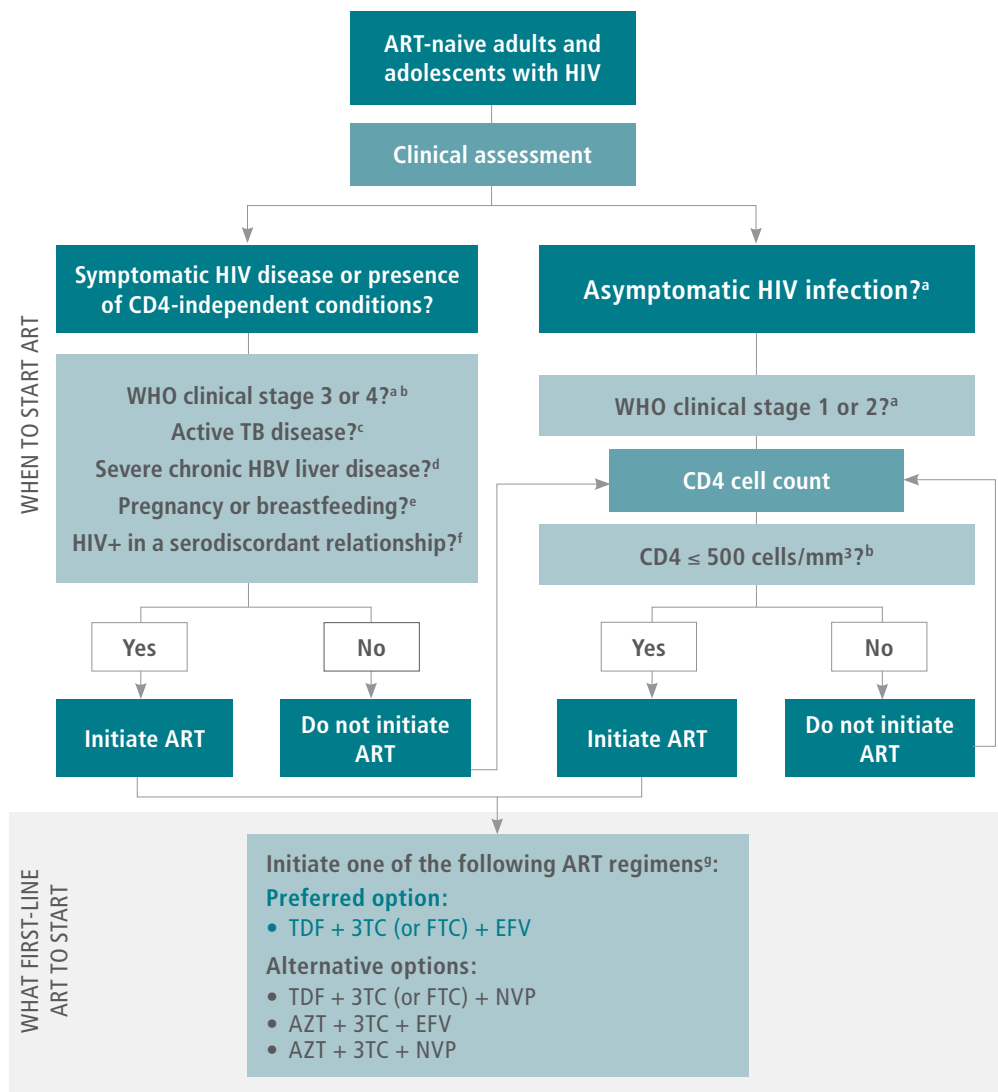
^a In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.

^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 5 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.

Annex 2. Algorithm for the 2013 recommendations for adults and adolescents



^a Annex 1 lists the WHO clinical staging for HIV disease.

^b ART initiation in individuals with severe or advanced symptomatic disease (WHO clinical stage 3 or 4), regardless of CD4 cell count, or with CD4 count ≤ 350 cells/mm³, regardless of clinical symptoms, should be prioritized.

^c Active TB disease refers to the time when TB breaks out of latency and causes disease. Latent TB infection refers to the period of time when the immune system has been successful in containing the *Mycobacterium tuberculosis* and preventing disease.

^d 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, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

^e For details on ARVs for pregnant and breastfeeding women with HIV (Option B and Option B+), see Annex 3 and sections 7.1.2, 7.1.3 and 7.2.2.

