

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.

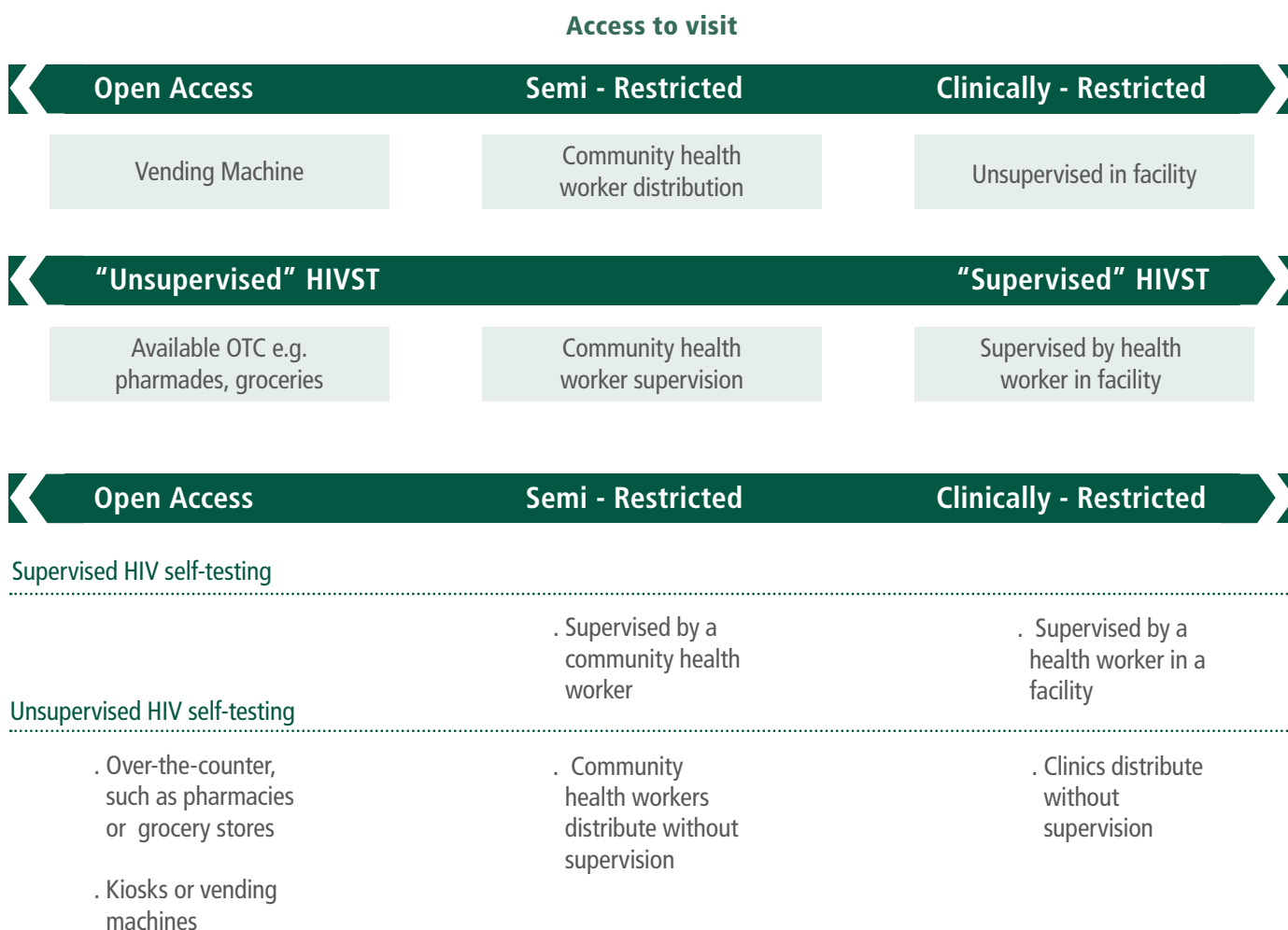
3. These terms describe approaches to HIV self-testing reported in current literature; they are not intended as WHO guidance or recommendations.

