1.1 EXECUTIVE SUMMARY

New HIV infections in children continue to occur globally and timely diagnosis and treatment of infants and children living with HIV remain critically important. The 2016 WHO ARV Consolidated Guidelines presented some innovative approaches, such as the use of nucleic acid testing (NAT) at or around birth for earlier diagnosis of HIV in infants, the introduction of point-of-care (POC) NAT for more rapid and decentralized diagnosis to enable prompt antiretroviral therapy (ART) initiation, and the use of enhanced postnatal prophylaxis (ePNP) to improve HIV prevention among infants exposed to HIV. To date, however, only a few countries have introduced these innovations and early lessons from the field have identified a number of implementation challenges that require careful review. Drawing on findings from a regional workshop held in Johannesburg, South Africa in 2017 and a follow-up expert meeting in Geneva, Switzerland in 2018, this programmatic update aims to describe changes in strategies for the identification, prevention and treatment of HIV in infants. This update will also highlight new information on the implementation of a postnatal package of care for HIV-exposed infants.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
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<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
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<td>ARV</td>
<td>antiretroviral drugs</td>
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<tr>
<td>AZT</td>
<td>azidothymidine (zidovudine)</td>
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<td>CTX</td>
<td>co-trimoxazole</td>
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<td>EID</td>
<td>early infant diagnosis</td>
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<td>ePNP</td>
<td>enhanced postnatal prophylaxis</td>
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<tr>
<td>FDC</td>
<td>fixed-dose combination</td>
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<tr>
<td>HCW</td>
<td>health-care worker</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HIVDR</td>
<td>HIV drug resistance</td>
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<tr>
<td>LPV/r</td>
<td>lopinavir/ritonavir</td>
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<td>MCH</td>
<td>mother and child health</td>
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<td>MTCT</td>
<td>mother-to-child transmission</td>
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<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child transmission</td>
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<td>NAT</td>
<td>nucleic acid test</td>
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<td>NVP</td>
<td>nevirapine</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>POC</td>
<td>point-of-care</td>
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<td>RAL</td>
<td>raltegravir</td>
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<tr>
<td>RDT</td>
<td>rapid diagnostics test</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<td>VL</td>
<td>viral load</td>
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2.1 BACKGROUND

2.1.1 Current status quo regarding pediatric HIV

The Global Plan Towards the Elimination of New HIV Infections among Children by 2015 and Keeping their Mothers Alive initiative has had a substantial impact, leading to a 60% reduction in new pediatric HIV infections in 21 high-burden countries in sub-Saharan Africa.\(^1,2\) Nevertheless, the burden of new HIV infections in children remains significant: in 2017, there were 180,000 new infections in children globally, and 70% of these children were in the same 21 priority countries. The Start Free, Stay Free, AIDS Free framework\(^3\) was developed to build on the progress of the Global Plan and to provide a roadmap to achieve fast-track targets towards ending the AIDS epidemic by 2030.

Following the adoption of the Option B+ policy\(^4\), the number of pregnant women on antiretroviral therapy (ART) has increased considerably across countries. This in turn has led to lower rates of vertical HIV transmission, now estimated to be less than 2% in non-breastfeeding populations, and less than 5% in breastfeeding populations.\(^5,6\) Despite the overall decrease in mother-to-child transmission (MTCT) of HIV, new pediatric infections continue to occur and transmission dynamics have now shifted towards a proportional increase in transmission during the postnatal period (Figure 1).\(^3,7\) Roughly half of all new infections among children occurs during breastfeeding. Although countries continue to make progress, challenges remain in retaining HIV-infected women in healthcare services and on effective ART throughout pregnancy and the breastfeeding period, as well as in detecting and preventing new HIV infections in women during pregnancy and breastfeeding. This shift in transmission dynamics has also raised issues concerning optimal testing in infants, with the identification of HIV-exposed and HIV-infected children continuing to present a significant bottleneck in several settings. Early infant diagnosis (EID) coverage globally still remains low: in 2016 only 43% of infants exposed to HIV received an HIV test within the first 2 months of life.\(^8\)

**Figure 1** MTCT transmission rates in the priority countries of the Start Free, Stay Free, AIDS Free framework in 2017 (Source: UNAIDS 2018 estimates)
Furthermore, although pediatric ART coverage has notably improved since 2010, only 51% of the estimated 1.8 million children living with HIV were receiving ART by the end of 2017. HIV-infected infants and younger children have an exceptionally high mortality without treatment, approximately 30% by the first year and 50% by their second year of life. Many HIV-related deaths in infants can be avoided by early identification of HIV and rapid ART initiation. Limited availability of optimal antiretroviral (ARV) formulations for preventing and treating HIV infection in newborn and young infants remains, however, an ongoing challenge in many countries.