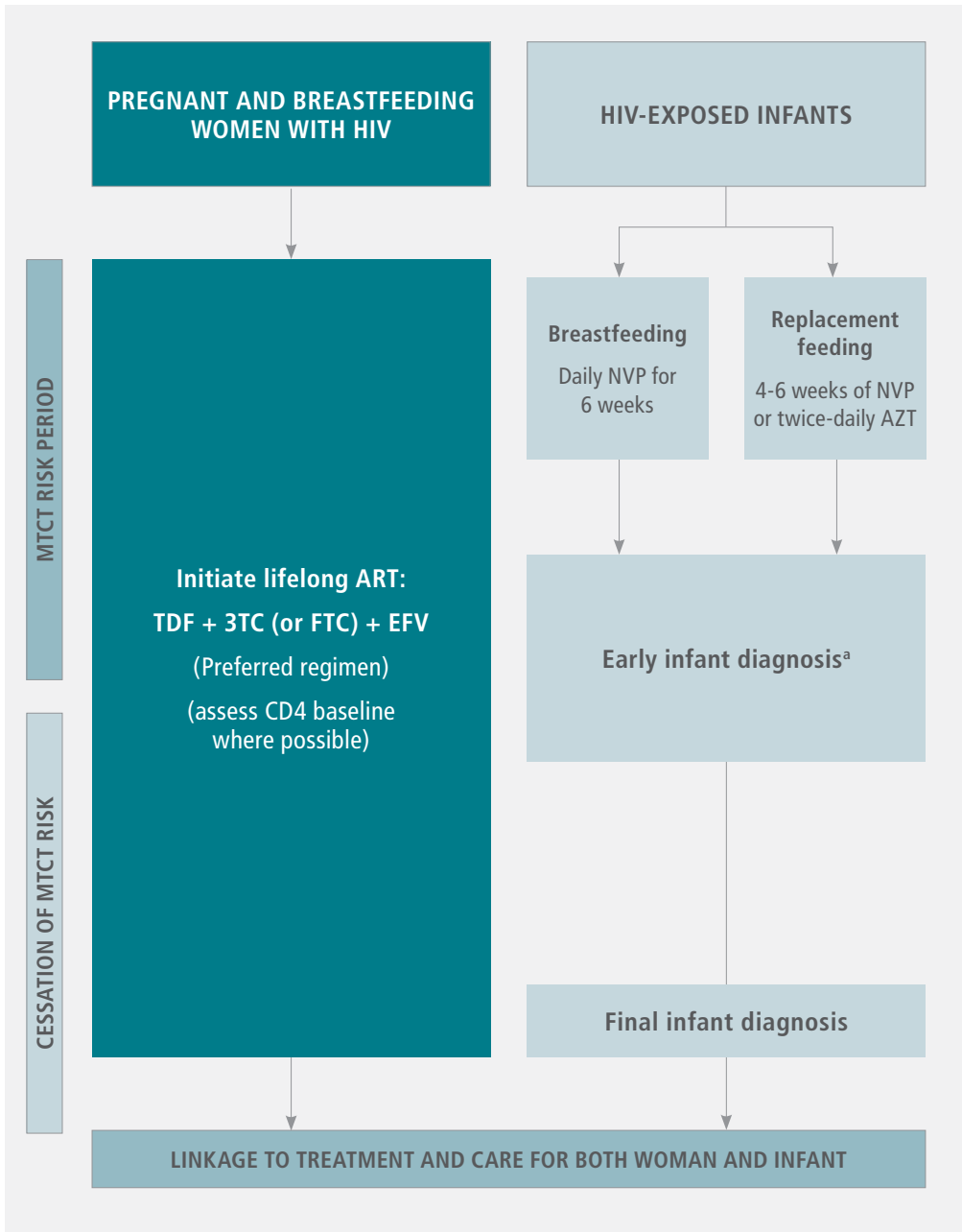
^f A HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.

^g For adolescents weighing less than 35 kg, refer to the algorithm for children in annex 4 which indicates the appropriate first-line ART regimen options.