“Supervised” or “unsupervised” self-testing³

“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



“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 an 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

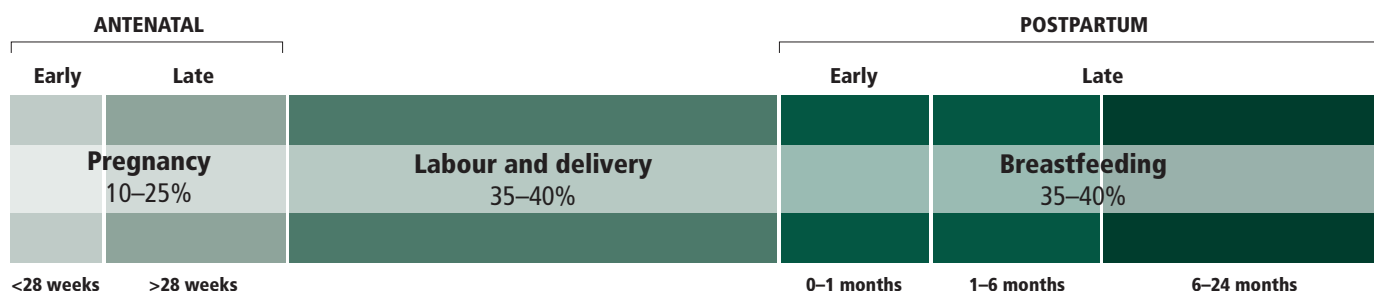
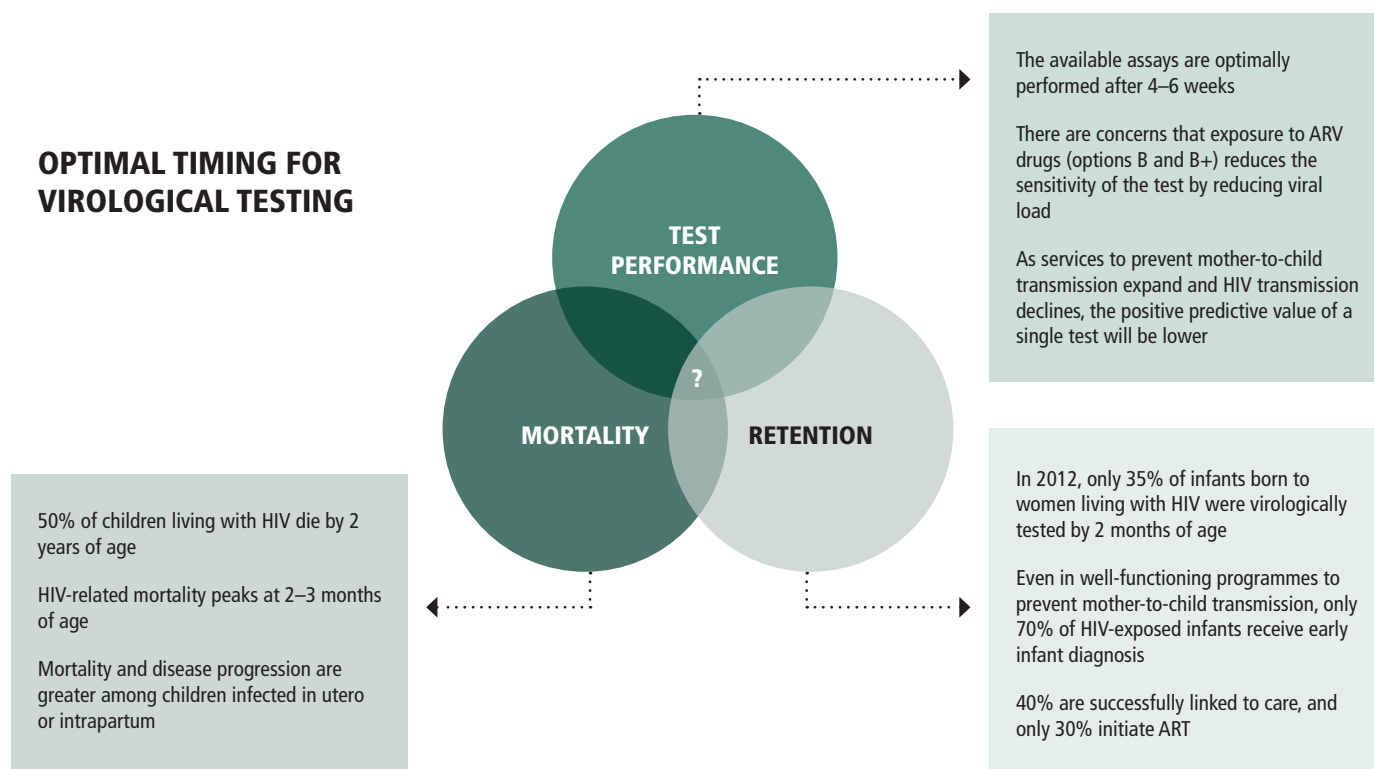


