CLINICAL GUIDELINES: HIV DIAGNOSIS

2

2 CLINICAL GUIDELINES: HIV DIAGNOSIS

2.1 Introduction

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

The overarching goals of HTS are as follows:

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

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

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

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

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

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

- **Counselling**: Pre-test information can be provided in a group setting, but all people should have the opportunity to ask questions in a private setting if they request it. All HIV testing must be accompanied by appropriate and high-quality post-test counselling, based on the HIV test result and HIV status reported. QA mechanisms as well as supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling.
- **Correct**: Providers of HIV testing should strive to provide high-quality testing services. Quality management systems (including QA) should be in place for all HTS, regardless of where testing takes place, to ensure that people receive a correct diagnosis. QA should include both internal and external measures, and should receive support from the national reference laboratory. All people who receive a positive HIV diagnosis should be retested to verify their diagnosis before initiation of HIV care or treatment.
- **Connection**: Linkage to prevention, treatment and care services should include effective and appropriate follow-up, including long-term prevention and treatment support.

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

2.2 Retesting prior to enrolment in care

Recommendations

- National programmes should retest all people newly and previously diagnosed with HIV before they enrol in care and initiate ART.
- Retesting people on ART is not recommended, as there are potential risks of incorrect diagnosis, particularly for in vitro diagnostics (IVDs) that use oral fluid specimens.

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

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

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

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

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

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

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

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

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

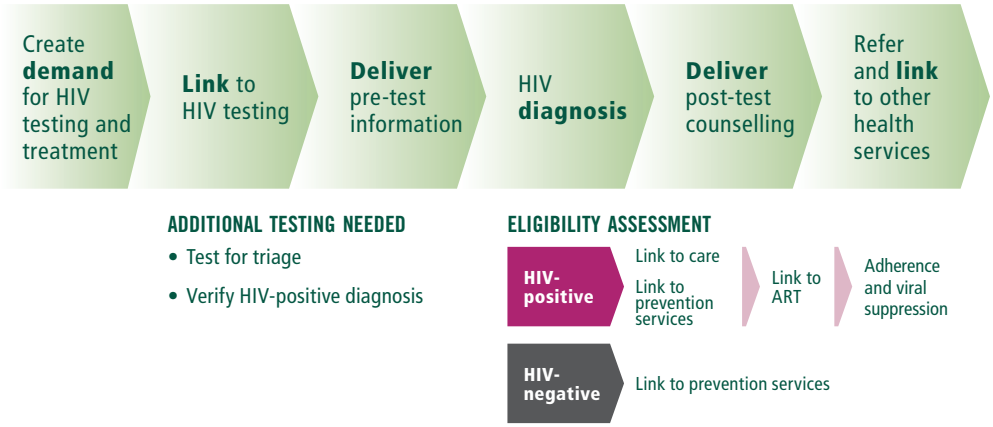
2.3 Pre- and post-test services

2.3.1 Overview

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

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

Fig. 2.1. Continuum of linkage to care and prevention



Recommendation

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

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

2.3.2 Pre-test services

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

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

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

- the services available in the case of an HIV-positive diagnosis, including where ART is provided;
- a brief description of prevention options and encouragement of partner testing;
- the fact that the test result and any information shared by the client are confidential;
- the fact that the client has the right to refuse to be tested;
- potential risks to the client, especially for those whose sexual or other behaviour is stigmatized;
- an opportunity to ask the provider additional questions; and
- provision of informed consent for testing.

2.3.3 Post-test services

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

- an explanation of the test result;
- information on methods to prevent HIV acquisition and provision of male and/or female condoms, lubricant and guidance on their use;
- emphasis on the importance of knowing the status of sexual partners and information about the availability of partner and couples testing services;
- referral and linkage to relevant HIV prevention services, such as needle and syringe programmes, opioid substitution therapy for people who inject drugs, post-exposure prophylaxis, pre-exposure prophylaxis and, in priority countries, voluntary medical male circumcision (VMMC);
- advice to people who test negative but report recent risky behaviour to return in 4 weeks for repeat testing; if they again test HIV negative after 4 weeks, people with ongoing risk should be advised to return for testing every 6–12 months;
- encouragement of partner testing when pregnant women test HIV negative in high-prevalence settings, as incident HIV in pregnancy and during the postpartum period is associated with a high risk of mother-to-child transmission; and
- no requirement for repeat testing (window period) for people who report no recent risk.