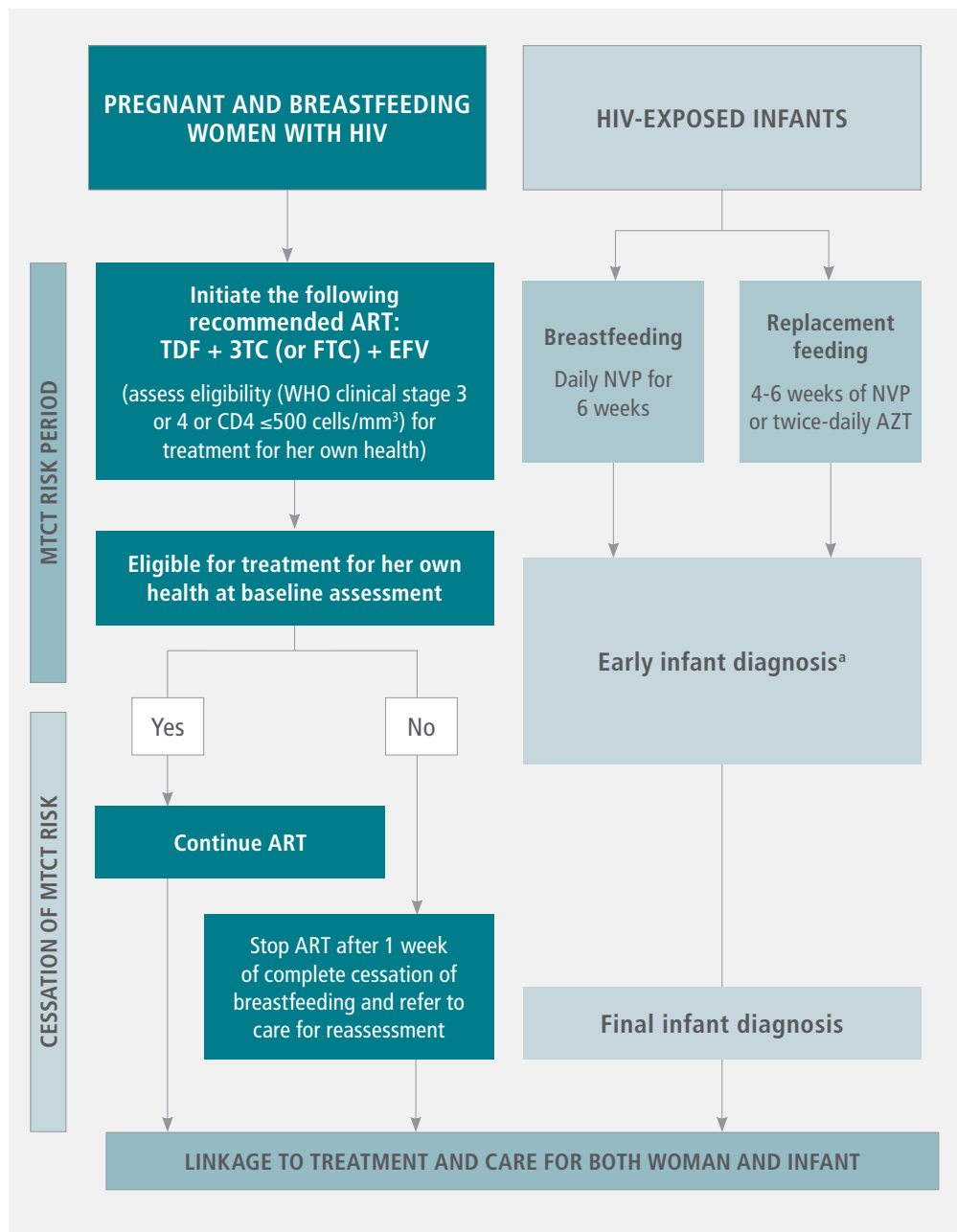
Annex 3. Algorithms for the 2013 recommendations for pregnant and breastfeeding women

Lifelong ART for all pregnant and breastfeeding women with HIV (Option B+)

