World Health Organization

SUPPLEMENT

MARCH 2014 SUPPLEMENT

TO THE 2013 CONSOLIDATED GUIDELINES

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

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
COBI	cobicistat
d4T	stavudine
ddI	didanosine
DRV	darunavir
DTG	dolutegravir
EC50	half maximal effective concentration
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EFV	efavirenz
ETR	etravirine
FDA	United States Food and Drug Administration
FTC	emtricitabine
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GSM	Global System for Mobile Communication
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
IVD	in vitro diagnostic medical devices
LPV/r	lopinavir/ritonavir
NASBA	nucleic acid sequence-based amplification
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse-transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PICO	population, intervention, comparison and outcome
PQ	prequalification
RAL	raltegravir
RPV	rilpivirine
RR	relative risk
RT-qPCR	reverse transcription real-time polymerase chain reaction
RTV	ritonavir
SMS	short message service
TAF	tenofovir alafenamide fumarate
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEE	tenofovir disoproxil fumarate plus emtricitabine plus efavirenz
TLE	tenofovir disoproxil fumarate plus lamivudine plus efavirenz
TNA	threose nucleic acid
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
XTC	3TC or FTC

FOREWORD

Countries have requested that WHO streamline, in a user-friendly manner, the development and release of HIV-related guidelines and of its technical and programmatic updates.

In response to this request, in June 2013, WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. This consolidation effort constitutes an innovative approach to WHO guidance and unifies previously disparate guidance on the use of antiretroviral therapy for adults, children, and pregnant and breastfeeding women. Another new feature is that it not only makes clinical recommendations on the use of ARV drugs (what to do) but also addresses operational aspects (how to do it) along the cascade of HIV-care related services. This includes testing, antiretroviral drugs for HIV prevention, linkage and enrolment into care, retention and adherence in general HIV care and treatment, management of comorbidities, when to start antiretroviral therapy and preferred ART regimens. The 2013 guidelines also provide, for the first time, recommendations on optimal service delivery and decision-making guidance for programme managers.

Since their release, many countries have responded very quickly, reviewed the implications of the new recommendations in their national context and, in many instances, adapted their national policies and guidelines. There is also rapid expansion of evidence and experience from both clinical and increasingly from implementation science research.

Another important aspect of the consolidation approach is that WHO now bundles its technical and programmatic updates and releases them once or twice a year, into supplements: this document, the March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, addresses new developments and implementation concerns regarding drug optimization, HIV testing, laboratory monitoring, toxicity and drug resistance surveillance, supply chain management and community delivery of antiretroviral therapy services. It constitutes the first of the supplements, builds on programme experiences, global consultations, and research and has been developed in collaboration with partners.

WHO is pleased to issue this document, which augments and complements a range of topics covered in the 2013 consolidated guidelines. I am confident that the materials contained in this supplement will be of good use to countries as they continue to expand and enhance the scope and scale-up of their HIV programmes.

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HIV self-testing

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Supplement as a whole

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EXECUTIVE SUMMARY

WHO guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection provide a public health approach for scaling up HIV care and treatment programmes and focus on simplified, harmonized and effective antiretroviral therapy (ART) regimens for use in resource-limited settings. In 2013, for the first time, WHO revised and combined guidelines for adults and adolescents, infants and children and pregnant women as well as other ARV-related guidance documents into one set of consolidated guidelines that addressed the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the broad continuum of HIV care.

The cascade of HIV care, treatment and prevention services is increasingly integrated with antiretroviral drugs used for treating people living with HIV as well as for preventing HIV transmission. The WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection provide recommendations on the use of ARV drugs for treatment and prevention and address other major aspects of HIV-related care. The guidelines also incorporate operational and service delivery guidance as well as guidance for programme managers on decision-making and programme planning.

The consolidated guidelines will be reviewed comprehensively every two years to incorporate the key clinical, operational and programmatic implications of new science and emerging best practices across populations, age groups and settings.

To ensure a timely dissemination of technical, policy and programmatic information, WHO will issue supplements to the consolidated guidelines. The materials included in these supplements can provide new recommendations, describe best practices and provide important updates that supplement the most recent consolidated guidelines and are intended for clinical and technical leaders as well as for programme managers.

The March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection provides complementary materials for the following chapters:

Chapter 5 – HIV diagnosis and ARV drugs for HIV prevention, including self-testing and early infant diagnosis;

Chapter 7 – Antiretroviral therapy, including optimizing ART for children and adults and the use of CD4 testing;

Chapter 9 – Guidance on operations and service delivery, including rolling out viral load testing, procurement and supply chain management concerns and community models of ART delivery; and

Chapter 11 – Monitoring and evaluation, including surveillance of ARV drug toxicity monitoring and surveillance of drug resistance.

WHO will issue the next supplement to the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in the second half of 2014. This later supplement will include sections related to diagnosing and managing major opportunistic and other HIV-associated infections as well as on adherence and retention. Future supplements will address the interactions between HIV and noncommunicable diseases, mental health and nutrition.

These guidelines continue to be 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. HIV SELF-TESTING

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 5 – HIV diagnosis and ARV drugs for HIV prevention

Key messages

- HIV self-testing has the potential to increase the number of people living with HIV who have access to testing, know their status, are diagnosed and initiate treatment.
- HIV self-testing shares many characteristics with current HIV testing and counselling approaches, including products, accuracy issues, linkage to care, potential benefits and risks and regulatory policies and frameworks.
- HIV self-testing is already formally and informally available, and it will likely become increasingly available. Countries should therefore be aware and informed about HIV self-testing.
- Research is continuing, but current evidence is limited. It is essential to develop a larger evidence base on HIV self-testing to inform the development of national policy and regulations as well as WHO normative guidance.
- There are several programmatic approaches and models for HIV self-testing, which vary as to type of support, range of access and site of sale or distribution. Although several models have been proposed, many others could be developed or adapted to suit the local context.
- Populations that may especially benefit from HIV self-testing include the general population and health workers in settings with a high prevalence of HIV infection, priority populations in all settings and those who frequently re-test due to ongoing risk.
- Key concerns regarding HIV self-testing also apply to all other types of HIV testing. The potential for harm can be minimized if HIV self-testing is provided along with adequate information, quality products and in a regulated way, within a human rights framework and with community involvement in decision-making.
- National policies and regulations can be adapted to include HIV self-testing in existing HIV testing and counselling strategies and policies.

Background

In June 2013, WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Chapter 5, "HIV diagnosis and ARV drugs for HIV prevention" summarizes diverse models of HIV testing and counselling services to increase access to HIV diagnosis that are presented in more detail in the WHO 2012 strategic HIV testing and counselling policy framework.

This technical update was prepared in November 2013 through the collaboration of the WHO, UNAIDS and key experts. Its primary objectives are to synthesize experiences, research and policies on HIV self-testing so as to inform stakeholders who are considering or already implementing HIV self-testing.

What is HIV self-testing and what could it accomplish?

HIV self-testing is a process whereby a person who wants to know his or her HIV status collects a specimen, performs a test and interprets the test result in private.[1] HIV self-testing does not provide a definitive diagnosis. Instead, it is a screening test for the presence of HIV-1/2 antibodies or HIV-1 p24 antigen. A reactive self-test always requires further testing according to relevant national testing algorithms *(1)*.[2]

HIV self-testing enables individuals to test themselves for HIV in private. By providing an opportunity for people to test themselves discreetly and conveniently, HIV self-testing may increase testing among people not currently reached by existing HIV testing and counselling services. Without access to HIV testing and counselling followed by prompt linkage to treatment and prevention services, people living with HIV risk ill health, death and the transmission of HIV to others.

Current status and research

There are a number of HIV rapid diagnostic tests available but, as of March 2014, only one rapid diagnostic test specifically packaged for self-testing has the approval of a stringent regulatory authority, the United States Food and Drug Administration *(2)*. Efforts are underway to develop or adapt other HIV rapid diagnostic tests for self-testing.

1. HIV self-testing differs from home specimen collection, in which individuals send their specimens to a laboratory where they are tested, and the laboratory returns the test result to an individual through a trained professional.

2. A testing algorithm describes the combination and sequence of specific HIV assays used within a specific HIV testing strategy.

Most rapid diagnostic tests have a 6- to 12-week window period: the time between suspected HIV infection and the time when the assay can detect HIV antibodies. However, several factors may affect the length of the window period.

Rapid diagnostic tests currently being considered for HIV self-testing are primarily whole blood–based (such as fingerstick/capillary) or oral fluid-based tests. However, other products for HIV self-testing could also be developed: for example, rapid diagnostic tests using other types of specimen collection, painless or integrated lancets, simplified sampling systems, integrated buffer delivery systems and shorter minimum reading time and maximum reading time.

Policy development regarding HIV self-testing is at varying stages across countries. A few, such as Kenya, have developed national HIV testing and counselling policies that include HIV self-testing *(3)*. Other countries, including Malawi, South Africa *(4)* and Zimbabwe *(5)*, are considering its introduction. The United States Food and Drug Administration approved over the counter sale and use of the OraQuick® In-Home HIV Test in the United States in 2012. In 2013, France and the United Kingdom announced plans to approve over-the-counter sale of HIV self-testing kits in 2014 *(6)*. In some countries, HIV self-testing is explicitly illegal *(7)*, but many others have no formal regulations or policies. Despite this, reports suggest that HIV rapid diagnostic tests have been "informally" available for self-testing for some time, and their availability and use are increasing.

Current evidence spans high-, middle- and low-income countries in Africa, Asia, Europe and North America. Findings are promising regarding acceptability and accuracy, but more evidence is needed to inform the development of policy, regulations and WHO normative guidance.

Studies generally report high levels of acceptability (74–96%), primarily with oral fluid–based rapid diagnostic tests *(8)*. In particular, good acceptability has been reported among the general population *(2,9–12)*, men who have sex with men *(13–18)*, health workers *(19–21)*, university students *(22,23)*, adolescents *(24)*, pharmacists who could provide HIV rapid diagnostic tests over the counter for self-testing *(25,26)* and couples or partners who want to self-test *(13,15,17,21,27)*. A study in Malawi reported that HIV self-testing combined with home-based ART initiation improved linkage to services, uptake of ART and care at a population level compared with facility-based HIV testing and counselling *(28)*.

Studies report that HIV rapid diagnostic tests for self-testing that use oral fluid are considerably accurate, with a sensitivity of at least 91.7% and specificity of at least 97.9% *(8)*. Although rapid diagnostic tests for HIV self-testing are generally accurate, the HIV prevalence of the population and operator errors affect their sensitivity and specificity and positive and negative predictive values. Operator error, which can take place with any test, occurs among both trained and untrained users of HIV rapid diagnostic tests and can cause incorrect test results.

There are many reports of trained health professionals making errors when performing HIV tests, regardless of the type of rapid diagnostic tests used, and their failure to follow standard operating procedures. For instance, a study of false-positive test results found that trained staff in the Democratic Republic of the Congo did not follow standard operating procedures *(29)*. In addition, a United States–based study of HIV rapid diagnostic tests using oral fluid used by trained health workers reported that user error was the most common cause of poor specificity, attributable to such factors as poor vision, poor lighting and not reading the results within the specified time period (reading either before 20 minutes or after 60 minutes) *(30)*. In studies of unsupervised HIV self-testing among untrained users, the rate of operator error was somewhat higher than when used by health professionals and ranged from 0.37% to 5.4% *(8)*. Errors reported include misinterpretation of test results and failure to follow instructions and perform the self-test correctly *(8)*.

Programmatic approaches and models

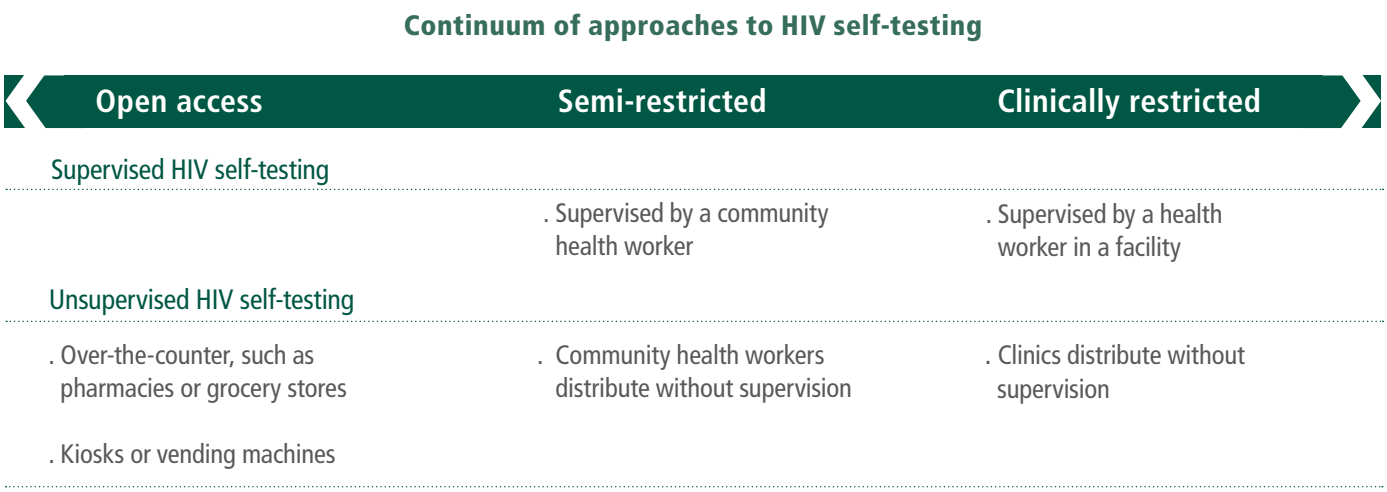
Researchers have proposed various approaches to delivering HIV self-testing *(1)*. These approaches differ as to: (1) how support is provided to users before and after testing (such as demonstration of the procedure, presence of peer supporter, telephone hotline); (2) how the test kits are distributed (facility, outreach, home-based or over the counter); and (3) how links are made from HIV self-testing to further HIV testing for confirming test results and for prevention, care and treatment as well as who is responsible for these links. Programmes may offer more or less support along a continuum, in combination with different levels of access and sites for distribution.

3. These terms describe approaches to HIV self-testing reported in current literature; they are not intended as WHO guidance or recommendations.

"Supervised" or "unsupervised" self-testing[3]

"Supervised" and "unsupervised" approaches to self-testing differ as to (1) the amount of support provided to test users and (2) how tests are administered or distributed.

Fig. 1.1. Continuum of approaches to HIV self-testing



"Supervised" self-testing involves support from a health worker or volunteer before or after individuals test themselves for HIV. Such support may include a demonstration, in a private setting, of how to use the test, pre- or post-test counselling and referrals to additional services.

"Unsupervised" self-testing refers to independent or open access to HIV self-testing. Support may or may not be indirectly provided, based on the user's initiative, such as telephone hotlines, leaflets, referral information, support groups, legal aid and HIV treatment, care and prevention services.

Access to self-testing

Three levels of availability of HIV self-testing have been proposed.

Clinically restricted: health professionals provide HIV rapid diagnostic tests for self-testing to only specific populations and groups, as decided by a country.

Semi-restricted: health workers or volunteers provide some pre-test instructions and counselling and then distribute the HIV rapid diagnostic test for self-testing to individuals, such as by health workers through a facility or through trained staff at pharmacies to patients or the general public. However, HIV self-testing is not necessarily openly available through the private sector.

Non-restricted (open access): HIV rapid diagnostic tests for self-testing are publicly available through many types of programmes and locations, such as pharmacies, clinics, groceries, convenience stores and vending machines.

Distribution and initiation of HIV self-testing

Three models for site of use or distribution of HIV rapid diagnostic tests for self-testing have been described.

Community-based HIV self-testing involves distributing HIV self-testing kits to community members through volunteers or community health workers. This approach involves some supervision through the support of a community health worker or volunteer before or after individuals test themselves for HIV in private. This support may include a demonstration of how to use the test and interpret the result, pre-test information on where and how to seek additional support, further testing and HIV prevention, care and treatment services as well as providing an opportunity for community members to disclose their result. This post-test support may include face-to-face counselling, peer support and referrals for additional HIV prevention, treatment and care services.

Facility-initiated or facility-based HIV testing approaches allow clients to use self-test kits at home or in a private setting in a health facility. Health care providers may encourage individuals to take self-test kits home for themselves and/or their spouses or partners. This model could also be used by health workers, their spouses or partners as well as health facility clients who want to self-test.

Alternative venue-initiated or venue-based approaches involve public distribution or sale of HIV rapid diagnostic tests for self-testing through pharmacies, groceries, the Internet and other venues – that is, the open access approach, which is currently employed in the United States *(2)*.

A modification of this approach could include access that is restricted to pharmacies, where HIV self-test kits are distributed by pharmacists or on-site nurses who have been trained to provide additional support and give information about sites for test confirmation and HIV care and support services. Further, rapid diagnostic tests for HIV self-testing could be clinically restricted and made available by prescription to specific individuals.

Weighing potential benefits and risks

Policy-makers and implementers need to weigh the potential benefits and risks related to introducing and scaling up HIV self-testing. Potential benefits include increasing access to testing, earlier diagnosis for people who do not have routine contact with health services where HIV testing is offered and greater convenience, autonomy and privacy for test users, some of whom are not using HIV testing and counselling services. Populations that may benefit are those who are currently underserved by existing HIV testing and counselling approaches and may include men who have sex with men, transgender people, people who inject drugs, sex workers, health workers and general populations in high-prevalence areas, couples or partners, serodiscordant partners, frequent re-testers and adolescents *(1)*. Some research suggests that HIV self-testing may reduce sexual risk behaviour *(15)* and increase testing frequency among men who have sex with men *(13,16)* and that HIV self-testing may also facilitate disclosure within couples in some settings *(27)*. These findings suggest that HIV self-testing may complement existing HIV testing and counselling and public health strategies to reduce the risk of exposure to and transmission of HIV.

To date, no serious adverse events or harm involving HIV self-testing have been reported—such as human rights violations from the misuse of HIV self-testing, violence or self-harm. However, some stakeholders have concerns about operational issues such as the slightly poorer sensitivity and specificity of rapid diagnostic tests in the hands of untrained or non-proficient users, risk of operator error, testing in the window period, misinterpretation of results and lack of linkage to care. There are also ethical, legal and social concerns, including potentially increased risks, such as inter-partner violence or coercive testing, for vulnerable populations. These considerations apply to all forms of HIV testing. WHO provides clear guidance on the critical requirements for all forms of testing, including the guidance that all testing must be voluntary. Mandatory or coerced HIV testing, including self-testing, is never warranted *(31)*.

Policy and regulatory considerations

HIV self-testing takes place in many countries that do not have regulations or policies on sale, distribution or use of HIV rapid diagnostic tests for self-testing. In order to improve both formal and "informal" HIV self-testing, a number of policies and regulations will likely need to be adapted or developed.

Key issues for policy-makers and implementers who are considering introducing HIV self-testing include the following.

- The sale, distribution and use of in vitro medical devices, in general, may need to be formally regulated.
- Access and consent policies may need to be adapted so that certain groups or populations can access HIV self-testing – for example, adolescents.
- Human rights and social protection laws, policies and regulations should address misuse and abuse, protecting individuals from coercion, discrimination and prosecution. Important social protections include safeguarding vulnerable populations, protecting users from mandatory or coerced testing and creating channels for reporting and redress in the event of misuse of self-test kits or of poor-quality or unregulated rapid diagnostic tests.
- Health care and managerial policies and regulations, national testing strategies and validated testing algorithms may need to be adapted or developed to address HIV self-testing, including policies to assure that health workers do not use self-tests as a first-line assay and policies on who can perform an HIV test and who can interpret and report an HIV test result. Health care providers and other staff of facilities and national programmes are likely to need guidance and training on how to include HIV self-testing in existing HIV testing and counselling frameworks.

Policy-makers, implementers and stakeholders also need to consider and address regulatory issues regarding HIV self-testing, including the following standards.

- **Regulation of HIV self-test kits and test-kit evaluation.** Self-tests must be evaluated with the intended users in the intended setting of use. Minimum standards for the delivery of HIV self-testing kits should be established, such as robust and clear pre- and post-test information for users.
- **Legal issues concerning disclosure of HIV self-testing results to others, including sexual partners.** Messaging and other information on testing should discuss the locally applicable legal implications of HIV self-testing and disclosure, keeping in mind that, where disclosure would be safe and beneficial, it should be encouraged.

- **Incorporating HIV self-testing into the national HIV testing strategy and national testing algorithms.** Policy-makers should consider a policy of requiring re-testing for confirming reactive HIV self-testing results. In accordance with existing HIV testing and counselling policies and national algorithms, re-testing is only needed for individuals with non-reactive self-test results if there is concern that they self-tested in the window period after potential exposure and/or if they are at ongoing risk for acquiring HIV infection.

- **Monitoring quality and adverse events.** Quality assurance indicators and procedures may need to be reinterpreted to include HIV self-testing. A strategy for monitoring social risk and harm must be put into place and regularly evaluated.

Other policy and programme considerations

HIV self-testing may provide an additional pathway for people to obtain care and treatment. Ways to facilitate links to care following HIV self-testing include pre-test information, counselling, post-test referrals and follow-up such as face-to-face counselling, telephone hotlines *(2,21)*, videos, Skype, short message service (SMS) *(32)* and computer programmes *(33)*.

An individual with a reactive self-test result should be advised to seek further testing to confirm the result according to the national testing algorithm. If the self-test result is non-reactive, the individual would be considered HIV-negative. However, as noted above, if an individual self-tests during the window period, had a recent exposure or is at ongoing higher risk, only then is re-testing recommended in accordance with national testing policies and algorithms. In addition, referral for counselling may be desirable for those with ongoing risk. To reduce the risk of HIV self-testing being used in practice as a first-line assay, policies and regulations may need to adapt national testing strategies and validate testing algorithms that include HIV self-testing. Further, health workers and health care facilities will need information on how to apply the national testing algorithm following HIV self-testing.

HIV self-testing accuracy is a priority concern for users and other stakeholders. The accuracy of test results depends on the type of HIV rapid diagnostic test, the specimen type (such as oral fluid or fingerstick whole blood), the sensitivity and specificity of the test, the way a rapid diagnostic test is used for self-testing and how test results are interpreted. HIV prevalence also affects accuracy: in a setting with low HIV prevalence, positive predictive values will be lower than in a high-prevalence setting, while the negative predictive values will be higher, and vice versa. Thus, the population and setting have implications for messages to the person using the HIV rapid diagnostic test for self-testing.

Appropriate and adequate messaging and instructions for use are critical to reducing user errors and maximizing the accuracy of HIV self-testing. Clear and concise printed instructions – written and/or pictorial – are essential to support correct use and interpretation. In particular, users need to understand that a reactive test result must be confirmed through further testing.

2. NEW STRATEGIES FOR DIAGNOSING HIV INFECTION AMONG INFANTS

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 5 – HIV diagnosis and ARV drugs for HIV prevention

Key messages

- The addition of virological testing at birth may provide an important adjunct to detect and treat infected infants earlier, but at increased cost and with unclear impact on overall programme outcomes.
- More evidence is needed to fully assess the performance of virological testing in the setting of more robust maternal combination antiretroviral regimens, prolonged infant antiviral prophylaxis and improved sensitivity of current HIV DNA- and RNA-based polymerase chain reaction (PCR) assays.
- HIV serological assays, including rapid diagnostic tests, are underused to detect HIV exposure, and their use should be encouraged to fast-track children to a definitive diagnosis, particularly if they are sick.
- Key innovations such as SMS printers and improved laboratory systems can greatly reduce turnaround times and improve programme efficiency.
- New platforms for virological testing (including for early infant diagnosis) that may be used nearer to the point of care could potentially provide a major advance in testing uptake and result in faster and more complete linkage to treatment but would require service reorganization, and it will be at least 1–2 years before these tests are widely available in countries.

Purpose of this section

This section summarizes key technical and operational developments in infant diagnosis since the release of WHO guidelines in 2010. It identifies key research gaps and operational issues and lays the groundwork for a complete review of new evidence and the publication of new guidelines expected by early 2015.

Context

Diagnosing HIV infection among infants and children requires overcoming a number of technical and operational challenges, particularly in resource-limited settings. The initiation of early antiretroviral therapy (ART) is critical in reducing mortality among infants living with HIV, and early infant diagnosis using molecular-based virological testing in the first few weeks of life is essential to starting early treatment. Serological HIV assays, including rapid diagnostic tests, which can be used to screen for HIV exposure among infants of unknown status and to diagnose older children, are underused. Despite efforts to scale up early infant diagnosis services and other testing services for infants and young children, overall early infant diagnosis coverage remains low, and this acts as one major bottleneck to improve the ART coverage among children.

Within this context, and in accordance with the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)*, The Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive *(2)* and the Treatment 2.0 Initiative *(3)*, WHO convened an expert review meeting in September 2013 to evaluate emerging literature on infant diagnosis and assess the need for new recommendations.

Background

Despite efforts to scale up antiretroviral therapy (ART) in resource-limited countries, coverage of treatment is lower among children than among adults. An estimated 647 000 children younger than 15 years were receiving ART in 2012 *(4)*, although coverage (34%) for those eligible for treatment was half that for adults (65%). The pace of scale-up for children has also been significantly slower than for adults.

One key bottleneck to scaling up treatment for children is access to timely HIV diagnosis for infants and young children (especially those younger than 18 months of age). Despite significant investment, among 104 countries reporting in 2012, only 35% of HIV-exposed infants underwent HIV virological testing within the first two months of life. Perinatally infected infants are at high risk of death in the first year of life *(5)*, and early initiation of ART reduces HIV-related mortality and long-term morbidity *(6)*. Based on these findings, WHO released guidance related to HIV testing in infants and children in 2010 *(7)*. These recommendations (summarized in part 1 of this section) include the following.

- Virological testing for HIV-exposed infants at 4–6 weeks of age should be performed using HIV DNA on whole blood specimen or dried blood spot; HIV RNA on plasma or dried blood spot; or ultrasensitive p24 antigen on plasma or dried blood spot.

- Virological testing is recommended for those who test positive at nine months of age with HIV serological testing.

- Children 18 months or older who are suspected of living with or being exposed to HIV should have HIV serological testing performed according to the nationally validated HIV testing algorithm for serological-based diagnosis used in adults.

- Infants and children younger than 18 months with unknown HIV exposure who have signs or symptoms suggesting HIV infection should undergo HIV serological testing and, if positive, virological testing.

Since these recommendations were published in 2010, there have been several important advances, including the following.

- Programmatic and operational experience with scaling up infant diagnosis has identified best practices for implementation but has also highlighted many challenges such as low testing coverage, slow turnaround time of results, poor quality of data systems to capture results and poor linkage of mother–infant pairs to care and treatment services.

- Emerging data on the optimal timing of infant testing suggest a potential benefit to testing soon after birth to quickly identify the infants infected in utero and prevent early mortality *(8)*.

- There are concerns about the potential lower sensitivity of virological testing in settings of expanded coverage of maternal ART and infant prophylaxis *(9)*.

- Virological testing platforms have evolved, with the possibility of testing for early infant diagnosis nearer to the point of care using innovative platforms, including the possibility that existing platforms for viral load monitoring can also accommodate both conventional or point-of-care early infant diagnosis testing.

- The Treatment 2.0 initiative aims to catalyse the next phase of HIV treatment scale-up and gives priority to providing testing nearer to the point of care as part of its framework.

- A case report of a "functional cure" of an infant living with HIV in Mississippi (USA) highlighted the urgent need to provide clear guidance on the testing strategies and programmatic management of HIV-exposed infants at birth *(10)*.

Based on these new advances, WHO convened an expert review meeting in September 2013 to evaluate emerging literature and develop a roadmap to guide the next set of WHO recommendations on infant diagnosis of HIV.

Technical considerations for infant diagnosis

The current WHO recommendations on infant diagnosis were developed in 2010 and were summarized in 2013 (Table 2.1 and Annex 2.1). Currently available HIV serological tests can be used to diagnose HIV among children aged 18 months and older. Since maternal antibodies cross the placenta to the fetus and may persist for up to 18 months, serological tests only demonstrate maternal infection and therefore infant HIV exposure but cannot confirm HIV infection among those younger than 18 months of age *(11)*. HIV serological testing can be used to screen for exposure among children younger than 18 months of age, but a definitive diagnosis of HIV infection among children younger than 18 months of age can only be confirmed with virological testing *(7)*.

Table 2.1. Summary of recommended testing approaches for infants (WHO 2013)

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 testing 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

Category	Test required	Purpose	Action
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

Infants who are HIV-exposed should have virological testing performed at 4–6 weeks of age or at the earliest opportunity thereafter, and ART should be initiated without delay in those testing positive. Current guidelines recommend the use of HIV DNA polymerase chain reaction (PCR) on whole-blood specimens or dried blood spot, HIV RNA on plasma or dried blood spot or ultrasensitive p24 antigen on plasma or dried blood spot. There are several operational advantages of using dried blood spot specimens that are well described in this supplement in the accompanying HIV viral load programmatic update *(12)*, and most programmes in resource-limited settings have opted for this approach. A confirmatory test on a new sample should be performed among those infants who test positive, but ART should not be delayed while awaiting results *(7)*. Importantly, for infants who have negative virological testing results, the definitive diagnosis of HIV infection should be determined when HIV exposure (usually through breastfeeding) ends, which is typically around 18 months, when serological testing, according to the national validated testing algorithm, can be used.

HIV serological assays (including rapid diagnostic tests) should be used to determine HIV exposure among any child in whom HIV is suspected (such as a child who is malnourished or has other symptoms compatible with HIV infection) and among all children with unknown exposure in a generalized epidemic setting. National programmes should follow existing national validated testing algorithms for serological diagnosis of HIV. Virological assays should be used to confirm HIV infection among children younger than 18 months of age who test positive on serological testing. When such virological assays are not available, the combination of serological testing and clinical symptoms in making a presumptive HIV diagnosis in infants and children less than 18 months of age is the recommended approach *(7)*.

WHO recommends provider-initiated testing and counselling as a key strategy to implement to identify people who need care and treatment *(13)*. This includes providing provider-initiated testing and counselling in routine infant care settings for additional case-finding, as some infants are not identified through programmes for preventing mother-to-child transmission as HIV-exposed or may be lost to follow-up even if known to be HIV exposed. Provider-initiated testing and counselling is particularly recommended for all children who are malnourished, have TB, are admitted to hospital or have other signs or symptoms of HIV infection *(13)*.

New developments

Since the 2010 guidelines on HIV diagnosis among infants and children were released, there have been a number of important advances, notably the release of the 2013 consolidated ARV guidelines *(1)*, which recommend (1) treating all children younger than 5 years living with HIV irrespective of clinical or immune stage and (2) ART for all pregnant and breastfeeding women living with HIV (option B), with consideration of lifelong treatment (option B+). Innovations such as simplified virological testing technologies open up the possibility of providing early infant diagnosis closer to the point of care and may facilitate expansion of infant diagnosis services and overcome some of the barriers in the diagnosis and care and treatment cascade. Virological testing at birth (as an additional test to the virological testing at 4–6 weeks in the diagnostic algorithm) has been proposed as a means of earlier case finding and a way to improve the retention in the cascade of care.

Virological testing among infants: early infant diagnosis

The optimal timing of virological testing to diagnose HIV infection in infants is a function of when infection occurs (in utero, intrapartum or postpartum during breastfeeding) but also of test performance, mortality risk by age and retention in the testing and treatment cascade (Fig. 2.1 and 2.2) *(8)*. It may also be influenced by operational considerations such as any contact with the health system when routine maternal and child health services are provided. Timing should optimize test performance and permit HIV treatment initiation among those for which nucleic acid is detected (HIV positive) before most early deaths occur. Ideally, the timing of testing should also align with the provision of routine maternal and child health services, such as scheduled immunization visits, and this was a key part of the rationale for the recommended timing put forward in the 2010 guidelines.

Fig. 2.1. Vertical transmission of HIV can occur in utero, intrapartum and postpartum at variable rates depending on the timing of infection and the availability of services for preventing mother-to-child transmission

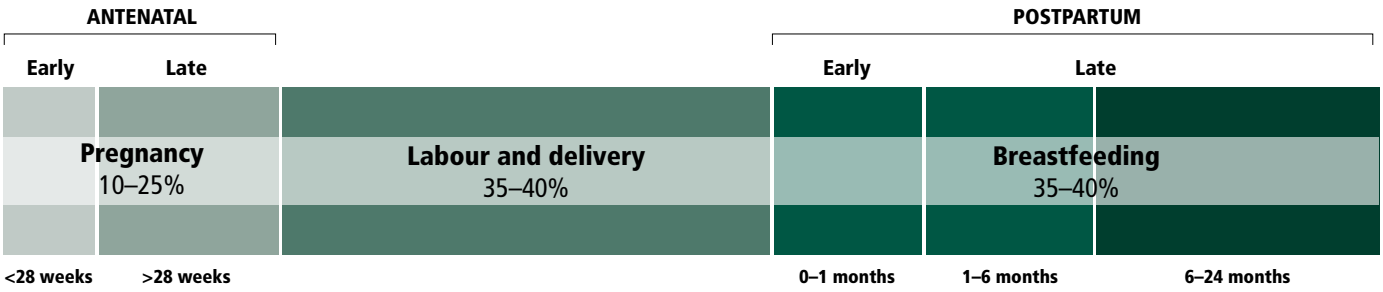
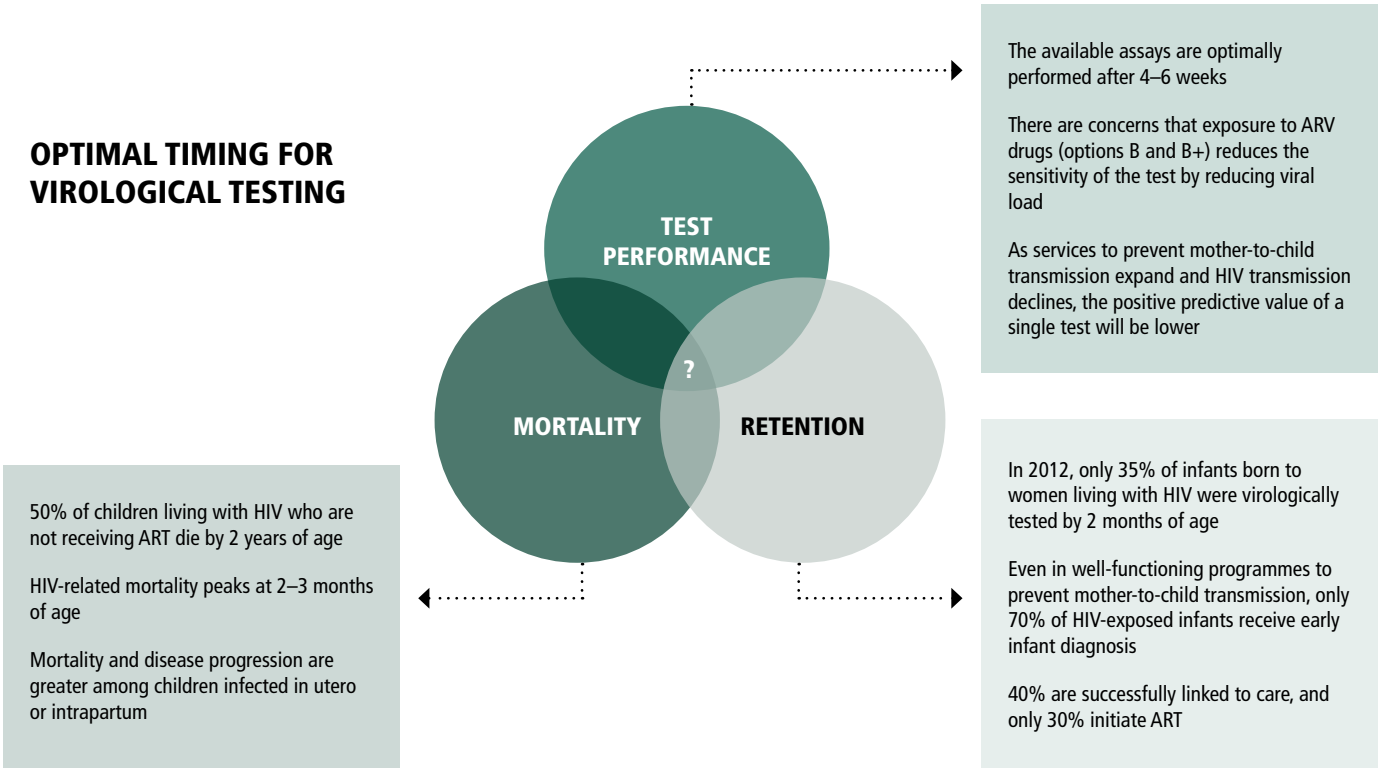


Fig. 2.2. Optimal timing of HIV virological testing depends on test performance, mortality patterns and retention in the treatment and care cascade



1. Test performance

The performance of an HIV diagnostic test is influenced by the intrinsic properties of the assays used (sensitivity and specificity), the quality and type of specimen and the underlying HIV prevalence in the population to be tested. For early infant diagnosis, in settings with well performing programmes for preventing mother-to-child transmission, vertical transmission rates may be as low as 2% at 6 weeks and the positive predictive value of a single test will be approximately 50%, meaning that only half of infants who test positive are truly infected *(7)*. For this reason, confirmatory testing is essential, especially as programmes for preventing mother-to-child transmission improve and the prevalence of HIV infection among HIV-exposed infants continues to fall.

Virological testing at 4–6 weeks of age will detect all in utero infections and nearly all intrapartum infections depending on the intervention for preventing mother-to-child transmission if provided *(14)*. For breastfed infants who will have ongoing exposure, virological testing at 4–6 weeks may detect, in addition to in utero and intrapartum infections, very early breastfeeding transmissions but will not detect later infections.

In untreated children living with HIV, viral replication is high, and HIV nucleic acid (RNA and DNA) and p24 antigen are therefore easily detectable in principle. By six weeks of age, almost all infants infected before birth, at birth or around birth can be identified by DNA, RNA, total nucleic acid or p24 antigen testing *(7)*. Assays that detect HIV DNA or total nucleic acid have good accuracy in whole blood and dried

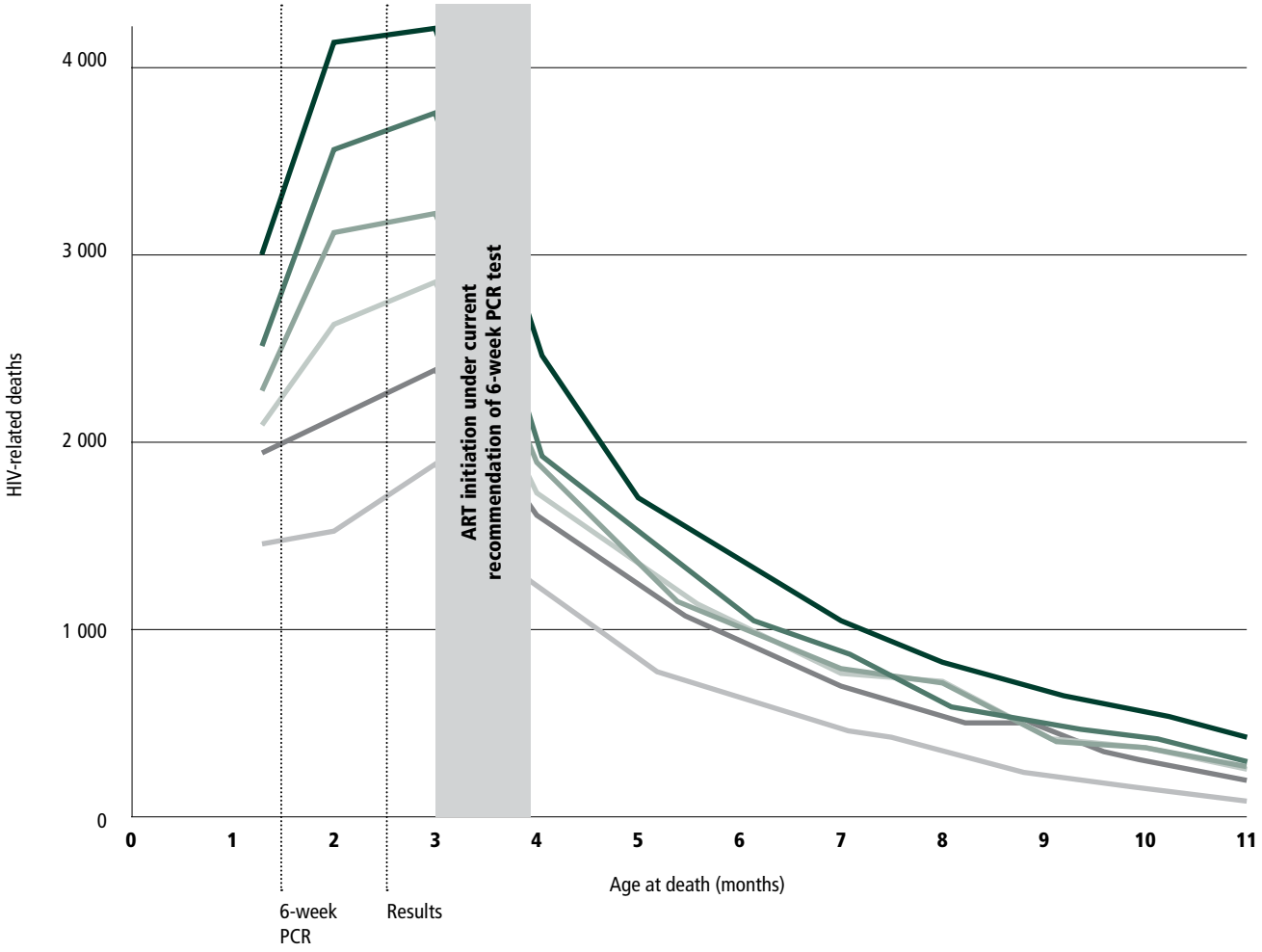
blood spots in almost all circumstances. Assays that detect RNA and p24 antigen, despite both having good accuracy, are of a concern in their use for testing infants exposed to neonatal prophylaxis and/or maternal ART, which may reduce significantly the amount of circulating virus and viral particles *(15)*.