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

- an explanation of the test result and diagnosis, giving the client time to consider the result and helping the client to cope with emotions arising from the diagnosis;
- discussion of immediate concerns and help for the client to decide who in his or her social network may be available to provide immediate support;
- assessment of the risk of intimate partner violence and discussion of possible steps to ensure the client's physical safety;
- assessment of the risk of suicide, depression and other mental health consequences of an HIV-positive diagnosis and referral to relevant services;

- clear information on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to access ART;
- arranging a specific date and time for active referral and follow-up of clients who are unable to enrol in HIV care on the day of diagnosis;
- information on how to prevent transmission of HIV, including information on the reduced transmission risks when virally suppressed on ART;
- provision of male or female condoms and lubricants and guidance on their use;
- discussion of the risks and benefits of disclosure, particularly among couples and to partners, and couples counselling should be offered to support mutual disclosure;
- encouragement and offer of HIV testing for sexual partners, children and other family members, which can be done individually, through couples testing, index case testing, family testing or partner notification;
- provision of or referral to prevention, counselling, support and other services as appropriate, including screening and treatment for tuberculosis (TB) and sexually transmitted infections (STIs), prophylaxis for opportunistic infections, contraception, antenatal care, opioid substitution therapy, and access to sterile needles and syringes; and
- offering time for the client to ask additional questions.

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

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

- discussion of childbirth plans and encouragement to deliver in a health facility for personal well-being and to ensure access to services for PMTCT;
- use of ARV drugs both for the client's health and to prevent transmission to the infant;
- the importance of partner testing and information on the availability of couples testing services;
- ensuring screening for TB and testing for other infections, such as syphilis and hepatitis B;
- counselling on maternal nutrition, including iron and folic acid, advice on infant-feeding options and support to carry out the mother's infant-feeding choice; and
- HIV testing for the infant and necessary follow up for HIV-exposed infants.

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

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

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

- tailored advice with linkage to HIV care and treatment;
- counselling, referral and linkage to specific psychosocial and mental health services tailored to both the situation in which infection happened and the developmental age of the individual;
- information on adolescent rights and responsibilities, especially the right to confidentiality;
- counselling, referral and linkage to specific sexual and reproductive health services, including contraception, and an opportunity to ask questions and discuss issues related to sexuality;
- individualized planning on how, when and to whom to disclose the HIV status; and
- referral for group counselling and peer support groups.

2.4 Principles of and approaches to service delivery

2.4.1 Improving quality and efficiency

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

- integration of HTS with other health services;
- decentralization of HTS to primary health-care facilities and outside the health system; and
- task-sharing of HTS responsibilities to increase the role of trained lay providers.

Integration

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

Decentralization

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

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

Task-sharing

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

Recommendation

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

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

2.4.2 HIV testing service approaches

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

Facility-based HIV testing services

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

Recommendations

Generalized HIV epidemic

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

Concentrated HIV epidemic

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

Regardless of epidemic type

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

Sources:

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

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

Community-based HIV testing services

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

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

Recommendations

Generalized HIV epidemic

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

Concentrated HIV epidemic

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

Sources:

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

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

HIV self-testing

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

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

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

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

2.5 HIV diagnosis in infants and children

2.5.1 Overview

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

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

Recommendations

- It is strongly recommended that HIV serological assays used for the purpose of clinical diagnostic testing have a minimum sensitivity of 99% and specificity of 98% under quality-assured laboratory conditions (strong recommendation, moderate-quality evidence).
- It is strongly recommended that HIV virological assays used for the purpose of clinical diagnostic testing (usually at or after 6 weeks of age) have a sensitivity of at least 95% and ideally more than 98%, and specificity of 98% or more under quality-assured, standardized and validated laboratory conditions (strong recommendation, moderate-quality evidence).
- It is strongly recommended that HIV virological testing be used to diagnose HIV infection in infants and children below 18 months of age (strong recommendation, high-quality evidence).
- In infants and children undergoing virological testing, the following assays (and respective specimen types) are strongly recommended for use: HIV DNA on whole blood specimen or DBS; HIV RNA on plasma or DBS; Us p24Ag on plasma or DBS (strong recommendation, high-quality evidence).
- It is strongly recommended that all HIV-exposed infants have HIV virological testing at 4–6 weeks of age or at the earliest opportunity thereafter (strong recommendation, high-quality evidence).
- In infants with an initial positive virological test result, it is strongly recommended that ART be started without delay and, at the same time, a second specimen be collected to confirm the initial positive virological test result. Do not delay ART. Immediate initiation of ART saves lives and should not be delayed while waiting for the results of the confirmatory test (strong recommendation, high-quality evidence).
- It is strongly recommended that test results from virological testing in infants be returned to the clinic and child/mother/caregiver as soon as possible, but at the very latest within 4 weeks of specimen collection. Positive test results should be fast-tracked to the mother–baby pair as soon as possible to enable prompt initiation of ART (strong recommendation, high-quality evidence).
- It is strongly recommended that all infants with unknown or uncertain[a] HIV exposure being seen in health-care facilities at or around birth or at the first postnatal visit (usually 4–6 weeks) or other child health visit have their HIV exposure status ascertained (strong recommendation, high-quality evidence).
- It is strongly recommended that HIV-exposed infants who are well undergo HIV serological testing at around 9 months of age (or at the time of the last immunization visit). Infants who have reactive serological assays at 9 months should have a virological test to identify HIV infection and the need for ART (strong recommendation, low-quality evidence).