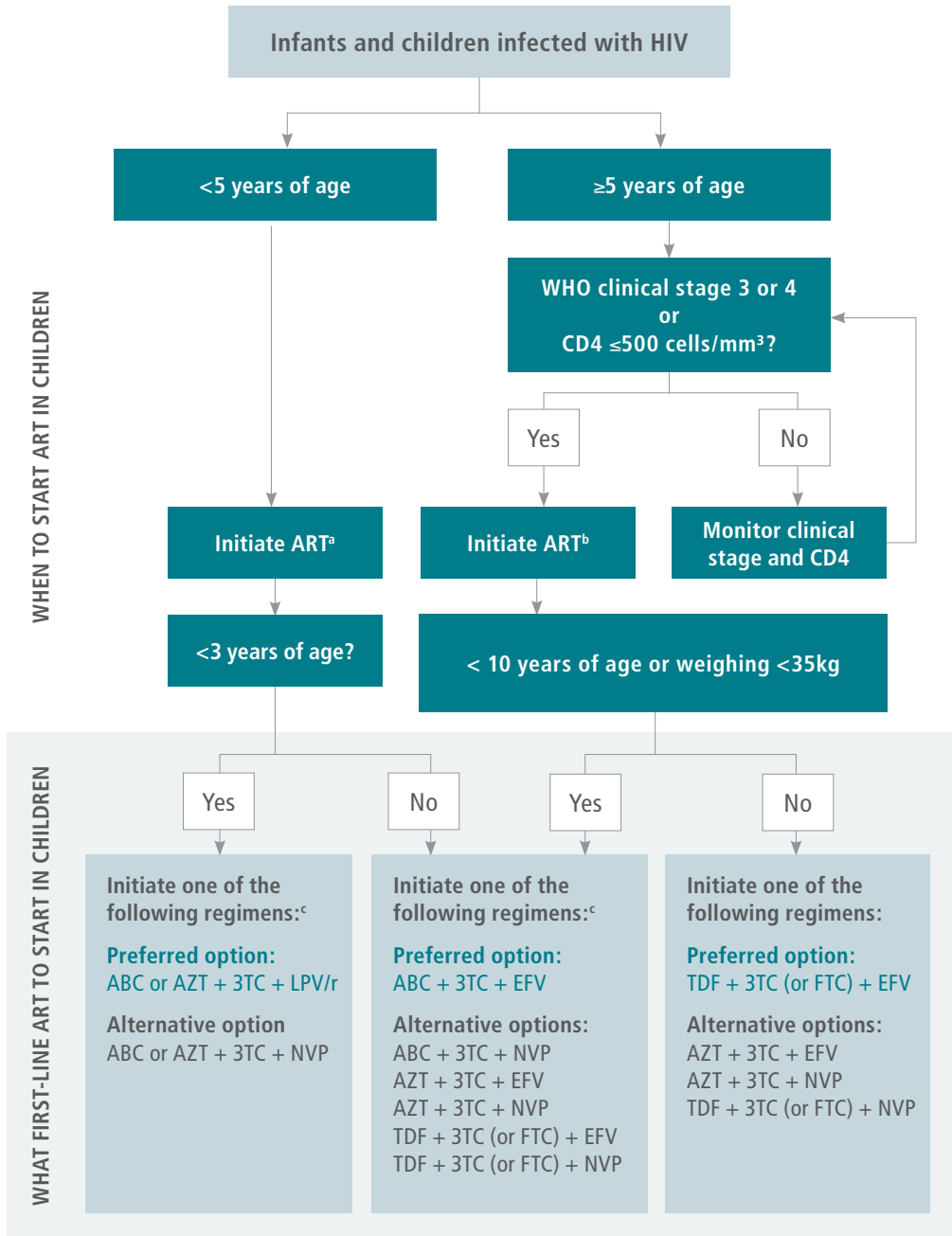


^a See Annex 5. Algorithm for early infant diagnosis

ART for women with HIV during pregnancy and breastfeeding (Option B)