Data from several cohorts, including non-breastfeeding infants, suggest that using combination ARV regimens to prevent mother-to-child transmission might delay the time to detect HIV DNA and/or RNA in the infants acquiring HIV despite interventions for preventing mother-to-child transmission *(9,16)*. A systematic review that assessed whether ARV exposure reduces the performance of assays that detect DNA and RNA (on dried blood spot specimens) found no evidence to suggest that these assays on dried blood spot underperformed at six weeks if infants were exposed to ARV drugs; there was also no evidence that assays that detect RNA on dried blood spot had lower performance than assays that detect DNA on dried blood spot as a result of exposure to ARV drugs. However, the quality of the evidence was determined to be low, since most of the studies did not include infants of mothers who are on three-drug ART regimens *(8,17–20)*. Future research is needed to address this issue.

2. Early mortality

Infants infected perinatally, including those infected in utero and intrapartum, have a high risk of rapid disease progression and death if not treated early *(21)*. Because HIV-related mortality peaks at around 2–3 months of age, the window of opportunity to identify and link infants living with HIV to ART is very narrow *(22,23)*. If virological testing is performed at 4–6 weeks of age and there are delays in returning test results and poor linkage to care, many infants living with HIV will die before having the opportunity to be treated. Virological testing at birth might allow ART initiation before peak mortality occurs, but numerous other factors should be considered (Fig. 2.3).

Fig. 2.3. Peak of mortality in South Africa and timing of virological testing and early treatment in different cohorts 1997–2002



Source: Bourne *(23)*.

3. Retention in the testing and treatment cascade

Programme experience has shown variable uptake of early virological testing of infants and high losses to follow-up among those who are tested *(24–27)*. Only 35% of HIV-exposed infants are reported to have received virological testing before the end of their second month of life, and among those tested, up to 45% are lost to follow-up before the mother receives her child's test result *(28)*. Studies in different settings are urgently needed to determine whether birth testing in addition to later testing can improve early treatment initiation and outcomes and to address the feasibility of this approach. In addition, tests that are nearer to the point of care and other strategies (such as the use of SMS printers) need to be evaluated as to whether they improve the cascade of care and infant outcomes.

HIV serological testing in children

The availability of HIV serological assays (such as rapid diagnostic tests) has resulted in increased HIV testing rates in adults, but such assays are not applicable for diagnosis in infants <18 months of age given the presence of maternal HIV antibodies *(29)*. Serological testing can be used to diagnose infection in children ≥18 months of age or to confirm final status among infants with known HIV exposure. Serological testing among infants <18 months of age can be used to determine HIV exposure and to exclude HIV infection. In settings where virological testing is not available, serological testing may be used along with clinical evidence of HIV infection to initiate life-saving ART quickly *(7)*.

The 2010 infant diagnosis guidelines recommended a number of outstanding issues for further research *(7)*. The expert consultation sought to determine whether additional data have become available on these topics. The findings are summarized below.

1. Assessing the performance of HIV combined antigen and antibody (fourth-generation) serological assays for diagnosis in breastfeeding infant populations: one study *(30)* found that this generation of assays offered no advantage over current antibody detection only assays in children.

2. Assessing the performance of different serological assays in infant populations: one study *(31)* found that Alere Determine HIV-1/2 (Alere Medical, Japan) had acceptable clinical sensitivity but that it was associated with delayed detection of seroreversion. Another study found acceptable performance of Alere Determine HIV-1/2 among infants in the United Republic of Tanzania aged 2–18 months with unknown HIV status who were admitted with an acute febrile illness *(32)*.

3. Assessing the use of oral fluid specimens to diagnose HIV in infants: one study that assessed two assays (OraQuick® HIV-1/2 – Rapid HIV-1/2 Antibody Test [OraSure Technologies, USA] and Aware™ HIV-1/2 OMT [Calypte Biomedical Corporation, USA]) found that these assays failed to detect about 13% of infections among infants *(33)*.

The 2010 guidelines also identified the need for more data on test performance among children who started ART in early infancy and to understand the rate of decay of maternal antibodies in breastfeeding infants *(7)*. Several studies *(34–37)* have highlighted that scaling up early ART among HIV-exposed infants and their mothers may influence the sensitivity of serological testing and timing of seroreversion. Further studies in this area are needed, including in different settings and populations. Finally, the 2010 guidelines made specific recommendations for the minimum sensitivity (99%) and specificity (98%) of HIV serological assays under quality-assured, standardized and validated laboratory conditions *(7)*. Since few data are available for infants and young children, and published data on how serological assays perform in this population are very limited, this remains an area of concern and an area in which additional data are needed.

Innovations

1. Birth testing to improve testing uptake and ART initiation and to accelerate the testing cascade

Programmes and policy-makers have promoted birth testing as a way of accelerating the testing cascade and starting more children on treatment in a timely manner. The report of a case of functional cure in an infant treated very early in life (at 30 hours of age) has stimulated further interest in testing infants at birth *(10)*. However, the feasibility of testing at birth is likely to be restricted to settings with a high rate of institutional delivery *(38)*, and treatment within hours of birth must still overcome barriers that include the turnaround time for testing, effective linkage to treatment and care, non-availability of appropriate neonatal dosing data for most ARV drugs (such as lopinavir/ritonavir or nevirapine given as treatment, as opposed to prophylaxis) and changes to programmatic and service delivery practices. For these reasons, birth testing may have little programmatic impact on the proportion of children who initiate timely ART and survive, unless it is coupled with improvements in the cascade of care and further health system strengthening.

Moreover, because intrapartum infections are generally not detectable at birth, virological testing at birth is approximately 70% sensitive for detection of early (defined as in utero and intrapartum) infections *(39)*. This is a particular concern for women who have not achieved viral suppression by the time of delivery. Therefore, a second virological test at six weeks, or at a later time that may better suit a new testing algorithm, would still be required to identify the substantial number of intrapartum infections that will be missed by testing at birth.

Preliminary data from a decision analytic modelling exercise developed to explore the potential performance and cost

implications of modifying the current algorithm by adding testing at birth (0–3 days old) highlighted the increase in investment that this may entail. Providing early infant diagnosis from birth to all HIV-exposed infants would increase the cost per HIV-infected diagnosis from US$ 458 to US$ 823. The proportion of HIV-infected children correctly diagnosed by 24 months (the parameter chosen for this model) would also increase, from 55% under the current algorithm to 69% with the addition of birth testing. However, due to reported high rates of dropout in the early infant diagnosis cascade, the proportion of pre-ART deaths and children living with HIV starting ART was more comparable (25% versus 27% and 37% versus 31% respectively). Adding early infant diagnosis at birth would therefore potentially increase the proportion of children living with HIV diagnosed but would offer limited improvements if not accompanied by improved retention and referral for initiation of ART *(40)*.

Pilot studies are underway or planned, in South Africa and Mozambique respectively, to better assess the true impact that birth testing can have in different settings, and how this could be best implemented; and similar studies are needed in other settings. In addition, further economic analyses are needed to help determine the optimal use of resources in settings with different HIV prevalence, coverage of services for preventing mother-to-child transmission or service delivery systems *(15)*.

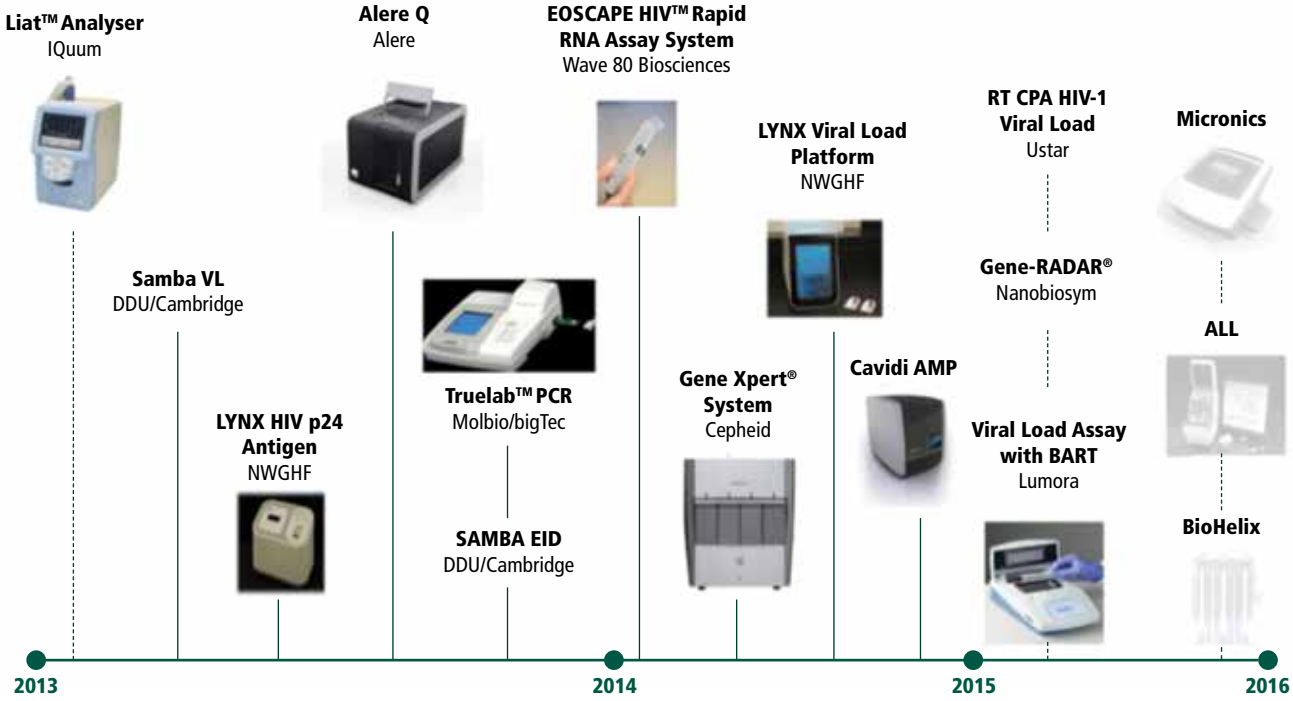
WHO currently recommends virological testing at 4–6 weeks of age *(7)* but encourages countries to consider pilot assessments and consideration of whether birth testing could be implemented in future. This area will be reviewed when the guidelines are updated in early 2015.

2. Use of point-of-care virological diagnostics to scale up infant testing

Current virological testing is laboratory based and technologically complex, and consequently requires considerable infrastructure, training and specimen transport networks even when using venous and/or capillary (heel-stick) dried blood spot specimens and optimal laboratory networks *(27)*. Despite several operational innovations, turnaround time remains long in many settings (contributing to a greater failure to return results and timely initiate ART) and there is underutilization of equipment and wastage in some settings. For these reasons, the possibilities of virological diagnosis nearer to the point of care hold great promise. To date, no testing platforms dedicated to early infant diagnosis that could be used at the point of care have been launched.

Many technologies for virological testing (DNA, RNA, TNA and ultrasensitive p24 antigen) that could be used closer to the point of care are being developed (Fig. 2.4). Two recent reviews provide a comprehensive update of what is in the pipeline and key considerations for country programmes *(41–43)*.

Fig. 2.4. Point-of-care viral load and early infant diagnosis products: available and in the pipeline*



--------- No market launch date set by company

* Estimated as of March 2013 - timeline and sequence may change

Source: UNITAID diagnostic landscape, semiannual update, November 2013.

Programmes need to consider where technologies that may be used closer to the point of care should be placed in the context of a tiered laboratory network and with an understanding of how this will change service delivery models and messages to stakeholders. The accompanying programmatic update on viral load technologies provides a systematic comparison of the advantages and disadvantages of centralized delivery using laboratory-based techniques compared with more decentralized delivery using simplified technologies close to the point of care *(12)*.

Lessons for future rollout efforts can be learned from recent experiences gained when implementing point-of-care or near point-of-care rollout, such as point-of-care CD4 and molecular techniques for diagnosing tuberculosis *(44)*. Although many platforms are currently being developed, their availability in programme settings is realistically still at least 1–2 years away *(41)*.

Operational considerations and innovations in infant diagnosis

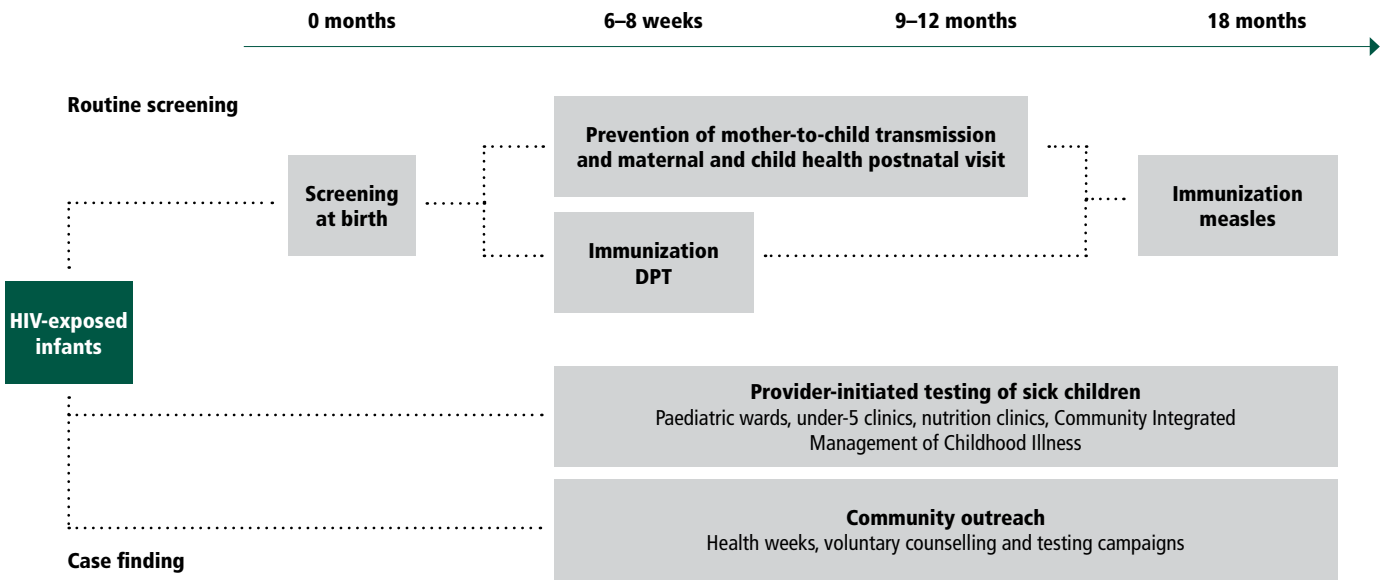
To maximize HIV testing coverage and linkage to care, a number of operational challenges need to be addressed in resource-limited settings. Although much attention has been given to optimizing testing platforms, enhancing service delivery strategies remains critical in achieving early ART initiation among infants living with HIV. Key operational elements in infant testing include (a) innovation and integration of programme services; (b) training health care workers in the appropriate use and interpretation of testing assays; (c) enhancing laboratory systems; (d) engaging community actors; (e) understanding operational considerations in various HIV prevalence settings; and (f) monitoring and evaluation. Further, the organization and feasibility of testing services need to take into account system capacity and consideration such as rural versus urban geographic disparities *(45)*. As there is now significant variation in early infant diagnosis coverage, additional attention should be given to the countries and regions where early infant diagnosis coverage remains the lowest.

Integration innovation of programme services

Programmes for preventing mother-to-child transmission present a key opportunity to test HIV-exposed infants, their siblings and their mothers' partners in addition to pregnant women as part of standard antenatal care *(46)*. However, not all women receive antenatal services and have access to programmes for preventing mother-to-child transmission and thus other entry points for infant testing integration have to be explored. A rapid assessment undertaken in 2010 in Swaziland, Uganda, the United Republic of Tanzania and Zimbabwe *(47)* found that only 5% of children initiating ART were identified through programmes for preventing mother-to-child transmission, despite 75% of children receiving virological testing through such programmes. This suggests that there are important missed opportunities to link infants who test positive within programmes for preventing mother-to-child transmission more effectively to ART *(48)* and to expand settings where virological testing may be offered to reach those infants who are sick and need ART more quickly.

The WHO Regional Office for Africa has developed operational guidance for African countries *(49)* for the integrated delivery of infant, child and adolescent testing by outlining a series of strategies to encourage more HIV testing and counselling for children, particularly by increasing access to HIV testing in existing inpatient or outpatient health care services and programmes for infants, children and adolescents and their families (Fig. 2.5). This guidance also outlines training health care workers to provide counselling and testing services for children and their parents or caregivers. Annex 2.2 highlights additional recommended HIV testing approaches.

Fig. 2.5. Entry points for offering HIV testing for infants and children



Source: adapted from Chewe Luo, UNICEF, presented at the International Conference on AIDS and STIs in Africa, December 2013.

HIV testing integration into child health care programmes, especially the Expanded Programme for Immunization services, is another way to identify HIV-infected infants. However, vaccine coverage indicators in the context of HIV testing integration should be carefully monitored to avoid affecting vaccine coverage as described in rural sites in the United Republic of Tanzania *(50)*. Swaziland, with high early infant diagnosis coverage, integrated the testing of HIV-exposed infants at six weeks of age into routine postnatal and under-five health care *(51)*. This resulted in a significant increase in the number of HIV-exposed infants tested within their first two months of life. In high-prevalence settings, HIV testing of infants should be made routinely available through child health services such as Expanded Programme for Immunization programmes, well-child services and services for hospitalized and all sick children. In all settings, provider-initiated testing and counselling should be offered to sick children with suspected HIV infection. In both cases, adequate human resources will be needed to ensure such testing is regularly available. Task shifting of testing and counselling responsibilities to trained lay counsellors is one promising approach *(52)*.

Strengthening laboratory systems

Optimizing infant diagnosis delivery will have to address how laboratory systems can be strengthened, particularly by examining practical issues around the use of current testing platforms, the advantages and disadvantages of decentralization versus centralization of laboratory testing, including the transport of specimens and return of the results, integration and the potential role of testing near the point of care and testing at birth. From a laboratory systems perspective, timely and efficient testing of infants and young children requires the following cascade of events: (1) identifying exposed infants through programmes for preventing mother-to-child transmission and other strategies (such as through provider-initiated testing and counselling); (2) offering the age-appropriate test (virological or serological) according to the setting; (3) proper specimen collection and storage; (4) specimen transport to the laboratory; (5) laboratory testing; (6) return the result to the health facility; (7) return the result to the caregiver; (8) linkage to appropriate care for both HIV-infected and HIV-uninfected people; (9) re-testing where required; (9) quality assurance; (10) reporting and monitoring; and (11) using laboratory-related data for laboratory and clinical programme evaluations.

A review of how early infant diagnosis services can be decentralized geographically and through different health system layers *(53)* concluded that decentralization alone is not sufficient to produce greater utilization of services at lower-level sites. Careful follow-up of infants is integral to counselling for preventing mother-to-child transmission, coupled with stronger early infant diagnosis linkages with the Expanded Programme for Immunization and accurate documentation of mothers' HIV status on health cards *(54)*.

A number of countries have begun to focus on simplifying testing methods and making specimen transport and management more feasible in rural settings. Box 2.1 describes Uganda's model system, which consolidated testing into a single high-volume laboratory but decentralized specimen collection and return of results *(54)*.

Box 2.1. Uganda's model for a national laboratory transport system

- Laboratory service reorganization (fewer testing sites and an improved system of specimen collection and results return) in 2011 resulted in significant reduction of turn-around time of results
- Reducing loss-to-follow up by integrating an early infant diagnosis care point either in maternal and child health or ART clinics
- Setting up a specimen transport system, with the use of a geographical information system, and establishment of hubs reaching out to health facilities resulted in reduction of transport costs of dried blood spot samples by 62% and improved turn-around time for specimen and result transport from over 40 days to 2 weeks
- Web-based programme monitoring to conduct analytics for stakeholders
- SMS messaging to remind mothers to collect their infant results
- GSM printers placed at the specimen transport hubs for transmission of results and follow-up of infants living with HIV

Early infant diagnosis technology that can be used near the point of care is anticipated to be available in the near future, and the selection and placement of such devices is a critical issue. Mozambique's experience in developing a selection tool for deploying point-of-care CD4 devices, which involved a scoring system of facilities throughout the country, could

serve as a model to develop strategies on where early infant diagnosis point-of-care platforms can be best placed *(55)*.

There is significant room for improvement to the current partly centralized and centralized testing systems *(56)*. It is likely that future infant testing will be performed by hybrid networks that include both laboratory-based and simpler technologies nearer to the point of care. The introduction of technologies nearer to the point of care will affect the efficiency and access to infant testing, but its success will depend on continual health system strengthening. Lastly, ensuring the documentation of best practices can improve laboratory systems and advocate for their adoption.

National policies and guidance on infant diagnosis

To understand national policies and practices related to infant diagnosis, WHO reviewed published national guidelines for 21 of 22 Global Plan countries and performed an e-survey of programme managers on current practices *(57)*. Box 2.2 summarizes the results.

Box 2.2. Results of a review of published national guidelines related to infant diagnosis, September 2013 and the results of an e-survey of programme managers

Results of a review of published national guidelines related to infant diagnosis

- All countries recommend virological testing at 4–6 weeks of age.
- Existing recommendations were found in a variety of national documents, which were at times inconsistent and lacking coordination.
- Most countries reported using HIV DNA PCR testing on dried blood spot (17 of 32); 19% (6 of 32) used HIV RNA PCR testing on dried blood spot.
- Only 5 of 21 countries recommend immediate ART initiation or referral clearly in their national policy document.
- Only 9 of 21 countries recommend HIV serological testing (including using rapid diagnostic tests) at 9 months of age.
- A number of good country examples were identified, including provider-initiated testing and counselling guidelines (Zambia), clear algorithms for different testing scenarios (Lesotho), and clear guidance on the important of different entry points for testing (Swaziland).

Results from an e-survey targeting programme managers

- Only 13 of 21 countries clearly recommend confirmatory testing of infants testing positive on a single test.
- HIV serological assays may be underused in programme settings to diagnose HIV exposure and infection in infants and children.
- The need for confirmatory testing of positive virological test results is not well understood in all countries.
- Clearer policies on key issues (such as serological testing at nine months and for final diagnosis) are needed in many countries.
- When asked to identify the greatest barrier to infant testing, respondents were divided between lack of services for preventing mother-to-child transmission (25%), families and communities not understanding the importance of early infant testing (24%), poor linkage to care and treatment for children (21%), lack of virological testing (18%) and slow turnaround time (12%).

Engagement of community structures

Community stakeholders play a critical role in raising awareness and improving utilization of services for preventing mother-to-child transmission, including the importance of infant diagnosis and links to treatment. Peer-to-peer mothers' support, service provision by community members including HIV testing and counselling, coupled with community-led monitoring and accountability are some of the ways communities have been actively involved at the grassroots level *(58)*. For children who do not benefit from programmes for preventing mother-to-child

transmission or who do not return for follow-up, community members are likely to make an important contribution to improve case finding and in tracing children and families who have been lost to follow up. There are some positive examples where community has supported innovative early infant diagnosis projects, including a pilot project in rural Zambia where automated SMS of the dried blood spot PCR results were reported to a point-of-care health facility or infant caregivers much faster than would have been possible by using a courier to deliver results by paper *(59)*.

Clear messaging around infant diagnosis and infant feeding to communities is critical. Disclosure of an HIV-positive diagnosis, whether to a woman about herself (through programmes for preventing mother-to-child transmission) or about her infant, is a difficult process, and women need ongoing support. Settings where women and infants may both be tested at maternity and shortly after birth pose particular challenges in ensuring adequate disclosure of the HIV status and supporting any emotional distress that may result. Maternity-based programmes should be considered during this critical period. It is also extremely important to ensure that all HIV-exposed infants receive a final definitive diagnosis. Parents and caregivers need to be informed that infant diagnosis is not a one-time test but is rather a process (particularly in the setting of ongoing exposure in breastfeeding populations).

Addressing the negative attitudes of health care workers is also critical, and they may require training and mentoring to provide high-quality and supportive care to women and families. Qualitative research is critical to better understand patient and community perspectives around infant testing. Lastly, male participation, coupled with community advocacy by networks of people living with HIV, should be factored into country-level efforts to implement infant diagnosis.

In settings with lower HIV prevalence in western Africa, acceptance of services for preventing mother-to-child transmission and infant testing has been a challenge in some programmes. In a study conducted in Abidjan *(60)*, routine screening for HIV exposure at postnatal visits was not effective because formal parental consent was low (15%). These findings suggest the need to engage fathers in the infant diagnosis cascade, coupled with a focus on patient education, which should start before birth.

Considerations for low-prevalence settings

The feasibility of HIV testing in infants is often described in the context of settings with high HIV prevalence in the general population and among pregnant women. However, the operational constraints and potential solutions for testing infants in settings of low HIV prevalence may pose unique challenges, including the need for different service delivery models. Confirmatory HIV testing in low HIV prevalence settings is essential, but once a definitive diagnosis is made, repeat testing is unnecessary.

Other key challenges in settings of lower HIV prevalence include services for key affected populations (such as pregnant women who inject drugs), the extent to which care is centralized, and perhaps a more exacerbated role of stigma. The suboptimal links between early infant diagnosis and treatment initiation are observed beyond sub-Saharan Africa, as in countries such as Ukraine *(61,62)*.

Monitoring and evaluation: what data do we capture?

As infant diagnosis is scaled up, all approaches demand careful monitoring and evaluation. Defining the outcomes of programmes for preventing mother-to-child transmission in programme settings has already been shown to be feasible in such settings as Zambia *(63)* but requires accurate documentation and analysis. The applicability of determining such outcomes to infant testing services may be particularly informative.

Table 2.3 lists the currently recommended indicators for infant diagnosis. The core indicator for infant diagnosis is virological testing of HIV-exposed infants within two months of birth. However, challenges to this indicator include (1) whether reported data include the number of children or the total number of tests, and (2) whether reported data include only children younger than two months of age when tested. Data on children tested after two months of age and on the final status of HIV-exposed

Table 2.3. Current indicators for infant diagnosis

Core indicator: early infant diagnosis coverage	
Numerator	Number of infants receiving a virological test within two months of birth
Denominator	Estimated number of HIV-exposed infants
Additional indicator: infant testing coverage	
Numerator	Number of infants receiving any serological or virological HIV test by 12 months of age
Denominator	Estimated number of HIV-exposed infants

Source: Indicator Registry (http://www.indicatorregistry.org/node/857, accessed 17 February 2014).

infants are seldom available in settings with a high burden of HIV, especially as this is the true measure of the success of interventions for preventing mother-to-child transmission. In addition, it is often difficult to link data for children to data regarding treatment and to maternal data. Such data are needed to assess the impact of services for preventing mother-to-child transmission and efforts to treat children as well as to pinpoint weak links along the cascade of care. These issues can be improved if patient registers are longitudinal and laboratory data are arranged to link individuals. Systems that link mother–infant pairs can also be extremely useful.

Currently, WHO is developing consolidated guidance on strategic information for release in mid-2014, and this will provide an opportunity to update recommendations on indicators related to infant and child testing, diagnosis and linkage to treatment. Future revisions should include testing rates and results by two months of age as well as better data on the final status of HIV-exposed infants.

Best practices in service delivery

Many programmes are successfully scaling up infant diagnosis and have developed innovative strategies to overcome various challenges. Box 2.3 highlights some of these best practices. Policy-makers should carefully consider the context of their epidemic (such as background prevalence) and existing health systems in place as they consider how to optimize infant diagnosis. It is equally important that other stakeholders, including community

Box 2.3. Best practices for implementation

1. One-stop care approach

- Linking mother–infant pairs (such as by ensuring that infants are followed in the same service as mothers who receive treatment through option B or option B+).
- The importance of linking early infant diagnosis with the Expanded Programme on Immunization (EPI) provides opportunities to find infected babies and ensure that testing coincides with immunization but requires engagement of EPI staff *(64)*.

2. Longitudinal continuum of care for mothers and infants by modifying policies and practices

- Strategies include better appointment systems (including SMS reminders) and monitoring systems to identify missed appointments and follow up of mothers by phone or home visits *(65)*.

3. Infant diagnosis expansion must go hand in hand with treatment services for children through greater decentralization of services for children, training and task shifting *(52)* and engagement of communities in infant and child follow-up.

4. Communities can provide critical support to children and families, through peer support, community health education and patient tracking to enhance retention *(66)*.

5. Reorganization of laboratory services can improve turnaround time and reduce logistics costs

- SMS printers, either one-way or two-way printers for result expediting and result requests
- Improved sample referral systems
- A dedicated telephone line in the national reference laboratory to expedite results return and HIV telephone hotline to support clinicians in the field with decision-making during patient care

6. Routine data should be used to review programme performance

- Unique patient identifiers and including HIV data elements on child health cards can improve longitudinal care and reduce missed opportunities
- Data from laboratory-based early infant diagnosis programmes can be used to assess programmes for preventing mother-to-child transmission performance (but should be interpreted with caution when early infant diagnosis programme coverage is low)

actors, become sensitized to the urgency of infant diagnosis and the need to ensure successful linkage and retention in the care and treatment services for infants living with HIV.

Roadmap to revising guidelines

Diagnosing HIV among infants and young children remains challenging and represents an important bottleneck to timely initiation of ART in children. A roadmap has therefore been developed that (1) identifies research gaps, (2) proposes key guidelines questions (such as including PICO questions) and (3) paves the way for revised recommendations. Box 2.4 describes the key research priorities.

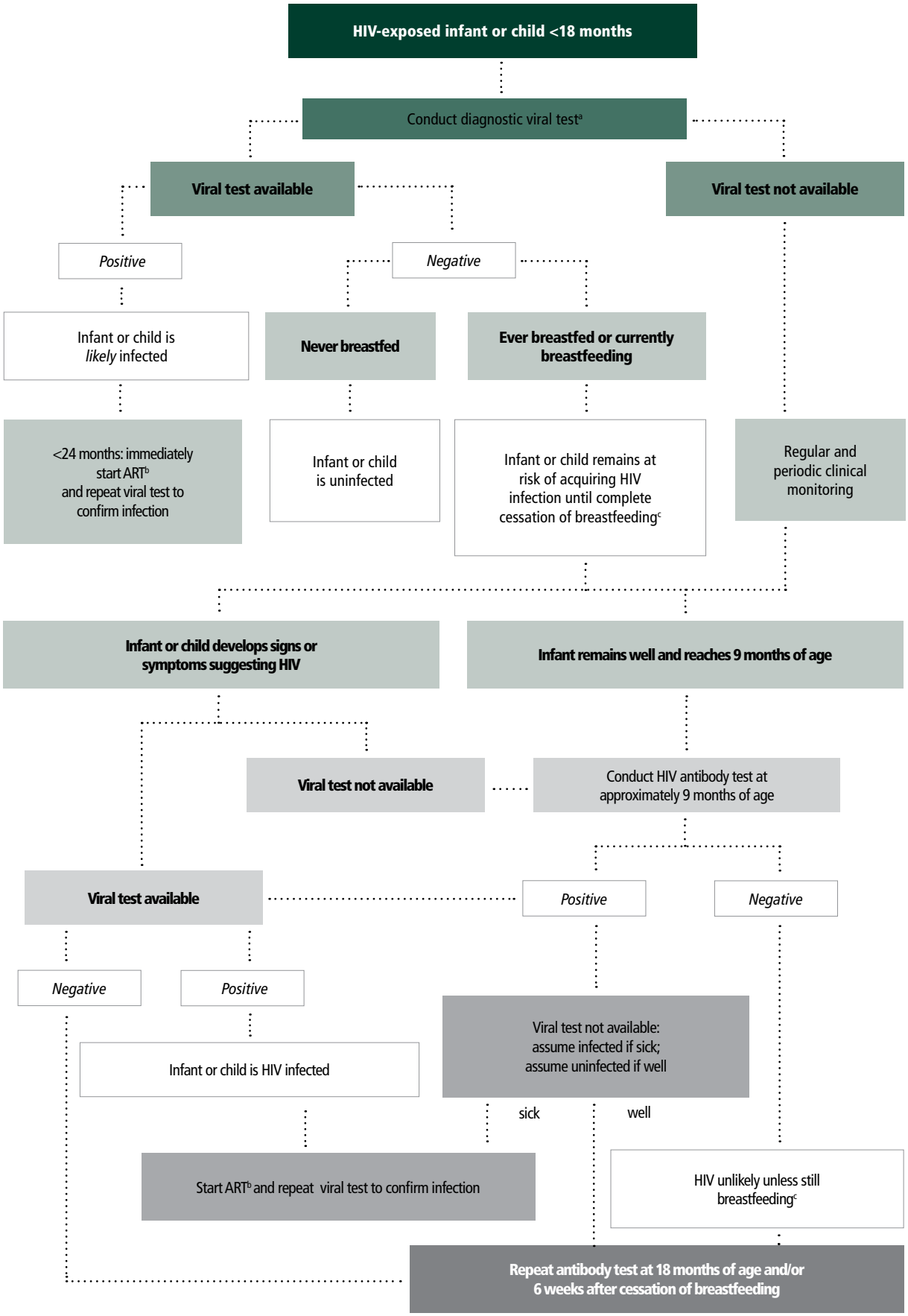
As new consolidated guidelines are anticipated in early 2015, clear questions were identified to frame the evidence review that is required to revise the current WHO recommendations in line with the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) requirements (http://www.gradeworkingroup.org) that have guided WHO's development of normative guidance since 2007.

Box 2.4. Research priorities

1. How does scale-up of effective intervention for preventing mother-to-child transmission impact the proportion of in utero, intrapartum and postnatal infections and what is the impact on optimal testing strategies?
2. Does virological testing at birth improve linkage and retention into treatment and care?
3. What is the impact of ART among mothers in the time to seroreversion among HIV-exposed but uninfected children?
4. What is the impact of early ART in infants living with HIV on HIV test performance?
5. What is the optimal timing (and testing strategy) to follow HIV-exposed infants to a final diagnosis?
6. How can we ensure that the performance of commercially available HIV serological assays is evaluated among infants and young children?
7. Do virological assays intended for use near the point of care improve linkage to care and patient outcomes?
8. What programme and laboratory data are critical to examine infant diagnosis and early infant treatment? How can data systems be better linked and designed to easily capture such data?
9. What are barriers and opportunities for women living with HIV, families, and communities to support testing of HIV-exposed infants and uptake of HIV treatment and related services?
10. What are the values and preferences of women living with HIV, families, and communities related to the diagnosis of HIV in infants and young children?

ANNEX 2.1.

Early infant diagnosis algorithm *(1)*



[a] For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks). See also Table 4.1 on infant diagnosis.

[b] Start ART, if indicated, without delay. At the same time, retest to confirm infection.

[c] The risk of HIV transmission remains as long as breastfeeding continues.

ANNEX 2.2.

Key entry points to HIV testing for infants, children, and adolescents

Settings for antenatal care and preventing mother-to-child transmission	
• All pregnant women • All infants of HIV-infected mothers • All infants with mothers of unknown status	• HIV serological (antibody) testing in the infant if the mother is of unknown HIV status • Virological assay for the infant if the mother is known to be positive or the infant tested HIV antibody positive: HIV DNA PCR or other virological test
Labour wards and delivery services	
• All pregnant women • All infants of HIV-infected mothers • All infants with mothers of unknown status	• Rapid serological HIV assay on mothers to determine HIV status and infant exposure. If infants HIV-exposed, for preventive treatment and virological HIV test at 4–6 weeks of age
Expanded Programme on Immunization	
• All infants born to HIV-infected mothers (if not previously tested) • All infants with mothers of unknown status	• Infants born to HIV-infected mothers (if not previously tested): virological assay: HIV DNA PCR or other virological test[a] • Infants with mothers of unknown status: HIV rapid serological test; if positive, confirmatory virological assay
IMCI, well-baby clinics and nutrition services	
• All infants of HIV-infected mothers (if not previously tested) whether symptomatic or not • All malnourished or underweight infants and children[b] • All children presenting with unusual or recurrent infections[b] • All children with signs and symptoms of HIV[b] • All children with TB[b] • All children with siblings and/or family members who are HIV- or TB-infected[b]	• Less than 18 months of age, status of mother or infant exposure unknown: establish exposure with serological test (HIV rapid test or HIV ELISA); if reactive confirm status with virological test (HIV DNA PCR)[a] • Less than 18 months of age, status of mother is known positive or known HIV-exposed infant: virological test (HIV DNA PCR)[a] • Older than 18 months: serological assay (HIV rapid test or HIV ELISA) • Previously negative but sick or breastfeeding: repeat test as appropriate for age
TB services	
• All infants, children and adolescents diagnosed with TB • All infants, children and adolescents with suspected TB	• Less than 18 months of age and of unknown exposure status: establish exposure with serological test (HIV rapid test or HIV ELISA); if reactive, confirm status with virological test (HIV DNA PCR)[a] • Less than 18 months of age and of known exposure status: virological testing. Consider initiating ART. • Older than 18 months: serological assay (HIV rapid test)
Sexual and reproductive health and family planning services	
• Adolescents presenting for contraception • Adolescents presenting with menstrual concerns • Adolescents presenting for treatment of sexually transmitted infections • Adolescents presenting for male circumcision	• Serological assay (HIV rapid test or HIV ELISA)
Orphans and vulnerable children	
• Orphans in institutional care • Disabled children in institutional care • Children who are the victims of sexual abuse	• Less than 18 months of age: establish exposure with serological test (HIV rapid test or HIV ELISA); if reactive, confirm status with virological test (HIV DNA PCR)a • Older than 18 months: serological assay (HIV rapid test or HIV ELISA)
Adult HIV testing and treatment services	
• Children and partners of adults living with HIV	• Serological assay (HIV rapid test or HIV ELISA)

Source: *Operational guidelines on HIV testing and counselling of infants, children and adolescents for service providers in the African Region (48).*

[a] When virological testing is unavailable, clinical algorithms along with serological testing allow for a presumptive diagnosis of HIV infection and for treatment with ART. if the mother is of unknown status, please either offer an HIV serological test to the mother or the infant. If the test is positive, then perform HIV virological testing.

[b] If HIV infection is clinically likely and HIV rapid test is positive, consider initiating treatment while HIV virological testing is being processed; this is particularly important among very young infants and children who have higher mortality from HIV infection.

3. PHARMACEUTICAL EQUIVALENCE AND CLINICAL INTERCHANGEABILITY BETWEEN LAMIVUDINE AND EMTRICITABINE

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Key messages

- Overall, the available evidence supports the clinical equivalence of 3TC and FTC in terms of efficacy and safety.
- Evidence with regards to drug resistance is inconclusive, with differences appearing to be small, and their clinical importance unclear.
- Currently, 3TC is available in more fixed-dose combination formulations than FTC.

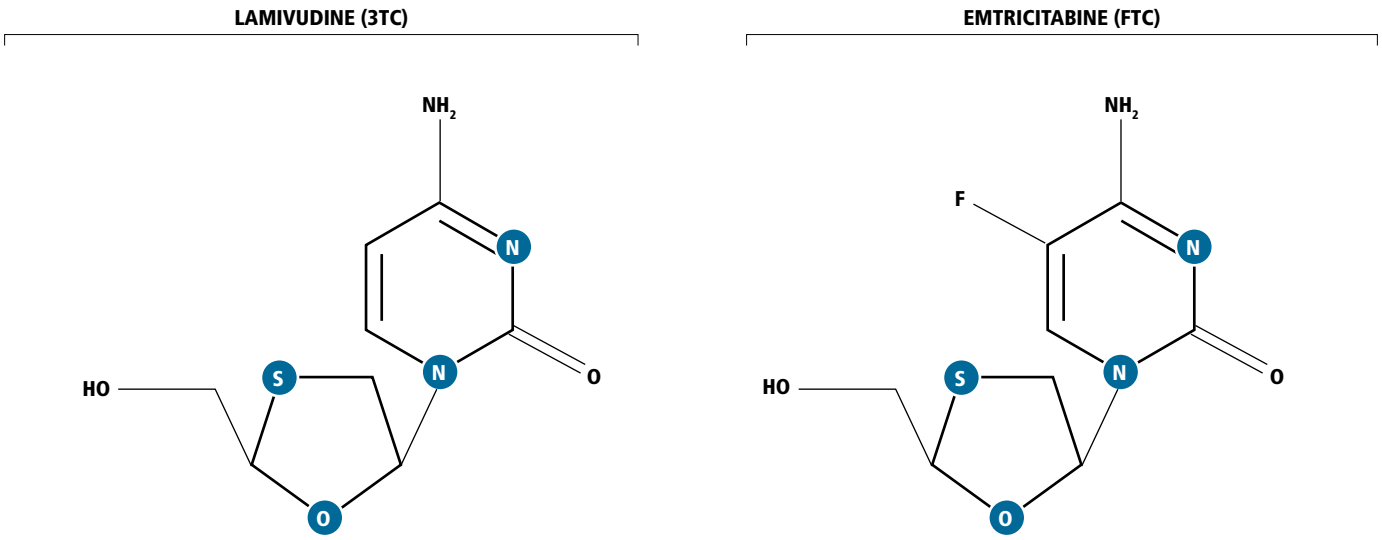
Context

The WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection consider lamivudine (3TC) and emtricitabine (FTC) as clinically equivalent, recommending either drug to be used as part of first-line once-daily triple drug therapy. However, early *in vitro* studies have suggested that there may be pharmaceutical differences between the two drugs, such as differences in binding affinities and drug half-life, that confer advantages to FTC. This review critically assesses these preclinical studies and summarizes findings from a systematic review and meta-analysis of comparative efficacy. This review also considers access issues such as patent barriers, drug pricing and the availability of 3TC and FTC as part of fixed-dose combination drug regimens.

Introduction

Lamivudine (3TC) and emtricitabine (FTC) are nucleoside reverse-transcriptase inhibitor (NRTI) antiretroviral drugs with similar chemical structures (Fig. 3.1*) (1,2)*. The latest antiretroviral therapy guidelines of the United States Department of Health and Human Services and WHO consider 3TC and FTC as clinically equivalent, recommending either drug to be used as part of first-line once-daily triple drug therapy *(3,4)*.

Fig. 3.1. Molecular structures of lamivudine (3TC) and emtricitabine (FTC)



3TC has been pivotal to all first-line ARV regimens in high-income as well as in resource-limited settings since the beginning of triple combination ART. It is safe, has an excellent toxicity profile, is non-teratogenic and is effective against hepatitis B virus *(5,6)*. It is widely available in fixed-dose combination regimens. FTC shares the same efficacy against hepatitis B virus, has the same toxicity profile and is available in fixed-dose combinations *(7)*.[4] However, laboratory studies suggest that FTC may have a longer half-life than 3TC and that FTC favourably interacts with tenofovir (TDF), further extending FTC's half-life, which could be advantageous *(8,9)*.