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

- It is strongly recommended that infants with signs or symptoms suggestive of HIV infection undergo HIV serological testing and, if positive (reactive), virological testing (strong recommendation, low-quality evidence).
- It is strongly recommended that children (18 months or older) with suspected HIV infection or HIV exposure have HIV serological testing performed according to the standard diagnostic HIV serological testing algorithm used in adults (strong recommendation, high-quality evidence).

Sources:

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

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

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

2.5.2 Timing of virological testing

NEW

Recommendation

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

Background

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

Rationale and supporting evidence

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

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

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

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

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

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

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

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

Implementation considerations

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

- collection of data on performance and feasibility of birth testing during implementation;
- improvement of uptake and retention in the testing-to-treatment cascade;
- active tracking of infants with negative NAT at birth to ensure that they return at 6 weeks for retesting and co-trimoxazole initiation; and
- retesting of infants who test positive at birth with a second specimen as soon as possible. ART should be started immediately after the first positive test, and if the second specimen tests negative, a third NAT should be performed before interrupting ART.

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

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

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

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

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

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

Point-of-care early infant diagnosis

NEW

Recommendation

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

Background

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

Rationale and supporting evidence

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

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

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

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

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

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

Implementation considerations

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

Rapid diagnostic tests for HIV serology

NEW

Recommendations

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

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

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

Background

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

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

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

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

Rationale and supporting evidence

Assessing HIV exposure in infants and children younger than 18 months

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

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

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

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

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

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

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

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

HIV diagnosis in children older than 18 months

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

Implementation considerations for the use of RDTs in infants and children

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

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

NEW

Recommendations

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

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

NEW

Good practice statement

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

Background

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

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

Rationale and supporting evidence

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

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

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

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

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

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

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

Implementation considerations

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

Research gaps

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

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

2.6 Other priority populations

2.6.1 Adolescents

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

Recommendations

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

Generalized HIV epidemic

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

Concentrated HIV epidemic

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

Sources:

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

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

2.6.2 Pregnant women

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

Recommendations

High-prevalence settings

- PITC for women should be considered a routine component of the package of care in all antenatal, childbirth, postpartum and paediatric care settings. In such settings, where breastfeeding is the norm, lactating mothers who are HIV negative should be retested periodically throughout the period of breastfeeding.
- All HIV-negative pregnant women should be retested in the third trimester, postpartum and/or during labour, because of the high risk of acquiring HIV during pregnancy.

Low-prevalence settings

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

Sources:

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

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

2.6.3 Couples and partners

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

Recommendations

- Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure. This applies also to couples and partners from key populations (strong recommendation, low-quality evidence).
- In antenatal care settings, couples and partners should be offered voluntary HIV testing services with support for mutual disclosure (strong recommendation, low-quality evidence).
- HIV testing services for couples and partners, with support for mutual disclosure, should be offered to individuals with known HIV status and their partners (strong recommendation, low-quality evidence for all people with HIV in all epidemic settings; conditional recommendation, low-quality evidence for HIV-negative people depending on the country-specific HIV prevalence).

Sources:

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

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

2.6.4 Men

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

2.6.5 Key populations

Recommendations

- HIV testing services should be routinely offered to all key populations in the community, in closed settings such as prisons and in facility-based settings.
- Community-based HIV testing services for key populations linked to prevention, treatment and care services are recommended, in addition to routine facility-based HIV testing services, in all settings (strong recommendation, low-quality evidence).