^a See Annex 5. Algorithm for early infant diagnosis

Annex 4. Algorithm for the 2013 recommendations for children



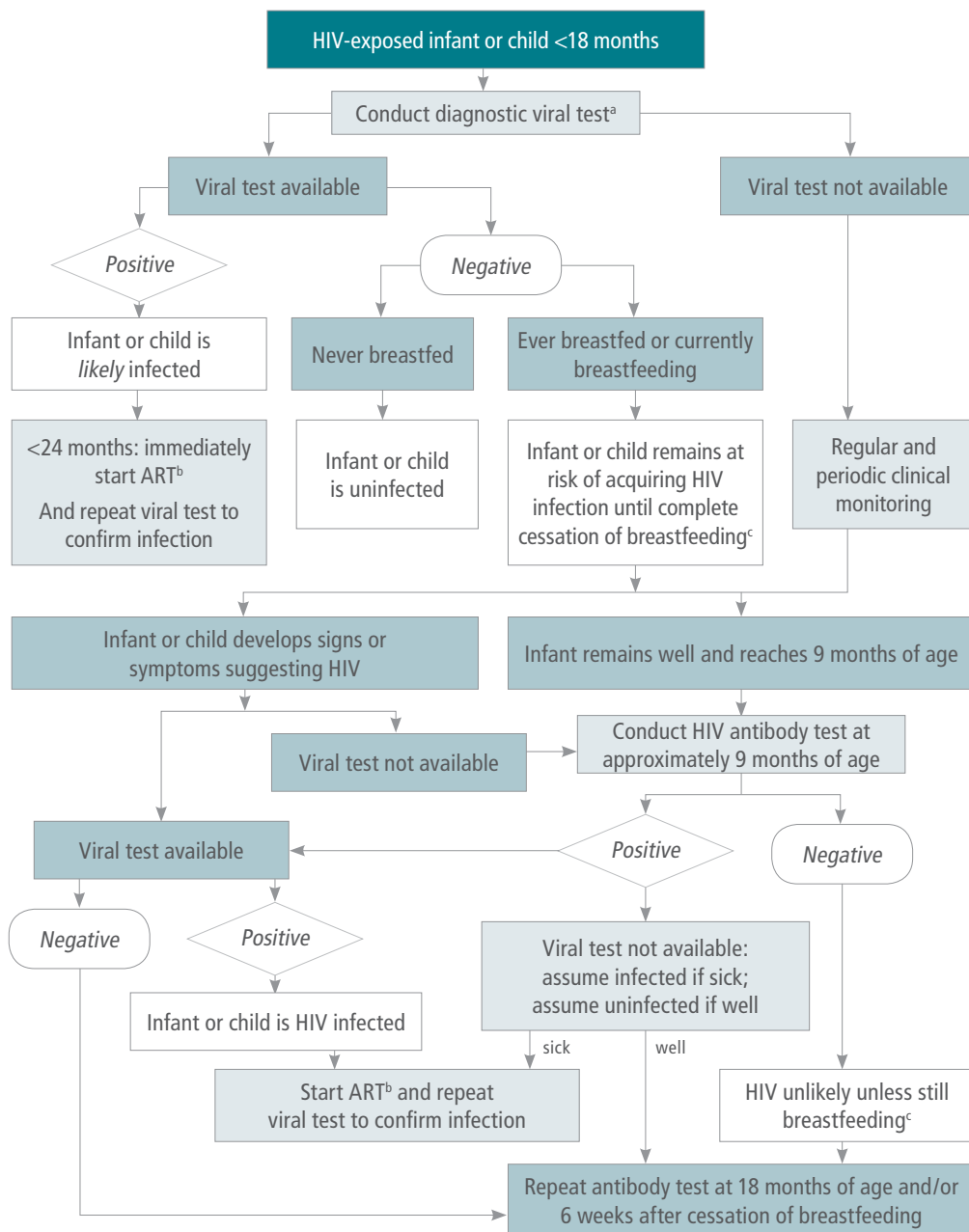
^a If this recommendation to treat all children between one and under five years of age is not adopted: initiate ART with WHO clinical stage 3 and 4 or with CD4 count ≤ 750 cells/mm³ or <25%, whichever is lower, regardless of WHO clinical stage (105).

^b If this recommendation is not adopted ART should be initiated at WHO HIV clinical stage 3 and 4 or with CD4 count ≤ 350 cells/mm³ regardless of WHO clinical stage (105, Chapter 7).

^c Special note: d4T use should be restricted to those situations where there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible.

Annex 5. Algorithm 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. Source: Adapted from *Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach*. 2010 revision. Geneva, World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf).



^aFor newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks). See also Table 5.1 on infant diagnosis.

^bStart ART, if indicated, without delay. At the same time, retest to confirm infection.

^cThe risk of HIV transmission remains as long as breastfeeding continues.

Annex 6. Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women

The 2013 consolidated guidelines recommend that all pregnant and breastfeeding women with HIV should initiate ART and, based on national programme decisions, that either all women continue ART as lifelong treatment or women not eligible for ART for their own health stop after the mother-to-child transmission risk period. 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 (adapted below), as well as a discussion guide, were developed by the United States President's Emergency Plan for AIDS Relief, and are included as part of the larger Elimination of Mother-to-Child Transmission Inter-Agency Task Team's *Toolkit: Expanding and Simplifying Treatment for Pregnant Women Living with HIV: Managing the Transition to Option B/B+*:

- Checklist Link: www.emtct-iatt.org/wp-content/uploads/2013/03/Toolkit-Section-2.pdf;
- Full Toolkit Link: www.emtct-iatt.org/toolkit

Recommended timing key:

Before implementation Early in implementation During implementation

POLITICAL COMMITMENT & POLICY ENDORSEMENT	Completed	In Process	Not yet started
Commitment to Global Plan goals (national and subnational)			
Full-time MoH staff responsible for PMTCT (national & possibly subnational)			
Functional technical working group inclusive of stakeholders from MNCH, PMTCT, and HIV treatment, including health care workers and people living with HIV			
National and subnational endorsement of ART for all pregnant and breastfeeding women (Option B or B+)			
Guidelines 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 minimum package of services to provide ART to all pregnant and breastfeeding women			
Assessment of system capacity (infrastructure, human resources, and commodities) to decentralize ART to MNCH settings, including absorbing women with HIV and their families			