Although both 3TC and FTC are associated with the emergence of the M184V resistance mutation, the most common NRTI mutation, it has been suggested that 3TC has a relatively low genetic barrier, meaning that specific resistance to 3TC evolves more frequently *(10,11)*. However, the clinical consequences of this mutation are unclear. While the M184V mutation is generally problematic for treatment, conferring resistance to 3TC and FTC and therefore reducing their antiretroviral activity, the mutation has also been shown to be beneficial in terms of increased reverse-transcriptase fidelity (reducing the chances of spontaneous mutagenicity of HIV) and lowered viral fitness *(12)*. Further, although in vitro M184V/I mutations cause high-level resistance to 3TC and FTC, and low-level resistance to didanosine (ddI) and abacavir (ABC), the mutation increases susceptibility to other drugs such as zidovudine (AZT), stavudine (d4T) and TDF *(13)*. These considerations informed the decisions to retain 3TC in second-line regimens in the 2010 and 2013 revisions of WHO guidelines on ART *(4,14)*.

However, pharmaceutical data are limited, particularly among adolescents, children and infants, and usually come from studies in high-income countries. Different genetic backgrounds, epidemiological settings, comorbidities and the balance between desired and undesired effects may not be comparable with populations in resource-limited settings.

In making a determination about the pharmaceutical equivalence and clinical interchangeability of 3TC and FTC, this technical update considered the following issues:

- evidence from preclinical and in vitro studies;
- clinical efficacy and safety data from randomized controlled trials;
- the development of resistance; and
- the relative availability of preferred fixed-dose combinations for use in resource-limited settings, including the existence of patents or other barriers.

Preclinical and in vitro data

There are several measurements used in virology to assess the potential potency of antiretroviral agents *(15,16)*. The EC_{50}, the half maximal effective concentration, measures the concentration of a drug required to inhibit 50% of viral growth. The binding affinity of an agent measures a drug's ability to bind itself to the target enzyme. The intracellular half-life of a drug is the time taken for a drug's intracellular concentration to halve. In order for an agent to be potent, it must bind to the target enzymes and enter and remain in the cell for a long enough period of time to exert its action, the inhibition of viral growth. It is also important that single drug agents be optimally combined with other drug agents to use the most effective triple combination drug regimen. Based on these factors, in vitro pharmacodynamic studies have suggested that FTC is more potent than 3TC *(15)*. However, antiviral effects in vitro are not reliable predictors of in vivo clinical activity *(17)*.

Binding affinity

The binding affinities of the active metabolites of FTC for reverse transcriptase are 10 times larger than those of 3TC, suggesting greater potency of FTC *(18)*. Further, the binding affinity of FTC for human mitochondrial DNA polymerase – associated with host toxicity *(7,19,20)* – was shown to be lower than that of 3TC in one study *(21)*. Two studies examining the effects of 3TC and FTC on mitochondrial structure or function in HepG2 cells *(22–24)* found no deleterious impact with either drug alone or in combination with TDF. It is thought that, although 3TC inhibits polymerase more than FTC, this inhibition occurs at such low levels that clinical differences are not apparent or important and that there are other factors other than mitochondrial disruption that play a part in toxicity *(21,25)*.

Intracellular half-life

The intracellular half-life of FTC's active metabolites (39 hours) – based on a once-daily dose of 200 mg – is longer than those of 3TC (15–22 hours) and is similar to that of TDF *(26–29)*. Further, the intracellular half-life of 3TC has been shown to be independent of the dosing regimen, with similar results obtained when the drug was administered twice daily (150 mg) or once daily (300 mg) *(15,29)*.

Inhibitory potency

On average, the EC_{50} of FTC is lower than that of 3TC, suggesting an 11-fold greater potency of FTC *(30)*. Dual HIV-1 infection/competition assays estimate that FTC has a 3-fold greater potency than 3TC *(31)*.

Synergy with TDF

With similar intracellular and plasma half-lives, it has been suggested that FTC and TDF make ideal companions as part of a combination drug regimen. For example, if two drugs with considerably different half-lives are used as part of the same dosing regimen and one drug's concentration falls to low levels before the other drug, the dual drug regimen would effectively become a single drug regimen, with potential

4. The United States Food and Drug Administration approved a fixed-dose triple combination of FTC, TDF and EFV on 12 July 2006 under the brand name Atripla®. Prescribing information, September 2011 available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021937s023lbl.pdf.

implications for the onset of drug resistance *(15)*. One in vitro study *(32)* suggested that FTC and TDF in combination had an additive to synergistic effect against HIV replication *(9)*. FTC in combination with TDF has also been shown to have a significantly superior inhibition of viral replication in vitro compared with a 3TC + TDF combination ($P < 0.0005$).

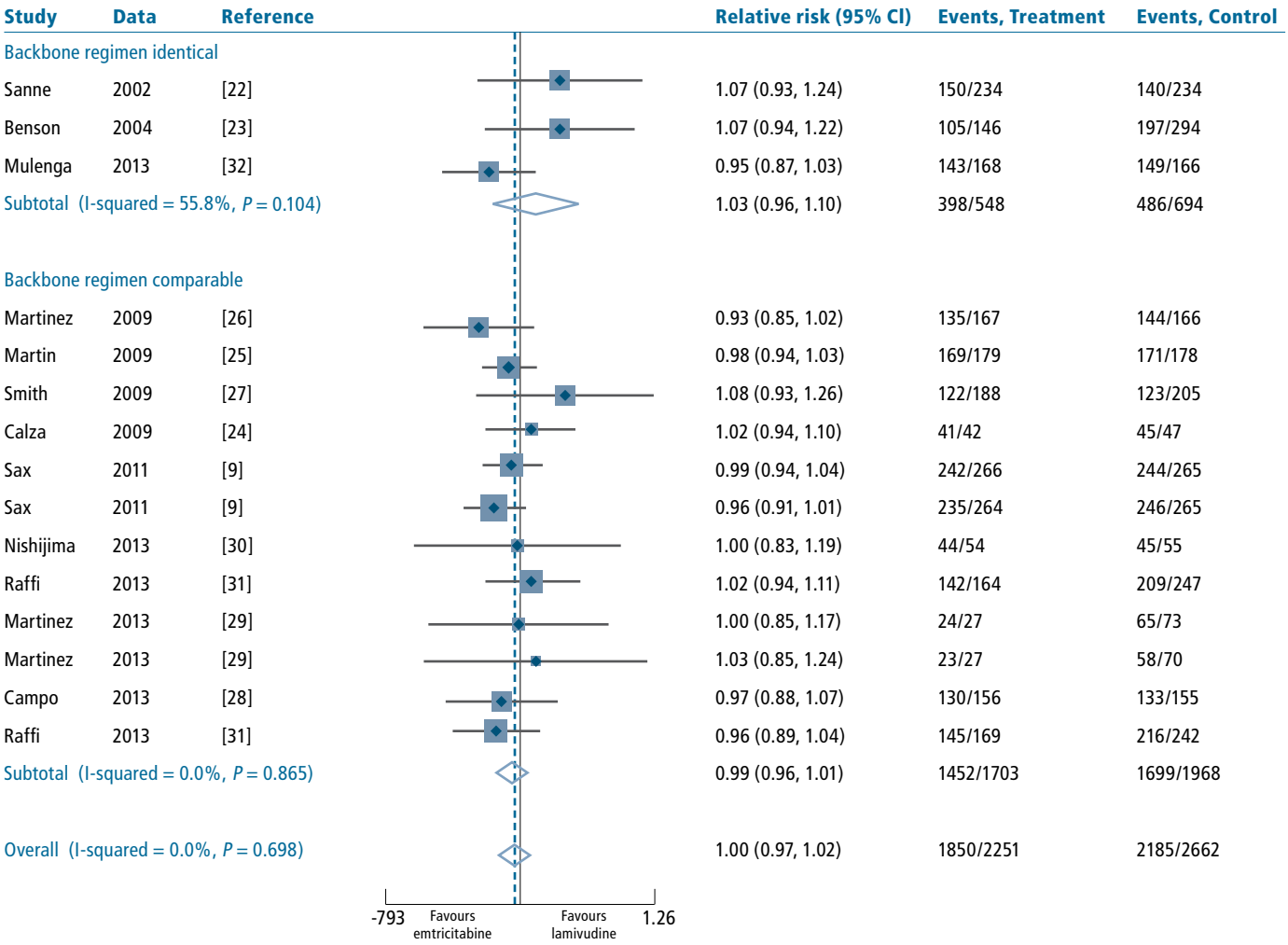
Clinical data: efficacy and safety

To date, three clinical trials have directly compared the clinical efficacy of 3TC and FTC among individuals with a baseline viral load <100 000 cells/ml *(35–37)*. In one double-blinded randomized trial, 468 treatment-naive people living with HIV were randomized to receive either 3TC or FTC, in combination with stavudine and nevirapine or efavirenz *(35)*. At 48 weeks, 65% and 60% of those taking FTC had an HIV RNA load of ≤400 copies/ml and ≤50 copies/ml, respectively, which was comparable to the 3TC arm, of whom 71% and 64% had an HIV RNA load of ≤400 copies/ml and ≤50 copies/ml, respectively. Another trial of 440 people living with HIV-1 initially stable on a twice-daily 3TC regimen who were randomized to either continue their regimen or switch to a once-daily FTC regimen also found no differences in outcomes at 48 weeks *(36)*. The rate of viral failure at 48 weeks was 7% for the FTC arm and 8% for the 3TC arm.

The third trial, an open-label, randomized non-inferiority trial, randomized 664 treatment-naive individuals to receive either FTC or 3TC in combination with TDF and EFV *(37)*. Viral suppression was achieved by 90.1% of those taking a FTC regimen and 85.3% of those taking a 3TC regimen at 48 weeks, suggesting comparable efficacy between the two drugs. Two of these three trials reported on adverse drug events *(35,36)* and found equivalent rates of severe adverse drug events between the FTC and 3TC arms.

A recent systematic review and meta-analysis *(38)* pooled the data from these three trials and found no significant differences overall between 3TC and FTC in terms of achieving treatment success (relative risk (RR) 1.03, 95% confidence interval (CI) 0.96–1.10). This result was maintained regardless of whether the pooling was carried out using a fixed-effects or random-effects model. This systematic review and meta-analysis also performed analyses on data from nine other trials – for a total of 12 trials – where the partner drugs could be considered to be comparable. When data from all 12 trials were combined, for a total of 15 direct comparisons, there were no differences in treatment success between 3TC and FTC arms (RR 1.00, 95% CI 0.97–1.02) (Fig. 3.2) *(38)*.

Fig. 3.2. Viral suppression comparing regimens including 3TC and FTC



Source: Ford et al. *(38)*.

Evidence on the development of resistance

The mechanisms for the development of resistance are similar for FTC and 3TC. Resistance to both drugs is usually caused by a single point mutation at position 184 of reverse transcriptase, causing methionine to be replaced by either valine or isoleucine, M184V or M184I mutations, respectively *(7)*.

Several studies infer a lower rate of resistance mutations (M184V) with FTC-containing regimens compared with 3TC-containing regimens *(32,39–42)*. The reasons cited were the greater potency or longer half-life of FTC compared to 3TC or potential pharmacokinetic differences, but no definite conclusions were reached.

The data from trials assessing the prevalence of M184V resistance mutations among those failing treatment where 3TC and FTC are directly compared or where 3TC and FTC were used with a comparable background regimen are inconclusive *(34–36,43)*. A systematic review and meta-analysis *(38)* pooled the results from these four trials, using a random-effects model, finding the overall pooled estimate of viral failure with the M184V mutation to be higher among people receiving 3TC (RR 1.41, 95% CI 0.6–33), but this was not statistically significant. The results should be interpreted with caution due to high heterogeneity between studies and due to the selective reporting of two of the four trials *(38)*.

Availability

A biowaiver[5] monograph for 3TC was published in 2011 *(44)*. Literature relevant to the decision to allow a waiver of in vivo bioequivalence testing for the approval of immediate-release solid oral dosage forms containing 3TC as the only active pharmaceutical ingredient was reviewed. The solubility and permeability data of 3TC as well as its therapeutic index, its pharmacokinetic properties, data indicating excipient interactions and reported bioequivalence and bioavailability studies were considered. A biowaiver was recommended for new 3TC multisource immediate release products and major post-approval changes of marketed drug products. This process is included in the WHO Prequalification of Medicines Programme and is detailed in the report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations *(45)*. This mechanism allows for the simplified approval of generic 3TC, thereby possibly making 3TC more readily available commercially. As of November 2011, FTC was identified by WHO Prequalification of Medicines Programme to be eligible for Biopharmaceutics Classification System (BCS)-based biowaiver applications *(46)*. The current WHO Prequalification of Medicines Programme (http://apps.who.int/prequal/default.htm) contains many approved 3TC formulations (with AZT, ABC, TDF, with AZT + ABC, AZT + EFV, d4T + EFV and d4T + NVP,[6] but a far more restricted list of FTC formulations (with TDF and with TDF + EFV).[7]

Access

The patent status of 3TC and FTC may be relevant to access. Access to patent information in relation to medical products has a major and growing importance for public health, to design access strategies, to assess for which products generic versions can be produced and marketed without infringing patents, and to determine with whom and the extent to which licenses have to be negotiated *(47)*.

Assessing the patent status of medical products is not always easy. The Medicines Patent Pool Patent Status Database for Selected HIV Medicines provides information on the patent status of selected antiretroviral medicines in many low- and middle-income countries.[8] It enables users to search by country and region, and by medicine, to obtain information on the key patents relating to each medicine.

The original patent covering both 3TC and FTC (EP0382526) expired in February 2010. A United Kingdom patent on the crystal form of 3TC (WO9111186) expired in June 2012 and a patent on FTC held by Emory University (WO9111186) expired in January 2011. However, there are patents on certain combinations of FTC or 3TC with other ARV drugs. The patent on the combination of abacavir (ABC) with 3TC (WO9630025) expires in 2016 and has been granted in many low- and middle-income countries. Combination patents have also been granted on TDF + FTC, TDF + FTC + RPV and TDF + FTC + EFV in several jurisdictions, which expire in 2024, 2024 and 2026 respectively. Voluntary licences on ABC + 3TC, TDF + FTC and TDF + 3TC + RPV have been issued that enable sale of generic versions of these combinations in many low- and middle-income countries.[9]

Data on global access and pricing can be found in the Médecins Sans Frontières report *Untangling the web of antiretroviral price reductions (48)*. The best prices for 300 mg of 3TC remain lower than for 200 mg of FTC. An oral liquid formulation of 3TC is available, but no similar formulation of FTC has been prequalified by WHO.[10] Combinations with 3TC are still less expensive than those containing FTC. However, the current best price for first-line combination regimens with either 3TC or FTC has declined considerably during the past five years (Fig. 3.3).

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5. A biowaiver is a document or process that demonstrates the bioequivalence by in vitro instead of more expensive and time-consuming in vivo pharmacokinetic studies for the simplified approval for immediate release generic solid oral products, allowing companies to forego clinical bioequivalence studies, provided that their drug product meets the specification detailed in the guidance (http://apps.who.int/prequal).

6. The use of d4T is no longer a recommended first-line option. However, many people are well controlled on d4T combinations and do not have an option to switch. The use of d4T will therefore continue for some time.

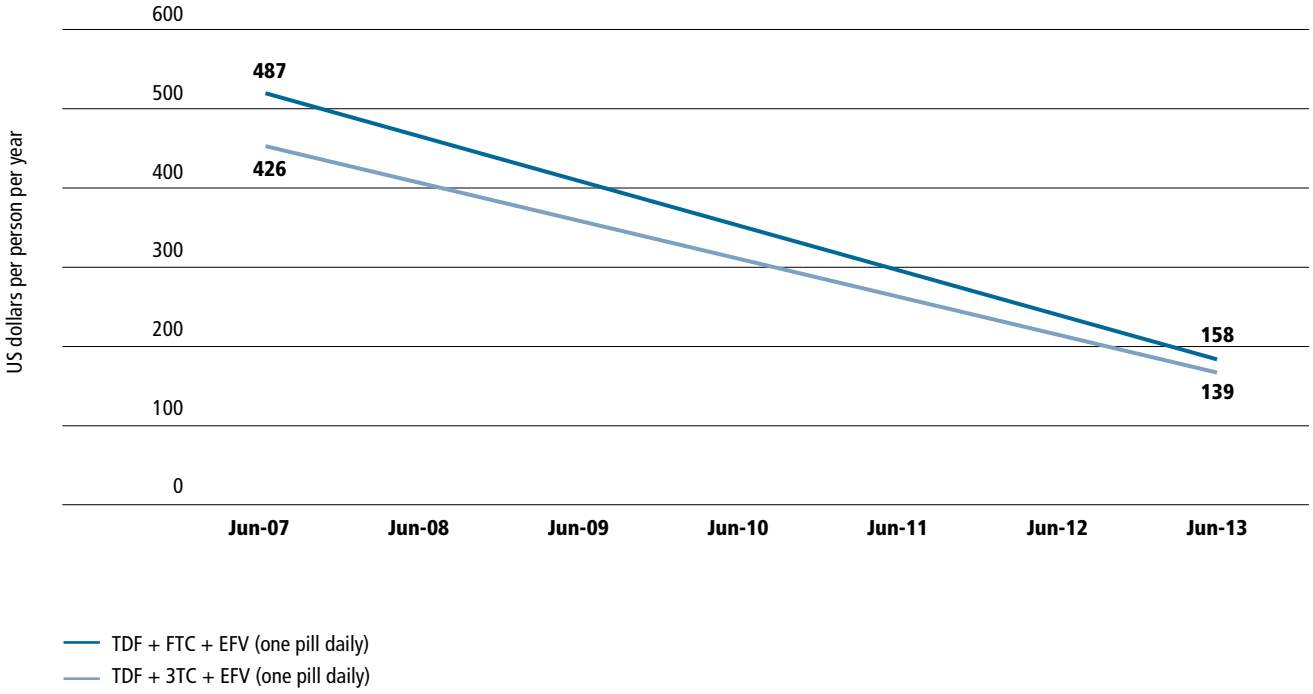
7. The United States Food and Drug Administration approved FTC + TDF + rilpivirine (Complera®) in August 2011.

8. http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs

9. Voluntary licences on ABC + 3TC cover 69 countries for adults and 118 for children. Licences on TDF + FTC and TDF + FTC + RPV cover 112 countries.

10. Médecins Sans Frontières has summarized the data for TDF + FTC (http://utw.msfaccess.org/drugs/tdf-ftc), TDF + FTC + EFV (http://utw.msfaccess.org/drugs/tdf-ftc-efv), TDF + 3TC (http://utw.msfaccess.org/drugs/tdf-3tc), TDF + 3TC + NVP (http://utw.msfaccess.org/drugs/tenofovir-disoproxil-fumaratelamivudinenevirapine) and TDF + 3TC + EFV (http://utw.msfaccess.org/drugs/tdf-3tc-efv).

Fig. 3.3. Price trends for TDF + 3TC + EFV and TDF + FTC + EFV



Source: Médecins Sans Frontières *(48)*.

Conclusions

Despite limited direct comparisons, the available data support the clinical and programmatic interchangeability of 3TC and FTC. The current edition of the WHO Model List of Essential Medicines (April 2013) *(49)* states that 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretroviral medicines. This supports the latest guidance provided by WHO and the United States Department of Health and Human Services[11,12] stating that 3TC may be substituted for FTC and vice versa.

11. Available at: http://www.who.int/hiv/pub/guidelines/en

12. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

4. USE OF EFAVIRENZ DURING PREGNANCY AS PART OF FIRST-LINE ANTIRETROVIRAL THERAPY: A PUBLIC HEALTH PERSPECTIVE

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Key messages

Overall, the available data and programmatic experience continue to provide reassurance that exposure to EFV in early pregnancy has not resulted in increased occurrence of congenital anomalies or other significant toxicity. In addition, evidence suggests that EFV is clinically superior to NVP, since it provides better long-term viral suppression and has fewer adverse reactions and less risk of resistance. Finally, the cost of EFV has decreased considerably, and it is now increasingly available as part of once-daily fixed-dose combinations. From a public health perspective and based on the available data and programme experience, this technical update summarizes the rationale for choosing EFV as the preferred NNRTI option in first-line treatment for adults and adolescents, including among pregnant women and those of reproductive age.

Background

The WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, published in July 2013 *(1)*, recommend efavirenz (EFV) as the preferred option for a non-nucleoside reverse-transcriptase inhibitor (NNRTI) in optimized first-line antiretroviral regimens for adults, including pregnant women and those of child-bearing potential. Concerns referenced in previous guidelines about EFV safety in early pregnancy had resulted in more complex treatment algorithms for women living with HIV who might become pregnant and for women in early pregnancy *(2)* and confusion regarding when to use EFV and when to use nevirapine (NVP). Recent evidence from systematic reviews provides reassurance regarding the safety of EFV in pregnancy and shows that EFV is superior to NVP in terms of safety and efficacy. The WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* emphasize simplification, harmonization and optimization of antiretroviral therapy, for a public health approach. There are multiple clinical and programmatic benefits of a switch to a harmonized one pill per day regimen for all adults, including pregnant women and those of childbearing potential. Switching to alternative and more complex antiretroviral regimens in pregnancy is no longer necessary, and the management of tuberculosis (TB) coinfection is simplified – unlike NVP, there are no clinically significant drug interactions between anti-TB drugs and EFV. Programmatic benefits include the simplification of treatment guidelines for health care providers and greater efficiency for drug procurement.

This section is a revised version of the technical update issued in 2012 *(3)* and summarizes the latest available data on the safety, tolerability and efficacy of EFV up to January 2014.

Introduction

In an effort to simplify and optimize HIV treatment and reflect the best available evidence, the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* recommend a once-daily simplified triple drug regimen – tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) + EFV – for all pregnant and breastfeeding women living with HIV for preventing mother-to-child HIV transmission, in accordance with the recommended first-line ART regimen for non-pregnant adults and adolescents. Further, the guidelines recommend that ART be continued for life after pregnancy or breastfeeding either for all women (option B+) or for those who meet eligibility criteria for their own health (option B).

Previous WHO guidelines for the treatment of HIV had recommended either NVP or EFV for adults *(4)* and that pregnant women or those planning pregnancy avoid EFV *(2,4)*, due to concerns about its safety in pregnancy (specifically the risk of neural tube defects) if taken early in the first trimester of pregnancy. Until recently, most people receiving ART in resource-limited settings have initiated NVP-based regimens *(5)*. The use of EFV is increasing in resource-limited settings as a result of its widespread availability as part of once-daily fixed-dose combinations, considerable reductions in drug price and the publication of the recent WHO guidelines recommending its use in preference to NVP.

This technical update summarizes the currently available evidence and experience that provided the basis for favouring EFV as the preferred NNRTI option in first-line therapy, including for pregnant women, and examines the broader anticipated benefits of this change in policy.

Rationale for this update

The 2013 WHO consolidated guidelines recommend a TDF-based first-line regimen in conjunction with 3TC (or FTC) and EFV as the preferred first-line treatment regimen for adults and pregnant women for treatment as well as for preventing mother-to-child transmission, as well as for adolescents, due to its more favourable clinical profile and programmatic advantages; a recent systematic review *(6)* showed that this combination has a better viral and treatment response compared with other once- or twice-daily regimens. EFV is now available in simplified formulations as part of a generic, fixed-dose, once-daily regimen (triple ARV regimens with NVP are available only in twice-daily formulations). This update provides current information regarding the safety and efficacy of EFV, including during pregnancy to present:

- an accumulation of evidence indicating that EFV has superior efficacy and tolerability compared with NVP, including when combined with TDF + 3TC (or FTC) as a once-daily regimen;
- substantial reductions in the price of EFV and increased availability of EFV as part of once-daily fixed dose combinations;
- updated data providing further reassurance about the safety of EFV during the first trimester of pregnancy;
- WHO-recognized benefit of using an EFV-based regimen for preventing mother-to-child HIV transmission harmonized with that for first-line adult ART *(7)* after programmatic experience highlighted the complications associated with switching pregnant women living with HIV and women living with HIV who may become pregnant from EFV to NVP; and
- increasing recognition of the benefits of initiating treatment among adults earlier, at higher CD4 counts (≤500 cells/mm^3) and for pregnant women to remain on lifelong ART after pregnancy.

Comparative data on the efficacy profiles of regimens containing EFV and NVP

In the 2010 WHO ART guidelines for adults and adolescents *(4)*, NVP and EFV were considered to have comparable clinical efficacy when administered in combination regimen and were recommended in combination with either zidovudine (AZT) or TDF plus either 3TC or FTC. This recommendation was based on a systematic review of seven randomized trials that concluded that there was no difference in clinical efficacy at 48 weeks; however, this analysis also noted a higher risk of non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance mutations among people taking NVP *(8)*. A more recent analysis of these trials over a longer period of follow-up together with consideration of cohort data suggested clinical superiority of EFV over NVP in terms of suppression of viral load and length of time to treatment failure; people taking an EFV-based regimen were also more likely to achieve viral success *(9)*.

Comparative data on the toxicity profiles of regimens containing EFV and NVP

EFV and NVP have different toxicity profiles, and both require clinical monitoring *(1,11)*. The main concern of EFV is central nervous system toxicity (such as depression or mental confusion *(1,12)*), which typically resolves after two to four weeks. However, in some cases it can persist for months or not resolve at all. Thus, EFV should be avoided for people with a history of depression or other mental disorders. NVP is associated with rash and with life-threatening reactions such as Stevens-Johnson syndrome and hepatic toxicity *(12)*, and there have been concerns that these risks are higher for women, particularly pregnant women with a higher CD4 cell count *(1,13,14)*.

A systematic review and meta-analysis of randomized controlled trials and prospective observational cohorts conducted in support of the WHO consolidated guidelines providing toxicity data on more than 26 000 adults receiving EFV or NVP drug regimens *(12)* found that those receiving taking NVP were more than twice as likely as those taking EFV to discontinue treatment because of any adverse event. Those taking NVP were more likely to experience any grade of hepatotoxicity and skin toxicity, severe hepatotoxicity and skin toxicity as well as severe hypersensitivity reactions compared with those taking EFV. The review also found that people receiving EFV were more likely to experience central nervous system–related adverse events, although these were mostly mild and rarely resulted in drug discontinuation.

Another systematic review specifically assessing the safety of NVP for pregnant women according to CD4 cell counts found a significantly higher risk of severe skin toxicity at CD4 cell counts above 250 cells/mm^3 *(14)*. The association between NVP-associated toxicity and higher CD4 counts led to a more complex "lead-in" dosing strategy for initiating NVP and recommendations urging caution when prescribing NVP to pregnant women and women who might be pregnant, using the drug only after the risks, benefits and available alternatives have been considered *(1)*. Although the evidence supporting the association between NVP toxicity and CD4 count is not entirely clear, routine monitoring of people with higher CD4 counts receiving NVP is recommended *(1)*. This, along with the complex lead-in strategy and the fact that NVP is unavailable as a once-daily triple drug regimen, favours the use of EFV in resource-limited settings *(1)*.

Managing adverse events is a challenge in resource-limited settings, since the capacity for clinical and laboratory monitoring may be limited. In addition, adverse events are a risk factor for poor adherence *(15)* and treatment interruptions initiated by the person living with HIV *(16)* and lead to more frequent regimen changes.

On balance, EFV appears to be better tolerated and has much less risk of severe adverse reactions than NVP. In addition, recent evidence shows that viral suppression with EFV is superior to that with NVP.

Cost and availability of EFV and NVP as fixed-dose combinations

The 2013 consolidated guidelines *(1)* have chosen a TDF-based first-line regimen in conjunction with 3TC (or FTC) and EFV as the preferred first-line treatment regimen due to its more favourable clinical profile *(6,17)*. The costs of both TDF and EFV have fallen substantially in recent years due to increased demand, improvements in the synthesis of the active ingredients and availability of generic formulations. In parallel with the decreasing cost of EFV as a separate compound (which is approaching the cost of NVP), the one-year treatment cost of generic formulations of once-daily TDF + 3TC (or FTC) + EFV has decreased to as low as US$ 112 *(18)*, close to the US$ 100 annual cost of twice-daily AZT + 3TC + NVP. However, access to affordable generic versions, particularly as fixed-dose combinations, remains a problem for some countries, where current drug patent laws and licensing agreements restrict purchasing options *(19)*.

Safety of EFV use during pregnancy

Although concerns persist about the safety of using EFV during pregnancy, particularly during the first 28 days, an analysis of all available data up to January 2014 provides reassurance of no evidence of increased harm. When the 2013 consolidated guidelines were developed, the evidence was considered sufficient to rule out more than a three-fold increase in risk. The overall prevalence of congenital anomalies reported in association with EFV is similar to that reported for other widely used ARV drugs and is consistent with rates reported in congenital anomaly registries from the general population *(20–22)*.

In practice, the likelihood of a newly diagnosed pregnant woman living with HIV being initiated on ART during the first trimester is relatively low. A report from Kenya and Malawi, for example, showed that 12–15% of women attended antenatal care within the first trimester of pregnancy *(23)*. Inadvertent exposure to EFV is more common, since the number of pregnancies among women living with HIV already receiving ART is increasing in both high-income *(24)* and low- and middle-income countries *(25)*, and a large proportion of pregnancies among women receiving ART may be unplanned *(26)*.

The latest systematic review and meta-analysis of congenital anomalies in infants with first-trimester EFV exposure, updated to January 2014 *(27)*, found no overall increased risk of congenital anomalies associated with EFV exposure during the first trimester of pregnancy (Fig. 4.1). Across 22 studies, women receiving first-trimester EFV had 44 birth defects (of any kind) among 2026 live births (1.63%, 95% confidence interval (CI) 0.78–2.48%), which is similar to that reported for women exposed to other, non-EFV-based regimens in the United States Antiretroviral Pregnancy Registry (2.6%) and in the general population (6%) *(20)*. The relative risk of congenital anomalies overall when comparing women on EFV-based and non-EFV-based regimens was 0.78 (95% CI 0.56–1.08%) *(27)*.

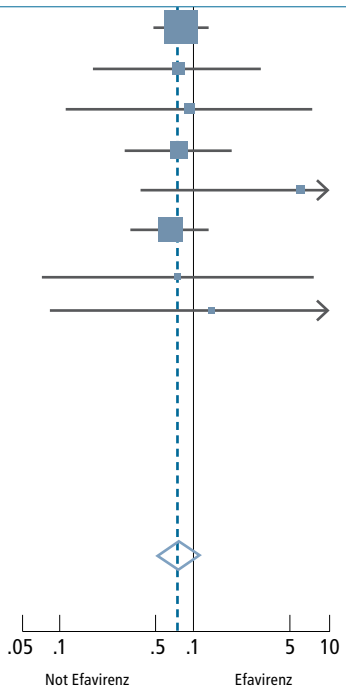
A recent unpublished report from France suggested an increased risk of nervous system defects (none of which were neural tube defects) among infants born to women receiving EFV during the first trimester of pregnancy *(28)*. However, no neural tube defects were reported in this cohort registry, and when these data were considered together with other available data in the latest systematic review, there was still no evidence of an increased risk of congenital anomalies associated with first-trimester exposure to EFV compared with exposure to other antiretroviral drugs *(22)*.

Among the study populations included in the meta-analysis, there is only one reported case of neural tube defect (myelomeningocele), yielding an incidence of 0.05% (95% CI <0.01–0.28%). Thus, the estimated pooled prevalence of neural tube defects among women living with HIV exposed to EFV during the first trimester of pregnancy was lower than that reported in the general population in the United States (0.04–0.06% before regular folic acid fortification *(29)*), United Kingdom (0.14% *(30)*) and South Africa (0.36% *(31)*). However, the low background incidence and the small number of events reported in available studies necessitate a larger sample size to definitively rule out a doubling of risk for this rare event *(22,27)*.

Congenital anomalies have not been consistently monitored in most low and middle-income countries, and in many resource-limited settings, the baseline risk of congenital anomalies remains unknown. Determining the additional risk due to the use of EFV or other ARV drugs cannot be established without prospectively following up a large number of pregnancies, both with and without the exposure of interest. To achieve this, WHO supports and encourages countries to implement a toxicity surveillance system and register the outcomes of drug use in pregnant women. A WHO technical brief was recently published *(32)* to provide technical guidance on the various approaches for the surveillance of ARV drug

Fig. 4.1. Relative risk of birth defects with EFV versus non-EFV regimens

Study	Year	Relative risk (95% CI)	Events, treatment	Events, control
Antiretroviral pregnancy registry	2013	0.79 (0.49, 1.28)	18/766	183/6160
Floridia et al	2013	0.74 (0.18, 3.10)	2/80	21/622
Bera et al	2010	0.90 (0.11, 7.43)	5/184	1/33
Townsend et al	2010	0.75 (0.30, 1.87)	5/204	48/1478
Machado et al	2010	6.22 (0.41, 95.10)	1/18	1/112
Gonzales-Tome et al	2010	0.65 (0.33, 1.26)	7/31	93/266
Bussmann et al	2010	0.75 (0.07, 7.78)	1/22	2/33
Patel et al	2010	1.33 (0.08, 21.51)	0/19	14/770
Cressey et al	2012	(Excluded)	0/4	0/21
Ekouevi et al	2011	(Excluded)	0/147	0/102
Phanupak et al	2011	(Excluded)	0/6	0/180
Shwartz et al	2012	(Excluded)	0/9	0/58
Overall		0.78 (0.56, 1.08)	39/1490	363/9835



The weights are from random effects analysis.

Source: Ford et al. *(22)*.

toxicity during pregnancy and breastfeeding, which cover a prospective pregnancy-exposure registry, a congenital anomalies surveillance programme and a prospective monitoring of cohorts of mother–infant pairs during the breastfeeding approach. A joint manual has recently been produced that provides a method to implement a congenital anomalies surveillance system *(33)*. In addition, UNAIDS, WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria are producing a technical brief note on toxicity surveillance of antiretroviral medicines within ART and programmes for preventing mother-to-child transmission to encourage standard procedures and integrating ARV toxicity surveillance into HIV funding proposals *(34)*. As part of the effort to detect any increased signal of birth-related or maternal-related toxicity, WHO is also promoting the development of a targeted spontaneous reporting for monitoring the toxicity of ARV drugs *(35)*.

While emphasizing the need for better data on congenital anomalies, the WHO Guidelines Development Group considered that the risk of increased congenital anomalies associated with EFV use was considered to be very low, the programmatic advantages and the clinical benefit of EFV in preventing HIV infection in infants and for the mother's health outweighed any potential risk of EFV when recommending EFV as part of first-line therapy among pregnant women and those of childbearing age *(1)*.

Programmatic benefit of favouring EFV as part of first-line treatment regimen in pregnant women

Recommending the use of EFV as part of first-line therapy in pregnancy is expected to result in a wide-range of programmatic benefits.

Decreased frequency of regimen changes with benefit for health-care workers and patients

A systematic review carried out in support of the WHO 2013 consolidated guidelines *(12)* compared the rates of switching regimens among the non-pregnant population and found that people taking NVP are more than twice as likely to switch regimens due to adverse events as those taking EFV. In settings where task-shifting strategies for managing HIV have been implemented, guidelines usually recommend referral to a higher-level health facility when managing severe side effects or when switching a person's regimen. This may increase the burden on health systems in terms of personnel and costs. Management of drug side effects and difficulties associated with regimen switches may increase the number of clinic visits; more travel may be required for more frequent monitoring, perhaps to a more distant facility. A regimen change may

result in a higher pill burden or more frequent dosing, both of which are inconvenient and could potentially lead to adherence problems *(36)*. These factors have been shown to lead to resistance, requiring a switch to a second-line ART regimen, which adds to the burden on the health system, in terms of both human and financial resources.

Simplifying and optimizing treatment for HIV and TB coinfection

TB is the most common opportunistic infection for people living with HIV, particularly in sub-Saharan Africa, where most new TB cases are among people living with HIV *(37)*. There are important drug interactions when NVP is given to people who are also receiving TB treatment. Unlike EFV, NVP concentrations are significantly reduced in the presence of rifampicin, which has been reported by many, but not all, studies *(38–40)* to reduce efficacy. Thus, EFV has been recommended as the preferred NNRTI for managing people with both HIV and TB *(1)*. Up to 40% of people starting ART in sub-Saharan Africa have TB *(41)*, and many of these are women of childbearing age *(42)*. Therefore, there is practical benefit in recommending EFV in pregnancy considering that many women of childbearing age are also coinfected with HIV and TB.

Potential decrease in the number of pregnancies terminated

Despite a clear statement in the 2010 WHO ARV guidelines for preventing mother-to-child transmission *(2)* that terminating pregnancy for first-trimester exposure to EFV is not recommended, in some settings there has been an increase in the number of pregnancies terminated among women exposed to EFV during pregnancy. A pooled analysis of three studies reporting the frequency of induced abortion among women living with HIV exposed to EFV- and non-EFV-based regimens *(22)* showed a nearly three times higher risk of induced abortions among women exposed to EFV. These studies suggest that the termination of pregnancy may have been based on concerns among providers and pregnant women of potential birth defects rather than on any confirmation of birth defects. WHO recommending the use of EFV in pregnancy is expected to alleviate some of the concerns health care providers and pregnant women taking EFV may have and may reduce the number of unnecessary terminations of pregnancy.

Simplifying and harmonizing treatment guidelines

Uncertainty about the safety of EFV in pregnancy resulted in increased complexity of previous guidelines and practices related to ART and preventing mother-to-child transmission *(2,4)*. These included the following.

- Which first-line ART regimen should be used for women of childbearing age who are unable or choose not to access contraception?
- Which first-line ART regimen should be used for women who are already pregnant, either during or after the first trimester?
- What guidance is appropriate for women already receiving an EFV-based first-line regimen who become pregnant and present to a health facility either during or after the first trimester of pregnancy?

Access to contraception in resource-limited settings is limited and, even when available, cultural barriers may prevent uptake. In sub-Saharan Africa, most people (approximately 60%) initiating ART are women, predominantly of childbearing age *(43,44)*. The proportion of unintended pregnancies among women living with HIV in sub-Saharan Africa ranges from 50% to 90% *(45)*.

These special considerations have prevented, until recently, one simplified and harmonized approach to first-line ART and prophylaxis for preventing mother-to-child transmission.

In an attempt to simplify and harmonise first-line therapy, the WHO 2012 technical update on the use of EFV in pregnancy *(3)* and the 2013 consolidated guidelines *(1)* recommended a once-daily fixed-dose combination regimen, with EFV as the preferred NNRTI for pregnant and breastfeeding women, in harmony with the recommendations for non-pregnant adults. This first-line regimen – TDF + 3TC (or FTC) + EFV – was chosen due to its relatively low cost, availability as a fixed-dose combination, safety for pregnant and breastfeeding women and their infants, good tolerability, low monitoring requirements, low drug-resistance profile and compatibility with other drugs in clinical care *(1)*. Recommending a harmonized treatment regimen is easier for programmes to implement and ensures that the programmes that do not have access to CD4 cell testing can initiate ART among pregnant women without delay, which benefits the mother and her infant.

Simplifying supply chain management

Previous guidelines had recommended that countries intending to use an EFV-based first-line regimen needed to maintain NVP as the preferred option for women of childbearing age who are planning to become pregnant, or who may become pregnant. As summarized in this update, the latest evidence, as well as important programmatic considerations, suggests that this is not necessary. Eliminating this requirement will simplify programmatic drug procurement and enable more unified supply chain management between ART and programmes for preventing mother-to-child transmission for first-line ARV drugs. NVP needs to be stocked only in small amounts for those (whether pregnant or not) who need to switch from EFV.

Summary comparison of EFV and NVP

Table 4.1 compares the key characteristics of EFV and NVP reviewed in this technical update. EFV has a more favourable profile than NVP for the first five of these characteristics: safety and tolerability, drug interactions, convenience, efficacy and drug resistance. Although EFV and EFV-containing fixed-dose combinations are still more expensive than NVP, the price gap has closed considerably.

Table 4.1. Summary of clinical characteristics of efavirenz and nevirapine

	Efavirenz	Nevirapine
Safety and tolerability	Central nervous system adverse events, which usually resolve after 2–4 weeks Potentially very low risk of congenital anomalies still cannot be ruled out	Hepatotoxicity, particularly among women with CD4 counts >250 cells/mm^3 Severe skin rash and hypersensitivity reaction (Stevens–Johnson syndrome)
Drug interactions	No significant interactions	NVP concentrations are reduced in the presence of rifampicin and complicate TB treatment
Convenience	Available as a once-daily, fixed-dose combination (with TDF and 3TC or FTC)	Twice-daily regimen (with AZT- or TDF-containing regimens) Requires lead-in dosing (use of half dose in the first two weeks of treatment)
Efficacy	Comparable efficacy in early clinical trials More recent data suggest greater efficacy for EFV in TDF-containing regimens	
Drug resistance (robustness)	Higher risk of NNRTI resistance mutations with NVP	
Cost (generic, annual, per patient)[a] Single drug	US$ 39	US$ 29
Fixed-dose combination	US$ 134 (TDF + 3TC + EFV once-daily fixed-dose combination)	US$ 101 (AZT + 3TC + NVP, twice-daily fixed-dose combination)

[a] Data from Médecins Sans Frontières *(46)*.

Conclusion and future directions

This technical update has reviewed the latest data relating to the use of EFV during pregnancy that form the basis of WHO's increased confidence in recommending EFV as the preferred NNRTI in the recommended first-line antiretroviral regimen, including in pregnant women and those of childbearing age.

EFV is an important, effective and relatively safe and well-tolerated drug and is currently the best available NNRTI to be included as part of combination first-line ART. Regarding the risks and benefits of using EFV in pregnancy, evidence supports the benefits of EFV against the known risks and complexities of alternatives such as NVP. The 2013 consolidated WHO guidelines recommend that EFV-based treatment no longer be avoided among pregnant women or those who want to conceive.

More countries are adopting TDF-based regimens that can be combined with 3TC (or FTC) and EFV in one tablet as a once-daily fixed-dose combination, in accordance with WHO's consolidated guidelines, which emphasize simplification, standardization and optimization of ARV regimens. This simplified regimen should facilitate improved adherence *(36)* and provide important programmatic advantages for use across different populations and in different settings *(47)*. Despite the development of second-generation NNRTIs such as rilpivirine (RPV), the recently demonstrated superior viral suppression with EFV will probably mean that EFV will remain the preferred first-line NNRTI for some time to come *(48,49)*.