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

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

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

2.7 Diagnostics

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

Recommendations

High-prevalence settings

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

Low-prevalence settings

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

All settings

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

Sources:

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

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

References

1 Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/, accessed 23 September 2015).

2 WHO reminds national programmes to retest all newly diagnosed people with HIV. WHO information note – 22 October 2014. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/vct/retest-newly-diagnosed-plhiv-full/en/, accessed 23 September 2015).

3 Jaspard M, Le Moal G, Saberan-Roncato M, Plainchamp D, Langlois A, Camps P et al. Finger-stick whole blood HIV-1/-2 home-use tests are more sensitive than oral fluid-based in-home HIV tests. PLoS One. 2014;9(6): e101148.

4 Malamud D, Friedman HM. HIV in the oral cavity: virus, viral inhibitory activity, and antiviral antibodies: a review. Crit Rev Oral Biol Med. 1993;4:461–6.

5 Stekler JD, O'Neal JD, Lane A, Swanson F, Maenza J, Stevens CE et al. Relative accuracy of serum, whole blood and oral fluid HIV tests among Seattle men who have sex with men. J Clin Virol. 2013:58(Suppl. 1): e19–22.

6 Guidance on HIV disclosure counselling for children 12 years of age and younger. Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/hiv_disclosure/en/, accessed 26 October 2015).

7 HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/adolescents/en/, accessed 26 October 2015).

8 Delivering HIV test results and messages for re-testing and counselling in adults. Geneva: World Health Organization; 2010 (http://www.who.int/hiv/pub/vct/hiv_re_testing/en/index.htm, accessed 15 November 2015).

9 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en/, accessed 23 September 2015).

10 Suthar A, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med. 2013; 10(8).

11 Statement on HIV testing and counseling: WHO, UNAIDS re-affirm opposition to mandatory HIV testing. 28 November 2012 (http://www.who.int/hiv/events/2012/world_aids_day/hiv_testing_counselling/en/, accessed 31 October 2015).

12 Marston M, Becquet R, Zaba B, Moutleon LH, Gray G, Coovadia H et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol. 2011;40(2):385–96.

13 Newell M, Coovadia H, Cortina Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004; 364(9441): 1236–43.

14 Moodley D, Bobat RA, Coutsoudis A and Coovadia HM. Predicting perinatal human immunodeficiency virus infection by antibody patterns. Pediatr Infect Dis J. 1995;14(10):850–2.

15 Chantry CJ, Cooper ER, Pelton SI, Zorilla C, Hillyer GV, Diaz C. Seroreversion in human immunodeficiency virus-exposed but uninfected infants. Pediatr Infect Dis J. 1995;14(5);382–7.

16 UNAIDS. Global AIDS Response Progress Reporting 2015. (In press) (http://www.unaids.org/en/resources/documents/2015/GARPR_2015_guidelines, accessed 31 October 2015).

17 Chatterjee A, Tripathi S, Gass R, Hamunime N, Panha S, Kiyaga C et al. Implementing services for early infant diagnosis (EID) of HIV: a comparative descriptive analysis of national programs in four countries. BMC Public Health. 2011; 11:553.

18 Penazzato M, Revill P, Prendergast AJ, Collins IJ, Walker S, Elyanu PJ et al. Early infant diagnosis of HIV infection in low-income and middle-income countries: does one size fit all? Lancet Infect Dis. 2014; 14(7): 650–5.

19 Ciaranello AL, Park JE, Ramirez-Avila L, Freedberg KA, Walensky RP, Leroy V. Early infant HIV-1 diagnosis programs in resource-limited settings: opportunities for improved outcomes and more cost-effective interventions. BMC Med. 2011;9:59. doi: 10.1186/1741-7015-9-59.

20 March 2014 Supplement to the 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and prevention HIV infection. Geneva; World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en/, accessed 16 October 2015).

21 Bourne DE, Thompson M, Brody LL, Cotton M, Draper B, Laubscher R et al. Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa. AIDS. 2009;23(1):101–6.

22 Innes S, Lazarus E, Otwombe K, Liberty A, Germanus R, Van Rensburg AJ et al. Early severe HIV disease precedes early antiretroviral therapy in infants: are we too late? J Int AIDS Soc. 2014;17:18914.

23 Burgard M, Blanche S, Jasseron C, Descamps P, Allemon MC, Ciraru-Vigneron N et al. Agence Nationale de Recherche sur le SIDA et les Hepatites virales French Perinatal Cohort. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. J Pediatr. 2012; Jan;160(1):60–-6.e1.