SERVICE DELIVERY MODEL	Completed	In Process	Not yet started
Timing and location of transition between PMTCT and long-term treatment services has been determined (including consideration of lifelong ART provision within MNCH)			
Systematic identification of ART clients who become pregnant and linkage to MNCH			
Testing and treating partners and family members within MNCH			
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/sharing for ART initiation and maintenance			
Assessment of human resource capacity (nurse, midwife, pharmacy, lab) 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			
Strategy for retention, retraining, and continuing professional development of health workers, especially those providing in PMTCT/ART			
ART REGIMEN CHOICE	Completed	In Process	Not yet started
Simplification and harmonization of PMTCT and adult treatment regimens			
Plan for alternate regimen for pregnant women not tolerant of 1st-line ART			
Optimization of 1st-line regimen for infants			
Establishment of pharmacovigilance system, where appropriate (see discussion guide)			
SUPPLY CHAIN MANAGEMENT	Completed	In Process	Not yet started
Supply chain gap assessment including quantification, distribution and stock management			
18 month forecast, quantification, and supply plan developed			
Stock management of ART in MNCH settings (training, capacity, and security)			
SUPPLY CHAIN MANAGEMENT	Completed	In Process	Not yet started
If modifying 1st line regimen, plan to 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 (ANC) and PMTCT register allows for documentation of initiation versus those already on ART			
ART register allows for documentation of pregnancy and breastfeeding status			
Tools and registers in MNCH allow for cohort monitoring of maternal ART retention and exposed infant retention in care			
Pregnant and breastfeeding women initiated on ART in MNCH settings are included in site and national level ART M&E systems			
System to track and measure linkages and transition between MNCH and long-term HIV care & treatment for mother and infant (for example, a mother-baby longitudinal registry, unique identifier)			
Program 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			
Harmonization of PMTCT and ART M&E systems and data review processes			
Standardized file or card for pregnant and breastfeeding women 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 program			
HIV TESTING AND COUNSELLING IN PMTCT SETTINGS	Completed	In Process	Not yet started
Quality assurance measures for rapid HIV testing in all PMTCT sites			
Policy decision on treatment of discordant couples			
Couples HTC and follow-up of discordant couples incorporated into PMTCT			
Strategy to link or register male partners with HIV in ART program			
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 in need ART for their own health who decline treatment for life			
LABORATORY AND CLINICAL MONITORING	Completed	In Process	Not yet started
Treatment monitoring capability for toxicity			
Availability of baseline CD4 (point of care or reliable sample transport)			
Algorithm for CD4 and/or viral load monitoring			

INFANT DIAGNOSIS AND PEDIATRIC TREATMENT	Completed	In Process	Not yet started
EID capacity paralleling PMTCT programme scale-up			
Strengthening of "EID cascade" – early diagnosis, rapid results return, active case finding of infants infected with HIV and initiation of treatment			
Retention of HIV exposed infants through end of breastfeeding including assuring final diagnosis			
Expand access to pediatric treatment			
RETENTION IN CARE AND TREATMENT	Completed	In Process	Not yet started
System to ensure that ALL pregnant and postpartum women with HIV are enrolled in ongoing HIV care and/or treatment			
Models of service delivery that consider harmonized mother-infant pair follow-up			
Facility- and community-based services to support adherence and trace defaulters			
Innovative solutions to improving the accessibility of ART			
FAMILY PLANNING	Completed	In Process	Not yet started
Assessment of family planning service availability and commodities			
Access to and uptake of voluntary family planning services in settings providing ART			
COMMUNITY INVOLVEMENT	Completed	In Process	Not yet started
Women living with HIV are engaged in the planning, implementation and monitoring at national, subnational and community levels			
Community-based activities and services to support PMTCT scale-up and retention			
Community structures to support orphans and vulnerable children			
ROLL-OUT STRATEGY	Completed	In Process	Not yet started
Roll-out strategy has been planned			
Real-time evaluation of implementation in order to inform further scale-up			

Acronyms used: MoH (Ministry of Health); MNCH (maternal, newborn, and child health); M&E (monitoring and evaluation); HTC (HIV testing and counselling); and EID (early infant diagnosis).

Annex 7. Dosages 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
Didanosine (ddI)	400 mg once daily (>60 kg) 250 mg once daily (≤60 kg)
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice 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)	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 or 600mg + 100 mg twice daily
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)	
Raltegravir (RAL)	400 mg twice daily

^aFor adolescents weighing less than 35 kg, see the next page for weight-based dosing for ARV formulations for children.