The current data review of safety of EFV in pregnancy is reassuring. Additional research and ongoing surveillance through pregnancy registries are needed, both to prospectively collect more data on congenital anomalies and other severe adverse reactions resulting from exposure to EFV and other ARV drugs and to better assess programme, provider and patient perspectives on the true risks and benefits of EFV use, especially in low- and middle-income countries.

WHO recognizes and emphasizes a public health approach for treating HIV and for preventing mother-to-child transmission of HIV. A simplified, harmonized and optimal treatment regimen results in substantial clinical and programmatic benefits. This translates into better health and improved survival for mothers and their infants.

5. OPTIMIZING ANTIRETROVIRAL DRUGS FOR CHILDREN: MEDIUM- AND LONG-TERM PRIORITIES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Background

Antiretroviral therapy (ART) for children living with HIV is associated with a host of pharmaceutical, clinical, service delivery and supply chain challenges, particularly in low- and middle-income countries. Global, regional, and national efforts are contributing to the scaling up of ART for children, with a sustained improvement in ART coverage for children. Nevertheless, the gap in treatment between children and adults persists, including in the 21 Global Plan priority countries in sub-Saharan Africa.

To support these efforts, reliable delivery of high-quality, affordable ART in doses and formulations appropriate for children is critical, as is the further development of child-friendly fixed-dose combinations.

Since 2010, a series of meetings has sought to address ways to optimize drug development and to harmonize regimens from childhood into adulthood. In June 2013, WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Chapter 7, "Clinical guidance across the continuum of care: antiretroviral therapy" included new guidance and recommendations on when to initiate ART for infants, children and adolescents as well as new recommendations regarding infant prophylaxis with ARV to prevent mother-to-child HIV transmission.

The Paediatric Antiretroviral Drug Optimization Conference was held in October 2013 to identify medium- and long-term priorities for the development of antiretroviral drugs for infants and children. The key outcomes of the meeting were as follows.

1. All stakeholders agree that accurate forecasting of demand for ARV drugs for children and quantification of drug needs are critical to ensuring adequate supply.

2. Accelerating the approval of new drugs and formulations suitable for children (such as shortening the gap between drug approval for adults and children) is essential.

3. Patent-sharing agreements are needed for dolutegravir (DTG), tenofovir alafenamide fumarate (TAF),[13] lopinavir/ritonavir (LPV/r) and ritonavir (as a stand-alone drug), in particular for development of fixed-dose combinations.

4. In the medium term, developing a triple fixed-dose combination of ABC + 3TC + EFV for use among children 3–10 years old should be given priority.

5. In the long term, DTG and TAF should be given priority, particularly in fixed-dose combination formulations.

6. Innovative ways need to be explored to generate age-appropriate pharmacokinetic data to extend antiretroviral indications for children to the neonatal period in order to facilitate earlier treatment initiation among infants and more potent postnatal prophylaxis regimens.

Collective engagement between researchers, manufacturers, funders and policy-makers will be critical in driving innovation in HIV treatment that meets the unique needs of infants and children and maximizes individual and public health benefits.

Context

Despite progress in scaling up the prevention of mother-to-child transmission of HIV under the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive *(1)*, an estimated 260 000 children were newly infected with HIV in 2012 *(2)*. Most of this transmission occurred in sub-Saharan Africa, where more than 90% of all children infected with HIV currently live. Of particular concern, the treatment gap between adults and children is widening, with latest estimates indicating that only 34% of children younger than 15 years eligible for ART (based on the 2010 WHO eligibility criteria) were receiving treatment compared with 61% ART coverage for adults. Moreover, the pace of scale-up in 2012 was slower for children than for adults – 14% compared with 21%. Scaling up treatment for children

13. TAF (formerly GS-7340) is an NRTI and a novel pro-drug of tenofovir.

living with HIV in low- and middle-income countries is challenging for several reasons, including poor access to early infant diagnosis, weak links between programmes for preventing mother-to-child transmission and ART programmes and the shortage of specialized providers. In addition to these programmatic challenges, the lack of appropriate ARV formulations for children remains a critical bottleneck.

In June 2013, WHO released consolidated guidelines on the use of ARV among adults, children and pregnant women for both prevention and treatment *(3)*. These guidelines incorporate important new treatment recommendations, including a recommendation that all children living with HIV younger than 5 years should initiate ART irrespective of CD4 count or WHO clinical stage. In addition, the consolidated guidelines advocate several new treatment approaches, including the use of protease inhibitor–based therapy for first-line treatment among all children younger than 3 years, the possibility to replace LPV/r with an NNRTI after viral suppression is sustained and once-daily treatment using tenofovir disoproxil fumarate (TDF) as a preferred regimen for children over 10 years (Table 5.1). Although first-line ART for children has been simplified, further simplification and harmonization between age groups remains challenging. Urgent efforts are needed to develop suitable formulations to make these recommendations easier to implement.

Table 5.1. Preferred and alternative first-line regimens for children according to the 2013 WHO consolidated guidelines

Age group	Preferred first-line regimens	Alternative first-line regimens
Children <3 years	ABC or AZT + 3TC + LPV/r	ABC or AZT + 3TC + NVP
Children 3–9 years and adolescents <35 kg	ABC + 3TC + EFV	ABC or AZT or TDF + 3TC (or FTC) + NVP or EFV
Adolescents (10–19 years) ≥35 kg	TDF + 3TC (or FTC) + EFV	ABC or AZT or TDF + 3TC (or FTC) + NVP or EFV

Fixed-dose combinations facilitate adherence to treatment and simplify prescribing and supply chain management and have long been used for adults. Fixed-dose combinations have been developed for use among younger children, including some dual NRTI scaled-down versions of adult formulations and dispersible formulations designed to dissolve in water. A triple-drug NVP-based fixed-dose combination was first developed and licensed by the United States Food and Drug Administration in 2007. Despite these improvements, there are still fewer ARV drugs and fixed-dose combinations approved for use in children compared with adults, and typically, the development and approval of indications for children lag many years behind adult indications. In addition, challenges arise from the slow transition by national programmes to adopt improved child-friendly fixed-dose combinations, thereby limiting the number of children able to benefit from them and threatening ongoing production and supply due to low demand.

The ARV landscape for children has to take into account the following factors.

- ARV metabolism in children is generally higher than in adults, so dose reduction by scaled-down weight ratios – particularly in the youngest age groups – might not always be a useful optimization strategy.
- ARV formulations need to be tailored to infants as well as older children.
- Both children living with HIV and HIV-exposed and uninfected children need ARV drugs, so optimization strategies should consider both treatment of children living with HIV and the use of ARV drugs for prophylaxis among infants born to women living with HIV for the needs of HIV-exposed and uninfected children.
- Earlier initiation of ART in the context of lifelong treatment requires careful consideration of each drug's toxicity and tolerability profile.
- The market for ARV drugs for children is fragmented, substantially smaller and will be virtually limited to low- and middle-income countries in the coming years.

Task shifting and integration of services have been identified as critical elements to enable the further scaling up of treatment and care. In this context, drug optimization should give priority to simplicity while ensuring efficacy, tolerability, robustness, cost–effectiveness, no overlapping resistance in treatment sequencing and convenience for both children and caregivers *(4)*.

Recent consultations on ARV drug optimization

The WHO and UNAIDS Treatment 2.0 framework has re-energized the public health approach to ART, with a vision of generating innovation in drug optimization,

diagnostics and service delivery (5). To guide innovation in drug development, short-, medium- and long-term targets and milestones are being identified through a series of expert consultations. Discussions on drug development priorities have largely focused on adults, despite the recognition that the pharmaceutical needs of children differ *(6)*.

In 2010, the Conference on Antiretroviral Drug Optimization set the stage for potential strategies for reducing drug costs, including (i) modification to the synthesis of the active pharmaceutical ingredient; (ii) use of cheaper sources of raw materials in synthesis of these ingredients; and (iii) innovations in product formulation to improve bioavailability thus needing less active pharmaceutical ingredient *(7)*.

In 2011, a WHO meeting on short-term priorities for drug optimization further refined the dose optimization strategy and provided recommendations on solid formulations for children such as LPV/r pellets, AZT + 3TC dispersible tablets and TDF + 3TC + EFV dispersible and scored tablets *(8)*. That same year, a meeting convened by Médecins Sans Frontières on ART sequencing identified a set of key principles for ART choice that included: simplicity, tolerability and safety, durability, universal applicability and affordability and heat stability *(9)*. In May 2012, WHO convened a think-tank meeting on drug optimization that identified treatment simplification as a critical element for scale-up and raised the issue of potentially aligning sequencing of first- and second-line regimens across populations *(4)*. Finally, in April 2013, the Second Conference on Antiretroviral Drug Optimization concluded with a set of recommendations that included the need for additional studies to examine the role of DTG and TAF in first-line therapy; greater research efforts to improve second-line therapy, particularly the role of dose-optimized ritonavir-boosted darunavir (DRV/r) *(10)* and continued research on oral and injectable long-acting formulations, nano-formulations and implantables is needed (Box 5.1).

Box 5.1. Conferences on Antiretroviral Drug Optimization

HIV Treatment Optimization, a collaborative project between the Clinton Health Access Initiative, the Johns Hopkins University School of Medicine and Pangaea Global AIDS Foundation, is funded by the Bill & Melinda Gates Foundation and has sponsored Conferences on Antiretroviral Drug Optimization in 2010 and 2013. These Conferences brought together process chemists, clinical pharmacologists, pharmaceutical scientists, physicians, pharmacists and regulatory specialists, and included participation of members of the WHO Department of HIV/AIDS. Although the Conferences were not specifically cosponsored by WHO, their deliberations and observations have been very helpful for the WHO guideline development process.

The first Conference in 2010 (http://www.who.int/hiv/pub/arv/short_term_priorities/en/index.html) focused on developing a research agenda to optimize the doses and combinations of existing approved drugs, including through role of process chemistry, and recommended a research development agenda for HIV drug optimization. The Conference identified a portfolio of projects with the potential to significantly optimize treatment while achieving major cost reductions. Projects included improvements in process and formulation chemistry and dose reductions as intermediate technologies with an imperative to focus future resources on developing better regimens and formulations.

The goals and objectives of the second Conference were to identify and facilitate the development of novel, affordable, optimized drug regimens in resource-limited settings, within a public-health approach. The participants looked further into the future, to review drugs in the development pipeline and to highlight gaps in the drug development programmes. Underpinning the meeting was the commitment to a single global standard for the equitable treatment of everyone, in both resource-rich and resource-poor settings.

The report and recommendations for the second Conference (http://hivtreatmentoptimization.org/sites/default/files/documents/2010-11/cado2meetingreportfinaljuly2013.pdf), while not specifically WHO-endorsed, are consistent with WHO work on drug optimization for adults and are complementary to the Paediatric Antiretroviral Drug Optimization. The second Conference recommended the following.

First-line treatment

Studies to determine fixed-dose combination regimens that are equally or more potent and more durable and affordable than TDF + XTC (either 3TC or FTC) + EFV including TAF + XTC + DTG and TAF + XTC + EFV.

Post-treatment failure

Studies to identify improved second-line regimens, particularly the role of fixed-dose boosted, dose-optimized DRV in replacing atazanavir or lopinavir as the protease inhibitor of choice.

A one-pill once-daily second-line regimen.
Studies of reduced-dose DRV/r, in combination with recycled nucleosides or an integrase inhibitor.

Enhancing trial participant criteria

Studies to reflect the characteristics of people in treatment access programmes, including girls and women of reproductive age, TB coinfection and comorbidity (such as hypertension).

Early engagement of private sector developers and manufacturers

To maximize pharmaceutical company expertise in drug development for global health priorities and to speed up the preparation for production, scale-up and incorporation of new regimens into global treatment programmes.

Longer-term research priorities

Continued research into the potential use of oral and injectable long-acting drugs (including GSK744) as well as nano-formulations and implantable devices (longer-term priority).

Paediatric ARV Drug Optimization Conference

Building on these drug optimization initiatives, the Paediatric ARV Drug Optimization Conference brought together a range of key stakeholders, including clinicians, scientists, funding agencies, representatives of health ministries from settings with a high burden of HIV, implementing partners, civil society and United Nations agencies. The main objectives of this consultation were:

- to provide an overview of the latest research on antiretroviral medicines for children with respect to market dynamics and the research and development pipeline;
- to identify medium- and long-term priority drugs and formulations for different age groups in light of the evolving HIV epidemic among children; and
- to develop a roadmap to streamline access to antiretroviral medicines for children by optimizing drugs.

Although the guidance described below constitutes expert opinion rather than WHO recommendations, it should nevertheless provide direction to industry and, over time, inform the development of WHO's recommendations for optimizing treatment for children.

Market dynamics and forecasting future ART needs for children

Successful efforts by programmes for preventing mother-to-child transmission have greatly contributed to preventing infants from acquiring HIV infection; however, the risk of mother-to-child transmission remains high in many countries. With recent changes to WHO treatment recommendations and country policies for preventing mother-to-child transmission, future projections of the potential number of children living with HIV and the proportion of those who would be eligible for ART initiation, stratified by age, as well as the number of infants who will require ARV drugs for preventing mother-to-child transmission, remains critical for forecasting future drug supply needs.

WHO and UNAIDS have used Spectrum[14] to develop scenarios to explore future changes in the numbers of children living with HIV and the overall number of children needing ART by 2020. A maximum scale-up scenario (95% ART coverage among adults, 95% coverage of services for preventing mother-to-child transmission and 100% ART coverage among children) was compared with a minimum scenario in which countries maintain their 2012 coverage rates. An intermediate scenario was also developed to reflect critical differences between countries in their current performance (Table 5.2).

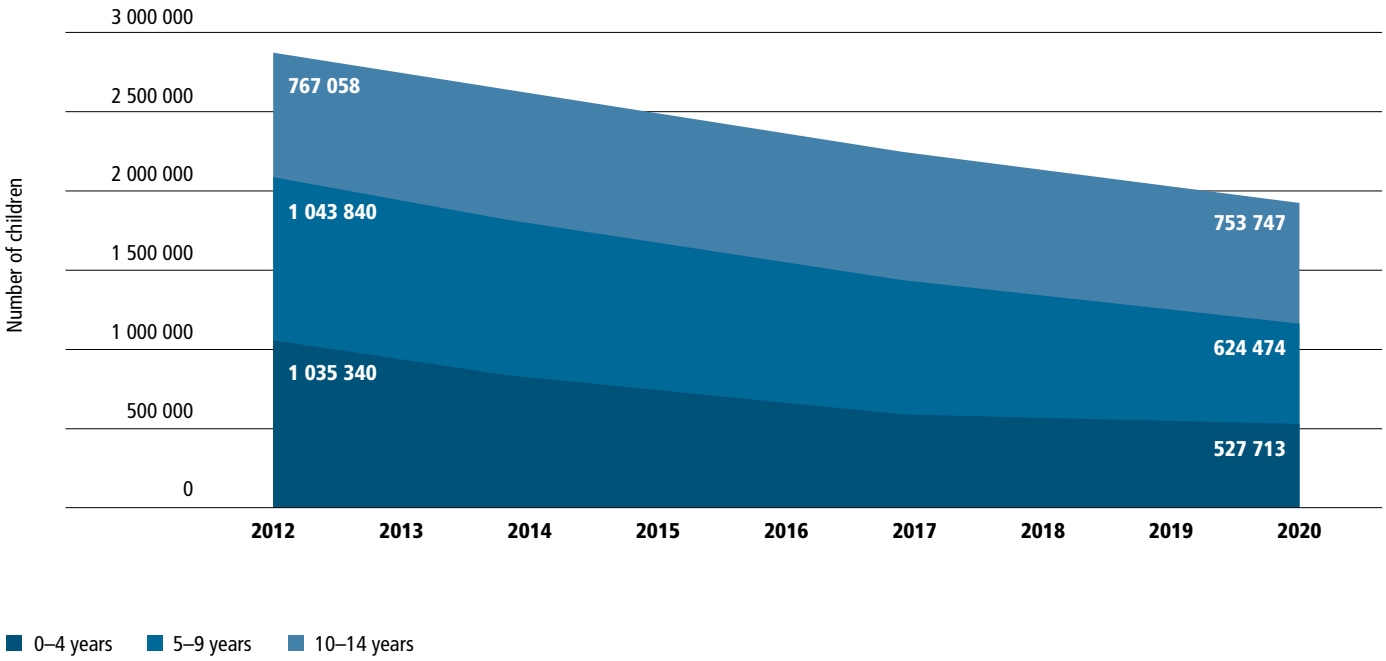
14. Spectrum is a modular program used by a variety of agencies to examine the consequences of current trends and future program interventions in reproductive health. UNAIDS uses Spectrum to estimate key HIV indicators based on HIV surveillance and surveys, programme statistics and epidemic patterns. These indicators include the number of people living with HIV, the number of people newly infected, the number of people dying from AIDS, the number of people orphaned by AIDS, the number of adults and children needing treatment the need for services to prevent mother-to-child transmission and how antiretroviral therapy affects survival.

Table 5.2. Assumptions used for the intermediate scenario: expected coverage by 2020 based on current coverage

ART for adults		Programmes for preventing mother-to-child transmission		ART for children	
If current ART coverage is:	Expected in 2020	If current ART coverage is:	Expected in 2020	If current ART coverage is:	Expected in 2020
>75%	95%	>75%	95%	>75%	100%
50–75%	90%	50–75%	90%	50–75%	90%
25–50%	85%	25–50%	80%	25–50%	80%
<25%	80%	<25%	70%	<25%	70%

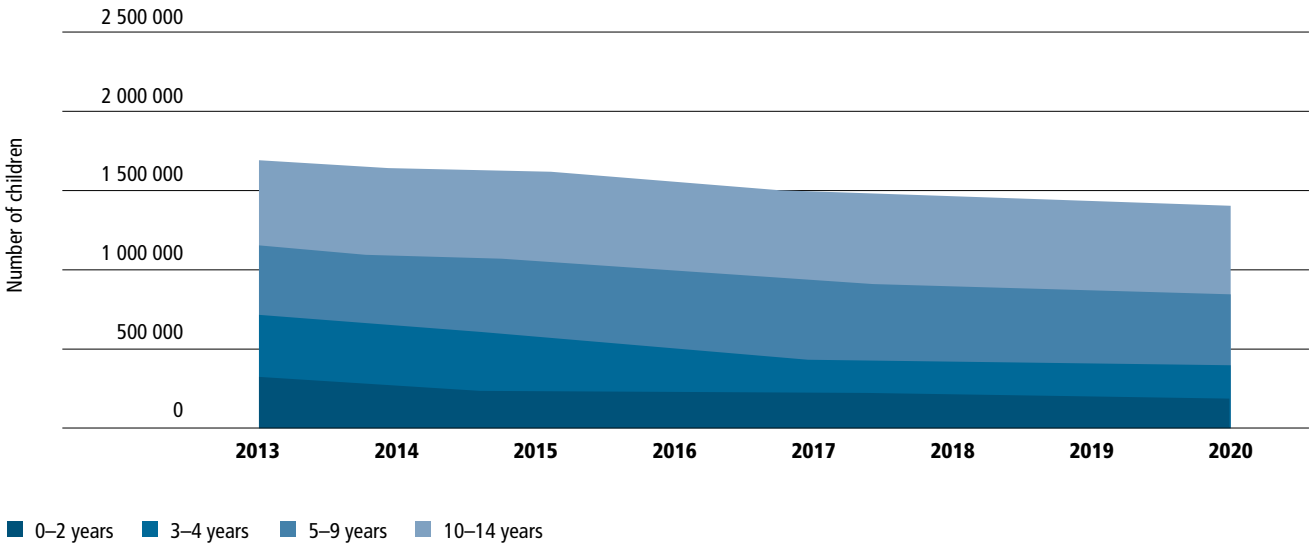
For the 21 sub-Saharan African priority countries, all three scenarios resulted in very similar projections. In 2020, there will be an estimated 1 931 768 children living with HIV (range 1 905 934–1 933 598) and an estimated 1 593 251 children needing ART (range 1 402 393–1 883 387) (Fig. 5.1 and 5.2) *(11,12)*. These estimates demonstrate that, even with expansion of programming for preventing mother-to-child transmission, new and current infections will contribute to a significant number of children living with HIV who will continue to require treatment, highlighting the need to maintain attention on development of appropriate drugs and formulations for infants and young children. An increasing proportion of children living with HIV will be older, and attention will need to focus on appropriate service delivery models for older children and adolescents.

Fig. 5.1. Number of children living with HIV in 21 Global Plan priority countries in sub-Saharan Africa (likely scenario, based on current performance)



Source: WHO and UNAIDS.

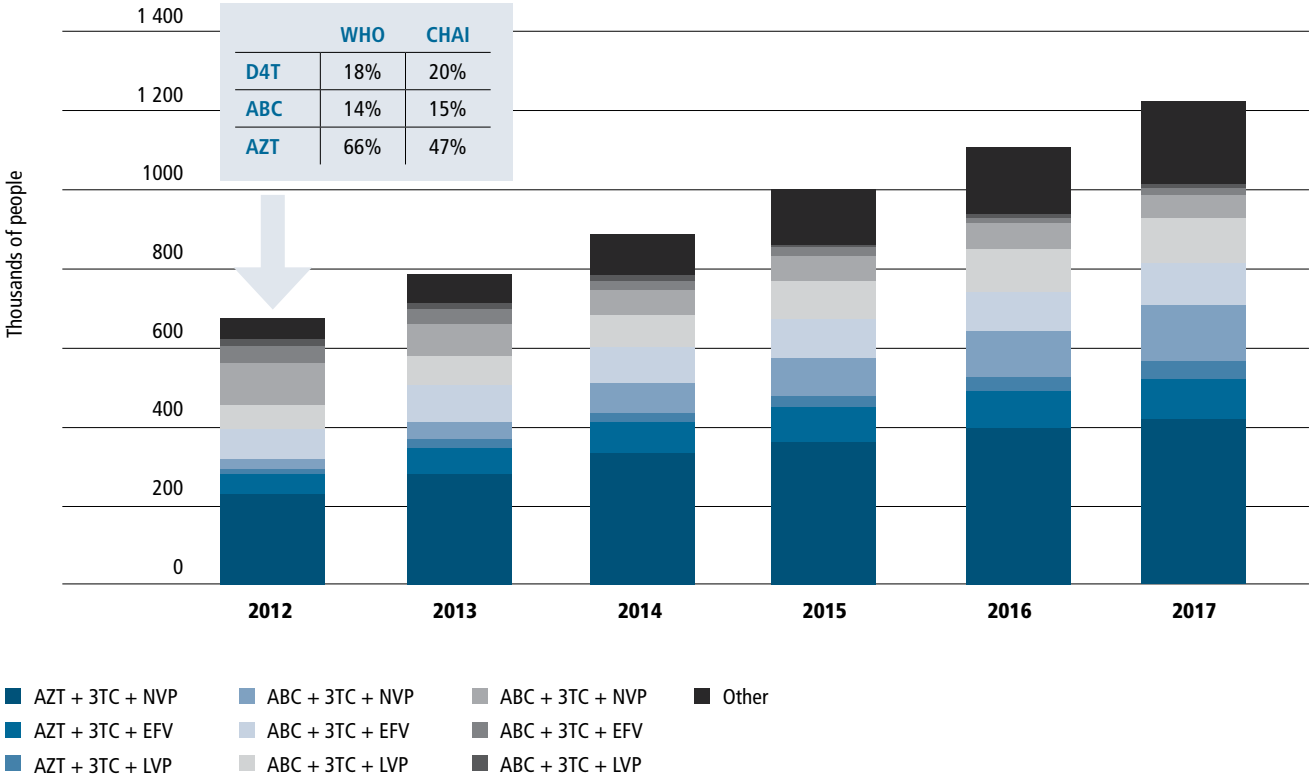
Fig. 5.2. Number of children living with HIV and eligible for treatment in 21 Global Plan priority countries in sub-Saharan Africa (likely scenario, based on current performance)



Source: WHO and UNAIDS.

Global ARV forecasting data by the Clinton Health Access Initiative (13) up to 2017 similarly highlight that a significant market for children will persist. The Clinton Health Access Initiative forecasting of regimens (Fig. 5.3) is intended to inform industry planning and country-level procurement. Notably, NVP and EFV demand will continue, reflecting the time lag between global guidance changes and likely uptake in national policy and practice. EFV demand may increase given the preference of the drug for children older than three years in accordance with the 2013 WHO guidelines, along with demand for LPV/r, AZT and ABC.

Fig. 5.3. Clinton Health Access (CHAI) Initiative forecasting indicating that AZT and ABC use will continue to increase into 2017



	WHO	CHAI
D4T	18%	20%
ABC	14%	15%
AZT	66%	47%

Source: Clinton Health Access Initiative.

Challenges in the development and uptake of drugs for children

Barriers to treating more children living with HIV include procurement and supply chain management systems, regulatory approval and intellectual property barriers. Drug forecasting, procurement and supply chain issues also need to be considered carefully to move new products and formulations more effectively from research and development to clinical practice.

Drug delivery

The ideal target product profile as well as user factors such as age and developmental stage have to be considered in designing and developing novel formulations and drug delivery systems. In addition, the technical difficulties of producing child-friendly fixed-dose combinations may be substantial.

Drug palatability is a well-recognized challenge in HIV treatment, particularly for younger children. Although palatability solutions (such as taste masking) generally are introduced as part of the drug formulation, they can also be included in the way a drug is delivered to a child, beyond the conventional use of oral tablets and syrups (such as spoons or straws with chemical changes that improve taste). Non-oral routes such as transdermal patches and long-acting ARV drugs are being explored and could play a role in improving adherence among children, especially adolescents. Currently, investigational long-acting injectable nanoformulations of rilpivirine and the integrase inhibitor GSK744 are in clinical development *(14)*. A recent study found that adults were generally receptive to the idea of long-acting injectable drugs, but in children this remains unknown.

Regulatory issues

From a regulatory standpoint, there are concerns over the widespread use of unlicensed and off-label medicines in children, including neonates, and WHO has issued guidance (linked to the List of Essential Medicines for children) to address these concerns *(15)*.

One key regulatory mechanism in place for drug developers is the paediatric investigation plan, serving as a development plan to ensure necessary study data are generated to support the approval of a medication for use in children. Pharmaceutical companies submit proposals for paediatric investigation plans directly to a stringent regulatory agency (the United States Food and Drug Administration or the Paediatric Committee of the European Medicines Agency).

Non-harmonized regulatory frameworks between countries create delays in accelerating the development of ARV drugs for children. In response to this, the Paediatric Medicines Regulators' Network has been set up and includes representatives from national medicines regulatory authorities from all regions. The Network has been convening regulators in interactive training sessions, on trials involving children. Regulatory networks such as the Paediatric Medicines Regulators' Network can also support companies in expediting drug trials in children and to address the extrapolation of data from adults to children, the modelling and simulation studies, and provide advice on specific ethical considerations.

Intellectual property

Intellectual property rights can be barriers for accessing affordable ARV drugs and developing fixed-dose combination. Innovative licensing models such as the Medicines Patent Pool are facilitating ARV access for children in resource-limited settings by soliciting voluntary licences from ARV patent owners and creating a pooled resource from which drug manufacturers and innovators can access the rights to manufacture or develop new and adapted formulations for sale in low- and middle-income countries.

Careful considerations of patent issues are important factors that may affect the availability of formulations for children. For instance, although the patent for LPV expires in 2017, formulation patents may last longer. RTV remains a top priority, as there is currently no voluntary licensing arrangement in place. Of note, the patents for DTG and TAF do not expire until 2026, challenging drug access; however, there are contingencies in place to address this issue.

Procurement guidance

Fragmentation of the market for ARV drugs for children, particularly for drug formulations, has been perceived as a disincentive to investment into the future development of drugs for children. Since children account for fewer than 7% of all individuals receiving ART *(2)*, the market for children is smaller and more vulnerable to supply disruptions than the ARV market for adults *(16)*.

With the goal of reducing market fragmentation and streamlining procurement of products for children, the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children developed an optimal list of ARV formulations for children in 2011 that serves as guidance to countries in procuring products that meet the needs of children within the context of WHO recommendations *(17)*. A recent revision of this list addressed the process of rationalizing available formulations by removing redundancies and focusing on a smaller number of formulation products that should facilitate procurement.

The Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children defined the criteria for what constitutes an optimal formulation (Table 5.3) and then evaluated all available products for children against these criteria.

Of the more than 50 products reviewed at that meeting, 10 formulations were identified for inclusion on a list of optimal ARV products for children – this list would include all WHO-recommended first- and second-line regimens for children. Additional products were recognized to be of limited use, and remaining products were listed as non-essential. Limited-use[15] products include formulations for children that may be needed in limited supply during transition periods and for special circumstances (such as didanosine). Non-essential products are formulations that are not recommended for procurement. Major implementing partners and procurement agencies have endorsed the optimized formulary list of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children. Procurement for ARV drugs for children has been transitioning from UNITAID and the Clinton Health Access Initiative to the Global Fund to Fight AIDS, Tuberculosis and Malaria, which is currently procuring an estimated 45% of these drugs, and this will rise to 60% by 2015. The Global Fund also has in place a market-shaping strategy, including the establishment of the Paediatric ARV Procurement Working Group, which provides market insight, coordinates ordering through a procurement consortium, engages with suppliers more directly and gives in-country support on forecasting and procurement planning.

Table 5.3. Selection criteria for inclusion in the optimal formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children

Criterion	Definition
Meets WHO requirements	Included in latest WHO guidelines for treatment for children
Allows for widest range of dosing options	Allows for flexible dosing across multiple weight bands and ages
Approved by a stringent regulatory authority or WHO prequalification	Availability of at least one product approved by a stringent regulatory authority
"User friendly"	Easy for health care worker to prescribe Easy for caregivers to administer Supports adherence
Optimizes supply chain management	Easy to transport Easy to store Easy to distribute
Available for resource-limited settings	Product is being manufactured and can be supplied to resource-limited settings
Comparative cost	Cost should not be a deciding factor; however, comparative cost of formulations of the same drug or drug combination should be considered

Country perspective on service delivery challenges

The gap in treatment coverage among children is a concern in both high and low burden countries. Country experiences highlight the challenges of identifying and diagnosing infants living with HIV in a timely manner and early infant diagnosis implementation is one of the major challenges to achieve wider uptake of ART. New models of service delivery in scaling up treatment for children (such as nurse-initiated ART management), simpler treatment options, giving priority to fixed-dose combinations and harmonizing treatment recommendations for children with adult regimens are programmatic innovations that will facilitate scale-up. At the patient level, palatability and food requirements are critical characteristics.

Toxicity monitoring

Toxicity monitoring has long been challenging due to lack of resources and infrastructure. As countries adopt the most recent WHO treatment recommendations and provide ART to a larger number of children, mechanisms to ensure that these regimens are safe must be strengthened. Although anaemia related to AZT is relatively easy to monitor, toxicity monitoring for other drugs, in particular, predicting

15. Limited-use formulations are categorized either as transition products (phasing in and phasing out of drugs, such as d4T) or products for use under special circumstances (specific to the person or situation, such as third-line formulations).

risk of ABC-related hypersensitivity reaction or monitoring TDF-induced bone toxicity, is currently not feasible in most settings. This challenge for monitoring has been reported as a significant barrier to the uptake of ABC (particularly in Asia) and TDF among children despite their well-recognized advantages in terms of sequencing and potential for harmonization. Although ABC toxicity was rarely observed in a large randomized control trial recently completed *(18)* in Africa, several studies *(19,20)* have described TDF-related reduction in bone mineral density, and more data to understand the clinical relevance of this and how to best monitor it are urgently needed. Giving priority to drugs with good tolerability and safety profiles and ensuring that systems to monitor toxicity are in place need to be carefully considered in the future strategies for optimizing drugs.

Recommendations of the Paediatric Antiretroviral Drug Optimization Conference

Considering both the critical barriers and the current pipeline of new drugs and formulations, the Paediatric Antiretroviral Drug Optimization Conference identified medium- and long-term priorities for drug and formulation development that can optimize drug delivery and treatment sequencing in children. Critical research gaps that will be essential to inform appropriate use of these products were also highlighted. Lastly, a roadmap to streamline both access and uptake of children-specific ARV in low- and middle-income countries was designed.

1. Medium and long-term priorities for children

Overarching criteria to set priorities for developing drugs and formulations have been identified, key elements to be included in a paediatric investigation plan, and the criteria for inclusion in the optimal list of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children should serve as a model for what an ideal drug or formulation should encompass (Table 5.3).

There is a need to explore more extensively the use of new products and formulations to the youngest age group (neonates), and innovative ways such as washout data (from babies being born to mothers taking ARV drugs) may be useful to collect when direct pharmacokinetic data for neonates cannot be obtained. Drugs with minimal food-related requirements that are suitable for alternative drug delivery systems and do not present chemical barriers for combination with other drugs should also be given priority. Further, ensuring a high genetic barrier and minimal drug–drug interactions, particularly with TB medications, is essential to guarantee adequate use of these drugs in low- and middle-income countries. Finally, harmonization with adult regimens should continue to be sought.

A. Formulations to be given priority

Given both the current WHO treatment recommendations for children living with HIV and the remaining gaps in products for children, the following formulations are to be given priority in the medium term (the next five years).

- **ABC + 3TC + EFV**
  A one-pill, once-daily formulation of the currently preferred regimen for children 3–10 years old would be highly desirable to enhance adherence and avoid unintentional mono- or dual therapy as a result of individual drug stock-out. EFV-based AZT-containing and NVP-based ABC-containing triple fixed-dose combinations may be of value but not a priority in light of the clear preference given to EFV and ABC by the new WHO guidelines and the potential limited market that these triple fixed-dose combinations may have.

- **AZT or ABC + 3TC + LPV/r**
  These formulations are needed to be able to offer fixed-dose combinations to children younger than 3 years who are prescribed one of recommended preferred regimens in this age group; this could also overcome palatability issues and remove supply chain barriers with the currently available formulation.

- **DRV/r**
  The current lack of a manageable alternative to LPV/r as part of a robust second-line regimen, particularly for children for whom a LPV/r-based first-line fails, make developing these formulations an urgent need.

- **RTV pellets**
  The possibility of a manageable alternative to the existing formulation to ease double-boosting in the context of a LPV-based regimen used as part of TB co-treatment.

Long term (beyond five years), given the existing formulations for children and dosing across the entire age spectrum for raltegravir (RAL), development of a fixed-dose combination containing RAL, 3TC with AZT or ABC should be encouraged. This would provide a second-line option in fixed-dose combination, particularly to the young children started on an LPV/r-based regimen that fail first-line therapy before the age of three years.

B. New drugs to be given priority

In consideration of the new molecules that are currently at advanced stage of development in adults or children (phase 3), and in light of key product characteristics, three new drugs for children were identified for which development should be given priority.

- **DTG**
  This integrase inhibitor has already been approved for use in adults and is currently under study for use from birth (P1093 trial). DTG does not require boosting and has so far shown good tolerability and high potency at doses as small as 50 mg for adults. Hence, there is growing interest in this drug for use in first- or second-line ART *(21)*.

- **TAF**
  A safer first-line alternative to TDF is a drug development priority. Preliminary data suggest that TAF may have lower renal and bone toxicity; however, more children-specific data are needed to confirm the more favourable safety profile and enable wider use of this drug in children. The opportunity to offer an alternative to ABC and further harmonize with adult regimens is an additional advantage, particularly if co-formulated with EFV or integrase inhibitors (preferably DTG).

- **Cobicistat**
  Cobicistat may potentially be a more child-friendly booster that could be combined with any protease inhibitor, particularly for the drugs for which co-formulation in dosing for children is still unavailable, such as ATV and DRV. Studies investigating this drug in formulations for children are planned.

The current timelines for development and potential approval of these priority drugs means that they are unlikely to be a viable treatment option before 2017. Therefore, these drugs represent the long-term vision. Although additional compounds such as elvitegravir and rilpivirine may well have value, at present it may be wise to give priority to fewer options that are more likely to meet the needs of children and better align with optimization principles.

C. Optimized sequencing

Given the age indications, known resistance profiles, potential for co-formulation and expected timelines of approval for most of the compounds being discussed, medium-term and long-term visions were developed on how to best sequence the priority drugs and formulations.

Although the current sequencing for children 3–10 years old remains a valid option in the medium term, better approaches are urgently needed for the younger age group (0–3 years) initiating an LPV-based first-line regimen. These younger children may be able to use an RAL-based or DRV/r-based regimen interchangeably for second- or third-line treatment, depending on whether first-line treatment fails before or after the third year of age to account for the age indication of these two drugs.

The long-term vision remains the opportunity to provide a potent, once-daily first-line option formulated in a fixed-dose combination containing DTG and 3TC in combination with either ABC or TAF (assuming that the age indication for the latter will be extended to newborns). This approach would not only allow complete alignment across the different age groups in children, but would most likely align with adult preferred regimens, thus representing for the first time full harmonization across populations (Table 5.4).

Table 5.4. Recommended sequencing options for younger and older children (medium and long term)

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">Age 0–3 years</th><th colspan="2">Age 3–10 years</th></tr>
<tr><th>Option 1</th><th>Option 2</th><th colspan="2"></th></tr>
<tr><td rowspan="3">Medium-term</td><td>First line</td><td>ABC + 3TC + LPV/r</td><td>AZT + 3TC + LPV/r</td><td rowspan="3">Continue using currently recommended regimens</td><td rowspan="3">Not applicable</td></tr>
<tr><td>Second line</td><td>AZT + 3TC + DRV/r</td><td>ABC + 3TC + RAL[a]</td></tr>
<tr><td>Third line</td><td>Optimized background regimen + RAL</td><td>Optimized background regimen + DRV/r</td></tr>
<tr><td rowspan="3">Long-term</td><td>First line</td><td colspan="4">TAF + 3TC + DTG or ABC + 3TC + DTG</td></tr>
<tr><td>Second line</td><td colspan="4">AZT + 3TC + LPV/r or ATV/r[b]</td></tr>
<tr><td>Third line</td><td colspan="4">DRV/r[c] + ETR or EFV</td></tr>
</table>

[a] If first-line failure occurs before three years of age.

[b] If first-line failure occurs before six years of age.

[c] Cobicistat can be considered a potential alternative for boosting, particularly if the DRV/r co-formulation is still unavailable.

Source: adapted from the recommendations of the Paediatric ARV DrugOptimization Conference, Dakar, Senegal, 22–23 October 2013.

2. Research priorities

The Paediatric Antiretroviral Drug Optimization Conference identified the following research priorities to address further drug optimization:

- DTG: establish dose, safety and efficacy in children;
- LPV/r in malnourished children: pharmacokinetics and implications for use;
- TB co-treatment in children: pharmacokinetics of ABC and newer drugs;
- drug interactions between ABC and LPV/r: impact on pharmacokinetics, efficacy and use;
- DRV/r ratios: pharmacokinetics of co-formulations for use by children;
- pharmacokinetics of EFV-based triple fixed-dose combination according to weight-bands dosing among children 3–10 years old;
- TAF and long-term TDF toxicity in young children (0–10 years): better understanding and clinical relevance;
- Cobicistat: pharmacokinetics and potential for co-formulations;
- head-to-head comparison between TAF and ABC among children of different ages; and
- rilpivirine: pharmacokinetics and efficacy and toxicity at higher dose to provide a more robust long-acting option particularly for older children and adolescents.

3. Roadmap to streamline access and uptake

A roadmap of actions with the objectives of facilitating access to drugs and formulations for children and ensuring adequate uptake of ART was developed at the Paediatric Antiretroviral Drug Optimization Conference, concerning the following four areas.

Speeding up the development and approval of drugs and formulations

There is a need to minimize the gap between the approval of new drugs for adults and children and neonates by engaging more effectively with ethics committees and industry. Harmonization of regulatory approval requirements across countries is critical to minimize the steps required for approval (harmonization of age categories and weight-bands). Establishing model paediatric investigation plans for regulatory bodies may further standardize and streamline the development and submission of adequate information. Lastly, fast-tracking mechanisms for priority products exist, and these systems should be more effectively used for children living with HIV to obtain regulatory approval (European Medicines Agency Article 58). International agencies such as WHO should ensure that priority products are identified and clearly flagged and use for fast-track approval.

Sharing patents

Although several patent-sharing agreements have already been negotiated,[16] additional agreements are urgently needed. Priority should be given to such drugs as DTG, TAF, new LPV/r and ritonavir (stand-alone) formulations. Other drugs identified as important by the group, such as RAL, should also be considered. There is a need to streamline clinical approval across age groups and to develop strategies that easily transition patent agreement from one age group to another. In addition, mechanisms should be put in place to ensure the continuity of coverage through adulthood in middle-income countries as much as in low-income countries.

Giving priority to procuring formulations for children

Coordination between health ministries, technical agencies, industry, procurement agencies and donors is essential to streamline the production and effective supply of formulations for children. Technical agencies and global partners should provide guidance on optimal drugs and formulations to be procured in alignment with WHO recommendations. Industry needs to be clearly informed on the selected priority formulations to best serve the needs of children living with HIV in the medium and long term.

Enhanced communication and adopting tools such as the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children optimal formulary list are expected to facilitate procurement, prevent stock-outs, reduce market fragmentation and ensure the necessary investment. Lastly, the role of donors and development agencies in securing the availability of low-volume products and encouraging the adoption of procurement tools on a global scale will be critical in ensuring the feasibility and sustainability of these changes.

Overcoming financial barriers

Since HIV infection among children is almost entirely a problem of low- and middle-income countries, alternative financial mechanisms need to be explored urgently at the global level, including the potential role of advanced market commitments and learning from other disease areas (such as polio) where efforts aiming to sustain a

16. Agreements to share patent information for other important drugs mentioned in this report, such as ABC + 3TC, ATV and COBI, have already been negotiated and are available through the Medicines Patent Pool.

diminishing market will be an important additional step. In this context, the group recommended that more accurate epidemic estimates be urgently sought to develop more reliable forecasting for ARV drugs for children and to ensure the mobilization of adequate and sustainable funding.

National governments should secure specific budgets for ARV drugs (for example, in South Africa, AIDS budgets are ring-fenced) and explore the potential for orders for children to be added on to orders for adults for drugs with the same active pharmaceutical ingredients.