Fig. 2.2. Optimal timing of HIV virological testing depends on test performance, mortality patterns and retention in the treatment and care cascade



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).

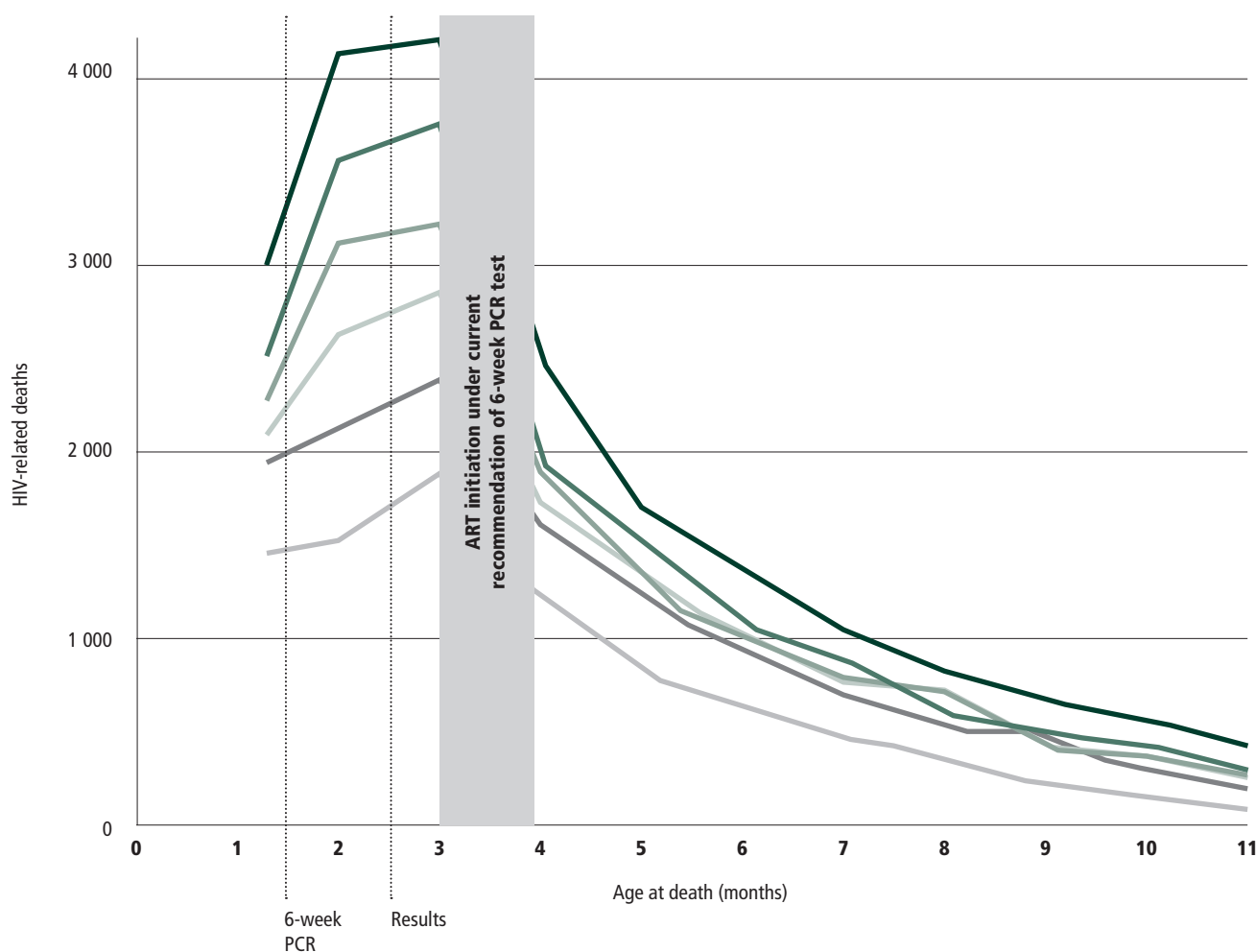
Data from several cohorts, including non-breastfeeding infants, suggest that using combination ARV regimens to prevent mother-to-child transmission might delay the time to detect HIV DNA and/or RNA in the infants acquiring HIV despite interventions for preventing mother-to-child transmission (9,16). 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