Weight-based dosing for antiretroviral formulations for children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on antiretroviral drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing. The work to develop and update simplified guidance on antiretroviral drugs for use in children has been undertaken by WHO 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 expert paediatric pharmacology consultations. For fixed-dose combinations, a dose-modelling tool (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 in no case would a child receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. For simplification, Antiretroviral drugs that are no longer considered preferred or alternative options for children such as didanosine and saquinavir are no longer included in the dosing guidance. In addition, dosing for postnatal prophylaxis for HIV-exposed infants is not provided here but can be found in Chapter 7, Table 7.8.

During the finalisation of these Guidelines FDA approval was granted for the use of EFV in children 3 months to 3 years old weighing at least 3.5 kg. While recognizing the opportunity to provide an additional option to children and allow further harmonisation across age groups, the GDG highlighted the need for further data prior to recommending EFV as a treatment option in children less than 3 years.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as further 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 in the Web Annex at www.who.int/hiv/pub/guidelines/antiretroviral2013/annexes.

Antiretroviral drugs and formulations are available from several companies, and the dose strengths of tablets, capsules and liquid formulations may vary from the information given here. In addition, the listing of a formulation in this annex does not equate to quality assurance of that formulation. National programme managers should ensure that any product procured for use is approved and of appropriate quality and stability. For guidance on the quality assurance of medicines, see the WHO medicines web site (www.who.int/medicines/areas/quality_safety/quality_assurance/about/en/index.html) and the Access to HIV/AIDS drugs and diagnostics of acceptable quality, which is available and updated at 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 antiretroviral drugs approved and tentatively approved by the United States Food and Drug Administration, see www.fda.gov/internationalprograms/FDAbeyondbordersforeignoffices/AsiaandAfrica/ucm119231.htm. For the policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance, see www.theglobalfund.org/en/procurement/quality/pharmaceutical.

¹ The current members are listed in the annex to the most recent Paediatric Antiretroviral Working Group meeting report: Paediatric Antiretroviral Working Group. Developing dosing guidance for new and upcoming formulations of paediatric antiretrovirals in line with Treatment 2.0 priorities. Meeting report, Paediatric Antiretroviral Working Group, Geneva, Switzerland, 25–26 October 2011. Geneva, World Health Organization, 2012 (http://apps.who.int/iris/bitstream/10665/75159/1/WHO_HIV_2012.8_eng.pdf, accessed 15 May 2013).

General principles

The principles followed in developing the WHO simplified tables include the following;

- It is preferable to use an age-appropriate fixed dose combination for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided where possible, especially if volumes are large – such as above 10 ml.
- 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.
- In general, young children should be switched to available solid oral dosage forms as soon as they are tolerated.
- Where children have to use adult formulations, care must be taken to avoid underdosing. Adult tablets that are scored are more easily split. For tablets that are not easily split, WHO recommends that this be done in the dispensing pharmacy using appropriate tablet cutters.
- Some tablets such as LPV/r 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 or crushed, since they lose bioavailability.
- Different dosing between morning and evening doses should be avoided where possible.
- Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or gain weight.

Table 1. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing among children

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	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg				
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM			
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	300/150	1	1
AZT/3TC/ NVP	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	300/150/200	1	1
ABC/ AZT/3TC	Tablet (dispersible) 60 mg/60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	300/300/150	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	600/300	0.5	0.5
d4T/3TC	Tablet (dispersible) 6 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	30/150	1	1
d4T/3TC/ NVP	Tablet (dispersible) 6 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	–	4	4

Table 2. Simplified dosing of child-friendly solid formulations for once-daily dosing in children

Drug	Strength of tablets (mg)	Number of tablets or capsules by weight band once daily					Strength of tablet (mg)	Number of tablets or capsules by weight band once daily
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		
EFV ^a	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200	2
	Tablet (double scored) ^b 600 mg	–	–	one third	one half	two thirds	600	2/3
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 + 300	1

^a EFV is not recommended for children younger than 3 years and weighing less than 10 kg. FDA approval for use in children less than 3 years weighing more than 3.5 kg was granted during the finalisation of these guidelines (3.5–5 kg two 50 mg capsules; 5–7.5 kg three 50 mg capsules; 7.5–15 kg one 200 mg capsule), however more data are urgently needed to inform recommendations for use of EFV in this age group.

^b The double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.

Table 3. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets by weight band morning and evening												Strength of adult tablet (mg)		Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		AM	PM				
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM						
Solid formulations																	
3TC	Tablet (dispersible) 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	150	1	1			
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1			
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1			
NVP ^a	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1			
LPV/r ^b	Tablet (heat stable) 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	100/25	3	3			
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 ^a	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–			
LPV/r ^b	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	–	–	–			

^a 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 2013). More definitive evidence is expected from an ongoing trial.