24 Nielsen-Saines K, Watts DH, Veloso VG, Bryson YJ, Joao EC, Pilotto JH et al. NICHD HPTN 040/PACTG 1043 Protocol Team. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med. 2012 Jun 21;366(25):2368–-79.

25 Mallampati D, Hannaford A, Sugandhi N, Markby J, Penazzato M. The performance of virological testing for early infant diagnosis of HIV: a systematic review [Poster]. 7th International Workshop on HIV Pediatrics, 2015; Vancouver, Canada, 2015 (http://www.who.int/hiv/pub/posters/ias2015-poster8/en/, accessed 15 November 2015).

26 International Community of Women Living with HIV (ICW) and Global Network of People Living with HIV (GNP+). Early infant diagnosis: understanding the perceptions, values and preferences of women living with HIV in Kenya, Namibia and Nigeria. 2015. (http://www.emtct-iatt.org/wp-content/uploads/2015/08/ICW-GNP-Early-Infant-Diagnosis-Perspectives-of-Women-Living-with-HIV.pdf, accessed 31 October 2015).

27 Ciaranello A on behalf of the CEPAC-Pediatric Team Massachusetts General Hospital. Strategies for early infant diagnosis (EID) among known HIV-exposed infants: model-based analyses. Web Supplement C.

28 Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171–80.

29 Mallampati D, Markby J, Doherty M, Penazzato M. The impact of adding a virological testing at birth to the existing WHO infant testing algorithm in the 21 Global Plan countries. In: International Workshop on HIV Pediatrics, 2015; Vancouver, Canada (http://www.infectiousdiseasesonline.com/7th-hivped-workshop_presentations/, accessed 15 November 2015).

30 Ochodo E, Mallett S, Soares-Weiser K, Kakourou A, Deeks J. A systematic review of point-of-care tests for early infant diagnosis (POC EID) of HIV. Web Supplement B.

31 Jani IV, Meggi B, Mabunda N, Vubil A, Sitoe NE, Tobaiwa O et al. Accurate early infant HIV diagnosis in primary health clinics using a point-of-care nucleic acid test. J Acquir Immune Defic Syndr. 2014;67(1):e1–4.

32 Odhiambo C, Zeh C, Ouma K. Evaluation of the simple amplification-based assay (SAMBA) qualitative point-of-care HIV-1 viral detection assay on whole blood among HIV-exposed infants in Western Kenya. ASLM International Conference 2014:44. [Oral session 3.3]

33 Hsiao NY, Kroon M, Dunning L, Myer L. Evaluation of the Alere q for point-of-care early infant HIV diagnosis in South Africa. In: Conference on Retroviruses and Opportunistic Infections 2015. 23–26 February 2015, Seattle, Washington [Abstract 34].

34 Herbert S, Carrick G, Edwards S, Copas A, George B, Long L et al. Enhancing services for HIV-positive patients: the role of point-of-care CD4 testing. HIV Med. 2011;12 (Suppl. 1):15. [Abstract P4].

35 Pinto IC, Sabidó M, Pereira AB, Mello MB, de Melo Xavier Shimizu A, Protti BL et al. Field evaluation of a point-of-care CD4 analyzer for monitoring HIV patients in the interior of the Amazon Region, Brazil. PLoS One. 2015;10(4):e0121400.

36 Mangwiro AZ1, Makomva K, Bhattacharya A, Bhattacharya G, Gotora T, Owen M et al. Does provision of point-of-care CD4 technology and early knowledge of CD4 levels affect early initiation and retention on antiretroviral treatment in HIV-positive pregnant women in the context of Option B+ for PMTCT? J Acquir Immune Defic Syndr. 2014;67 (Suppl 2):S139–44.

37 Garcia-Prats AJ, Draper HR, Sanders JE, Agrawal AK, Mohapi EQ, Schutze GE. False-negative post-18-month confirmatory HIV tests in HIV DNA PCR-positive children: a retrospective analysis. AIDS. 2012;26(15):1927–34.

38 Essajee S, Vojnov L, Penazzato M, Jani I, Siberry G, Fiscus R et al. Reducing mortality in HIV-infected infants and achieving the 90.90.90 target through innovative diagnoses approaches. J Int AIDS Soc. 2015, 18 (Suppl 6):20299.

39 Kuhn L, Schramm DB, Shiau S, Strehlau R, Pinillos F, Technau K et al. Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. AIDS. 2015;29(9):1053–60.