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

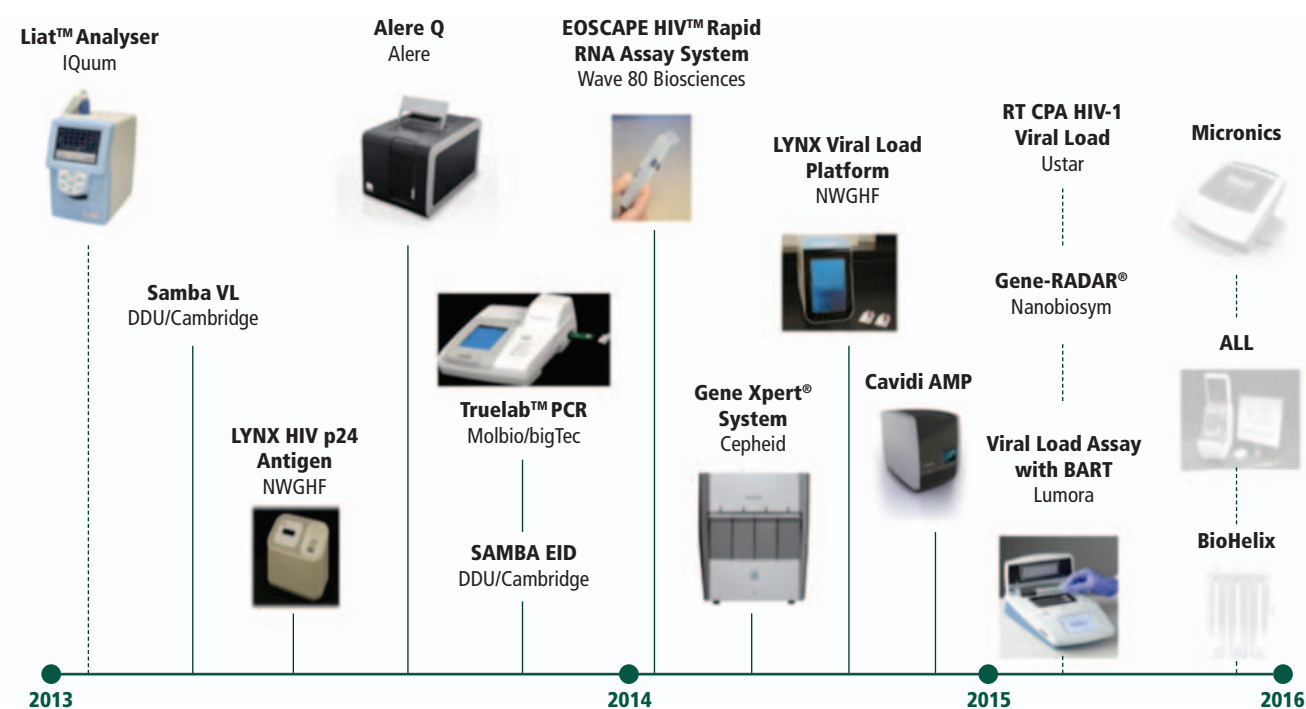
assessments and consideration of whether birth testing could be implemented in future. This area will be reviewed when the guidelines are updated in early 2015.