^b 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 or crushed.

Table 4. Simplified harmonized dosing for currently available TDF formulations for children

Drug	Size of powder scoop (mg) or strength of tablet (mg)	Number of scoops or tablets by weight band once daily					Strength of adult tablet (mg)	Number of tablets by weight band
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		
TDF ^a	Oral powder scoops 40 mg/scoop	–	–	3	–	–	300 mg	25–34.9 kg
	Tablets 150 mg or 200 mg	–	–	–	1 (150 mg)	1 (200 mg)	300 mg	1 (200 mg) ^b or 1 (300 mg)

^aTarget dose: 8 mg/kg or 200 mg/m² (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.

^b200-mg tablets should be used for weight 25–29.9 kg and 300 mg tablets for 30–34.9 kg.

Table 5. Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX) prophylaxis

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of scoops or tablets by weight band once daily					Strength of adult tablet (mg)	Number of tablets by weight band
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	25–34.9 kg
CTX	Suspension 200/40 per 5ml	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	–	one half	one half	1	1	400/80 mg	2
INH/CTX/B6 ^a	Tablets (scored) 800/160 mg	–	–	–	one half	one half	800/160 mg	1
	Tablets (scored) 960 mg/300 mg/25 mg	–	–	–	one half	one half	960 mg/300 mg/25 mg	1

^aThis formulation is currently awaiting regulatory approval, and a scored junior tablet (480 mg/150 mg/12.5 mg) is also under development.

The need for new formulations

The work of the Paediatric Antiretroviral Working Group has highlighted the urgent need for formulations, especially fixed-dose combination formulations containing LPV/r in solid forms, suitable for treating younger children, scored tablets of TDF and TDF-based fixed-dose formulations for children. In addition, the availability of ATV/r and DRV/r in heat-stable fixed-dose combination formulations is becoming more critical to facilitate treatment sequencing. Access to a heat-stable formulation containing 30 mg of RTV is also important for “super-boosting” LPV in the setting of rifampicin-based TB treatment. The table below contains some duplication of formulations. For example, a scored adult fixed-dose combination of TDF + 3TC + EFV is not needed if a formulation for children is available. However, the Paediatric Antiretroviral Working Group recognized that, although a child-specific formulation may be ideal, a scored adult formulation may be easier to develop as a first step.

The recent approval of EFV for use in children 3 months to 3 years old has provided an additional option for young children and offers further opportunity for harmonisation. As more data are obtained to inform the best use of this drug in young children, sprinkles formulation should be made available in resource limited settings.

In moving towards the joint UNAIDS/WHO Treatment 2.0 initiative, 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.

Table 6. Simplified dosing for urgently needed ARV drugs for children recommended by the Paediatric Antiretroviral Working Group

Drug	Strength of tablet or sprinkle sachet or capsule (mg)	No. of tablets or sprinkle capsules/sachets by weight band											
		3–5.9kg		6–9.9kg		10–13.9 kg		14–19.9kg		20–24.9kg		25–34.9kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC/NVP	60mg/30mg/50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	4	4
LPV/r sprinkles	40mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	–
ABC/3TC/LPV/r	30mg/15mg/40mg/10mg	2	2	3	3	4	4	5	5	6	6	–	–
AZT/3TC/LPV/r	30mg/15mg/40mg/10mg	2	2	3	3	4	4	5	5	6	6	–	–
DRV/r	240/40mg	–	–	–	–	1	1	1	1	2	1	–	–
ATV/r	100/33mg	–	–	–	–	1	1	1	1	2	1	–	–
ABC/3TC	120/60mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	–	–
TDF/3TC	75mg/75mg	–	–	–	–	1.5	1.5	2	2	2.5	2.5	3–3.5 ^a	3–3.5 ^a
TDF/3TC/EFV	75mg/75mg/150mg	–	–	–	–	1.5	1.5	2	2	2.5	2.5	3–3.5 ^a	3–3.5 ^a
TDF/3TC adult double scored ^b	300mg/300mg	–	–	–	–	one third	one third	one half	one half	two thirds	two thirds	1	1
TDF/3TC/EFV adult double scored ^b	300mg/300mg/600mg	–	–	–	–	one third	one third	one half	one half	two thirds	two thirds	1	1

^a 3 tablets for 25–29.9 kg and 3.5 tablets for 30–34.9 kg.

^b A double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling it to be divided into thirds or halves as needed



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Chapter 7

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Chapter 8

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Chapter 9

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Chapter 10

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Chapter 11

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