Conclusions

Although programmes for preventing mother-to-child transmission continue to succeed in reducing vertical transmission globally, there are currently 1.2 million children living with HIV eligible for ART who do not receive it, and the number of children acquiring HIV infection will remain significant, with an estimated 1.8 million children living with HIV by the end of 2020. An urgent and appropriate response to the specific needs of children is therefore urgently needed.

More strategies will be required to tackle treatment-experienced children living with HIV and to address the challenges and needs of adolescents living with HIV. In addition, ongoing acquisition of HIV infection will continue to contribute a significant number of children eligible for treatment in the coming years. As the use of early infant diagnosis improves, more data will be required to fully inform the use of ARV among neonates and young children.

In addition to the need to improve currently available formulations, new drug delivery systems have the potential for further optimizing drugs, and this promising work needs to move beyond academic research and into drug development. Better alignment of first- and second-line treatment options for both younger and older children also will be critical to facilitate the scale-up of ART for children and to ensure that treatment optimization enables new models for service delivery, such as task-shifting and decentralization, to reach more children earlier. Finally, efforts in advancing the research agenda on treatment for children, particularly in the context of new formulations and drugs, will require coordinated efforts between stakeholders, including academe, funders, regulators, industry, civil society and the affected communities.

6. CHANGING ROLE OF CD4 CELL COUNTS IN HIV CARE AND TREATMENT

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy

Key messages

- Assessment of baseline CD4 cell counts continues to play a role in stratifying risk and guiding clinical decisions about starting prophylaxis and screening for opportunistic infections.
- Assessment of CD4 cell count is still necessary to guide initiation of ART outside of certain clinical situations.
- HIV viral load, when available, is a more reliable tool for monitoring adherence to treatment and efficacy of ART than CD4 cell counts.
- Recent evidence demonstrates that, once people living with HIV receiving ART are virally suppressed, their CD4 cell count does not decline over time, suggesting that, in situations in which viral load is available routinely, CD4 monitoring could be reduced or stopped altogether.

Purpose of this section

As reflected in the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO now recommends ART initiation regardless of CD4 cell count for a number of clinical or programmatic indications. WHO further recommends HIV viral load measurement as the preferred approach to treatment monitoring *(1)*, and there is a concerted effort to support the scaling up of viral load capability in resource-limited settings.

With access to viral load becoming increasingly available, the role of CD4 monitoring is increasingly being questioned. Several studies have recently suggested that CD4 monitoring has little added value in situations where viral load is available and patients are virally suppressed *(2,3)*. In September 2013, WHO held an expert consultation on the future role of CD4 testing for ART monitoring. This technical update summarizes the evidence to date and the key findings of this consultation and is intended for clinicians and programme managers to assist them in decisions about the relative priorities of CD4 testing in settings in which viral load capacity exists or is being phased in.

National HIV programme policies for ART monitoring

During the past decade, WHO guidelines on antiretroviral therapy (ART) in low- and middle-income settings have evolved towards recommending that countries phase in viral load for treatment monitoring, although it has been acknowledged that the complexity of the technologies and the cost have limited access *(4)*. The latest guidelines, released in June 2013, recommend that countries use HIV viral load as the preferred approach to ART monitoring *(5)*.

Current guidelines for ART monitoring vary from country to country. The Democratic Republic of the Congo, Guinea and several other countries currently rely on CD4 alone, whereas several countries including Kenya, Lesotho, Mozambique, Swaziland and Zimbabwe rely on routine CD4 cell monitoring and use viral load only in a targeted way to confirm treatment failure among people with immune or clinical failure, and Malawi and South Africa rely on viral load for long-term monitoring; in the case of South Africa, discontinuation of routine CD4 is now recommended after one year for people stable on ART unless continued CD4 results are needed for decisions regarding stopping opportunistic infection prophylaxis *(6)*. Monitoring strategies can also differ between the public and private sectors; in India, for example, targeted use of viral load is provided in the public sector, whereas routine viral load monitoring is offered in the private sector. The frequency of both CD4 and viral load tests performed for ART monitoring also varies substantially between countries.

Prospects for increasing access to viral load monitoring

Several middle-income countries – notably Botswana, Brazil, South Africa and Thailand – were early adopters of HIV viral load monitoring. Viral load monitoring has been integrated into the guidelines of national HIV programmes in countries with a high burden of HIV more broadly since 2010, when WHO guidelines first recommended that countries should phase in viral load for routine treatment monitoring *(7)*. In practice, however, access to viral load remains limited due to the complexity of current technologies and cost.

Currently, it is estimated that less than 20% of the people receiving ART in Africa receive routine viral load testing *(8)*. The anticipated arrival of point-of-care technologies from 2014 onwards should help overcome some of the technological limitations to improving access to viral load, particularly in remote rural areas. As of June 2013, nine point-of-care technologies were in the pipeline, with six anticipated to receive market authorization by 2016 *(9)*. Other approaches that have been taken to increase capacity and access include the use of dried blood spot sample collection and sample pooling *(10,11)*.

An important barrier to scaling up viral load testing remains the cost, which can range from US$ 10 to more than US$ 50 per test. The African Society for Laboratory Medicine recommends several approaches to reducing the cost of viral load testing, including negotiating volume-based regional or country-wide pricing for test supplies, encouraging competition by using multiple suppliers to negotiate lower prices and using automated technology to improve test quality and increase test throughput *(8)*.

A key approach to increasing resource availability for phasing in viral load testing is to decrease the overall cost of laboratory test monitoring by reducing the overall number of tests performed. Recent studies from South Africa *(12)* and the United States of America *(13)* have suggested that reducing the frequency of CD4 testing can substantially reduce costs; in resource-limited settings, these resources could be directed towards increasing access to viral load testing.

The value of baseline CD4 measurements

Consistent with the trend towards policies of earlier initiation of ART, the median baseline CD4 count at which people start ART has risen during the past decade in all WHO regions, and most markedly in the lowest-income countries; however, many people enter into HIV care late, with advanced immunosuppression. The proportion of people initiating ART with very low CD4 counts remains high, with more than one in four people starting ART at CD4 ≤100 cells/mm^3 across all regions *(14)*.

People first presenting to HIV care with a low CD4 cell count are at increased risk of death in both low- and high-income settings *(15,16)*, and CD4 determination currently has an important role in decisions for screening and prophylaxis for major opportunistic infections. A low CD4 count predicts several diseases associated with higher mortality, including cryptococcal meningitis, *Pneumocystis* pneumonia, toxoplasmosis, *Mycobacterium avium* complex and disseminated cytomegalovirus disease. CD4 test results can help stratify the clinical care requirements for people presenting late to care and support diagnostic decision-making at baseline and among people for whom ART is failing or who are returning to care after a period of treatment interruption.

For example, cryptococcal meningitis remains a leading cause of mortality among people with HIV, contributing up to 20% of AIDS-related deaths in low- and middle-income settings *(17)*, and WHO recommends systematic *Cryptococcus* antigen screening for everyone with CD4 ≤100 cells/mm^3 and pre-emptive treatment for those with positive antigen test *(18)*.

WHO recommends providing co-trimoxazole prophylaxis to everyone presenting to care with a CD4 count ≤350 cells/mm^3 (as well as for those with WHO clinical stage 3 or 4). Co-trimoxazole improves survival by reducing the risk of death from a range of infections, including malaria, severe bacterial infections, *Pneumocystis* pneumonia and toxoplasmosis *(19)*.

CD4 cell count and treatment initiation

The 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* recommend that ART be initiated for all patients with CD4 ≤500 cells/mm^3, and initiated immediately regardless of CD4 for children up to five years old, people with active TB or coinfected with hepatitis B virus with severe chronic liver disease and people living with HIV in serodiscordant partnerships. The guidelines further recommend that ART be offered to all pregnant and breastfeeding women living with HIV *(20)*.

Most countries with a high burden of HIV are in the process of adopting and adapting these new recommendations according to their epidemic setting and resource availability. While there is a trend towards an increasing number of CD4-independent ART initiation scenarios, ART for all irrespective of CD4 cell count remains the exception rather than the rule and, for most countries, CD4 measurements continue to play an important role in determining eligibility for ART.

Value of CD4 for ART monitoring

Recent evidence from randomized trials and observational cohorts suggests that, once people living with HIV receiving ART are virally suppressed, CD4 cell counts do not decline over time for most of them.

An analysis of data from the Artemis trial found that, of the 449 people with sustained HIV-1 RNA suppression and CD4 ≥200 cells/mm^3 followed for 192 weeks, only 1% experienced reductions in CD4 count below 200 cells/mm^3. These reductions were transient, with follow-up results >200 cells/mm^3 *(3)*. A cohort study from the United States found that, among 832 people followed for a median of 7.7 years, those with an initial CD4 ≥300 cells/mm^3 and who were virally suppressed on ART had a 99.2% probability of a durable CD4 ≥200 cells/mm^3 at year 5, after excluding non-HIV causes of lymphopaenia *(2)*. Similar studies from the United Kingdom *(22)* support these findings. Unpublished data from resource-limited settings further confirm that CD4 declines are rare and mostly transient among people who are virally suppressed. Although data for children are lacking,

there is no reason to expect that these dynamics will differ substantially. A recent model-based algorithm *(23)* suggests that the frequency of CD4 cell count measures could also be reduced in children, using last CD4 count, last viral load and age to predict clinical disease progression risk.

Criteria for stopping CD4 for treatment monitoring

Although a CD4 cell count at baseline continues to be important for initial clinical management decisions, once ART is initiated and people have achieved viral suppression and stabilized on treatment, the additional value of CD4 testing in the presence of routine viral load monitoring is questionable. CD4 cell counts rarely decline over time once viral suppression is achieved, even for people presenting late for care. The extent of immune recovery depends on nadir CD4 count before treatment initiation *(24)*, but most people can be expected to achieve a reasonable degree of immune recovery after several years of ART provided that viral load remains suppressed *(25–27)*. A minority of people may fail to increase CD4 despite viral suppression *(28,29)*, but if viral load is suppressed, this variability in CD4 recovery would not alter treatment decisions, as there is no evidence for changing ART among those with a discordant immune and viral response.

There is a growing consensus that CD4 monitoring adds little additional value to viral load monitoring once patients are stable on ART with viral suppression. Guidelines issued by the Southern African HIV Clinicians Society recommend that, for people being monitored with viral loads, once the CD4 count is >200 cells/mm^3 and viral load is suppressed (two consecutive undetectable viral loads), there is no need to continue CD4 testing. CD4 testing is recommended if viral or clinical failure occurs *(6)*.

Community considerations

In addition to guiding clinical decisions, CD4 cell counts are a central part of current approaches to treatment literacy, and considerable emphasis has been placed on using CD4 as a way to explain to people why ART is needed, the importance of maintaining good adherence and as a measure of a positive response to treatment.

If viral load is to be used as the principal means of monitoring ART, treatment literacy efforts will be needed so that demonstration of viral suppression can take the place of rising and subsequently stable CD4 as the main way that people living with HIV understand how they are responding to ART. However, both clinicians and people living with HIV recognize that CD4 cell counts can fluctuate significantly due to both the inherent variability of CD4 levels and the inconsistency of results obtained by CD4 tests, and this can be an unnecessary source of anxiety for the people living with HIV *(30)*. Successful pilot programmes have already shown that, with appropriate communication materials, the relationship between viral load and treatment success is easy to convey and readily understood *(31)*, and groups of people living with HIV have expressed a willingness to support a reduction in or stopping of routine CD4 monitoring for people in stable condition provided that this is accompanied by clear messaging that they can understand.

Conclusions

CD4 cell counts have been the main tool for making decisions about ART initiation and monitoring the response to treatment and have had considerable value for both clinicians and people living with HIV. However, the utility of ongoing CD4 monitoring among people stable on ART whose viral load is also being monitored is increasingly being questioned.

More than 10 million people are currently receiving ART, and more than 1.5 million people were newly initiated on ART in 2012 alone. Life expectancy studies from both high-income *(32)* and low-income *(33–35)* settings have concluded that, with timely ART initiation, people living with HIV can expect near normal life expectancy. There is therefore a pressing need to identify the most rational and cost-effective way to provide laboratory monitoring of HIV treatment over time.

CD4 counts will continue to play an important role in initial decisions around ART initiation and clinical management, particularly for the people presenting late to care, and will remain an important tool for treatment monitoring in settings where viral load monitoring is limited. Although CD4 cell levels provide an important indication of disease progression and death among people living with HIV but not receiving ART, once treatment has been initiated, the key focus is ensuring viral suppression.

In settings where both CD4 and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or eliminating them altogether from routine use for monitoring treatment response once people are stable on ART. Countries in the process of phasing in viral load monitoring capacity should consider reducing the indications for and frequency of CD4 cell measurements at the same time and redirect these resources towards expanding access to viral load monitoring.

When access to viral load testing is assured, the WHO consultation endorsed the move to reduce routine CD4 monitoring for adults who are on ART and are immunologically stable. For children, the decision to stop CD4 is more complex both due to risk of disease progression, particularly for younger children, and determination of immune recovery. A working definition of stability on ART for children may need to be age dependent, and this is an important area for further research.

7. SCALING UP VIRAL LOAD TESTING IN RESOURCE-LIMITED SETTINGS

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 7 – Antiretroviral therapy.

Key messages

- HIV viral load testing is the preferred monitoring approach to diagnose ART treatment failure.
- Options for phasing in viral load testing are varied and will increase as new technologies become available.
- Viral load scale-up is context specific, and programme managers and laboratory experts need to collaborate closely at the national level.
- The selection of a viral load platform will be affected by cost, robustness, low threshold accuracy and the ability to ensure expeditious delivery of samples to the viral load laboratory.
- The availability of point-of-care technologies over the next several years may impact early infant diagnosis and treatment monitoring.
- More detailed technical guidance is forthcoming to complement this programme update.

Introduction

By the end of 2012, 9.7 million people were receiving ART in low- and middle-income countries. This increase in the number of people receiving ART during the past decade has been achieved through political commitment, community mobilization and significant domestic and international financial support. Despite this success, more needs to be done to reach the target of 15 million people receiving ART by 2015 set by United Nations Member States in June 2011. Further, with the introduction of the 2013 WHO guidelines recommending a higher initiation threshold of CD4 ≤500 cells/mm^3 for everyone and ART for certain people living with HIV regardless of CD4 count (including pregnant women and members of serodiscordant couples), the number of people eligible for ART is now estimated to have risen to 25.9 million.

In addition to expanding access to ART for everyone eligible, it is important to ensure that those receiving ART remain in care and on effective therapy if treatment programmes are to continue to have a sustained impact on morbidity, mortality and the transmission of HIV. Viral load, the gold standard for monitoring ART response in high-income settings, is increasingly recognized as an important and accurate tool for managing ART in resource-limited settings as a way to diagnose poor adherence and treatment failure early *(1)*. Guidelines for ART management issued by WHO have recognized the importance of viral load monitoring since 2003, and routine viral load monitoring is now strongly recommended as the monitoring strategy of choice *(2)*.

Most countries with a high HIV burden and lower-income countries still rely on clinical and immunological criteria to define treatment failure. However, a recent systematic review concluded that clinical or immunological criteria for treatment failure have low sensitivity and positive predictive value for identifying individuals with viral failure, particularly for children, and people who are identified with immunological failure may in fact have adequate viral suppression and risk being misclassified and switched unnecessarily to second-line therapy *(3)*.

There are a number of challenges to implementing viral load monitoring in resource-limited settings, including complex technical requirements to perform the test, logistics of sample transport and cost. Nevertheless, recent operational experience has demonstrated the feasibility of performing viral load monitoring in a range of resource-limited settings, and provides strategies to overcome these challenges. Interest in the use of dried blood spot samples for viral load testing and a robust pipeline of near-to and point-of-care technologies will likely provide further opportunities for increasing access to viral load testing, particularly in settings that do not have easily accessible referral laboratories. The first commercially available point-of-care viral load technologies are expected to become available before the end of 2014 *(4)*.

This section outlines key considerations for national programme managers as they consult with laboratory services experts for phasing in routine viral load monitoring and for selecting HIV viral load testing platforms that will be best suited for their national or local contexts. Programme managers and laboratory experts will need to evaluate how they can increase access with currently available technologies and how expected increased numbers of newer technologies, such as point-of-care viral load testing, might affect current priority-setting. WHO is collaborating with several technical partners to issue a more detailed technical update on viral load platforms that will complement this programme update.

Box 7.1. WHO 2013 recommendations for monitoring people receiving ART

- 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.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (2).*

Viral load monitoring is increasingly recommended in policy, including by WHO (Box 7.1), but availability remains limited. A 2012 survey of 23 countries with a high burden of HIV found that, although 13 countries include viral load for routine monitoring in their national guidelines, only three of these (Botswana, Brazil and South Africa) had the capacity to implement this as a nationwide policy *(4)*. These three countries have been able to institute efficient and regular specimen collection systems and have decentralized viral load testing to provincial level laboratories, usually relying on fully automated platforms.

Where viral load monitoring is not routinely available, national guidelines generally recommend CD4 testing every six months to monitor treatment efficacy, but in practice many programmes perform significantly fewer than half of the number of CD4 tests that would be expected based on treatment monitoring guidelines *(5)*. The reasons for this range from inconsistent test-ordering practices among health care providers, lack of regular or reliable sample transport, stock-outs of sample reagents, inadequate throughput capacity and lack of maintenance for the laboratory equipment. National programme planners and laboratory experts will benefit from understanding the challenges in accessing CD4 testing as viral load testing is scaled up *(5)*.

Developing a strategy for scaling up access to viral load testing

Based on recommendations that, if feasible, expanding viral load testing capacity will facilitate patient monitoring, a range of stakeholders will need to collaborate to develop a country-specific situational analysis that defines plans for scaling up viral load testing. The issues related to expanding viral load testing are complex but include choice of platform(s), degree of decentralization of laboratory equipment, scope and scale of viral load testing expansion, issues of sample type and collection, logistical and infrastructure needs, laboratory staffing requirements, training needs for clinicians, modification of clinical tools and elaboration of monitoring and evaluation systems.

The choice of viral load testing platform will be affected by cost, robustness in country-specific conditions, accuracy at lower viral load thresholds, availability of maintenance contracts and ability to use different sample types. Annexes 7.1 and 7.2 describe the operational characteristics of the most common viral load platforms. Deciding which viral load platform is the most appropriate requires considering not only price but also servicing needs and availability, quality, subtype and ability to meet the technical and throughput needs of the local context. Harmonization of platforms should be defined by the health ministry in collaboration with clinicians, laboratory staff and policy-makers. Finally, plans to introduce new approaches to increase viral load capacity should also consider how best to use existing equipment to maximize capacity.

Simplifying sample transport for centralized viral load testing

An important limitation to scaling up viral load testing

in resource-limited settings has been the complexities of transporting samples. Plasma obtained from EDTA anticoagulated whole blood remains the preferred sample type *(6)*; however, obtaining plasma in peripheral clinics is often not feasible due to the lack of electrical centrifuges and cold-chain storage. One possible alternative to EDTA is a plasma preparation tube, although this does require centrifugation within 6 hours. When blood is collected at a peripheral clinic without centrifugation capacity in an EDTA tube, or in a plasma preparation tube, samples can be transported at room temperature but must reach the district laboratory within 6 hours *(7)*.[17]

Once centrifuged, samples can be stored up to 5 days at room temperature with a plasma preparation tube and up to 14 days at 2–8°C from EDTA-derived tubes, and longer if frozen at –20°C or –80°C. Stability under these conditions can facilitate sample transport if testing is performed at referral laboratories. These cold-chain limitations for the different sample types will need to be factored into costing sample storage and transport *(8)*.

The practical implications of these various requirements are that, if sample transport does not occur daily, patients are either asked to visit their clinic again on a specific specimen collection day or are required to travel to the nearest hospital with a laboratory with centrifugation and plasma specimen storage and transport capacity, to have blood drawn.

Use of dried blood spots for viral load testing

A strategy to simplify sample transport for early infant HIV diagnosis for using DNA qualitative testing assays for HIV DNA has been to prepare whole-blood samples on dried blood spots on appropriate filter paper. Dried blood spot samples offer multiple operational advantages: they can be stored and transported at room temperature for long periods without affecting nucleic acid stability *(9)*; they can be prepared by non-laboratory staff with limited training, either from capillary or venous blood; and the small volume of blood needed to impregnate the filter paper reduces the biohazard risk related to sample collection *(10)*.

For quantitative viral load monitoring, HIV RNA testing is needed. Both dried blood spots and dried plasma spots for quantitative viral load measurements have been extensively evaluated with different viral load assays *(11)*. An important limitation of dried blood spots is the presence of cell-associated nucleic acids (DNA and RNA), particularly in samples with lower levels of viral load (≤5000 copies/ml), that, compared with plasma, can lead to elevated results when using methods relying on total nucleic acid extraction (DNA and RNA) reverse-transcriptase PCR methods rather than RNA-specific extraction methods.

Dried plasma spots have been proposed as an alternative to dried blood spots, with studies showing good correlation with plasma *(12,13)*; however, its applicability in primary health clinics is limited owing to the need for centrifugation for plasma preparation.

Tradeoffs therefore exist with each sample type, and these should be balanced against clinical and operational considerations. For example, dried blood spots may allow decentralization of viral load testing, but this may restrict the type of viral load platform to be used and the applicable clinical thresholds. For use of EDTA-derived plasma rather than whole blood, small and inexpensive battery-operated centrifuges may be a solution but, where logistics for adequate sample transport to a laboratory do not exist, this will require dedicated staff at the clinic level trained in phlebotomy, sample processing, storage and transport as well as safety precautions associated with sample manipulation and waste management.

Rapid plasma preparation devices may in the future provide an alternative to obtaining plasma without the need for electrical centrifuges, but their applicability for viral load testing has not yet been evaluated *(14,15)*.

The challenge of selecting a technique-specific, reliable threshold that is above the currently recommended lower limit of 1000 copies/ml to identify treatment failure (and higher transmission risk) can be overcome to some extent by using RNA-specific methods such as nucleic acid sequence-based amplification (NASBA). At present, the NucliSENS EasyQ HIV-1 v2.0 assay is the only commercially available RNA-specific NASBA-based viral load testing technology and the only viral load test with regulatory approval to use dried blood spots as a sample type. Other manufacturers are adapting their tests for use with dried blood spots. Fig. 7.1 outlines the sample transport considerations for the different sample types.

Reducing the cost of viral load testing

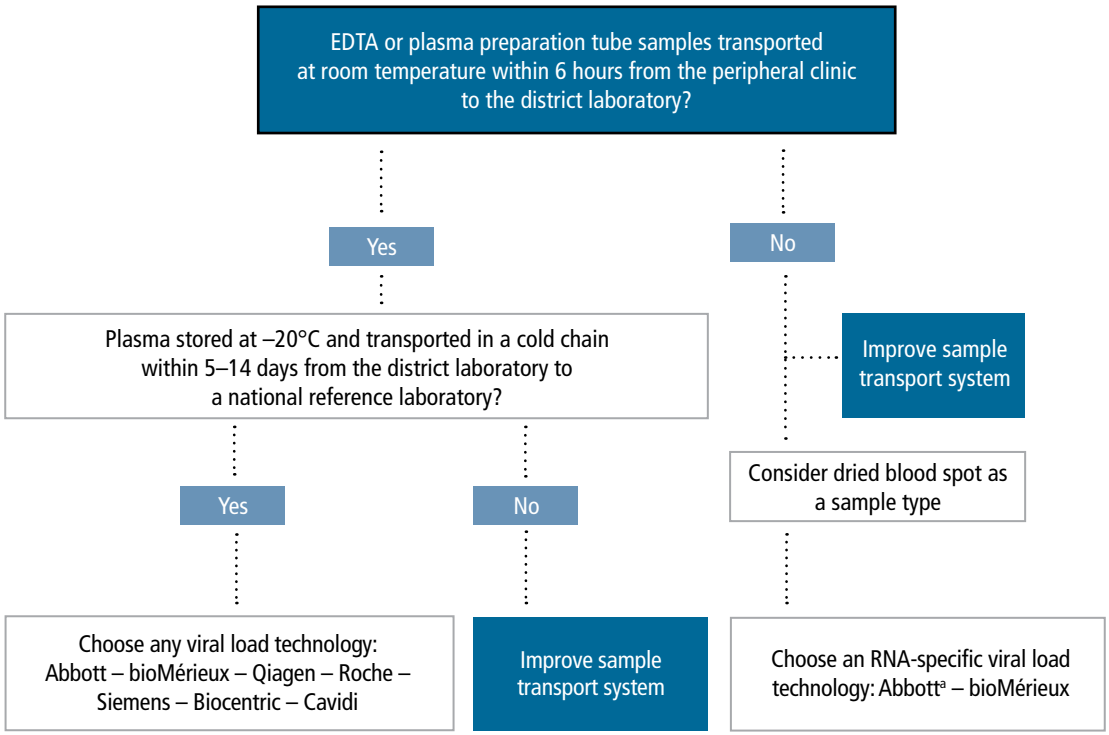
The cost of viral load testing per sample has declined in recent years. Programme managers must factor in many cost centres when evaluating the most cost-efficient testing platform and strategy. From a clinical and programmatic standpoint, several options may reduce the cost to the national programme.

Viral load pooling

Viral load pooling can reduce the total number of tests being performed by combining sample aliquots – for example, for five individual patient samples – and analysing them according to a standard operating procedure. A pool deemed negative – below the applicable threshold – does not require further testing, and all samples are considered

17. Some studies suggest that EDTA whole-blood samples can be stored at room temperature for up to seven days, with negligible impact on RNA stability. These results only apply to samples with high viral loads (≥5000 copies/ml); thus, further investigation is needed for samples with low viral loads (≤5000 copies/ml).

Fig. 7.1. Sample transport considerations for scaling up access to viral load testing



[a] Although Abbott uses a reverse-transcription PCR technique, the extraction method is more RNA-specific, with about 90% RNA recovery from a sample to total nucleic acid, and co-amplification of DNA is therefore attenuated when dried blood spot samples are used.

below the threshold. A pool deemed positive – above the applicable threshold – will require individual testing of each patient sample. The number of tests saved will therefore depend on the proportion of "detectable" samples found. Further operational and clinical research is required to evaluate the feasibility of pooling in resource-constrained settings, particularly in high-throughput settings. Although this approach requires further validation for routine monitoring, it is already being used in Malawi.

Reduced frequency of testing

The cost–effectiveness of viral load testing in comparison to clinical or immunological monitoring is sensitive to the frequency of testing, with annual viral loads being more cost-effective than six-monthly viral load testing *(16)*. Current guidance recommends performing viral load monitoring routinely at month 6 following ART initiation and then yearly thereafter, and more frequent monitoring is not indicated. Currently, there is little evidence on the clinical impact of differing monitoring frequencies; however, as part of the phased approach to scaling up routine viral load testing, a decrease in frequency of monitoring may allow increased coverage *(17)*.

Reducing CD4 monitoring in the presence of viral load monitoring

CD4 testing remains necessary for the staging of immune status and vulnerability to opportunistic infections, and this information is frequently used to guide initiation of prophylaxis for opportunistic infections. For people receiving ART, an increasing number of countries are considering reducing or stopping the use of CD4 testing for treatment monitoring as a way to free up funds for scaling up viral load testing. A growing body of evidence suggests that people who have achieved a degree of immune reconstitution and who maintain viral suppression are unlikely to experience a

subsequent drop in CD4 count *(18)*. The latest ART guidelines issued by the Southern African HIV/AIDS Clinicians Society recommend that CD4 be checked initially and at 12 months after ART initiation; subsequent monitoring is through yearly viral load alone. This approach was endorsed by a recent WHO consultation on the changing role of CD4 cell counts in HIV care and treatment *(19)*.

Pricing

The prices of viral load testing vary considerably. Although the market is very fragmented, with a wide range of prices paid both within and between countries, the recent prices for viral load tests quoted to low-income countries average US$ 15 per test (including all reagents and consumables) and may even include complimentary instrumentation. Price negotiations are usually subject to confidentiality agreements such that pricing information per country is not publicly available, and many additional costs may be added to this, including distribution costs, tax or duties and procurement overhead.

Comprehensive test price calculations should include laboratory overhead, human resource expenses, maintenance costs, consumables required for the test but not included in the kit, sample collection consumables, sample transport costs and data management costs. Some countries have been able to negotiate price decreases with manufacturers using a combination of competition between manufacturers and volume scale-up – to prices as low as US$ 10 per test (including all reagents and consumables) – volume discounts may increase as scale-up occurs, and preliminary work suggests that manufacturing costs can be further lowered through economies of scale *(20)*.

Using early infant diagnosis to scale up viral load testing

Traditionally, early infant diagnosis has been performed using a qualitative virological test for HIV DNA. However, several molecular platforms are now available that are more automated and sensitive and can do DNA or RNA testing or total nucleic acid testing. The advantage of using reverse-transcriptase quantitative PCR is that the quantitative result will be more informative for clinicians since a baseline viral load in infants will be established as part of monitoring treatment efficacy.

Although the same platform can be used for both quantitative and qualitative PCR, some platforms will require running different batches for each test type, since plasma and dried blood spot samples may not be able to be tested simultaneously in all platforms; for example, the Roche COBAS® AmpliPrep/COBAS® TaqMan® (CAP/CTM) version 2 allows simultaneous testing of plasma and dried blood spots, but the Abbott and other platforms do not. Similarly, the combined testing volume for HIV viral load and early infant diagnosis testing required on the same platform needs to be considered to maximize efficiency and the turnaround time of the results. For example, if viral load and early infant diagnosis samples must be batched separately, and early infant diagnosis testing is typically much lower throughput – although more urgent – than viral load testing, operational space will need to be made for early infant diagnosis testing in between batches of viral load samples while still trying to maximize the efficiency of processing. Alternatively, should a national programme have more than one instrument available, individual platforms could be dedicated to either early infant diagnosis or viral load testing.

Options for phasing in viral load testing

Several approaches for phasing in viral load testing capability can be considered depending on patient load, sample transport constraints, financial resources and equity considerations. Phase-in could be achieved in several ways, depending on the country-specific challenges to scaling up. Depending on the context, a mix of approaches may be used.

Confirming treatment failure

In situations in which sample transport concerns are not the prime factor and viral load capacity is limited, the first priority should be to confirm viral failure in patients with suspected treatment failure due to clinical progression or significant deterioration in immune status. WHO has put forward criteria for defining treatment failure based on clinical and immunological grounds but recognizes that these criteria have low specificity and sensitivity for predicting viral failure. Confirmatory testing using a viral load test is therefore important to avoid unnecessary switching to second-line treatment.

Routine viral load testing

Current WHO guidelines recommend that viral load be checked after six months on ART and yearly thereafter to enable earlier and more accurate detection of treatment failure *(2)*. Challenges, particularly in sample transport, may lead to selecting specific populations for the initial roll-out of routine viral load testing, although a blend of strategies may be chosen in practice.

Geographical tiered approach

To establish laboratory capacity, specimen collection and result delivery, internal and external quality assurance and adequate training of clinical and counselling staff, a tiered

approach to phase-in may be chosen. Health facilities with easy access to laboratories with existing or easily implemented viral load testing capability could be chosen to implement routine viral load testing, with a gradual decentralization to peripheral sites once systems are established and practical implementation lessons learned. Such an approach will allow for a stepwise approach to training, sharing of experiences in implementation and avoid multiple facility-specific changes in messaging for health staff on viral load testing algorithms.

Phasing in according to target populations

An alternative approach to phasing in routine viral load testing could be to target specific populations at higher risk. Children, adolescents, pregnant or breastfeeding women and people identified as being at higher risk for early poor adherence might benefit selectively from receiving routine viral load testing if capacity does not exist for monitoring everyone receiving ART in the initial phases. Depending on the setting, a combination of approaches may be preferred.

Pregnant women. Higher maternal viral load is associated with elevated antenatal and postnatal transmission, with an estimated 29% greater transmission rate for every $\log_{10}$ unit increase in viral load *(21)*.

Children and adolescents. Rates of viral failure tend to be higher among children and adolescents than among adults *(22)*. Identifying the children with viral failure early would enable them to receive more targeted adherence interventions, or changes in regimen, early.

Identification of early poor adherence. Poor adherence soon after initiating ART has been found to predict short- and long-term viral failure *(23)*. Early identification through viral load testing and intensive adherence intervention may prevent the future development of resistance and decrease the time before switching treatment.

Targeting specific populations still requires functioning sample transport systems for all sites, training and supervising all site staff members and clinical staff being able to systematically identify the subgroups requiring monitoring. Where ART care has been task-shifted to lower-level health workers and/or extensively decentralized, top-down roll-out may be the better option, since it does not add the programmatic complication for clinicians to triage access within a specific facility.

Emerging technologies – point-of-care viral load testing

Viral load testing has been confined so far to centralized laboratories and performed by trained laboratory technicians. Although some platforms are highly automated, the availability of point-of-care viral load technologies in the coming years will provide increased opportunities for viral load testing at the district or primary care level. Table 7.1 outlines the main issues for national programmes to consider when deciding whether to introduce point-of-care technologies, once available, for routine viral load testing, in addition to centralized testing. The decision-making will be affected by the specifications of the particular point-of-care platform that is chosen.

Point-of-care testing for early infant diagnosis could allow ART initiation for infants on the same day of HIV testing and diagnosis, a critically important issue because of the high risk of mortality associated with HIV infection among infants. Point-of-care testing can reduce the risk of loss to follow-up before diagnosis, whether exposed infants are tested at birth or at 4–6 weeks *(24)*.

Once point-of-care testing is widely available and validated, programme managers will need to make judicious choices regarding the balance between point-of-care and more centralized laboratory viral load testing.

When a point-of-care technology is being considered, the total number of sites requiring viral load testing and the daily throughput of each individual site need to be assessed, including workload considerations for the clinical staff. If throughput at a given site is very low, it may not justify the investment required to install and maintain a point-of-care device. Similarly, in settings with a high prevalence of HIV infection, where a single point-of-care test at the clinic or district level is unlikely to meet daily throughput needs, and many instruments would place an undue burden on staff, a high-throughput laboratory-based instrument at provincial level may be the preferred choice. Policies to allow task shifting of laboratory tasks to nurses and lay workers will facilitate the use of point-of-care devices at the health facility level, accompanied by appropriate training and supervision.

Comparative costing studies should be undertaken to inform these decisions. The price per test is minimized when instruments are used efficiently; if a point-of-care test can be performed eight times per day but would only be used twice per day at clinic level, then it may be better to install the point-of-care test at the district level to process samples from several clinics per day.

Table 7.1. Programmatic considerations for different tiers of the health care system for viral load monitoring

	Centralized or partly decentralized laboratory-based viral load testing	Point-of-care viral load testing
Advantages	• Provides high-throughput testing • Facilitates the storage and analysis of results in a centralized database • An existing sample collection and result delivery system could be used • A centralized approach simplifies quality assurance • Fewer machines mean fewer maintenance contracts and simpler supply chain for reagents and commodities	• Same-day result for patient at time of testing • No sample transport but a result delivery system required • Simplicity allows task-shifting to low cadres More suitable in: • Low-throughput settings • Restricted number of treatment sites • Sites that will be difficult to reach via sample transport • Vulnerable groups for treatment failure (such as children and adolescents or populations at high risk of loss to follow-up)
Disadvantages	• Sample transport and result delivery system has to be established • No immediate result • Batch testing required • Cost per test linked to the efficiency of testing (preferably using the instrument at least at 50% capacity) • Skilled laboratory staff required • Preventive maintenance may be costly	• Widespread training, supervision, supply chain, quality assurance, maintenance and connectivity for central reporting are required • No experience with viral load point-of-care use to date • Cost (not currently determined) • Increased workload for already overloaded health care workers due to task shifting • Limited number of tests per day

Procurement

Laboratory test quality relies on the availability of laboratory equipment, reagents and consumables that meet minimum quality standards as well as a quality assurance policy, including quality assurance policies established by funding agencies. In an effort to enhance quality and promote efficient resource use, equipment selection should be standardized wherever possible in a tiered laboratory network *(25)*. The health ministry should define harmonization and procurement policies in collaboration with clinicians, laboratory staff and policy-makers. Standardizing the type of platform for viral load testing across different laboratory levels offers many benefits. Ideally, a list of prequalified vendors would be established based on WHO guidelines and/or the list of products from the WHO prequalification of diagnostics. A team of laboratory technicians should provide input, and along with procurement specialists, should develop technical specifications for equipment acquisition. It is advisable to include at least two different platforms on the national approved procurement list to avoid problems in case of quality or distribution issues, and to account for differences in capacity between laboratory tiers within a decentralized viral load testing network. Post-procurement, national quantification and forecasting should be performed to inform future budgeting and procurement.

A local service provider should be available to facilitate training and support, either in the form of local representatives of the company or a third party designated by the manufacturer for procurement, training and maintenance.

It is advisable to investigate whether a local or regional office is available for the product of interest and to negotiate a favourable maintenance contract with the manufacturer. If national and/or donor regulations permit, an instrument leasing option or reagent rental option may be preferable to purchasing expensive instrumentation outright. This option will also allow for end-user flexibility to adopt newer and more efficient technologies as they emerge in the market.

In settings in which molecular testing for multiple pathogens is required, a polyvalent platform may be the preferred choice. Most manufacturers of commercially available laboratory-based platforms (such as Abbott, bioMérieux, Qiagen, Roche, Siemens, Biocentric and Cavidi) offer multiple kits for different diseases: typically HIV DNA (for early infant diagnosis), hepatitis B and C, human papillomavirus, chlamydia and gonorrhoea, for use on their single molecular instruments (Annexes 7.1 and 7.2). Point-of-care instruments will initially be sold for single use, but there are plans to design additional test cartridges for other diseases, such as TB or hepatitis B and C. The GeneXpert instrument by Cepheid offers a substantial test menu already, with a robust pipeline for the future.

Open platforms can be used on various real-time PCR instruments, thereby allowing other tests to be run on the same platform. Open platforms offer the possibility for ordering reagents and instrumentation separately and from multiple manufacturers. This has the advantage of both sourcing the best-priced item and optimizing the test for best performance in the particular population where it will be used. For example, viral load testing must be able to detect all HIV subtypes and circulating recombinants that are present locally. A limitation of this approach is that, once optimized, the test must be standardized for routine use and for submission to a strict regulatory authority.

Although current real-time PCR technologies are comparable in terms of analytical performance (lower limit of detection, linear range and HIV subtype detection), they differ in terms of technology used, level of automation, throughput capabilities, costs, infrastructure and human resource requirements and ability to process different sample types. These differences are important considerations for implementing and scaling up of viral load testing nationwide.

Preparing for second-line ART as treatment failure is diagnosed

A major programmatic challenge associated with scaling up viral load monitoring is the likely increase in identification of treatment failure and the need to budget for more expensive second-line ART. Even in settings in which targeted viral load is used, programmes have not reliably switched those diagnosed with viral failure due to ongoing adherence concerns, poor implementation of the clinical algorithm or loss to follow-up *(26)*. Establishing an effective decentralized approach to switching to second-line therapy should be part of any strategy for scaling up viral load testing. Job aids and training of clinicians on the use of second-line regimens for both adults and children are needed to ensure familiarity with second-line regimens.

Preparing health providers

Successfully rolling out routine viral load testing requires appropriate action by health providers, for which training and supervision are critical. User-friendly clinical algorithms and simple schematics are useful to assist health care providers in ensuring that people living with HIV are routinely tested for viral load and that the results are acted on appropriately. In addition, adequate supervision, through monitoring and evaluation and site visits, is needed to ensure that the treatment failure and second-line therapy algorithms are systematically implemented. Providing laboratory-generated lists of people receiving ART with viral load >1000 copies/ml to clinic coordinators and programme supervisors may aid follow-up to ensure that the people who will benefit from intensified adherence interventions or initiation of second-line therapy are being managed appropriately.

Preparing counsellors

The algorithm recommended in the WHO 2013 consolidated guidelines proposes that an adherence intervention be implemented for the people receiving ART with a viral load >1000 copies/ml. Although many countries have adopted this principle, the types, intensity and uptake of adherence interventions vary. The ART clinic team should clearly identify who is responsible for addressing adherence barriers for those patients who have detectable viral loads.

Principles of enhanced adherence counselling

Based on the workload of the staff providing adherence support and their competencies, the number of sessions, the mode and the content should be adapted. Adequate monitoring and supervision of the implementation of the enhanced adherence intervention are essential for effective roll-out. Adherence interventions are context-specific and need to be adapted to the local resources available *(27)*. Enhanced adherence support interventions should aim to identify the behavioural, cognitive, socioeconomic or emotional problems affecting people's adherence. At the same time, individualized strategies should be identified with the person to overcome these barriers. Ideally, follow-up counselling over a further one or two sessions should be provided to evaluate strategies implemented by the person living with HIV.

Preparing people living with HIV

Patient literacy on the need for and interpretation of viral load to monitor their treatment response is essential to support the demand for viral load and is likely to aid adherence. For many people, changes in CD4 values have been the way to understand treatment efficacy, and changing this paradigm will require concerted patient literacy and counselling, both within the clinic and from community-based awareness-raising. Visual tools to explain the concept of viral load may aid understanding as well as having clear written instructions on patient-held records as to when viral load should be tested *(28)*.

Establishing a viral load implementation plan

Viral load testing may be scaled up nationally, regionally or within a specific referral hospital laboratory and primary health centre network. A situational analysis should be performed to identify existing capacity, utilization and need. There are key steps that programme planners, laboratory workers, clinical manager and other service providers can then follow to ensure that a comprehensive scale-up plan is developed and implemented (Fig. 7.2).