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

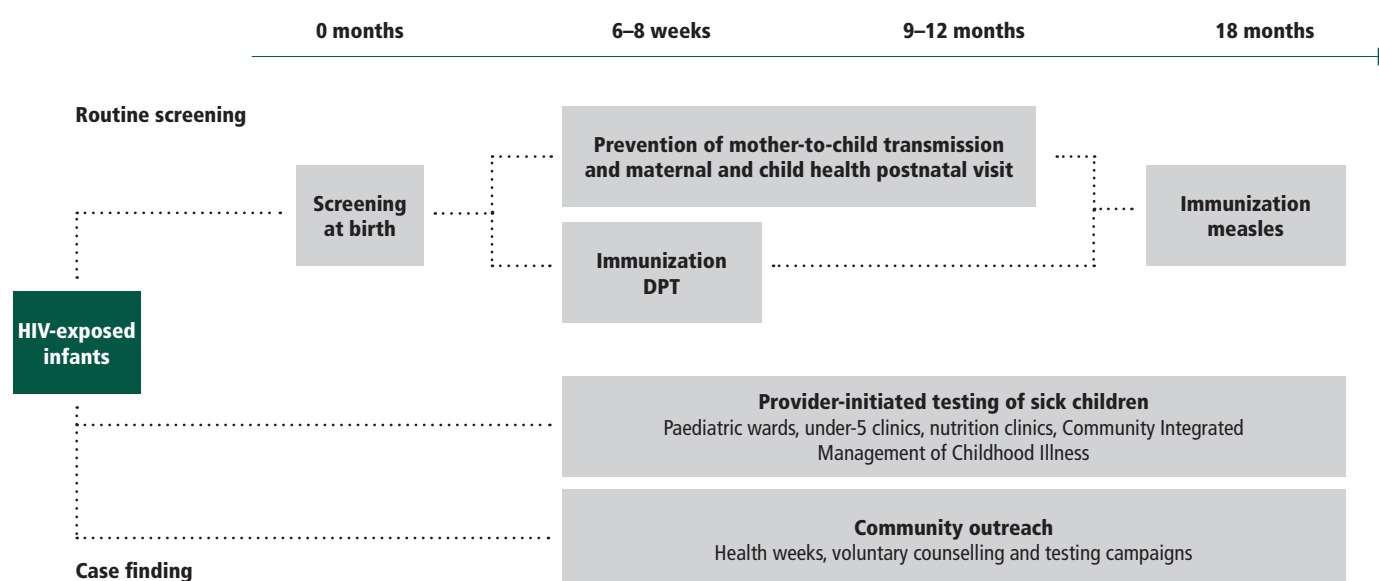
geographic disparities (45). As there is now significant variation in early infant diagnosis coverage, additional attention should be given to the countries and regions where early infant diagnosis coverage remains the lowest.

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



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

- 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 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

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

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 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.

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)

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.