40 Payne H, Mkhize N, Otwombe K, Lewis J, Panchia R, Callard R et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the Children with HIV Early Antiretroviral Therapy (CHER) trial: a retrospective analysis. Lancet Infect Dis. 2015;15(7):803–9.

41 WHO recommendations on the diagnosis of HIV infection in infants and children. Geneva: World Health Organization; 2010 (http://www.who.int/hiv/pub/paediatric/diagnosis/en/, accessed 16 October 2015).

42 Deeks J, Mallett S, Perez Gonzalez M. A systematic review of rapid antibody tests for infant and childhood diagnosis of HIV exposure and infection. Web Supplement B.

43 Sanders GD, Anaya HD, Asch S, Hoang T, Golden JF, Bayoumi AM et al. Cost-effectiveness of strategies to improve HIV testing and receipt of results: economic analysis of a randomized controlled trial. J Gen Intern Med. 2010;25(6):556–63.

44 Schackman BR, Neukermans CP, Fontain SN, Nolte C, Joseph P, Pape JW et al. Cost-effectiveness of rapid syphilis screening in prenatal HIV testing programs in Haiti. PLoS Med. 2007;4(5):e183.

45 Uzochukwu BS, Obikeze EN, Onwujekwe OE, Onoka CA, Griffiths UK. Cost-effectiveness analysis of rapid diagnostic test, microscopy and syndromic approach in the diagnosis of malaria in Nigeria: implications for scaling-up deployment of ACT. Malar J. 2009;8:265.

46 Batwala V, Magnussen P, Hansen KS, Nuwaha F. Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. Malar J. 2011;10:372.

47 Cohn J, Whitehouse K, Trang T, Tuttle J, Lueck K. Where to test? Targeting pediatric HIV testing beyond PMTCT: a systematic review. Web Supplement B.

48 McCollum ED, Johnson DC, Chasela CS, Siwande LD, Kazembe PN, Olson D et al. Superior uptake and outcomes of early infant diagnosis of HIV services at an immunization clinic versus an "under-five" general pediatric clinic in Malawi. J Acquir Immune Defic Syndr. 2012;60(4):e107–10.

49 Asafo-Agyei SB, Antwi S, Nguah SB. HIV infection in severely malnourished children in Kumasi, Ghana: a cross-sectional prospective study. BMC Pediatr. 2013;13:181.

50 Sweeney S, Obure CD, Maier CB, Greener R, Dehne K, Vassall A. Costs and efficiency of integrating HIV/AIDS services with other health services: a systematic review of evidence and experience. Sex Transm Infect. 2012;88(2):85–99.

51 Ramirez-Avila L, Noubary F, Pansegrouw D, Sithole S, Giddy J, Losina E et al. The acceptability and feasibility of routine pediatric HIV testing in an outpatient clinic in Durban, South Africa. Pediatr Infect Dis J. 2013;32(12):1348–53.

52 Kranzer K, Meghji J, Bandason T, Dauya E, Mungofa S, Busza J et al. Barriers to provider-initiated testing and counselling for children in a high HIV prevalence setting: a mixed methods study. PLoS Med. 2014;11(5):e1001649.

53 Ndirangu J, Bärnighausen T, Tanser F, Tint K and Newell ML. Levels of childhood vaccination coverage and the impact of maternal HIV status on child vaccination status in rural KwaZulu-Natal, South Africa. Trop Med Int Health. 2009; 14(11):1383–93.

54 Goodson JL, Finkbeiner T, Davis NL, Lyimo D, Rwebembera A, Swartzendruber AL et al. Evaluation of using routine infant immunization visits to identify and follow-up HIV-exposed infants and their mothers in Tanzania. J Acquir Immune Defic Syndr. 2013;63(1): e9–e15.

55 UNAIDS. Global AIDS Response Progress Reporting 2015. (In press). (http://www.unaids.org/en/resources/documents/2015/GARPR_2015_guidelines, accessed 31 October 2015).

56 Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach. Geneva: World Health Organization; 2012 (http://www.who.int/hiv/pub/guidelines/9789241501972/en/, accessed 23 September 2015).

57 Laboratory quality management system: handbook. Geneva: World Health Organization; 2011 (http://www.who.int/ihr/publications/lqms/en/, accessed 16 October 2015).

58 Improving the quality of HIV-related point-of-care testing: ensuring reliability and accuracy of test results. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/199799/1/9789241508179_eng.pdf, accessed 11 February 2016).