Fig. 7.2. Steps for rolling out viral load testing at the national level

	Implementation plan for viral load testing	Year 1				Year 2			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Coordinate efforts and define priorities	Internal consultation within the health ministry and consultation with laboratory national strategic plan								
	Consultation with donors and partners: funders, suppliers, laboratories, clinicians and economists								
	Establish working group, analyse prevalence for selecting sites and adapt clinical algorithm								
	Develop funding proposal								
	Develop a pilot and phased plan: analyse strengths, weaknesses, opportunities and threats								
	Develop a procurement plan and negotiate with suppliers								
	Assess the human resources required: laboratory and clinical								
	Verify instruments when required								
	Set up or improve systems for transporting samples and delivering results (SMS)								
Prepare sites	Prepare training materials, standard operating procedures, external quality assessment and instrument interface								
	Modify the database to handle viral load results								
	Sensitize provincial and city hospitals about the viral load testing programme								
	Pilot viral load accreditation criteria at provincial and city hospital laboratories								
	Select initial sites to begin routine viral load testing and enhanced adherence counselling								
	Pilot enhanced adherence counselling at selected sites								
	Pilot viral load training at selected sites								
Initiate sites	Install instruments and laboratory information system and verify instruments								
	On-site training and parallel clinic training								
Build capacity for training (laboratory and clinic) support resources	Commence testing at sites								
	Transport coordination and system for delivering results								
	Biweekly meeting with the laboratory team and the supplier								
Monitoring and evaluation framework Collect data and evaluate the project	Monthly monitoring and evaluation								
	Data analysis, instrument use and quality control								
	Monthly and quarterly report and review of plans								
Scale up viral load testing	Initiate routine viral load testing in more clinics								
	Initiate further viral load testing laboratories								

ANNEX 7.1.

Operational characteristics of the most common automated molecular HIV RNA viral load platforms

Company	Abbott	bioMérieux	Roche	Siemens	Biocentric
Assay	RealTime HIV-1 assay	NucliSENS EasyQ HIV-1 v2.0	COBAS Ampliprep/ COBAS TaqMan HIV-1 monitor v2.0	VERSANT HIV-1 RNA 1.0 assay (kPCR)	Generic HIV viral load assay
Principle	RT-qPCR	NASBA	RT-qPCR	RT-qPCR	RT-qPCR
Storage of EDTA blood before testing	≤6 h (15–30°C) or ≤24 h (2–8°C)	≤24 h (15–30°C)	≤6 h (2–25°C)	≤6 h (15–25°C)	≤6 h (2–25°C)
BD plasma preparation tubes validated	Yes	No	Yes	Yes	No
Storage of plasma preparation tubes before centrifugation	6 h (2–25°C)	Not applicable	6 h (2–25°C)	≤6 h (15–25°C)	Not applicable
Storage of plasma preparation tubes after centrifugation	Frozen in situ until testing	Not applicable	5 days at 25°C	5 days (4–8°C)	Not applicable
Extraction automation	+++	++	+++	+++	+++
Amplification automation	++	+	+++ (with docking station)	++	+
Number of tests in one run	M2000sp: 96 M24sp: 24 M2000rt: 96 (93 test samples)	EasyMAG: 24; EasyQ: 48 (46 test samples)	Ampliprep: 21 test samples; Taqman 48: 48 (42 test samples); Taqman 96: 96 (84 test samples)	SP module: 96 (89 test samples) AD module: 96 (89 test samples)	Nordiag Arrow: 12Thermocycler: 96 (82 test samples)
Number of plasma tests in one day (8-h shift)	279	EasyMAG: 168 (lysis on board workflow) / 240 (lysis in tube workflow); EasyQ: 192	Taqman 48: 100; Taqman 96: 250	178	192
Regulatory approval	WHO PQ, CE-IVD, US-FDA-IVD, Canada-IVD, CFDA (plasma)	WHO PQ, CE IVD (plasma and EDTA DBS)	WHO-PQ, CE-IVD, US-FDA-IVD (not m24sp), Canada-IVD, Japan-IVD (plasma)	CE-IVD (plasma)	Commercialized but currently research use only (WHO PQ and CE mark in process)
Cost of the test in resource-limited settings	US$ 25, subject to negotiations	US$ 24	US$ 11–25 (applicable to all least developed countries or countries in sub-Saharan Africa with a high burden of HIV infection, otherwise US$ 35–90)	US$ 54–72	US$ 16
Approximate cost of equipment (extraction and amplification)	US$ 200 000	US$ 150 000	US$ 250 000	US$ 200 000	US$ 55 000 (US$ 70 000 with two automated nucleic acid extractors)

Company	Abbott	bioMérieux	Roche	Siemens	Biocentric
Rooms or work areas needed	2	2	Taqman 48: 2 Taqman 96: 1 (with docking station, otherwise 2)	2	2
Technology applicable for dried blood spots qualitative DNA-PCR (using the early infant diagnosis kit)	Yes	No	Yes	No	Yes
Regulatory approval for dried blood spots viral load	No (research use only)	Yes	No (research use only)	No (research use only)	No (research use only)

Source: *Putting HIV treatment to the test (29).*

WHO-PQ: WHO prequalification. CE-IVD: CE marking for in vitro diagnostic medical devices. US-FDA-IVD: United States Food and Drug Administration for in vitro diagnostic medical devices.

ANNEX 7.2

Polyvalency of currently available commercial viral load platforms

Tests commercially available	Abbott (m2000)	BioMérieu (EasyQ)	Qiagen (QS-RGQ)	Roche (CAP/CTM)	Siemens (VERSANT kPCR)
HIV quantitative RNA (viral load)	Yes	Yes	Yes	Yes	Yes
HIV qualitative (early infant diagnosis)	Yes	No	No	Yes	No
Mycobacterium tuberculosis	No[a]	No	Yes	Yes	No
Hepatitis B virus	Yes	No	Yes	Yes	Yes
Hepatitis C virus	Yes	No	Yes	Yes	Yes
Chlamydia trachomatis and *Neisseria gonorrhoeae*	Yes	No	Yes[b]	Yes[b]	Yes

[a] In development.

[b] For chlamydia only.

8. PHASING OUT STAVUDINE: PROGRESS AND CHALLENGES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery

Key message

- Countries should discontinue initiating new people on d4T-containing regimens and accelerate the pace of phasing out the use of d4T in people who have already initiated ART.

Introduction

In 2010, WHO guidelines for antiretroviral therapy *(1)* recommended that countries take steps to progressively reduce the use of stavudine (d4T) because of its well-recognized toxicity. This recommendation was supported by a WHO technical brief issued in 2010 *(2)* that outlined several guiding principles for phasing out d4T.

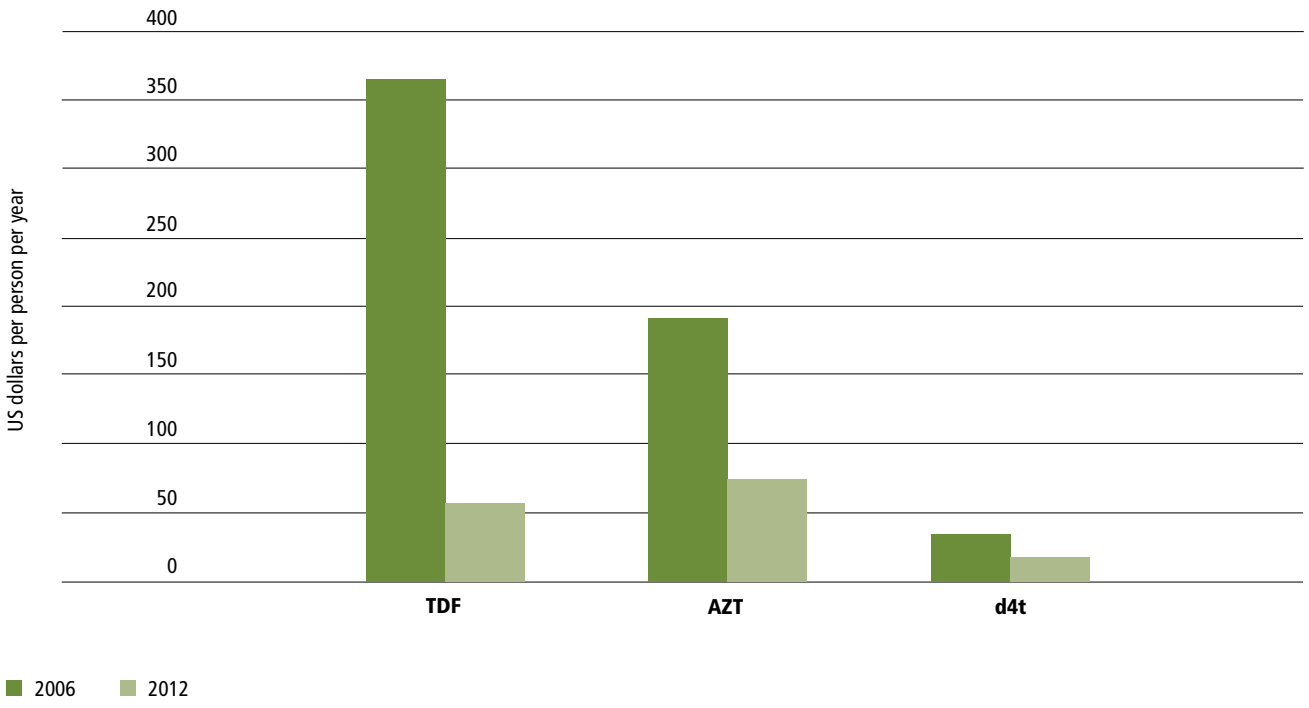
Since that time, most countries have moved towards phasing out d4T, but progress is varied and consumption overall remains high. At the same time, there is a growing appreciation of the need to move towards standardized, more tolerable and robust regimens to support the next phase of scaling up of antiretroviral therapy (ART). In 2013 WHO issued consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(3)* that further simplify the regimen choices for all groups of people living with HIV.

This section provides an overview of the evidence supporting the 2010 d4T phaseout recommendation, outlines progress to date and summarizes the main challenges and potential solutions for countries to reach the goal of completely phasing out the use of d4T in first-line ART.

Why phase out d4T use?

The fact that d4T use is associated with important types of toxicity has been known for some time. WHO guidelines for antiretroviral therapy as early as 2003 recognized that among the nucleoside reverse-transcriptase inhibitors (NRTIs), d4T was most consistently associated with metabolic toxicity and long-term complications, in

Fig. 8.1. Trends in antiretroviral drug prices, 2006 and 2012



Source: Global Price Reporting Mechanism, AIDS Medicines and Diagnostics Service, WHO, 2013.

particular lipoatrophy, peripheral neuropathy and lactic acidosis. Since that time, an accumulation of evidence and experience from resource-limited settings has highlighted the problems associated with d4T use within a simplified public health approach to scaling up ART *(4–8)*. Nevertheless, the low cost and simplicity of d4T-containing regimens led to it becoming one of the most widely used ARV drugs, with over half of all people taking first-line ART in low and middle-income settings receiving d4T in 2010 *(2)*.

In late 2006, WHO issued advice recommending that countries switch to a lower dose of d4T (30 mg) as a way to minimize side effects. Although this lower dose resulted in some improvement *(5)*, the overall frequency of side effects remains high and increases with longer use of the drug *(4,9)*. An accumulation of evidence from low- and middle-income countries has demonstrated the negative programmatic effects of d4T toxicity in terms of increased regimen substitution, treatment interruption, suboptimal adherence and the need for expert clinical supervision. This evidence, combined with the substantial price reductions in ARV drugs in recent years, has reinforced the imperative to replace d4T with less toxic alternatives, such as tenofovir (TDF), in first-line antiretroviral therapy (Fig. 8.1).

Risk of severe and life-threatening toxicity

The 2010 WHO recommendation was based on the acknowledgement that cumulative exposure to ART has the potential to cause disfiguring, painful and life-threatening side effects, such as lipodystrophy, peripheral neuropathy and lactic acidosis *(10,11)*, often associated with long-term d4T use *(12)*. Similar safety concerns exist for adolescents, children and infants. In Europe and the United States, d4T use has declined sharply during the past decade *(13)*, and its use today is restricted to people for whom there are no appropriate alternatives and for the shortest possible time *(11)*.

Increased regimen switches

d4T is associated with the highest rate of toxicity-driven substitutions *(14)* of all ARV drugs, which can be more than 10 times higher than for most other ARV drugs *(15)*. In South Africa, 21% of the people taking d4T had changed to another drug within three years due to symptomatic hyperlactataemia (5%), lipodystrophy (9%) or peripheral neuropathy (6%) *(16)*. In Lesotho, people taking d4T were almost six times more likely to experience a toxicity-driven switch than people taking TDF *(17)*. In Botswana, treatment-modifying toxicity strongly predicted death and was most commonly associated with d4T regimens *(18)*. In Cambodia, more than 90% of the people taking d4T had switched from it within six years of initiating therapy due to toxicity *(19)*, mainly due to lipoatrophy *(8)*.

Suboptimal adherence and treatment interruptions

Drug toxicity is a recognized cause of non-adherence to medication *(20)*. A systematic review of barriers to adherence reported by medication users found that 11% stated that side effects were a barrier to adherence, and 12% reported that complicated regimens were challenges to adherence *(21)*. d4T use has specifically been associated with increased likelihood of non-adherence *(22,23)* and defaulting from care *(24)*. In addition, drug-related toxicity is the leading cause of treatment interruption, accounting for more than one third of all treatment interruptions reported in a systematic review of the issue *(25)*.

Limited monitoring capacity

It has been suggested that d4T use could be continued with close monitoring of toxicity to save drug costs. However, the high rates of regimen substitution suggest that this is not cost-effective in the long run. Moreover, capacity for toxicity monitoring remains limited in many settings with a high burden of HIV. A study from Malawi found substantial underreporting of side effects, suggesting that the true incidence of toxicity of d4T in clinical practice may be underreported *(26)*.

Limited monitoring capacity has also been reported as a reason for the slow phasing out from d4T to preferred regimens. In Lesotho, patients in health centres were more than twice as likely to be receiving a d4T-based regimen compared with those in hospitals, and this was partly explained by the challenge of assessing baseline creatinine before switching people from d4T to TDF *(27)* (despite this not being a requirement according to WHO guidelines *(3)*). Another report, also from Lesotho *(28)*, found that use of d4T decreased significantly once nurses were provided with simple algorithms to support the management of TDF; the use of TDF instead of d4T was found to facilitate task shifting and decentralization, since less clinical management was required.

Earlier initiation of ART

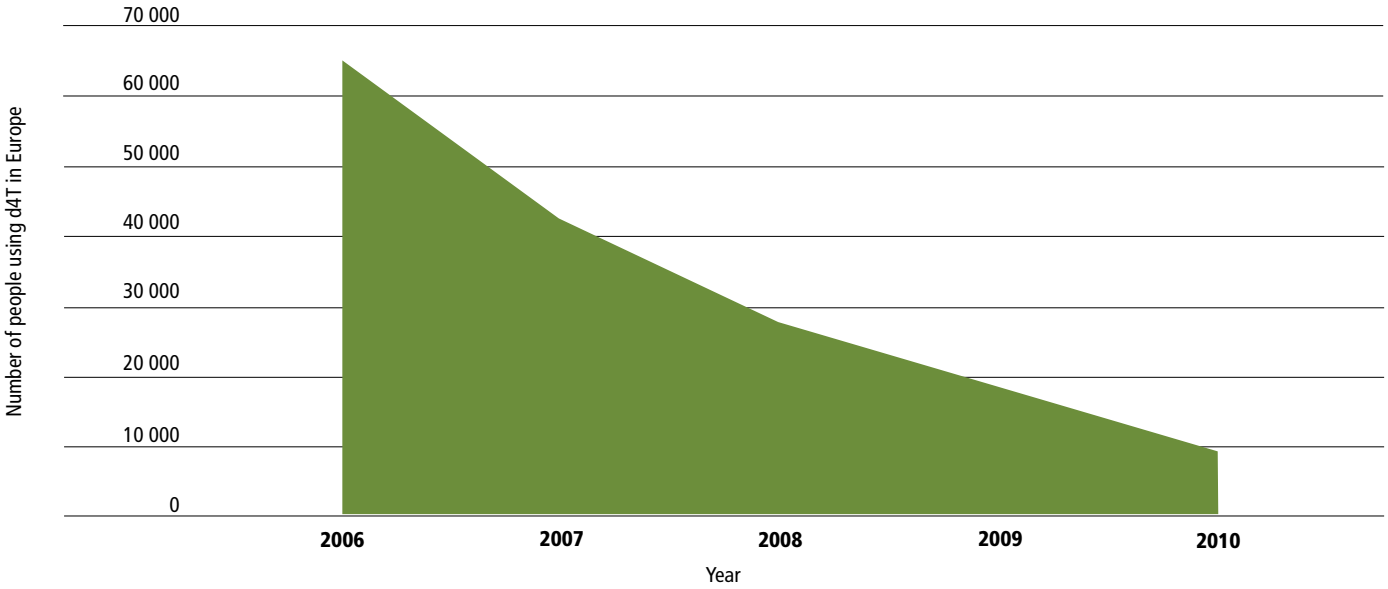
Risk–benefit considerations for providing ARV drugs to people earlier in the course of their disease need to take into account the potential harm of exposing people to medicine toxicity *(29)*. Following a systematic review of the evidence regarding morbidity and mortality, the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(3)* now recommend that countries move towards earlier initiation of ART for clinical benefit, at CD4 <500 cells/mm^3. These considerations become even more important when the main reason for initiating therapy is not for the person's own health but to prevent HIV transmission to others. An

accumulation of evidence in the last few years has led to WHO recommendations for preventing HIV transmission in serodiscordant couples even at higher CD4 counts and preventing mother-to-child transmission and has been suggested for other groups at high risk of HIV infection *(30)*. Several countries are already in the process of revising initiation criteria to include treatment-as-prevention options. Earlier treatment, which leads to longer exposure to ARV, when considered, should be coupled with a move to less toxic regimens.

Progress in phasing out d4T use to date

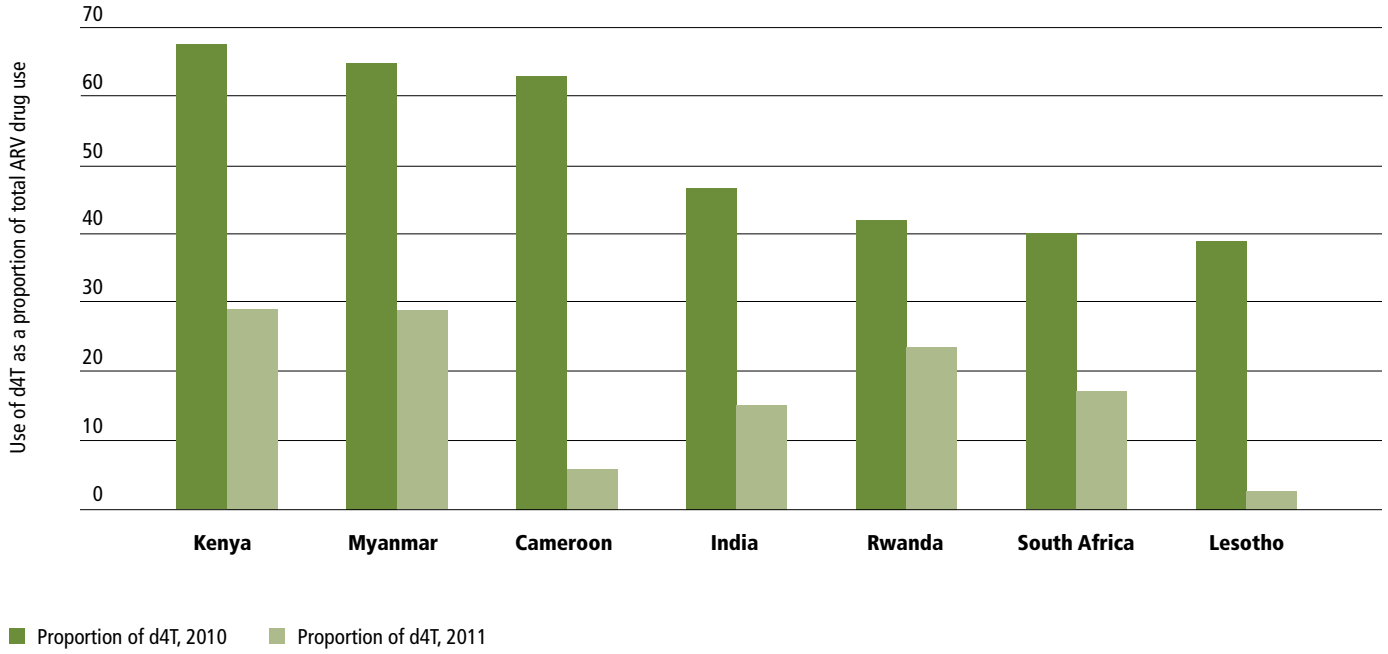
In higher-income settings, where regimen choices and resources are greater, d4T use has been progressively reduced during the past decade. Between January 2005 and March 2010, an estimated 56 000 people were exposed to d4T in Europe (Fig. 8.2). This is less than the total number of people initiating d4T in Zambia in 2011 (64 552) and highlights the fact that d4T use has largely been confined to resource-limited settings for many years.

Fig. 8.2. d4T use declines in Europe, 2006–2010



Source: data from: CHMP renewal assessment report: Zerit® (stavudine). London, European Medicines Agency, 2011.

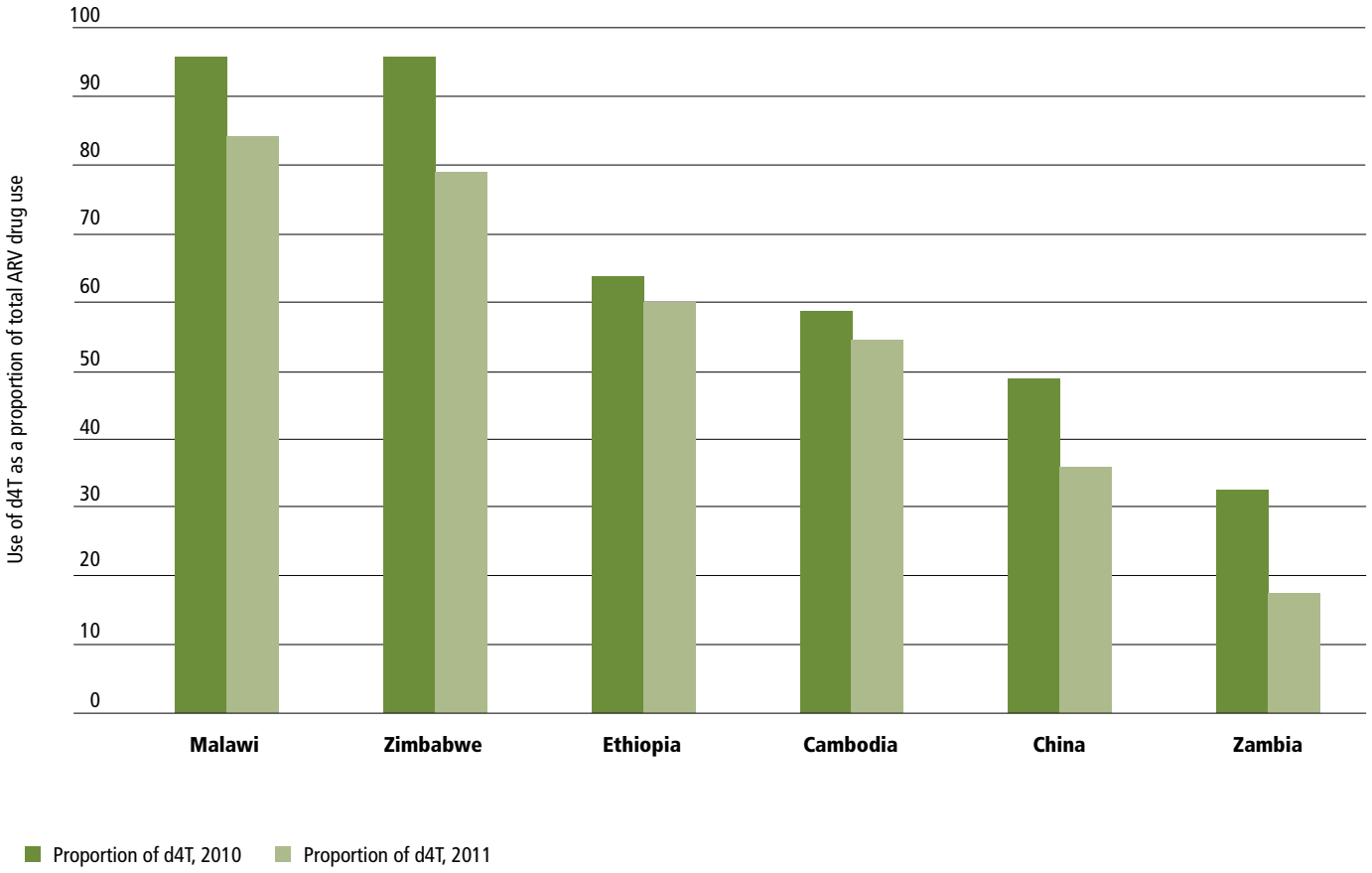
Fig. 8.3. Countries reducing d4T use >50% between 2010 and 2011



Source: WHO annual global antiretroviral survey, 2012.

Since 2010, most countries have reduced the proportion of people initiating d4T-based regimens. However, the rate of change has differed markedly in different countries. Fig. 8.3 and 8.4 show the change in use of d4T in some key countries between 2010 and 2011. Some countries (such as Cameroon, Kenya and Zambia) made further progress in phasing out d4T in 2012, but in a few countries with a high burden of HIV, d4T continues to be prescribed to substantial numbers of people, and the continued scaling up of treatment has meant that, overall, the absolute number of people initiating d4T in 2011 increased compared with 2010.

Fig. 8.4. Countries reducing d4T use <50% between 2010 and 2011



Source: WHO annual global antiretroviral survey, 2012.

Despite progress, in 2011, 1.1 million people newly initiated d4T-based first-line regimens, the vast majority in resource-limited settings in Africa with a high burden of HIV infection.

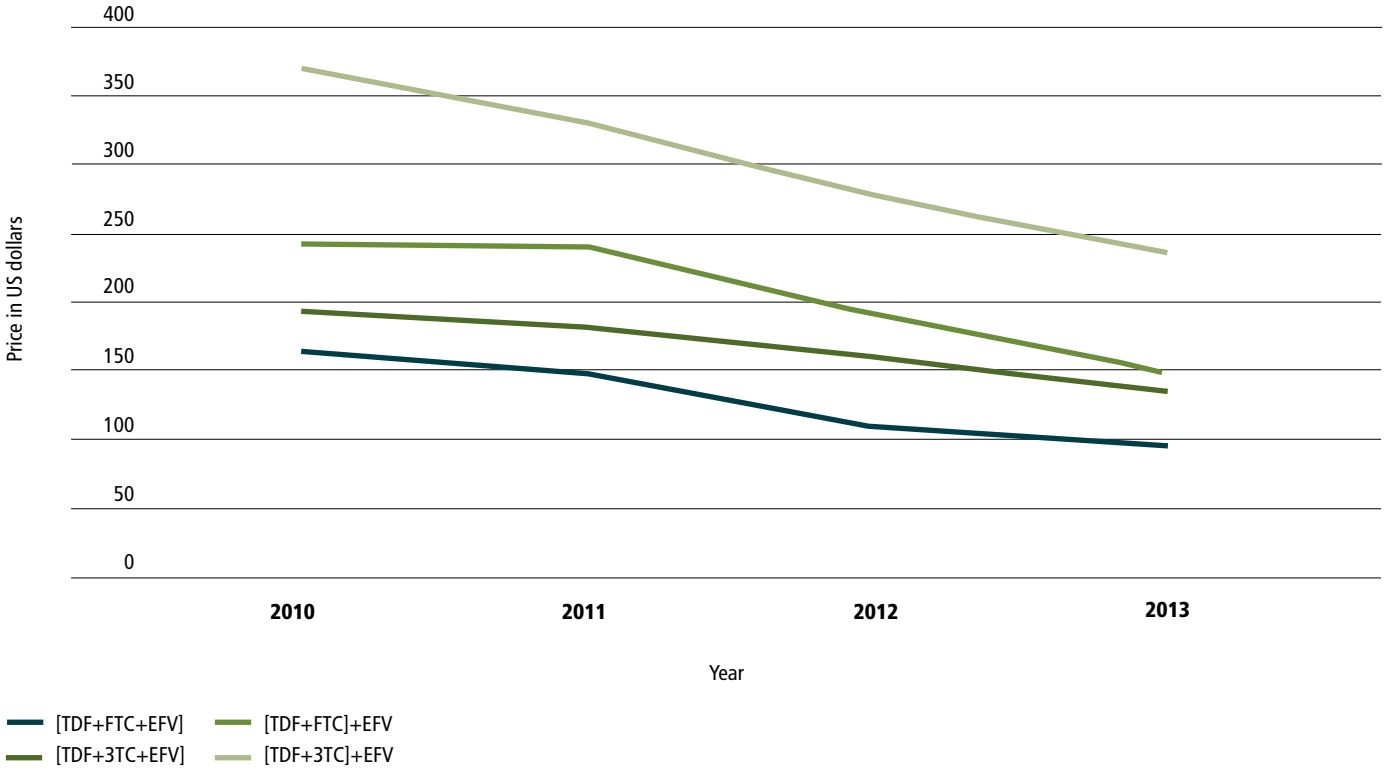
Overcoming challenges to phasing out d4T

Several countries have reported barriers to phasing out d4T. These include: the high cost of AZT or TDF compared with d4T *(31)*, uncertainties regarding whom to give priority to for phaseout *(32)*, the need for donor support *(33)* and the need to reduce stockpiles of d4T *(32)*.

Higher cost of alternative drugs

The speed of transition away from d4T has mainly been limited by the higher cost of the alternative drugs AZT and TDF. However, the cost of TDF-based regimens has declined substantially. The best available price for TDF globally has dropped from US$ 365 per person per year in 2005 to US$ 57 in 2012; similarly, the cost of TDF-combinations recommended by WHO for first-line therapy have all declined substantially in recent years (Fig. 8.5) *(34)*.

Fig. 8.5. Trends in the prices (in US dollars) of preferred antiretroviral drugs and regimens, 2010–2013



Although d4T remains the most affordable drug in terms of absolute cost, several studies have concluded that a switch away from d4T-based regimens is cost-effective if health service costs associated with managing side effects are considered. A study from South Africa concluded that d4T use was not cost-effective due to decreased quality-adjusted survival *(35)*. Similar results have been reported from Lesotho *(36)* and India *(37)*. In Myanmar, the higher cost of TDF was offset by the reduced need for laboratory tests and clinic visits *(38)*.

Uncertainty regarding which people to give priority to for phaseout

Several countries face the challenge of transitioning a large number of people from d4T, raising questions of who should take priority. From a clinical perspective, people with d4T related side effects and those coinfected with hepatitis B virus are most clearly going to benefit from an immediate switch to TDF (given the anti–hepatitis B virus properties of this drug). Beyond these two groups of people, there is no strong rationale for favouring certain groups over others, and while incremental phaseout may be necessary based on operational and feasibility considerations, the goal should be to move entirely away from d4T use and reserve it for use only in exceptional situations.

Funding the switch

Recently, the Global Fund for AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief have clearly committed to supporting countries in moving away from d4T. Programmes supported by the United States President's Emergency Plan for AIDS Relief already report a sharp decrease in the purchase of d4T in the past few years *(39)*. Existing donor grants have already been reprogrammed in several countries with a high burden of HIV, and this will facilitate phaseout.

To facilitate phaseout, countries should develop national plans that identify key priority groups for immediate change and include timelines for subsequent phaseout. The overall operational plan for phaseout should be costed, including estimates of additional domestic and external resources required to fund the switch.

Stockpiles of d4T

Stockpiles of d4T exist in several countries and are a major reason for slow phaseout. This challenge has been confronted in other disease areas: for example, when countries were recommended to shift away from chloroquine towards artemisinin-based combination therapy for treating

malaria *(40)*. Several countries used chloroquine stockpiles as buffers for delays in artemisinin-based combination shipments or in cases of stock-outs while progressively introducing artemisinin-based combination therapy into clinics across the country. Similarly, WHO recommends discontinuing ordering d4T-based formulations and that national stakeholders determine the future use of remaining stockpiles; one solution would be to reserve stocks for back-up situations for individuals who may require d4T in the absence of alternative choices.

Preferred ARV drugs for replacing d4T

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(3)* give preference to TDF over AZT for first-line ART regimens based on an accumulation of evidence and experience. Although both TDF and AZT are associated with toxicity, in countries in which both regimens have been used, TDF has been found to be the better tolerated regimen. AZT, like d4T, is a thymidine analogue, and although it is better tolerated than d4T, it has similar known metabolic and mitochondrial toxicity *(17,41)*. In Uganda, among people changed to AZT because of d4T toxicity, 6.6% subsequently had to be changed to TDF (3.4% because of anaemia and 3.1% because of failure) *(42)*. A review comparing TDF and AZT in first-line therapy found that TDF was superior in immune response and adherence, and resistance emerged less frequently *(43)*. Several studies *(44,45)* have assessed the comparative cost–effectiveness of WHO-recommended TDF and AZT-based first-line options and concluded that TDF is cost-effective *(46,47)*.

Finally, for people already receiving first-line therapy, switching from d4T to TDF is preferred over AZT when considering the potential for cross-resistance of mutations that are known to accumulate among people exposed to d4T *(48)*. A recent analysis of resistance mutations associated with d4T-containing ART from 35 cohorts *(49)* concluded that, in settings in which genotype resistance testing is not available, TDF is more likely to be effective than AZT.

Phasing out d4T among children

There has been some suggestion that d4T toxicity is less severe in children than adults. Studies from Uganda *(50)* and Cameroon *(51)* found no difference in the frequency of adverse events among children, comparing AZT- and d4T-based regimens. Nevertheless, about one third of the children experienced an adverse event on either regimen. Lipodystrophy was the most commonly reported adverse event, similar to other African cohorts *(52)*.

Until recently, concern about the limited number of formulations for children provided a potential justification for continuing to support d4T use in children. However, the number of approved formulations for children has increased in recent years, and with the recent approval of TDF for children ≥2 years, all NRTIs currently in use for adults are available for use among children. There is no longer a rationale for making different recommendations for children versus adults. This alignment of regimens as much as possible between children and adults to further simplify treatment has been endorsed through the treatment recommendations in the 2013 WHO guidelines *(3)*. Therefore, although d4T may be of use for individual children, as for adults, overall the WHO advice to phase out d4T applies equally to adults and children alike.

Phasing out other ARV drugs

Through the Treatment 2.0 strategy, WHO is promoting the rationalization of first-line ART to simplify procurement and prescribing and maximize health service efficiency. The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(3)* further simplify options by promoting a single, preferred first-line regimen based on TDF + XTC + EFV for adults and older children (>3 years).

According to data from the WHO sixth annual survey on the use of ARV drugs and diagnostics, the number of first-line ART regimens per country ranged from 4 to 38. In some regions, countries continue to procure ARV drugs that are no longer recommended as preferred options, such as indinavir, saquinavir and fosamprenavir *(53)*.

Although it is important to retain alternative regimens in case of poor tolerability or contraindications, countries are encouraged to develop phaseout plans for other drugs that may no longer be preferred to simplify and standardize first- and second-line ART as far as possible.

Conclusions

Since 2010, WHO has recommended that countries phase out d4T in favour of less toxic regimens. During the past two years, progress on phasing out d4T has been variable, with some countries making rapid and substantial progress and others taking a phased approach. Although countries face different barriers to phaseout, WHO recommends that countries discontinue initiating new people on d4T-containing regimens and accelerate the pace of phasing out d4T use in people already receiving ART, particularly the countries in which d4T remains the main first-line option and in which policies of earlier initiation of ART are being implemented.

9. TRANSITION TO NEW HIV TREATMENT REGIMENS – ISSUES RELATED TO PROCUREMENT AND SUPPLY CHAIN MANAGEMENT

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery

This section was developed to advise a phased approach to implementing partners, antiretroviral therapy programme managers, procurement managers and other relevant parties. The ultimate purpose is to ensure a continuous supply of antiretroviral (ARV) drugs and to ensure rapid and efficient implementation of the new WHO HIV treatment guidelines, with smooth transitioning to new recommended ARV regimens, while reducing the wastage or expiry of products that are no longer recommended.

Background

WHO's recent consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach *(1)* recommend a preferred treatment regimen based on tenofovir (TDF) in combination with lamivudine and efavirenz (TLE), or TDF with emtricitabine and efavirenz (TEE), preferably as fixed-dose combinations. Comparative systematic reviews showed that these two regimens are associated with less risk of severe adverse events and better antiviral and treatment response compared with other once- and twice-daily options currently available. Evidence also indicates that EFV has superior efficacy and tolerability to NVP, including when combined with TDF + 3TC (or FTC) as a once-daily regimen. In addition, WHO recommends that countries discontinue stavudine (d4T) as a preferred first-line option, because of its cumulative mitochondrial toxicity. The implementation of these new recommendations implies transition of the nearly 1 million people who were still receiving d4T at the end of 2012 to tenofovir-based regimens. A decision on how to deal with the 2 million to 4 million people who received zidovudine (AZT)-containing regimens and the 4 600 000–5 800 000 people receiving NVP-containing regimens is needed. As has been seen with previous regimen changes, any such major transition is a significant undertaking that requires careful procurement and supply chain management planning, coupled with clear guidance to inform prescribing practices.

The recommendations in support of option B+ in preventing mother-to-child transmission and adult treatment initiation at a CD4 count of 500 cells/mm^3 or lower, will also potentially increase the demand for ARV drugs.

Challenges

Three key challenges face the supply chain with these new recommendations.

1. The currently approved[18] suppliers of fixed-dose combination formulations of TEE and TLE expect that their production capacity will be sufficient to satisfy the increased demand for these formulations in 2014, as in 2013 new capacity to produce TLE and TEE has been brought on line. However, in the short term, their supply is still constrained, since buffer stocks held by countries that switched to TDF-based first-line treatment have not been built up yet.

2. At present, order to delivery lead times for TEE and TLE formulations are averaging 4–8 months, including manufacturing time and delivery to country.

3. Purchasers and implementing partners with people receiving d4T-, AZT-, and NVP-based regimens have stocks and orders in process that should be considered in the transition process to avoid the occurrence of stock-outs and also wastage or expiry of usable products.

Recommendations

Programmes should plan carefully and discuss with their suppliers the pace at which increased quantities of TDF- and EFV-based products can be made available. This will require a graduated process of transition. To ensure that supply is available to meet anticipated demand, a phased programme is highly recommended. Suggested approaches are the following.

1. Initiate new people eligible for antiretroviral therapy on TDF-based regimens, with preference for the fixed-dose combinations of TLE or TEE.

2. Transition people currently receiving d4T-based regimens to a TDF-based regimen:

- For people with clinical evidence of d4T-related toxicity: immediate replacement with TEE or TLE is recommended.

18. Either approved or tentatively approved by the United States Food and Drug Administration or prequalified by WHO.

- For people with evidence of treatment failure, shift to second-line treatment with TDF + 3TC or TDF + FTC plus LPV/r or ATV/r as recommended by the 2013 WHO guidelines *(1)*.

- For people with minimal or no d4T-related toxicity, replace the d4T-based regimen with TEE or TLE as soon as possible, in a phased programme to enable the use of current d4T stocks and orders. No new procurement orders of d4T-based formulations should be planned.

3. People currently receiving AZT- and/or NVP-based regimens to TEE or TLE should be transitioned in a phased programme to enable the use of current stocks and orders and taking into account the speed at which increased deliveries of TDF products can be ordered and delivered; in practice, it is suggested that national ART programmes consider the following sequence.

- For people with evidence of treatment failure, shift to second-line therapy with TDF + 3TC (or TDF + FTC) plus LPV/r or ATV/r (with monitoring of renal function) as recommended by the 2013 WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection *(1)*.

- For people with clinical evidence of AZT-related or NVP-related toxicity, immediate change to TEE or TLE is recommended. New procurement orders of AZT- or NVP-based formulations should be planned only in the context of alternative first-line and/or second-line therapy needs.

- For people developing TB while being treated with AZT + 3TC + NVP, switch to TLE or TEE immediately, since NVP is not recommended as a preferred option and using TEE or TLE reduces the pill count and increases adherence to HIV and TB treatment.

- For people without toxicity or treatment failure, replace with TEE or TLE as soon as possible. AZT is also associated with mitochondrial toxicity that can emerge more slowly than with d4T. EFV is clinically superior to NVP in terms of suppression of viral load and length of time to treatment failure; people taking an EFV-based regimen were also more likely to achieve antiviral success. In the absence of treatment failure, switching to a regimen containing TDF and EFV is not detrimental from the perspective of developing HIV drug resistance.

It should also be recognized that not all countries can transition at the same time or at the same pace and that they also differ in other aspects. In areas with a high prevalence of HIV-2 infection, for example, the procurement and use of two-drug fixed-dose combinations (TDF with 3TC, TDF with FTC and AZT with 3TC) might still be a preferred option, since this provides flexibility to combine the NRTI backbone with protease inhibitors in first-line therapy for people living with HIV-2. Advice on these challenges and on how countries and programmes can coordinate their transitions and product requirements is available from:

- WHO: AIDS Medicines and Diagnostic Service: Vincent Habiyambere (habiyamberev@who.int);

- United States of America Government: Supply Chain for Health Division, Office of HIV/AIDS at the United States Agency for International Development: Christine Malati (cmalati@usaid.gov), Mike Hope (mhope@usaid.gov) or for questions USGTx@usaid.gov;

- the Global Fund to Fight AIDS, Tuberculosis and Malaria: Martin Auton (Martin.Auton@theglobalfund.org) or Ade Fakoya (ade.fakoya@theglobalfund.org); and

- UNITAID: Taufiqur Rahman (rahmant@unitaid.who.int).

Conclusions

The transition to the new regimens will ensure that people receive the most effective treatment. This transition can be achieved if it is well planned and coordinated. Full transition cannot happen in all countries and across all groups of people living with HIV immediately, but the constraint on the supply side for the new TDF- and EFV-containing formulations has progressively become less critical. However, since their supply is still somewhat constrained, it is important to ensure that people do not risk treatment interruption. To achieve a smooth transition in as short a time as possible, without treatment interruption, significant collaboration between programme managers and their suppliers is essential.

10. TRANSITION TO 2013 WHO ANTIRETROVIRAL THERAPY REGIMENS FOR CHILDREN – PROCUREMENT AND SUPPLY CHAIN MANAGEMENT ISSUES

Key messages

- When available, age-appropriate fixed-dose combinations for any regimen are preferable for children.
- Oral liquid formulations should be avoided in favour of solid oral dosage forms when available.
- Dispersible tablets (also known as tablets for oral solution) are the preferred solid oral formulations
- Fixed-dose combinations of ABC + 3TC (60 mg + 30 mg) in both dispersible and non-dispersible scored tablets are available. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children (IATT) lists the dispersible formulation as the preferred option.
- Two formulations of LPV/r are available for use among young children: LPV/r 100 mg/25 mg heat-stable tablet for children >10 kg who are able to swallow whole tablets, and LPV/r oral liquid 80/20 mg per 1 ml for use among infants.
- Country programmes are urged to limit the procurement of ARV products for children to formulations included on the Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children.