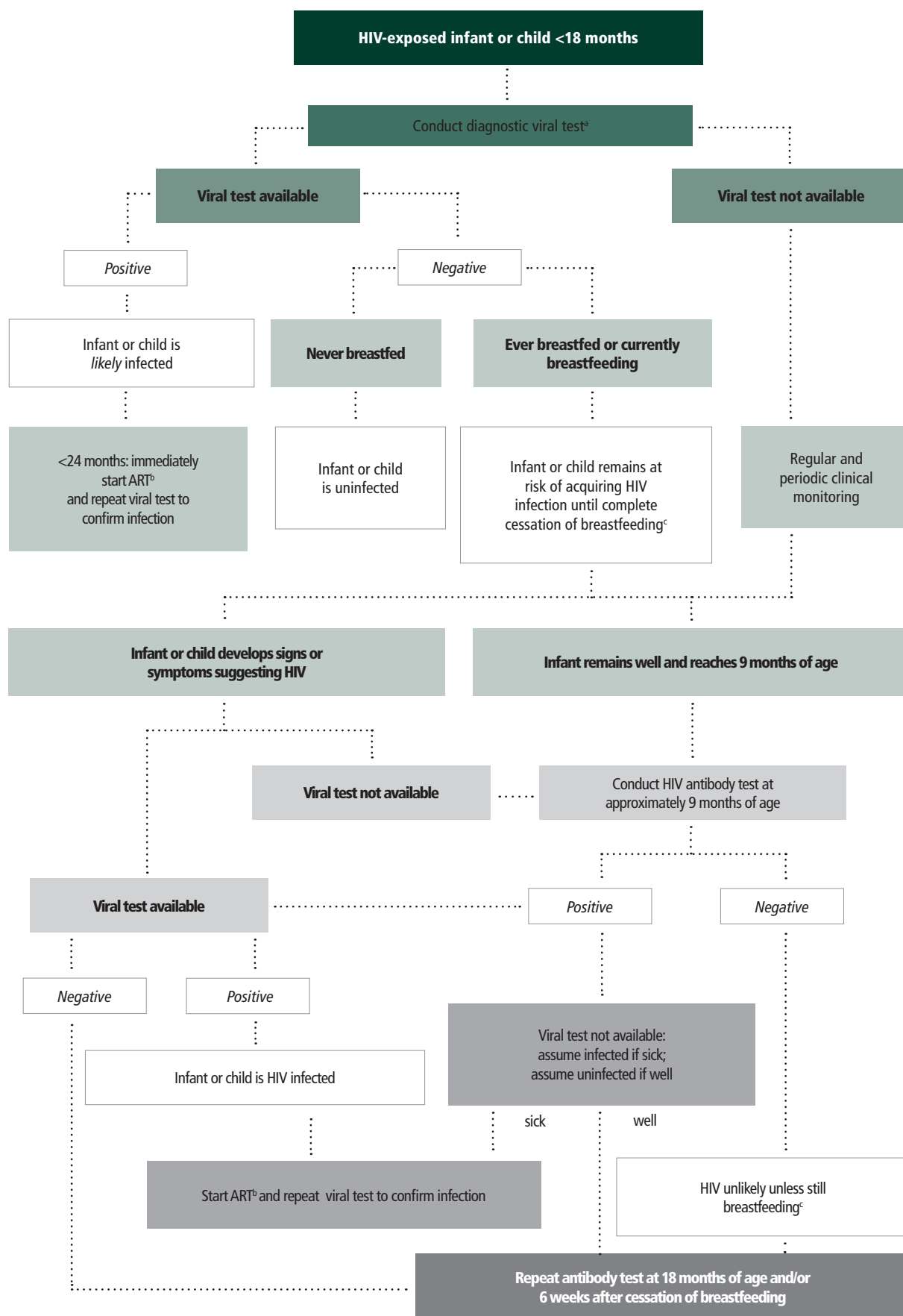
As new consolidated guidelines are anticipated in early 2015, clear questions were identified to frame the evidence review that is required to revise the current WHO recommendations in line with the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) requirements (<http://www.gradeworkinggroup.org>) 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 a care and preventing mother-to-child transmission	
<ul style="list-style-type: none"> All pregnant women All infants of HIV-infected mothers All infants with mothers of unknown status 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> All pregnant women All infants of HIV-infected mothers All infants with mothers of unknown status 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> All infants born to HIV-infected mothers (if not previously tested) All infants with mothers of unknown status 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> All infants, children and adolescents diagnosed with TB All infants, children and adolescents with suspected TB 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> Adolescents presenting for contraception Adolescents presenting with menstrual concerns Adolescents presenting for treatment of sexually transmitted infections Adolescents presenting for male circumcision 	<ul style="list-style-type: none"> Serological assay (HIV rapid test or HIV ELISA)
Orphans and vulnerable children	
<ul style="list-style-type: none"> Orphans in institutional care Disabled children in institutional care Children who are the victims of sexual abuse 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> Children and partners of adults living with HIV 	<ul style="list-style-type: none"> 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.