This policy brief was developed to advise implementing partners, managers of antiretroviral therapy (ART) programmes, policy-makers and other relevant stakeholders on the current global availability of antiretroviral (ARV) drug formulations for children needed to implement the HIV treatment recommendations for infants and children living with HIV that are described in the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* at the national programme and facility levels. This policy brief provides information regarding the availability of preferred first-line formulations for children of abacavir (ABC), tenofovir (TDF) and lopinavir/ritonavir (LPV/r) included in the WHO 2013 consolidated guidelines and products being phased out of use.

Context

The WHO 2013 consolidated guidelines recommend preferred and alternative first-line ARV regimens for children as well as second-line regimens. In addition, although the guidelines in general recommend once-daily fixed-dose combinations, when possible, to facilitate procurement and supply chain management logistics, as well as adherence, additional logistic and programme factors should be addressed for national programmes to select optimal formulations. To ensure smooth implementation of the recommended first-line regimens for children and adolescents, it is critical for policy-makers and implementers to consider the availability of ARV formulations for children when determining appropriate specific drug formulation recommendations for children.

General principles in the selection of ARV products for children include age-appropriate fixed-dose combinations for any regimen when such a formulation is available. Oral liquid formulations should be avoided in favour of solid oral dosage forms when available; dispersible tablets (also known as tablets for oral solution) are the preferred solid oral formulations.

In light of continuing challenges of ensuring availability of ARV formulations for children, the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children provides guidance on optimal ARV products for children to promote a secure and sustainable supply. The group met in September 2013 to revise and update the 2011 Optimized Paediatric ARV Formulary *(2)*; Annex 10.1 presents an updated formulary.

Update of the availability of ARV formulations for children

Formulations of ABC for children containing fixed-dose combinations

a) ABC is now included among the preferred non-nucleoside reverse-transcriptase inhibitors (NRTI) for first-line ART among children younger than three years and as the preferred NRTI for children 3–10 years old in combination with lamivudine (3TC) and either LPV/r, nevirapine (NVP) or efavirenz (EFV).

b) Currently there are fixed-dose combinations of ABC + 3TC (60 mg + 30 mg) in both dispersible and non-dispersible scored tablets. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children lists the dispersible formulations as the preferred option.

c) To provide a complete regimen, the ABC + 3TC fixed-dose combinations must be combined with a suitable formulation of NVP, EFV or LPV/r.

Formulations of TDF for children

a) TDF is now approved by stringent national pharmaceutical regulatory agencies, including the United States Food and Drug Administration for use among children older than two years of age.

b) WHO recommends TDF-containing regimens as an alternative first-line regimen for children 3–10 years of age and as a preferred first-line regimen for adolescents older than 10 years and weighing more than 35 kg (in alignment with preferred first-line regimens for adults).

c) A TDF-containing fixed-dose combination for children is currently not available.

d) TDF is available in three different formulations for children for use across different weight bands. The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children lists the dispersible formulations as the preferred option (Table 10.1).

d) At present, TDF formulations must be combined with two additional single-component ARV formulations to achieve a complete regimen for people weighing less than 35 kg. This will significantly complicate the use of TDF-based regimens among children until a suitable fixed-dose combination becomes available.

Table 10.1. TDF dosing using currently available formulations for children

Weight band	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–29.9 kg	30–34.9 kg
Formulation	3 powder scoops	One 150-mg tablet	One 200-mg tablet	One 200-mg tablet	One 300-mg tablet

Formulations of LPV/r for children

a. WHO strongly recommends the use of LPV/r as part of first-line ART for all children living with HIV younger than three years.

b. Only two formulations of LPV/r are currently available for use among young children.
a. There is a LPV/r 100 mg/25 mg heat-stable tablet for children >10 kg who are able to swallow whole tablets. These tablets must be swallowed whole and must not be chewed, crushed or dissolved.
b. LPV/r oral liquid 80/20 mg per 1 ml can be used for infants; however, this has poor palatability and is not heat-stable. LPV/r oral liquid 80/20 mg per 1 ml should be shipped and stored between 2°C and –8°C. After dispensing, storage at 2–8°C is preferred, but the product can be kept at up to 25°C for up to two months.

Formulations for children pending approval

The following formulations have been filed for regulatory approval with the United States Food and Drug Administration; however, the timeline and outcome of this process cannot be predicted:

a. Fixed-dose combination tablets for children contain TDF + 3TC + EFV (75 mg/75 mg/150 mg).

b. A heat-stable formulation of LPV/r (40 mg/10 mg) pellets.[19] These heat-stable pellets are similar in formulation to the 100 mg/25 mg heat-stable tablets currently in use; the pellets must be swallowed whole and must not be chewed, crushed or dissolved. Safety and acceptability data from the CHAPAS-2 trial are available for ages two months to 12 years *(3,4)*.

c. Although new formulations are being developed, the time between regulatory approval and product availability in specific countries is unpredictable. Once the product obtains regulatory approval from a stringent regulatory authority, the steps for manufacturing commercial batches, adoption into national guidelines, national regulation and procurement processes must be taken into account.

Drugs being phased out

Didanosine (ddI)

a. ddI is no longer recommended as an alternative NRTI in adult or child second-line regimens because of toxicity, lower efficacy and inconvenient dosing requirements.

b. Countries should transition people currently receiving ddI to more optimal regimens as soon as possible. For example, 3TC can replace ddI in WHO-recommended second-line regimens.

19. This formulation has been referred to as a "sprinkle" or "minitab".

Stavudine (d4T)

a. d4T is no longer recommended for adults or children except in special circumstances in children when AZT cannot be used due to toxicity and ABC is not available.

b. Countries should transition people currently receiving d4T-based regimens to more optimal regimens as soon as possible.

Conclusions

The Optimized Paediatric Formulary of the Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers, and their Children has been updated based on the WHO 2013 consolidated guidelines. Countries are encouraged to limit the procurement of ARV drugs for children to the products listed on the Optimized Paediatric Formulary to simplify the supply chain and aggregate global demand to stabilize global supply of ARV drugs for children.

ANNEX 10.1.

Optimal and limited-use lists of ARV formulations for children

Optimal

Drug class (or fixed-dose combination)	Product	Formulation	Dosage	Rationale for being on the list
NRTI	AZT	Oral liquid	50 mg/5 ml	For use in preventing mother-to-child transmission
NNRTI	EFV	Tablet (scored)	200 mg	
NNRTI	NVP	Tablet (dispersible, scored)	50 mg	
NNRTI	NVP	Oral liquid	50 mg/5 ml	For use in preventing mother-to-child transmission
Protease inhibitor	LPV/r	Tablet (heat-stable)	100 mg/25 mg	
Protease inhibitor	LPV/r	Oral liquid	80 mg/20 ml	
Fixed-dose combination	AZT + 3TC	Tablet (dispersible, scored)	60/30 mg	
Fixed-dose combination	AZT + 3TC + NVP	Tablet (dispersible, scored)	60/30/50 mg	
Fixed-dose combination	ABC + 3TC	Tablet (dispersible, scored)	60/30 mg	
Fixed-dose combination	ABC + 3TC + AZT	Tablet (non-dispersible, scored)	60/30/60 mg	

Limited-use

Drug class (or fixed-dose combination)	Product	Formulation	Dosage	Rationale for being on the list
NRTI	3TC	Tablet (dispersible)	30 mg	To be used with TDF single formulation
NRTI	TDF	Oral powder[a]	40 mg/scoop	For use in special circumstances when ABC or AZT cannot be used or for people with hepatitis B, until an appropriate fixed-dose combination becomes available

[a] Product is administered as an oral powder, not reconstituted with liquids.

Drug class (or fixed-dose combination)	Product	Formulation	Dosage	Rationale for being on the list
NRTI	TDF	Tablet	150 mg	See above
NRTI	TDF	Tablet	200 mg	See above
NNRTI	ETV	Tablet	25 mg	Special circumstance in third line where appropriate
NNRTI	ETV	Tablet	100 mg	See above
Protease inhibitor	RTV	Oral liquid	400 mg/5 ml	For boosting of non-co-formulated protease inhibitors and super-boosting protease inhibitors during TB coinfection
Protease inhibitor	ATV	Solid oral dosage form	100 mg	Use in alternative second line for children older than six years old when boosting with separate RTV is available
Protease inhibitor	ATV	Solid oral dosage form	150 mg	See above
Protease inhibitor	DRV	Tablet	75 mg	Special circumstances in third line where appropriate and when boosting with separate RTV is available
Integrase Inhibitors	RAL	Chewable tablet (scored)	100 mg	For use in third line where appropriate
Fixed-dose combination	d4T + 3TC + NVP	Tablet (dispersible, scored)	6/30/50 mg	Special circumstances where people cannot be transitioned to a preferred or alternative NRTI
Fixed-dose combination	d4T + 3TC	Tablet (dispersible, scored)	6/30 mg	See above

11. COMMUNITY-BASED DELIVERY OF ANTIRETROVIRAL THERAPY

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 9 – Guidance on operations and service delivery.

Key messages

- Community-based models of ART delivery can benefit people living with HIV and decongest facilities in settings with a high burden of HIV infection.
- There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important, and models need to be flexible and responsive to the needs of people living with HIV.
- Bidirectional referral is essential so that people in stable condition can be moved out of the clinic into the community and those who experience health problems can be referred back to facility care.
- A conducive national policy and regulatory framework around providing ARV drugs is essential to the success of community-based ART delivery.
- Countries should consider measures to retain and enhance the performance of community-based staff with new or increased responsibilities.
- Simplified, integrated monitoring and evaluation systems are necessary to ensure the success of community-based models.

Background

During the past decade, antiretroviral therapy (ART) has been scaled up, and this has been particularly rapid in low- and middle-income countries – growing from 300 000 people in 2002 to 9.7 million by the end of 2012 *(1)*. The greatest scale-up of ART happened in sub-Saharan Africa. By the end of 2012, more than 7.5 million people in the region were accessing ART, an increase of more than 90% since the end of 2009 *(2)*.

In addition to the need for continued scale-up of access to ART, there is growing emphasis to improve the retention of people who have already initiated treatment. In most settings, HIV programmes are faced with the challenges of retaining a growing number of people in care. Retention is a challenge in all stages of the HIV care cascade, from HIV testing to long-term treatment *(3,4)*. There is increasing recognition that attrition is threatening the effectiveness of ART programmes and is growing in some settings. For ART programmes to continue to expand while retaining people in care and achieving high level of treatment adherence, novel models of service delivery are needed.

Reflecting the need to respond to these challenges, the WHO 2013 guidelines *(5)* recommend decentralized HIV treatment delivery with initiation of ART at peripheral health facilities and the option of maintenance treatment at community level and task shifting to include trained and supervised community health workers to dispense ART[20] between regular clinic visits. With the expansion of access to ART and sustained adherence, people living with HIV can expect a near normal life expectancy, including in resource-limited settings. To support lifelong care, there is a growing realization that, for most people receiving treatment, models of service delivery need to be adapted to support the management of HIV as a chronic condition. Out-of-clinic or community-based models of care show great promise in supporting adherence and retention for lifelong ART. There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important and models need to be flexible and responsive to the needs of people living with HIV.

WHO held a consultative meeting on community ART delivery in eastern and southern Africa from 5–7 December 2013 in Cape Town, South Africa. This update is based on this consultation and developed to advise national programmes and their stakeholders in settings with a high burden of HIV on implementation considerations for community-based ART delivery and share some lessons learned. The target audience is national policy-makers and HIV programme managers, health care providers and other relevant stakeholders. The main purpose is to support country programming and scale-up by describing key operational and programmatic considerations for effective and sustainable community-based ART delivery. WHO is currently consolidating guidance for key populations.

Evidence for WHO recommendations

Growing evidence indicates that decentralized models of HIV care can provide ART services comparable to those in hospital-based settings. A systematic review on the impact

20. Dispensing ART in this context includes assessment for any new signs and symptoms, adherence monitoring and support and dispensing medication to people who are already receiving ART between regular clinic visits.

of decentralization on ART delivery identified evidence that people who initiated ART at a hospital and maintained at a health centre were more likely to be retained in care than people initiating and maintained at the hospital level (overall estimate RR 1.12, 95% CI 1.08–1.17). The review from cluster randomized controlled trials shows moderate quality of evidence, with similar mortality rates at 12 months (RR 1.03, 95% CI 0.64–1.65) for maintenance ART delivered at the health facility or in the community. The risk of mortality did not different significantly at six months (RR 1.44, 95% CI 0.81–2.57) and 24 months (RR 1.50, 95% CI 0.91–2.47) in the cohort study. Comparable attrition (overall RR 1.01, 95% CI 0.99–1.03) was observed after 12 months in two trials with ART maintenance in the community *(6)*. Fig 11.1 summarizes the pooled relative risk for retention by model of decentralization.

These studies are supported by similarly positive outcomes reported by programmes piloting community ART delivery. Another review, assessing models that engage laypeople in ART delivery, indicates that such programmes can overcome barriers to retention and decongest health facilities with a high disease burden *(7,8)*.

Programmatic and implementation considerations

More and more programmes in sub-Saharan Africa are exploring innovative community ART delivery models, which aim to remove some of the structural and economic barriers to accessing facility-based HIV services. Such models of ART delivery have led to a shift away from primarily specialized (hospital-based) service delivery models to (1) decentralize ART to primary health facilities, with concomitant task-shifting, expansion and strengthening of links to community systems; and (2) out-of-clinic models of HIV treatment that engage community providers in essential tasks, including ART distribution, peer adherence and social support to supplement conventional models of ART delivery, particularly in settings where shortages of care providers create bottlenecks in service delivery *(9–11)*. Annex 11.1 summarizes selected models of community ART delivery and with corresponding outcomes where available.

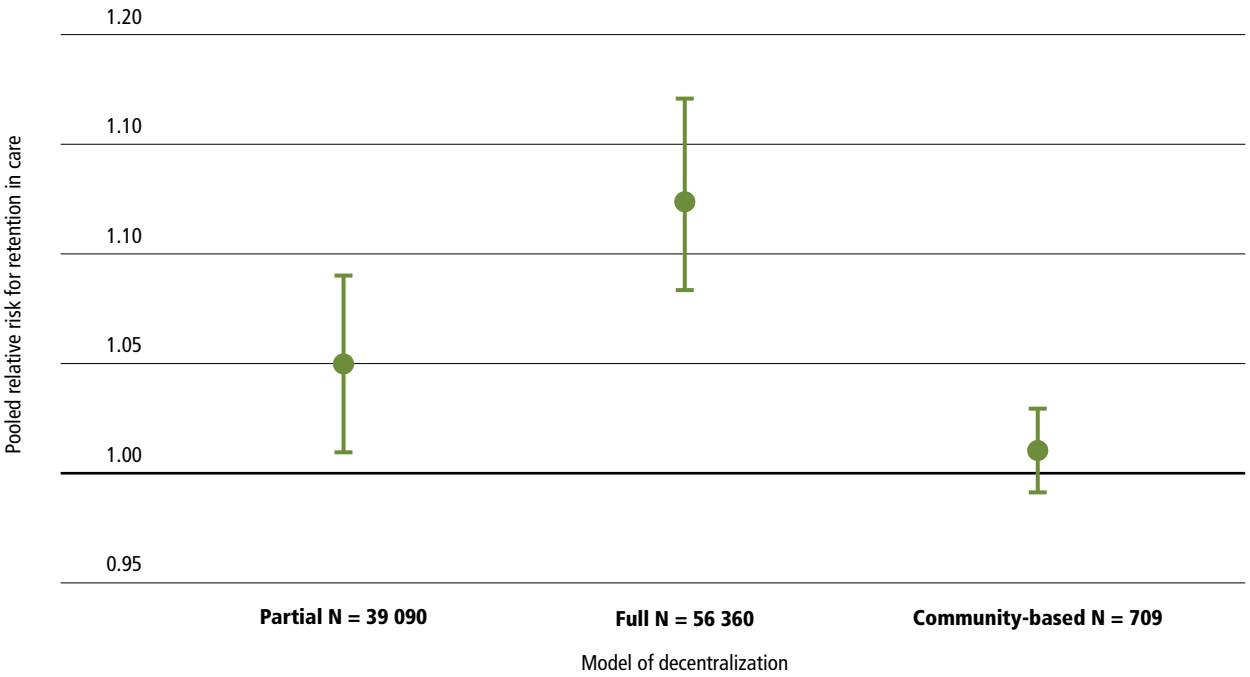
Several programmatic and implementation considerations are common to the successes reported by community-based models of ART delivery:

- community-based ART services delivered as an extension of facility-based ART services;
- a reliable and flexible ARV drug supply system;
- appropriate human resources; and
- adapted monitoring and evaluation linked to facility-level information systems to tracking input and outcomes.

Community-based ART delivered as part of facility or clinic ART services

Community-based models of ART delivery are designed to benefit service users and health care delivery systems, and as such there is substantial overlap in strengthening health systems and community systems. Community ART delivery needs input from and linkage with health facility staff, people living with HIV and communities at large. Flexibility is therefore necessary for people living with HIV to move along the care pathway between facility- and community-based models. Strengthening systems

Fig. 11.1. Summary of decentralization and retention in care



Source: Suthar et al. *(12)*.

for bidirectional patient referral is essential, such that stable people living with HIV can be moved out of the clinic into the community, while those who experience health problems are efficiently and timely referred back to clinical care. In addition, packaging community-based ART services as an extension of the facility will ensure clinical and programme accountability. Community models of ART delivery are not a replacement of facility-level care but complementary services. People living with HIV in the community model must feel welcomed in clinic settings, and involvement of respective facility staff (in designing and implementing community ART delivery models) is necessary to ensure a supportive environment. They have increased capacity for peer support and community involvement, which can facilitate improved retention in care and support for people living with HIV.

Reliable and flexible drug supply system

The success of models of community ART delivery depends on reducing the workload for both people living with HIV and providers by allowing for longer dispensing intervals and for community workers to dispense ARV drugs between clinic visits. A conducive national regulatory environment around the provision of ARV drugs is therefore essential to the success of community-based ART delivery. Countries and national regulatory bodies need to address policy and regulatory frameworks for who can dispense or distribute ARV drugs, the frequency required for ART prescription and who can refill ART prescriptions.

Appropriate human resources

Community ART models of care may help alleviate the workload of clinical teams but require additional work by some cadres of health workers, usually trained community health workers or "lay" providers. Health workers and staff involved in community-based ART services need to be appropriately supported, both in terms of training, supervision, management and incentives and remuneration. Since community-based models are an extension of facility services, they often require task shifting or task sharing. Successful models have included ways to ensure appropriate recognition for those involved as well as management systems that support the community-based ART delivery. In many settings, "lay" cadres and community health workers may be under different regulatory frameworks than health professionals and are mostly funded through short-term projects. This often leads to gaps in sustainability and contributes to high attrition of health workers. WHO recommends that countries consider measures such as financial and/or non-financial incentives, performance-based incentives or other methods as means by which to retain and enhance the performance of health workers with new or increased responsibilities, commensurate with available resources in a sustainable manner *(13)*.

People living with HIV play a key role in delivering ART at the community level, including acting as role models to others who need HIV treatment and providing peer support, which in some cases contributes to reducing stigma and seeking HIV services.

Monitoring and evaluation systems to track outcomes and ensure accountability

Simplified, integrated monitoring and evaluation systems are necessary to ensure reliable drug supply, track input and programme effectiveness, and for programme accountability. Such systems need to be integrated within the existing health information systems and simplified for community health workers and people living with HIV themselves to complete them accurately and timely. Where possible, reporting requirements from community based services should be limited to the most vital and necessary, to minimize the workload that may discourage the involvement of care providers and people living with HIV.

Knowledge gaps and research priorities in community ART delivery

There are knowledge gaps and questions that need to be answered both in trials and from observational and implementation studies. First, across the literature and programmes, judgement differs regarding what defines a "stable patient" and how rigid such inclusion criteria should be applied for referral to community-based ART services. Also unknown is the proportion of people who meet these "stable patient" criteria. Of the nearly 10 million people receiving ART at the end of 2012, it is unknown what proportion have been on treatment for extended periods of time and could be managed with less frequent clinical contact; however, this is likely to be the majority.

Second, limited data exist on the preferences for community ART delivery systems and how these models of care enable patient empowerment and human rights. In addition to the need to document patient experiences, documenting processes and inputs needed for scaling up and implementing these models at the district, regional and national levels can support programme learning.

Third, there is considerable interest in how out-of-clinic community models can support underserved populations who often experience inequitable access to ART, including but not limited to men, children, adolescents, pregnant women, sex workers, men who have sex with men and people who inject drugs.

Fourth, data on the long-term effectiveness of these models in relation to patient outcomes are needed. Community models can offer benefits not just for the targeted stable ART population but also potentially for improving outcomes at different levels of the treatment cascade. Although evidence supports the provision of community-based HIV testing and ART maintenance, evidence is needed to assess the ranges of other HIV services that could safely be delivered at the community level.

Finally, more cost information is needed. Although community models are not primarily designed to save costs, it is important to determine what their costs are and their cost–effectiveness in different settings. In addition, understanding the resources needed to implement these models needs to be documented. This includes health workers' time and workload analyses to further clarify resource requirements in different settings.

Continued innovation will be necessary to support the growing cohort of people living with HIV who are receiving ART. The current community models of care are an initial step of what and how services can potentially be provided closer to the homes of people living with HIV. Complementary to this innovation is the role of technology in supporting and engaging people living with HIV and communities.

Conclusion

There is no one-size-fits-all approach to community models of ART delivery. The context in which they operate is important, and models need to be flexible and responsive to the needs of people living with HIV. Community models are also designed to strengthen facility-based models by providing appropriate decentralized care, by minimizing congestion of health facilities and by allowing clinicians to see only the people who would benefit from clinical consultation. The needs of people living with HIV may vary over time, and links between community and facility models of care are necessary to ensure quality along the care pathway. Community models of ART delivery are not intended to replace existing services and very much need to operate as part of a continuum of care with facility-based care models. In addition, multiple community-based models might be implemented depending on local context.

The sustainability of community models of care is essential to ensure their long-term effectiveness. Although many models have been innovative and piloted by not-for-profit organizations, governments increasingly recognize that these models can be successfully implemented without huge external resources. Sustainability depends on appropriate support for the models of care, by incorporating such models in national programming and health care delivery systems.

ANNEX 11.1.

Summary of examples of models of community ART delivery

Model of care	Country, implementer and year	Criteria for delivering ART	ART refill interval	Frequency of clinic visit	Patient–provider ratio, human resources used and organization	Remarks
Community adherence groups *(14,15)*	Mozambique (Ministry of Health) Lesotho, Malawi, South Africa and Zimbabwe (Médecins Sans Frontières) 2011–present	Stable on ART Piloting inclusion of pre-ART people living with HIV	Monthly (Lesotho and Mozambique), every 2 months (Malawi), every 3 months (Zimbabwe)	Every 6 months (Lesotho, Malawi and Mozambique), annually (Zimbabwe)	Self-forming groups of 6–10 people living with HIV rotate to collect ART for the group. Groups formed with support from clinic staff and local networks of people living with HIV	
Community adherence groups – pilot for the above *(15)*	Mozambique Médecins Sans Frontières 2008–present	>6 months on ART, absence of adverse drug events, no opportunistic infection, CD4 >200 cells/ mm^3	Monthly	Every 6 months	Self-forming groups of six people living with HIV rotate to attend the clinic and collect ART for the group	93.4% retention rate in care at 3 years and 91.8% at 4 years *(16)*; children in community adherence groups reporting 94% retention *(11)* Uptake around 50%

Model of care	Country, implementer and year	Criteria for delivering ART	ART refill interval	Frequency of clinic visit	Patient–provider ratio, human resources used and organization	Remarks
Adherence support *(17,18)*	South Africa Khet'impilo 2004–present	All people living with HIV	Not reported	Not reported	80–120 per community health worker All people living with HIV receive regular support in their homes from their community health worker	Lower rates of mortality and loss to follow-up, higher rate of viral suppression
Community drug distribution point	Uganda, TASO 2006–present	ART ≥10 weeks, defined as stable by clinician at the individual level	Every 2 months	Not reported	Not reported	Reported 70% accessing ART
Community-based *accompagnement* for ART	Rwanda Partners in Health 2005–2006	All people living with HIV at ART initiation	Daily, directly observed therapy by community workers	Every 6 months	6 people living with HIV per community health worker	92% retention in care after 24 months Currently exploring approaches to reduce the frequency of home visits
Adherence clubs – expansion	South Africa Provincial department of health and partners 2011–present	≥18 years, ART ≥12 months, two consecutive suppressed viral loads, no clinical condition requiring more frequent clinical consultation	Every 2 months	Annually	20–30 people living with HIV per club Number of clubs and community health workers not reported In the community, clubs meet outside the health facility in community venues	Expansion to >20 000 people living with HIV over 18 months, and one fifth are now managed in a club 10–40% of the people living with HIV in each facility are accessing ART using this model
Community ART distribution	Democratic Republic of the Congo Médecins Sans Frontières 2010–present	Receiving ART for >6 months, absence of opportunistic infections, CD4 >350 cells/mm^3	Every 3 months	Annually	Not reported People living with HIV provide refills, adherence support and follow-up	Retention 89% at 12-month follow-up 43% of patients accessing ART in this model Reduced personnel cost and reduced transport and time cost for people living with HIV *(11)*.
Adherence clubs – home-based expansion *(9)*	South Africa Médecins Sans Frontières 2012–present	≥18 years, ART ≥12 months, 2 consecutive suppressed viral loads, no clinical condition requiring more frequent clinical consultation	Every 2 months	Annually	10–15 people living with HIV per adherence club that meet in people's homes	10 home-based clubs to date

12. SURVEILLANCE OF THE TOXICITY OF ANTIRETROVIRAL DRUGS DURING PREGNANCY AND BREASTFEEDING

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Main messages

- Surveillance of the toxicity of ARV drugs during pregnancy and the breastfeeding period aims to assess the risk of adverse reactions in pregnant women and adverse reactions to the fetus exposed in utero and to the infant exposed to ARV drugs during breastfeeding.

- Three surveillance approaches are suggested to assess these risks: (i) a prospective pregnancy-exposure registry; (ii) a birth-defect surveillance programme; and (iii) a prospective monitoring of cohorts of mother–infant pairs, during the breastfeeding period in sentinel sites.

- The national decision on whether surveillance of the toxicity of ARV drugs during pregnancy and the breastfeeding period should be undertaken, and on which approach to use, should be informed by local needs; health system characteristics; treatment-seeking behaviour of women; the available financial, human and technical resources; and the ability to link the required recording systems.

- To ensure that the data provide prompt, robust evidence for policy-makers, nationally and internationally, the data collected should be of consistently high quality. To ensure that data can be pooled to inform national and international policies, it is desirable that they be collected in a standardized manner.

- The commitment and support of national policy-makers, programme managers and health care staff at sentinel sites are critical to the success of any of these approaches.

- The sustainability of the surveillance system depends critically on communication and feedback of the data and findings to relevant stakeholders, including women and their communities; health care providers; drug regulators and other policy-makers; donors; and international agencies.

- WHO provides advocacy tools, technical guidelines and technical assistance to countries and technical organizations planning to implement ARV toxicity surveillance during pregnancy and the breastfeeding period. WHO also collaborates with scientific and research agencies to implement strengthened surveillance and research in the area of toxicity of ARV drugs in pregnancy and during breastfeeding, to inform future guidelines on the use of ARV drugs.

Purpose of this section

Chapter 7 of the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)*, "Clinical guidance across the continuum of care: antiretroviral therapy", describes evidence from the systematic reviews conducted on the safety of ARV drugs in pregnancy and breastfeeding. The guidelines briefly discuss the surveillance of the toxicity of ARV drugs during pregnancy and the breastfeeding period, in particular in Box 7.2 on surveillance of ARV drug toxicity. The guidelines *(1)* also recommend that toxicity surveillance and additional research be conducted on the safety and acceptability of lifelong ART for pregnant and breastfeeding women, and their infants, especially in resource-limited settings, where malnutrition and comorbidity are more common that in resource-rich countries, and monitoring capacity is limited.

Based on current evidence, WHO determines that the benefits of using ARV drugs during pregnancy are considerable, in terms of both avoiding infant HIV infection and benefits to the mother, and greatly outweigh the potential low risks, including the risk of congenital malformation. However, to decrease uncertainty and provide more confidence around the level of risk, if any, and strengthen the motivation of both health care providers and people living with HIV to use ART during pregnancy and the breastfeeding period, WHO recommends that toxicity surveillance activities and additional research be conducted.

This section expands on the information provided in the guidelines with an overview of proposed approaches for assessing the safety of ARV drugs used during pregnancy and the breastfeeding period. It is intended for national HIV/AIDS programme managers and implementing partners, such as nongovernmental organizations and academic institutions, that are responsible for implementing systems to monitor the safety of ARV drugs. The proposed approaches include the development and maintenance of (i) a prospective pregnancy-exposure

registry; (ii) a birth-defect[21] surveillance programme; and (iii) a prospective monitoring of cohorts of mother–infant pairs, during the breastfeeding period at sentinel sites.[22] This section describes briefly the methods employed, their strengths and limitations, tools available for implementing them and practical issues that would need to be considered for a particular setting or country.

Why is surveillance of the toxicity of ARV drugs in pregnancy and during breastfeeding important?

The recommendations for use of ARV drugs in pregnancy and during breastfeeding in the 2013 consolidated ART guidelines will result in earlier and more prolonged exposure to ARV drugs for women, as well as increased exposure to ARV drugs for infants during the breastfeeding period *(2)*. The likelihood of first-trimester exposure of the fetus to the new recommended regimen will increase, as women newly diagnosed with HIV initiated on treatment during one pregnancy are likely to remain on treatment during subsequent pregnancies. In addition, the 2013 guidelines recommend starting ART earlier (CD4 count of 500 cells/mm^3 or less) and regardless of CD4 cell count for all people with HIV with active tuberculosis, with severe hepatitis B and for serodiscordant couples. This will also increase the number of infants born following exposure to ARV drugs during the first trimester of pregnancy. The first trimester is a critical period of exposure because organogenesis occurs during this time and exposure to teratogenic medicines can cause major congenital anomalies *(3)*. Although, based on current data, WHO currently determines that ARV drugs do not, or minimally, increase the risk of congenital anomalies, more data would provide confidence about the level of risk, if any *(1)*. Finally, pregnant women are known to be at increased risk of side effects of drugs, in particular those that affect the liver, kidney and blood pressure and mental side effects (Box 12.1).

Goals and objectives of monitoring the toxicity of ARV drugs in pregnancy and during breastfeeding

The goal of toxicity surveillance in HIV programmes is to ensure that the ART regimens are safe, including when used for preventing mother-to-child transmission by pregnant and breastfeeding women and for their babies.

To obtain reliable national data that contribute to national treatment guidelines and global policies, surveillance of the toxicity of ART during pregnancy and the breastfeeding period needs to include the following three areas of focus:

- maternal health outcomes: serious toxicities associated with ART in pregnant women;
- birth outcomes: on the fetus in utero, manifesting as stillbirths, preterm births and low birth weight or manifesting as birth defects; and
- infant and child outcomes: health outcomes among infants and young children exposed to ARV drugs via breast-milk, including effects on growth and development.

The specific objectives are:

- to determine the incidence of important types of drug toxicity associated with using (and introducing new) ARV drugs, including maternal mortality, in women exposed to ARV drugs during pregnancy;
- to monitor birth outcomes, including preterm births, stillbirths, low birth weight and infant mortality among women exposed to ARV drugs during pregnancy compared with women not exposed to these medicines during pregnancy;
- to assess the nature and risk of major congenital anomalies in the infants of women exposed to ARV drugs during pregnancy compared with women who are not exposed to these medicines during pregnancy; and
- to monitor the effect on growth and development in infants of exposure to ARV drugs via breast-milk and the toxicity associated with such exposure compared with infants not exposed to ARV drugs.

Surveillance approaches

Based on the priority toxicity issues to be addressed by the surveillance system, health care–seeking patterns of pregnant women and mothers, and available resources, surveillance systems could comprise of any or all of the following approaches:

- a prospective pregnancy-exposure registry for toxicity among pregnant women and neonates;
- a birth-defect surveillance system for assessing birth outcomes; and
- a prospective monitoring of cohorts of mother–infant

21. Congenital anomalies, also known as birth defects, are structural or functional abnormalities, including metabolic disorders, that are present from birth. Congenital anomalies are a diverse group of disorders of prenatal origin that can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies. The terms "congenital anomalies" and "birth defects" are used interchangeably in this section.

22. The surveillance of the toxicity of antiretroviral medicines within antiretroviral therapy programmes is addressed in the next section (Surveillance of the toxicity of antiretroviral medicines within antiretroviral therapy programmes).

pairs for toxicity from birth throughout the breastfeeding period, including significant growth and developmental delays.

In all of the above approaches, recruiting and assessing a concurrent group of controls comprising pregnant women not exposed to ARV drugs (women not infected with HIV) is essential to understand the relative contribution of ARV drugs to the toxicity of interest and establish whether there is any additional risk. Since many of the adverse outcomes of interest are rare, it is important to pool the data collected from several sites across several countries to obtain sufficient data to determine whether or not treatments contribute to the risk of these rare adverse outcomes. Standardized data-collection approaches that comply the norms and standards of surveillance *(4)*, including using standard terms such as those used in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) *(5)* for defects of interest, should therefore be used to enable the pooling of core data across sites and countries.

Box 12.1. Pregnancy-related toxicity concerns

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* identified that more data are desirable on:

- the risk of serious, life-threatening and fatal skin and hepatic reactions among pregnant women exposed to nevirapine during pregnancy;
- the risk of serious reactions such as seizures and nervous system and mental effects among pregnant women exposed to efavirenz-based ART regimens during pregnancy;
- the comparative risk of preterm delivery, stillbirths and small for gestational age births associated with various ARV regimens used during pregnancy;
- very low risk of neural tube defects in infants exposed in utero to efavirenz-based regimens;
- risk of renal and bone toxicity in infants exposed in utero or during breastfeeding to tenofovir-based regimens; and
- risk factors for serious and life-threatening anaemia in pregnant women exposed to zidovudine during pregnancy and the impact on birth outcomes.

Basic technical requirements for the three surveillance approaches

Prospective pregnancy-exposure registry

- At selected antenatal clinics, pregnant women are enrolled from their first antenatal visit and followed up to term, including delivery.
- At the first visit, information is obtained from the woman on her medical, obstetric and drug-exposure history.
- The fewest number of women are enrolled if there are an equal number of exposed women (cases) to unexposed women (comparators). This approach is recommended.[23]
- At each later antenatal visit, information on infections, treatments and folate supplementation[24] is updated, and any new clinical conditions or diagnoses are recorded.
- Antenatal staff members are trained to obtain and record comprehensive and precise drug and medical histories.
- Women are encouraged to attend all follow-up antenatal visits and to deliver at the health care facility.
- Any adverse reactions occurring during pregnancy are actively solicited and systematically recorded and reported.
- At delivery, all liveborn or stillborn babies have a standard, surface examination, which establishes any

23. Sample-size estimations based on background incidence, case–comparator ratio and anticipated risk, including continuity correction, are documented in the protocol for a drugs exposure pregnancy registry for implementation in resource-limited settings *(6)*. See also the European Medicines Agency *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (7)*.

24. Folic acid supplementation is recommended before pregnancy and in the first three months, to prevent neural tube defects and other congenital malformations in the fetus among all women *(8)*.

external and visible birth defects and identifies neonates needing immediate medical or surgical attention *(9)*.

- These data are recorded on standardized data-collection sheets.
- All suspected major congenital anomalies are photographed.
- Experts in birth defects later provide diagnoses of any birth defects after reviewing the documentation and photographs.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during pregnancy (Box 12.2).

Box 12.2. Prospective pregnancy registry in South Africa

South Africa is implementing a national pregnancy registry to assess the safety of the ARV regimens and other medicines commonly used in pregnancy. Concerns about medicines such as co-trimoxazole and anti-tuberculosis drugs, and other conditions that may predispose women to risks of adverse birth outcomes, have dictated the need for a prospective approach with a scope beyond ARV drugs.

At sentinel sites, all new antenatal women are recruited into the registry. The maternity case records used at the sites facilitate systematic collection of relevant information at each antenatal visit on drug exposure, occurrence of adverse reactions, comorbidity, ultrasound and other diagnostic tests and birth outcomes. A bright sticker on maternity records identifies the woman as a pregnancy registry woman and allows referral facilities and other sites to rapidly recognize women who are part of the registry so that they can inform the pregnancy registry site coordinator regarding the pregnant woman or her neonate and data entered into the registry database.

Health care staff members at the sentinel sites are trained to (i) elicit and document medical, obstetric and drug histories and other clinical information in the maternity case records; (ii) conduct and document a systematic surface examination of each neonate, using training materials developed by WHO; and (iii) take photographs and record birth defects and refer infants appropriately. A national birth-defect panel will review all reported major congenital anomalies and determine whether the cases should be included in the analyses related to teratogenicity.

The National Health Research Ethics Council has waived the need for informed consent by women enrolled in the registry, except for permission to photograph babies born with a birth defect.

Birth-defect surveillance

- A few facilities are selected that provide good obstetric care and with many deliveries.
- All women presenting for labour at these selected facilities are included.
- At delivery, all liveborn or stillborn babies have a standard, surface examination, which establishes any external and visible birth defects and identifies neonates in need of immediate medical or surgical attention.[25]
- All suspected congenital anomalies are photographed.
- Before discharge, information is obtained from the woman and/or from her medical records about her medical and obstetric history and the use of medications (including ARV drugs) during the course of her pregnancy.
- These data are recorded in a standard data-collection sheet.
- Experts later provide diagnoses of any congenital anomalies after reviewing the clinical documentation and photographs.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during pregnancy (Box 12.3).

25. The WHO Tropical Diseases Research and Reproductive Health and Research Programme has produced a video guide to a stepwise surface examination of neonates, to train health care workers to assess a neonate for birth defects *(9)*. It supports a new protocol for a pregnancy registry *(6)*.

Box 12.3. Birth-defect surveillance in Malawi

Malawi is implementing a birth-defect surveillance system in two hospitals with high numbers of deliveries (>10 000 deliveries per year). The system aims to establish a baseline prevalence of neural tube defects and other major birth defects among neonates and to compare this to the observed prevalence in ARV-exposed pregnancies. All births, both live and stillborn, delivered at the participating institutions will be systematically assessed for birth defects within a few hours of birth. The sample size will be calculated based on assumptions regarding the prevalence of HIV, the prevalence of neural tube defects and the percentage of women exposed to ARV drugs and the goal of ruling out a twofold increased risk of neural tube defects with efavirenz exposure. A structured data-collection form, including photographs, will be used at the sites to record the assessment of every facility-based birth. There will also be a uniform approach to ascertaining ARV exposure in the first trimester. There will be uniform classification and coding of birth defects using ICD-10 *(5)*, and birth-defect experts will validate diagnoses.

Prospective monitoring of cohorts of mother–infant pairs during the breastfeeding period

- Cohorts of mother–infant pairs (infants exposed and unexposed to ARV drugs during pregnancy and breastfeeding) are enrolled at birth and followed up over the course of the breastfeeding period (typically 18–24 months).
- Depending on the ARV regimen used for breastfeeding women and infants, case definitions should be developed to assist health care staff in identifying targeted types of toxicity that should be monitored.
- Enrolled infants are assessed in a standardized, systematic manner, for bone growth, renal function (where feasible), nervous system development and HIV infection, at all facility visits (such as immunization visits, paediatric services, emergency room visits or hospitalization) during the breastfeeding period, at specific times.
- All findings, including reports of HIV infection, growth parameters, fractures, seizures and hospitalizations, are recorded.
- The data are analysed to determine whether any additional risk of adverse outcomes in infants can be attributed to the exposure to ARV drugs during breastfeeding.
- Settings with a fairly stable population, with reasonable access to care and where home-based follow-up is possible are the most suitable for this approach (Box 12.4).

Box 12.4. Malawi breastfeeding cohort

In Malawi, a surveillance programme will monitor infant growth and neurocognitive development within a cohort of breastfeeding mother–infant pairs receiving regimens including tenofovir or efavirenz. Active surveillance will be conducted for parameters that indicate growth and development problems among infants exposed to ARV drugs via breast-milk. This component has been introduced in two ongoing cohort studies conducted in Malawi that will each recruit and follow up about 1500–2000 pregnant women living with HIV until 18–24 months postpartum. All women in these cohorts will receive ART (tenofovir, lamivudine and efavirenz) according to the Malawi national protocol. The studies will implement interventions to improve the retention of mothers throughout the postpartum period.

Important considerations when developing a surveillance system

Countries with a moderate to high prevalence of HIV infection among pregnant women, and high coverage of ART during pregnancy, for preventing mother-to-child transmission; countries using efavirenz- or nevirapine-based regimens as first-line treatment among pregnant women and women of childbearing age; and those adopting option B or option B+ as a policy for preventing mother-to-child transmission should consider implementing one or more of these surveillance systems.

Decision-makers need to give priority to the key toxicity issues of concern. If there are toxicity issues concerning the pregnant woman (such as risk of hypersensitivity reactions with nevirapine), a pregnancy-exposure registry should be considered. If the priority concerns are regarding birth outcomes, a birth-defect surveillance or pregnancy-exposure registry would be suitable. If there are concerns about breastfeeding exposure, prospective cohorts of mother–infant pairs are appropriate. Logistical issues, such as availability of surveillance staff, budget, timelines for funding and sample-size requirements, need to be considered, to assess the feasibility of the different approaches. The process for decision-making related to which of these approaches to adopt at the national level depends on various factors.

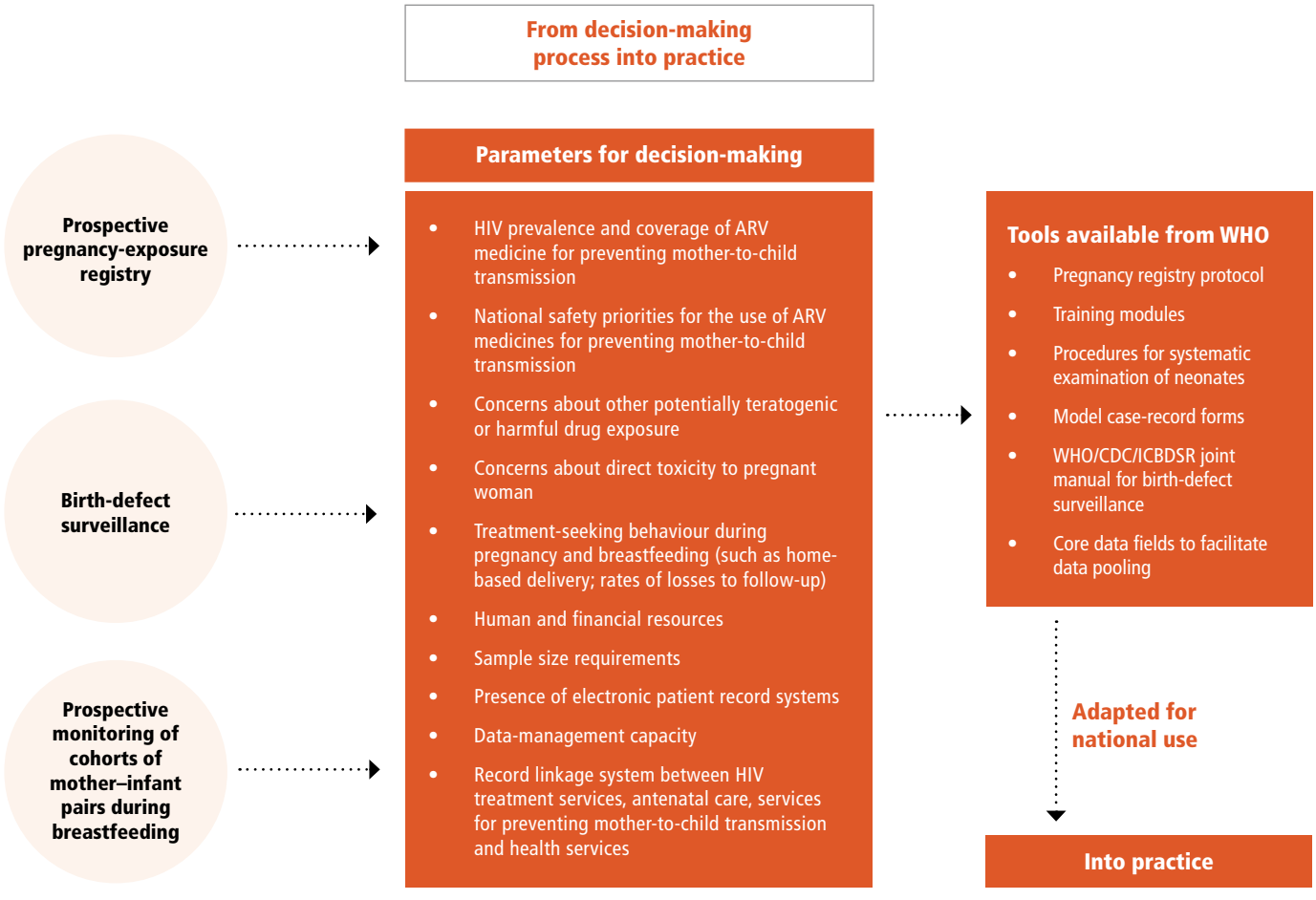
The pregnancy-exposure registry has the potential to collect information on serious adverse reactions occurring among women during their pregnancies. The ability to detect and collect information on such reactions depends on the diagnostic capacity available at the antenatal clinic, awareness of safety issues among health care staff, record linkage and continuity of care between clinical services (such as emergency rooms and medical wards) and antenatal services. Programmes need to consider these issues, as well as the priority toxicity concerns in pregnant women, when determining the type of data that are collected during the pregnancy as part of the pregnancy-exposure registry.

The birth-defect surveillance approach in a setting with high HIV prevalence, high coverage with ART during pregnancy and many deliveries will allow reporting on a large number of births more quickly. If there is good record-keeping and record linkage between antenatal, labour and delivery and postnatal care, and if drug exposure during pregnancies is systematically recorded, birth-defect assessment at the hospital and organizing the data flow may the only incremental efforts required to set up birth-defect surveillance.

Both pregnancy-exposure registry and birth-defect surveillance require rigorously examining the neonate, accurate information about drug exposure and comorbidity during pregnancy and many assessments to assess the risk to the fetus of exposure to ARV drugs.

The breastfeeding mother–infant cohorts also require proper assessment of the infant, drug exposure, breastfeeding patterns and clinical history-taking throughout the breastfeeding period. Standardized but simple assessments for growth and nervous system development need to be implemented at specific times during the growth of the breastfeeding infant. Ongoing validation and quality-assurance activities need to be implemented, to ensure that the data continue to be of good, reliable quality (Fig. 12.1).

Fig. 12.1. Parameters for planning for a toxicity surveillance system of antiretroviral drugs during pregnancy and breastfeeding



Before initiating any approach, it will be important to consult with the national health research ethics committees on whether there is any need for written informed consent from pregnant women included in the pregnancy-exposure registry or birth-defect surveillance or whether written informed consent can be waived on the grounds that surveillance forms part of routine care and is in the interest of safety. In general, written or oral permission to take photographs of babies with a birth defect is likely to be required.

Responding to methodological and programmatic challenges in establishing ARV toxicity surveillance

Table 12.1. Surveillance challenges and how to address them

Challenge	Solutions
High rates of home births and high rates of loss to follow-up	Intensify interventions to encourage facility-based births Address known barriers to accessing care – such as transport and ambulance services. Use automated SMS reminders to women during the pregnancy to attend scheduled visits and to prepare for delivery at a health care facility. Train antenatal clinic health care staff and community health nurses to visit or telephone women who miss scheduled visits.
Late presentations for antenatal care during pregnancy (pregnancy-exposure registry only)	Select sites with a high proportion of early uptake of antenatal services. Consider a birth-defect surveillance approach only, as the quality of information on first-trimester exposures is unlikely to differ between pregnancy-exposure registry and birth-defect surveillance.
Incomplete or poorly completed antenatal and labour or delivery records do not routinely collect the data required for the surveillance system	Design data-capture forms or systems that are easy to use and train staff in their use. Frequently or automatically verify data for completeness at sites. Validate data using other data sources. If feasible, identify other than routine health care staff for data capture.
Poor record linkage between antenatal and labour and delivery services	Flag maternity case records (antenatal cards) to alert staff to link records. Introduce an integrated patient-record system used by all sites and services.
Poor-quality data capture from source documents	Train and supervise staff capturing data. Provide feedback to staff involved on issues relating to data recording.
Sustainability	Provide frequent feedback to health care facility staff, women, administrators and policy-makers. Identify and address site staff concerns about the system on an ongoing basis. Integrate the system in the routine delivery of care. Limit the reporting requirements (such as with electronic practice management systems).

Engaging stakeholders in establishing surveillance systems

A comprehensive communication strategy that identifies target groups, communication objectives and a practical communication approach (means of communication, type and frequency of outputs) needs to be developed that guides programme staff on how to engage with key stakeholders. Target groups include the pregnant women; their communities and health care providers; academic and professional associations; the national regulatory authority; nongovernmental organizations and other partners; and

the mass media. Issues around data sharing, publication agreements and dissemination of findings should be discussed and agreed on at the onset of such programmes.

Collaborative links with the regulatory pharmacovigilance systems, related programmes, such as maternal and child health programmes, and clinical services need to be established or strengthened. Programmes need to allocate adequate resources and attention to these collaborative activities, to ensure a consolidated approach to addressing issues of patient safety without duplication of efforts.

What is WHO doing?

The Sixty-third World Health Assembly in 2010 endorsed a report by the Secretariat on birth defects. This report describes the basic components of a national programme for the prevention and care of birth defects before and after birth and the priority actions recommended to the international community to assist in establishing and strengthening these national programmes *(10)*.

In this context, WHO is working with the National Center on Birth Defects and Developmental Disabilities of the United States Centers for Disease Control and Prevention, the International Clearinghouse for Birth Defects Surveillance and Research, EUROCAT and health ministries in participating countries with high HIV prevalence to provide technical expertise at the country level for surveillance of birth defects. WHO has produced a guiding protocol *(6)* and training video *(9)* on the conduct of a systematic surface examination of newborn infants, for countries planning to implement a pregnancy registry. A joint manual has been produced that provides methods for implementing a congenital anomalies surveillance system *(4)*.

WHO is an active member of an ARV Birth Defect Task Team with 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. The task team provides national programmes for preventing mother-to-child transmission with coordinated technical assistance in planning and implementing birth defect surveillance programmes *(11)*.

WHO provides advocacy tools, technical guidelines and technical assistance to countries and technical organizations implementing ARV toxicity surveillance during pregnancy and breastfeeding. WHO encourages countries to include ARV toxicity surveillance activities under the monitoring and evaluation component of the new Global Fund to Fight AIDS, Tuberculosis and Malaria funding model, to mobilize funding to support ART toxicity surveillance within ARV treatment and programmes for preventing mother-to-child transmission *(12)*.

WHO is convening a Steering Group on ARV Toxicity Surveillance, comprising international experts and representatives of research agencies. The Group will advise WHO on producing normative guidance and technical updates and enhanced collaboration on toxicity surveillance to inform the future clinical guidelines process.

13. SURVEILLANCE OF THE TOXICITY OF ANTIRETROVIRAL DRUGS WITHIN ANTIRETROVIRAL THERAPY PROGRAMMES

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Main messages

- ARV toxicity surveillance is an integral component of monitoring and evaluation within ART programmes. Technical requirements, including data collection, reporting, data outputs and feedback should be incorporated into HIV monitoring and evaluation activities of the programme.
- Three surveillance approaches are suggested to assess ARV toxicity: (i) targeted spontaneous reporting; (ii) active surveillance for specific types of toxicity within sentinel cohorts; and (iii) cohort event monitoring.
- National priorities and objectives should dictate the type of monitoring approaches used in ARV toxicity surveillance; local needs, health system characteristics and available human, financial and technical resources should guide the selection of priority toxicity questions and the monitoring approaches used to address them.
- Targeted spontaneous reporting and active surveillance within cohorts are complementary approaches and, where resources permit, adoption of both approaches should be considered.
- Communication with and feedback to relevant stakeholders, including patients receiving ART, health-care providers, drug regulators and policy-makers, donors and international agencies, is an essential component of the performance and sustainability of the surveillance system.
- Collaboration with partner organizations, national and international monitoring systems, cohort consortiums and clinical trial agencies should be considered because it allows sharing of technical expertise and pooled analyses of toxicity data.

Purpose of this section

Chapter 7 of the WHO 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)*, "Clinical guidance across the continuum of care: antiretroviral therapy" describes evidence from the systematic reviews conducted on the toxicity of ARV drugs. Based on current evidence, WHO has determined that the risk of harm from the recommended antiretroviral regimens is small and outweighed by their benefits. The reviews conducted for the guidelines highlighted that available evidence is restricted to studies with limited sample size and short duration, mainly in industrialized or high-income countries. The guidelines also highlight remaining evidence gaps and sensitive questions about toxicity that require attention.

The guidelines briefly discuss the surveillance of the toxicity of ARV drugs within ART programmes and programmes for preventing mother-to-child transmission of HIV, especially in Box 7.2 on surveillance of ARV drug toxicity. This section provides guidance on surveillance of the toxicity of ARV drugs. It is intended for national HIV programme managers and implementing partners, such as nongovernmental agencies and academic institutions, that are responsible for implementing systems to monitor the safety of ARV drugs. It focuses on approaches that address the particular needs of the HIV treatment programmes to monitor the toxicity of ARV drugs. The proposed approaches include developing and maintaining (i) targeted spontaneous reporting; (ii) active surveillance for specific types of toxicity within sentinel cohorts; and (iii) cohort event monitoring.

The section describes briefly the methods used, their strengths and limitations, tools available for implementing them and practical issues that would need to be considered for particular settings or countries.

Why is surveillance of the toxicity of ARV drugs within ART programmes important?

The new recommendations of the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* aim at, and will result in, an increased and prolonged exposure to ART among people living with HIV.

The guidelines recommend implementing toxicity surveillance within ART programmes, to provide data and assess the frequency and clinical relevance of specific types of toxicity associated with both the short- and long-term use

of ART; increase confidence in the use of the drugs; identify populations with risk factors; and plan preventive strategies. It is notably essential to implement toxicity surveillance in low-resource settings, where toxicity may present a different pattern in association with environmental or behavioural factors and the prevalence of other conditions and where ARV drugs are used in association with other medicines.

Goals and objectives of monitoring the toxicity of ARV drugs

The goal of monitoring is to support the safe use of ART, thus improving the quality of care and treatment outcomes, and to inform national guidelines and global policies on the use of ART in adults, adolescents and children (Box 13.1).[26]

The specific objectives are:

- to determine and minimize the incidence of drug toxicity associated with the use of new and older ARV medicines;[27]
- monitor the effect of toxicity on treatment outcomes, including treatment discontinuation, medical significance, disability or incapacity, hospitalization or prolonged existing hospitalization, life-threatening illness and death and congenital anomalies;
- determine the impact of risk factors, including other types of comorbidity, and the association with other medicines or traditional medicines on the incidence, nature or severity of ARV toxicity; and
- identify rare types of toxicity or toxicity associated with long-term use that have not previously been identified.

Box 13.1. Toxicity concerns

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* identified that more data are desirable on:

- the renal and bone toxicity associated with the long-term use of tenofovir;
- the bone, growth and renal toxicity of tenofovir among children and adolescents;
- the toxicity associated with efavirenz, in particular on the central nervous system;
- the safety of the use of efavirenz- and tenofovir-containing regimens during pregnancy and in breastfeeding mothers;
- the severe skin rash and hypersensitivity reactions associated with nevirapine;
- the long-term toxicity associated with the use of second- and third-line drugs; and
- the best methods for monitoring renal function in individuals using tenofovir-containing regimens.

Surveillance approaches

National priorities and objectives should dictate the type of monitoring approaches used in ARV toxicity surveillance. Local needs, health system characteristics and available human, financial and technical resources should guide the selection of priority toxicity questions and the monitoring approaches used to address them. The following are complementary approaches to surveillance.

Targeted spontaneous reporting

Targeted spontaneous reporting *(3)* elicits reports of specified and serious adverse drug reactions from health care workers. Targeted spontaneous reporting approach cannot be used to determine the incidence of serious adverse drug reactions because the denominator used to calculate it – the number of people exposed to the ARV drugs used – is unknown, and because the quality of reports may vary and underreporting is likely to occur. However,

26. In 2010, WHO recommended that countries shift away from using stavudine because of issues with toxicity and instead opt for zidovudine- and tenofovir-based regimens. The toxicity concerns have led to a progressive decline of stavudine globally during the past five years. Continued efforts are needed to replace stavudine by a tenofovir-based regimen in line with the 2013 WHO guidelines *(1,2)*.

27. Section 11 in this supplement addresses the surveillance of toxicity of ARVs in pregnancy and breastfeeding.

if a targeted toxicity is reported at a frequency equal to or higher than a rough estimate of its expected incidence would suggest, this would warrant formal assessment of its incidence and, if serious, immediate remedial decision and action.

"Serious" reactions include those that result in death, are life-threatening, result in hospitalization or prolongation of hospitalization or result in permanent harm or disability. Adverse reactions that result in treatment discontinuation and a change in ART regimen are also monitored as serious. Standardized case definitions for specific solicited adverse reactions are used and should be included in training for health care workers, in guidance on reporting and on reporting forms.

This approach can be used across all sites nationally where ART is delivered or in a specific geographical region or site, depending on the specific objectives of the system and resources available. A well-functioning targeted spontaneous reporting system will allow programme managers to determine the major drug toxicity concerns of health care workers and respond to those concerns, by providing direct feedback and support, requesting further studies, retraining or revising treatment guidelines and training materials. The approach promotes safety awareness among clinical staff and provides a forum for clinicians to raise their concerns about treatment regimens.

This approach differs from the traditional spontaneous reporting approach used by medicines regulatory authorities, since reports of specific types of toxicity associated with a specific group of drugs or in a specific group of people are encouraged, for example, monitoring of renal function and growth parameters among children taking tenofovir. However, similar to traditional spontaneous reporting, targeted spontaneous reporting can also be a means of detecting signals of adverse reactions that have not previously been reported. Box 13.2 illustrates an example of a targeted spontaneous reporting approach.

Box 13.2. Targeted spontaneous reporting in Western Cape Province in South Africa

A targeted spontaneous reporting system was implemented in early 2005, coordinated by the provincial government in collaboration with the Medicines Information Centre of the University of Cape Town. The system was designed to collect data on toxicity suspected for ARV drugs and other medicines among people concurrently being treated with ARV drugs.

Case definitions of each of the solicited types of toxicity (such as lactic acidosis, hepatotoxicity, nephrotoxicity, major birth defects, etc.) are provided on the case-reporting form as well as simple guidance on reporting procedures (the what, when, how and where of reporting). The system is constantly evaluated according to the changing needs of the programme: for example, when tenofovir was introduced into the treatment programme, the reporting form was updated to include nephrotoxicity. Feedback is provided to reporters in the form of an annual newsletter. Data derived from the system are routinely reported to the national programme managers and to the medicines regulatory authority.

Targeted spontaneous reporting should be incorporated into the routine monitoring and evaluation reporting requirements of ART programmes and be clearly differentiated from the existing national spontaneous reporting system. Targeted spontaneous reporting programmes should share its results with the latter system.

Active surveillance for specific types of toxicity within sentinel cohorts

Cohorts selected for active surveillance of toxicity need to have a reliable system for capturing clinical and toxicity data. Active surveillance for specific types of toxicity nests within existing cohorts set up in a country for research or monitoring and evaluation purposes. This approach determines the incidence of important drug toxicity, since there is reliable denominator data on the number of people exposed to the drug of interest and the duration of exposure.

Working with existing cohorts, with a focus on exposure to one drug and the incidence of one or few types of toxicity of interest, enables the cohort size to be optimized (which needs to be large when the defined toxicity is rare, but can be small if the toxicity is known to be relatively frequent). A focus on a relatively small number of types of toxicity can also improve the accuracy of their assessment. Toxicity can be detected from routine laboratory assessment, active case finding or tracking regimen changes. Regardless of the approach adopted within the cohort, it is important that individual reports be assessed for causality in a scientifically sound, standardized manner.

Maintaining sentinel cohorts is resource intensive. Limiting the number of people studied, such as by selecting sentinel sites, limits the costs and increases the efficiency of the system. However, in sites that have a functioning electronic patient-monitoring system, it is increasingly possible to limit the cost, since these electronic monitoring systems can be reliably assessed, and including the reporting of defined toxicity and serious adverse reactions would add very little to their running costs. Box 13.3 illustrates one example of this approach.

Box 13.3. Active surveillance of specific types of toxicity in sentinel cohorts in Western Cape Province in South Africa

Data from two existing sentinel HIV cohorts in Gugulethu and Khayelitsha, Cape Town, were used to explore the time to, and reason for, single ARV drug substitutions among people receiving first-line ART. Single drug substitutions were used to indicate significant drug intolerance. This cohort analysis included 2679 individuals, all of whom were receiving therapy based on non-nucleoside reverse-transcriptase inhibitors. This study found that substitutions from toxicity occurred early for nevirapine, efavirenz and zidovudine, with 8%, 2% and 8% of people respectively having substitutions by three years. The rates of substitution for stavudine (owing to symptomatic hyperlactataemia, lipoatrophy and peripheral neuropathy) continued to accumulate over time, reaching 21% by three years. Women weighing more than 75 kg and receiving ART for more than six months were found to be at increased risk of hyperlactataemia *(4)*. This, and other cohort studies, provided data that led to recommendations to avoid stavudine in obese women, and subsequently to tenofovir being recommended in WHO treatment guidelines in place of stavudine.

Cohort event monitoring

The cohort event monitoring approach is a prospective observational cohort study of adverse events[28] associated with one or more medicines. In cohort event monitoring, all adverse events occurring to a person taking ARV drugs are collected, irrespective of the causality or relationship with the ARV drugs. Cohort event monitoring would optimally involve recruiting about 15 000 to 20 000 people receiving an ARV regimen.

The advantages of cohort event monitoring (over spontaneous reporting) include the ability to produce rates of events, early detection of signals, fewer missing data and less reporting bias *(5)*.

However, cohort event monitoring requires a comprehensive cohort follow-up structure to be set up and therefore extensive financial and human resources. Where existing cohorts of people living with HIV receiving treatment are being monitored, efforts to include event monitoring into their existing monitoring and research activities may be reasonably cost-efficient. However, developing new cohorts exclusively for toxicity surveillance is not recommended. Box 13.4 presents an example of a cohort event monitoring approach.

Box 13.4. ART cohort event monitoring in the United Republic of Tanzania

The United Republic of Tanzania has started cohort event monitoring for ARV drugs, with 300 people being monitored at each of 10 implementing sites. Data-collection tools have been developed and introduced to various sites, with development of a cohort event monitoring manual and standard operating procedures and training of health care providers. Health care staff at participating sites have been trained on the use of CemFlow (a tool for collecting cohort event monitoring) for data management, and continuous monitoring and site supervision are now taking place.

Important considerations when developing a surveillance system

Surveillance priorities should be chosen for the local context, in consultation with national or regional clinical and epidemiological experts and WHO guidance. It is very important to choose surveillance approaches that are appropriate for these objectives and to integrate toxicity surveillance into routine monitoring and evaluation activities to efficiently use of resources. Targeted spontaneous reporting and active surveillance for specific types of toxicity within cohorts are complementary approaches and, where resources permit, adopting both approaches should be considered. Cohort event monitoring could be pursued when cohort studies with very large scope are planned or ongoing.

Individual monitoring for toxicity should be integral to delivering high-quality care. Facility-based records can

28. An adverse event is defined as "Any untoward medical occurrence that may present during the treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" *(9)*.

provide valuable information, if regular and accurate records are kept of key aspects of the care and treatment offered. Patient-monitoring systems also record information on clinical and laboratory toxicity monitoring for individual case management. When electronic medical record systems for people receiving ARV regimens are implemented, they will enable data extraction and aggregated reports generated through these systems could contribute towards documenting the impact of ARV-related toxicity on treatment outcomes *(6)*.

Data arising from spontaneous reports, other regulatory data and investigator-initiated research often contribute towards better understanding of the data derived from programmatic toxicity surveillance systems. Moreover, programmatic surveillance data can be used to improve the quality, efficacy and safety of medicines used nationally, by contributing to regulatory decision-making. Programme managers, drug regulators, academic researchers and pharmaceutical manufacturers therefore need to develop platforms that facilitate the exchange of information on the efficacy and safety of medicines used.

Table 13.1. Surveillance challenges and how to address them

Challenges	Solutions
Underreporting, poor quality of reports and reporter "fatigue" will occur within targeted spontaneous reporting systems	Solicit reports of important types of toxicity for a specific window in time. Field-test reporting forms and procedures before implementation. Provide training and information on why reporting priority types of toxicity is important. Give feedback so that stakeholders can appreciate that their reports are of value to the programme. Provide reporting guidelines, clinically appropriate case definitions and simple reporting procedures to all staff.
Poor quality of the denominator within sentinel cohorts	Provide necessary resources, to ensure accurate data for calculation of incidence. Use triangulation of approaches – use patient cohort data, pharmacy records and clinic registers to estimate denominators.
Wide differences among facilities in the ability to conduct both laboratory and clinical monitoring	Assess the availability of laboratory monitoring and diagnostic capacity at candidate sentinel sites. Match the surveillance approach to laboratory and clinical monitoring capacity.
Obtaining reliable and standardized causality assessment and decisions about the implications of findings for policy	Adopt an internationally recognized standardized and systematic approach to causality assessment. Establish a panel with the necessary expertise to review individual and collective data.
Sustainability	Provide frequent and relevant feedback to all stakeholders. Identify and address site staff concerns about the system on an ongoing basis. Limit reporting requirements (such as with electronic management systems).

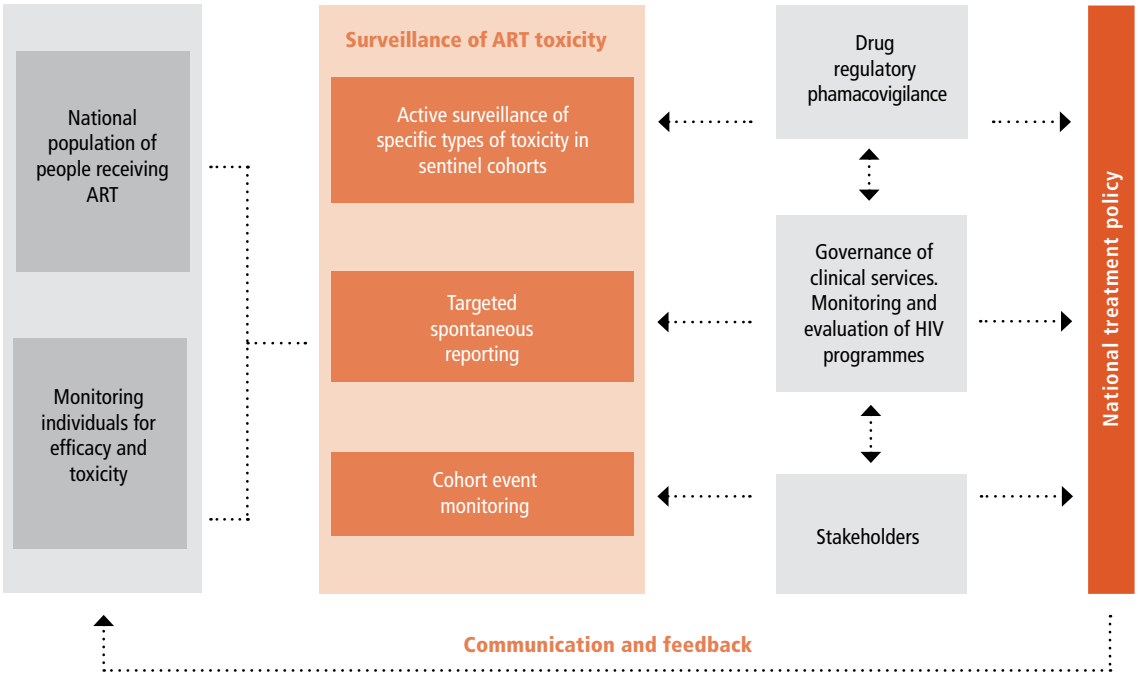
Improving care and informing national and global HIV treatment and prevention policies

The value of a national toxicity surveillance system lies in its ability to inform policy and improve clinical care (Fig. 13.1). This can be achieved by ensuring continual feedback and communication with relevant stakeholders, including patients and their communities, health care staff, district, state, provincial and national authorities, the medicines regulatory agency, pharmaceutical manufacturers, the media and the national and international scientific community.

All public communication with stakeholders needs to be skilfully prepared and relevant expertise used to ensure that messages are clear, informative, contextual and delivered in the appropriate format and forum.

A comprehensive communication plan, including a crisis-communication plan, needs to be developed as part of the surveillance system. If, for instance, the surveillance system identifies new significant risks associated with recommended treatment regimens that may warrant a revision of national guidelines, procedures should already be in place on how to handle such issues.

Table 13.1. Surveillance challenges and how to address them



What is WHO doing?

The 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)* recommend strengthening toxicity surveillance activities to increase evidence and inform future guidelines on toxicity in key areas.

In this context, WHO provides advocacy tools, technical guidance and assistance to countries and partner organizations for developing and implementing ARV toxicity surveillance and its inclusion into the monitoring and evaluation effort of antiretroviral therapy programmes.[29]

WHO is convening a Steering Group on ARV Toxicity Surveillance, comprising international experts and representatives of research agencies. The Group will advise WHO on the production of normative guidance and technical updates and enhance collaboration on toxicity surveillance to inform the clinical guidelines process.

WHO encourages countries to include ARV toxicity surveillance activities under the monitoring and evaluation component in the new Global Fund to Fight AIDS, Tuberculosis and Malaria funding model, to mobilize funding to support ART toxicity surveillance within ART programmes and programmes for preventing mother-to-child transmission *(7)*.

Pilot projects on toxicity surveillance that WHO has supported in several countries since 2011 informed the content of this briefing note. More information on these projects can be found at: http://www.who.int/hiv/topics/arv_toxicity/en/index.html.

29. WHO is working on a consolidated HIV monitoring and evaluation framework and global reporting that will include ARV toxicity monitoring as a key component. Technical consolidated guidance for monitoring and evaluation in HIV programmes will be available in 2014.

14. SUPPORTING THE DEVELOPMENT OF NATIONAL STRATEGIES FOR SURVEILLANCE OF HIV DRUG RESISTANCE

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 11 – Monitoring and evaluation

Key messages

- Preventing and assessing HIV drug resistance should be integrated into every national HIV programme. WHO recommends that countries put in place a comprehensive strategy to monitor the emergence and transmission of HIV drug resistance.
- Each element of the overall HIV drug resistance monitoring and surveillance strategy has been designed to support optimal programme management at every step along the treatment cascade, from treatment initiation to long-term viral load suppression. HIV drug resistance data should ideally be available to support global and national decision-making as ART guidelines for adults and children are regularly updated.
- Grants from the United States President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria can be used to facilitate the establishment or expansion of a national HIV drug resistance strategy. Investments in HIV drug resistance surveillance and monitoring should fall well within the monitoring and evaluation budget for ART programmes.
- Early-warning indicators for HIV drug resistance should be monitored at all facilities where ARV drugs are provided in the country.
- In the first quarter of 2014, WHO will release tools to assist programme managers design and cost HIV drug resistance surveillance adapted to their country contexts and needs.

Context

The 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection provide clinical and programmatic recommendations for scaling up antiretroviral therapy. Chapter 11 – "Monitoring and evaluation" – describes adaptations to monitoring and evaluation frameworks and systems that are needed to track the implementation and impact of these recommendations.

Surveillance of HIV drug resistance provides critical information to assess the performance of HIV treatment and prevention programmes, to support effective regimen selection and to optimize patient monitoring protocols. Specifically, HIV drug resistance surveillance is essential to predict the population-level efficacy of current and future first- and second-line therapy and pre- and post-exposure prophylaxis; reduce unnecessary switches to more costly and less well-tolerated regimens; optimize strategies for monitoring the people receiving treatment (such as frequency of viral load monitoring); and implement targeted interventions to improve care, treatment adherence and minimize HIV drug resistance.

The WHO global strategy for the surveillance and monitoring of HIV drug resistance comprises five key elements (Fig. 14.1):

- monitoring early-warning indicators;
- surveillance of HIV drug resistance in recently infected populations;
- surveillance of pre-treatment HIV drug resistance in populations initiating ART;
- surveillance of acquired HIV drug resistance in populations receiving ART; and
- surveillance of HIV drug resistance among children younger than 18 months of age.

Components of a comprehensive HIV drug resistance surveillance and monitoring strategy

Early-warning indicators

Early-warning indicators are indicators of the quality of care that assess factors associated with the emergence of HIV drug resistance. Early-warning indicators are designed to

be monitored at all ART clinics as part of routine monitoring and evaluation. Early-warning indicators can alert clinics and ART programmes to situations favouring the emergence of HIV drug resistance and provide an opportunity for corrective action to be taken. In 2011, the number of HIV drug resistance early-warning indicators was reduced from eight to five: (1) on-time pill pick-up, (2) retention in care, (3) pharmacy stock-outs, (4) dispensing practices and (5) viral load suppression (if viral load is routinely monitored). Standardized definitions and performance targets have been developed for each indicator, along with a colour-based scorecard system (Table 14.1).

Fig. 14.1. Five key elements of the WHO global strategy for the surveillance and monitoring of HIV drug resistance

Table 14.1. List of early-warning indicators and associated clinic-level targets

Early-warning indicator	Target
1. On-time pill pick-up	Red: <80% Amber: 80–90% Green: >90%
2. Retention in care	Red: <75% retained after 12 months of ART Amber: 75–85% retained after 12 months of ART Green: >85% retained after 12 months of ART
3. Pharmacy stock-outs	Red: <100% of a 12-month period with no stock-outs Green: 100% of a 12-month period with no stock-outs
4. Dispensing practices	Red: >0% dispensing of mono- or dual therapy Green: 0% dispensing of mono- or dual therapy
5. Viral load suppression at 12 months	Red: <70% viral load suppression after 12 months of ART Amber: 70–85% viral load suppression after 12 months of ART Green: >85% viral load suppression after 12 months of ART

Additional information to support country planning, including a more comprehensive description of indicators and associated targets, can be found at http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/index.html.

Surveillance of transmitted drug resistance in recently infected populations

This surveillance is designed to provide a national prevalence of transmitted HIV drug resistance among individuals likely to have been recently infected with HIV (within about three years of diagnosis) and unlikely to have been exposed previously to ARV drugs. The prevalence of transmitted drug resistance should be reported by individual drug class and overall. Data on transmitted HIV drug resistance to the classes of drugs being used in a country, together with data on HIV drug resistance in people for whom ART is failing, are essential to predict the likely efficacy of regimens used for pre- and post-exposure prophylaxis at the time of the survey.

For cost and feasibility reasons, WHO suggests that countries integrate transmitted drug resistance surveillance into pre-existing HIV surveillance systems or routine diagnostic testing activities (if the reporting system is centralized and the reporting rate exceeds 90%) to ensure the widest possible geographical reach. Examples of routine nationwide HIV surveillance activities designed to estimate HIV prevalence into which the surveillance of transmitted drug resistance may be integrated include: surveillance of HIV in men and women performed as part of a national household survey (such as Demographic and Health Surveys), surveillance of HIV prevalence among women attending antenatal clinics (antenatal surveillance), surveillance of HIV among people newly diagnosed with HIV infection (women and men) attending voluntary counselling and testing sites, or special populations, such as sex workers, men who have sex with men and people who inject drugs, often conducted as part of bio-behavioural surveys. A sample size of at least 200 specimens meeting eligibility criteria is recommended to provide the precision needed for adequate planning and programming.

Surveillance of pre-treatment drug resistance in populations initiating ART

Pre-treatment drug resistance surveys are designed to calculate a nationally representative prevalence estimate of HIV drug resistance among ARV-naive populations initiating ART. Information on previous exposure to ARV drugs will be collected from everyone enrolled in the survey and will be used to separately assess the resistance among individuals without previous ARV exposure. This distinction is justified by the fact that higher levels of HIV drug resistance are anticipated among ART initiators with previous ARV exposure. The results of pre-treatment drug resistance surveys inform the selection of optimal first-line regimens to maximize population-level impact.

Pre-treatment drug resistance surveillance is based on a cross-sectional survey, which involves observing a representative subset of a population at one specific point in time and uses a method known as a two-stage cluster design. In the first stage, 15–40 clinics are sampled from a list of all clinics that initiate ART in the country. In the second stage, consecutive eligible people initiating ART on or after a predefined survey start date are sampled and their specimens genotyped. The number of people to be sampled varies according to several factors. For budgeting purposes, countries can use 350 as an approximate number of specimens to be genotyped. It is recommended that the duration of sampling be limited to six months to ensure that the results are available in a timely fashion.

Surveillance of acquired drug resistance in populations receiving ART

The objective of surveys of acquired drug resistance is to calculate nationally representative point prevalence estimates (with associated confidence intervals) of viral load suppression and prevalence of HIV drug resistance in populations receiving antiretroviral therapy for 12 (±3) months and ≥48 months. According to programme needs and the feasibility of patient sampling, countries can decide whether to sample only populations receiving ART for 12 (±3) months or also sample people who have received ART for ≥48 months.

Acquired drug resistance surveillance is based on a cross-sectional survey, which involves observing a representative subset of a population at one time and uses a method known as a two-stage cluster design. First, 17–40 clinics are sampled from a list of all clinics dispensing ART in the country. Second, once clinics have been selected, consecutive eligible people receiving ART for 12 (±3) months and/or ≥48 months on or after a predefined survey start date are sampled. The specimens of those individuals for whom ART is found to be failing (defined as having a viral load above 1000 copies/ml) are subsequently genotyped. To correct for any potential survivor bias and to improve comparability across countries and over time, a representative estimate of retention, developed by reviewing a predefined number of patient files at the participating clinics, will be used to adjust the prevalence of viral load suppression among observable people for the proportion of individuals who have been lost to care. It is recommended that the duration of sampling be limited to six months to ensure that the results are available in a timely fashion.

Surveillance of HIV drug resistance among children younger than 18 months of age

The purpose of this survey is to calculate nationally representative point prevalence estimates (with associated confidence intervals) of initial drug-resistant HIV among children younger than 18 months of age and newly diagnosed with HIV. As ARV use for preventing mother-to-child transmission increases, the proportion of children who become infected with HIV despite prophylaxis for preventing mother-to-child transmission tends to decrease. However, among those infected, an increasing proportion is expected to harbour drug-resistant HIV. Data on HIV drug resistance among this population are therefore critical to inform the selection of optimal first-line ART regimens for children.

The default survey method is retrospective, since stored remnant dried blood spot samples collected for PCR diagnosis of children will be used for genotyping. In contrast to surveys of pre-treatment drug resistance and acquired drug resistance, the sampling unit in this case is the diagnostic laboratory and not the clinic where specimens were collected. When possible, all early infant diagnostic laboratories in the country should participate in the survey and thus contribute to the overall sampling.

The main survey outcome is the prevalence of HIV drug resistance, along with 95% confidence intervals, of relevant mutations and combinations of mutations leading to classifications of high, intermediate or low resistance to relevant drug classes and drugs. A generic protocol has been developed and is already available for country review and adaptation. It is available at http://apps.who.int/iris/bitstream/10665/75202/1/WHO_HIV_2012.17_eng.pdf.

Identifying the target populations

Each survey targets a specific population:

- transmitted drug resistance surveys: ARV-naive individuals likely to have been recently infected;
- pre-treatment drug resistance surveys: ARV-naive and ARV-exposed individuals initiating first-line ART (for their own health, preventing mother-to-child transmission, etc.);
- acquired drug resistance surveys: populations receiving ART at different time points (such as 12 (±3) months and/or ≥48 months); and
- surveys of children: children living with HIV younger than 18 months of age newly diagnosed with HIV by early infant diagnosis testing.

In concentrated epidemics with well-identified key populations at higher risk for HIV infection, such as men who have sex with men, sex workers and people who inject drugs, activities for preventing and assessing HIV drug resistance could be planned to target specific populations.

Strategy review and development

HIV drug resistance surveillance and monitoring should be integrated into every national HIV programme. Grants from the United States President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria can be used to facilitate the establishment of a national HIV drug resistance strategy, to maintain or expand existing programme activities or to add new programme components.

Country priorities may differ depending on their type of epidemic and on the status and coverage of their national ART programmes. Countries may also choose to stagger the implementation of the various survey components. Nevertheless, it is desirable that all ART clinics annually report early-warning indicators, although this can be accomplished in stages as clinic capacity is built. HIV drug resistance data should ideally be available to support national decision-making as ART guidelines for adults and children are regularly updated to ensure the delivery of the most effective interventions to everyone in need.

The development of a robust plan involves (1) performing situation analysis to take stock of the country's existing HIV drug resistance monitoring and assessment strategy, (2) reviewing available data describing the prevalence and patterns of transmitted, pre-treatment drug resistance in adult and infants, and acquired drug resistance among adults and children, (3) identifying any data gaps that must be addressed given the country's programmatic priorities and (4) developing a costed strategy, aligned with the broader national HIV strategy, outlining how the various elements of the HIV drug resistance strategy will be implemented and how they will be funded.

Various factors influence the cost of an HIV drug resistance survey, such as the number of specimens to be genotyped, the number of sites included in the survey as well as the prices of genotyping and, when applicable, viral load tests. However, it should fall well within the accepted proportion of an ARV programme's budget that should be allocated to monitoring and evaluation activities. A more detailed briefing note, with budget examples, has been developed to assist countries as they prepare their national strategies and will be available online on the WHO website.

Table 14.2 provides a summary of HIV drug resistance surveys and their relevance for optimal programme management.

Table 14.2. Summary of drug resistance surveys

Type of survey	Population of interest	Measure	Programmatic relevance
Transmitted drug resistance	ARV-naive, recently infected individuals	National estimate of level and patterns of transmitted HIV drug	Transmitted drug resistance can compromise the effectiveness of ARV drugs in preventing HIV transmission among uninfected individuals and may compromise the efficacy of first-line ART when recently infected populations require it.
Pre-treatment drug resistance	ARV-naive individuals initiating ART	Nationally representative estimates of HIV drug resistance among ARV-naive individuals about to start ART	The presence of HIV drug resistance before ART initiation can compromise both the therapeutic as well as the prevention benefits of first-line ART.
	ARV-exposed individuals initiating ART	Regional or global estimates of HIV drug resistance among ARV-exposed individuals about to start ART	
Acquired drug resistance	Individuals receiving antiretroviral therapy for 12 (±3) months and/or ≥48 months	Nationally representative estimate of viral load suppression and levels and patterns of HIV drug resistance among individuals receiving treatment at 12 (±3) and/or ≥48 months	Acquired drug resistance may compromise the effectiveness of second-line ART among individuals receiving ART and may, if transmitted, negatively affect the effectiveness of first-line ART among individuals starting first line in the future, as well as that of pre-exposure prophylaxis and post-exposure prophylaxis.
HIV drug resistance among children younger than 18 months	Children living with HIV younger than 18 months newly diagnosed with HIV by early infant diagnosis testing	Estimate of HIV drug resistance among newly infected children undergoing early infant diagnosis	As ARV drug use for preventing mother-to-child transmission increases, the proportion of children who become infected with HIV despite prophylaxis for preventing mother-to-child transmission tends to decrease. However, among those infected, an increasing proportion is expected to harbour drug-resistant HIV strains. HIV drug resistance data are thus essential to select optimal first-line ART regimens for children.

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Supplementary sections to Chapter 5 – HIV diagnosis and ARV drugs for HIV prevention

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Supplementary sections to Chapter 9 – Guidance on operations and service delivery

Chapter 8. Phasing out stavudine: progress and challenges

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Supplementary sections to Chapter 11 – Monitoring and evaluation

Chapter 12. Surveillance of the toxicity of antiretroviral drugs during pregnancy and breastfeeding

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