2.1.2 Rationale for this technical update

The 2016 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection presented innovative approaches to diagnosis and treatment; however, to date only a few countries have started to implement these innovations. In addition, evidence from early adopter countries has raised a number of issues that require careful consideration and have generated lessons learned that may be useful for countries planning to adopt these interventions.

- Reduction in MTCT rates has led to a decrease in the positive predictive value of nucleic acid testing (NAT), resulting in higher proportions of false-positive test results. There is currently no specific recommendation on what level of viremia should be considered a true-positive result in infants and whether there is benefit in defining an indeterminate range for NAT.
- Significant drug exposure due to implementation of the Treat All policy and enhanced postnatal prophylaxis (ePNP) could cause delays in antibody development in infants with HIV infection. These dynamics may complicate the use of rapid diagnostic tests (RDTs) in infants to determine exposure and/or infection and affect how RDTs are used and interpreted in infants under 18 months of age.
- Addition of NAT at birth to the national infant testing algorithm has been considered by a number of countries. Several operational challenges have emerged and a critical review of these will be important to support the strategic introduction of birth testing where feasible and most appropriate.
- ePNP for high-risk infants is being implemented in a number of countries but challenges persist with identifying infants at high-risk and providing ePNP with existing formulations. This has led to simplified approaches, currently being considered by a number of countries, that may have an impact on infant testing.
- Greater emphasis should be placed on strengthening the postnatal package of care for HIV-exposed infants and their mothers. There are opportunities to consider combining successful interventions into packages in order to support service delivery, and placing greater importance on promoting the integration of services to ensure that infants are retained in care until final diagnosis.

Following the WHO regional workshop in Johannesburg, South Africa (June 2017), an expert meeting was convened in April 2018 to provide insight and promote discussion on these matters. This programmatic update aims to detail important changes and new implementation considerations arising since the publication of the 2016 WHO ARV Consolidated Guidelines.

3.0 KEY CONSIDERATIONS

3.1 Infant diagnosis

The complexity of EID testing is now growing due to significant scale up of Treat All (including pregnant and breastfeeding women), implementation of ePNP, reduced MTCT rates and the increased relative contribution of postnatal transmission. EID can no longer be considered primarily a one-test process, since it now requires additional testing over the duration of exposure. Accordingly, several additional key considerations will be necessary to strengthen the EID testing cascade through the entire exposure period. This includes ensuring that ART initiation is not delayed in those infants found to have HIV infection.

3.1.1 Minimising false-positive results by introducing an indeterminate range for EID

Although infant diagnosis is being scaled up globally, with increased access to Treat all, declining MTCT rates and low viremia observed in infants found to be infected with HIV mean that false-positive test results are increasingly being reported in programs. Some infants may therefore be incorrectly diagnosed as having HIV infection and started on lifelong ART unnecessarily. There is currently no specific recommendation on what level of viremia should be considered a true-positive result in infants and whether there is benefit to adding an indeterminate range to minimize false-positive test results (see Box 1).
A systematic review of 32 studies using an indeterminate range found 14,753 non-negative test results of which 2,436 (16.5% [95% CI 15.9–17.1%]) were indeterminate (data unpublished); one study reported the final diagnoses of indeterminate cases found that 76% of infants with an initial indeterminate test result were negative on repeat testing, suggesting these infants were not HIV-infected despite the initial non-negative test result. These data indicate that in countries not implementing an indeterminate range for NAT and where MCTC rates are low (<5%), 12.5% (76% of 16.5%) of non-negative results could be false-positive on initial testing with affected infants being potentially started on lifelong treatment unnecessarily.

Typically, EID assays detect the presence of HIV using real-time NAT technologies that often report cycle thresholds. Reported cycle thresholds represent the PCR cycle at which amplification is first observed and are inversely correlated to the amount of virus in the sample. The approximate equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay was selected as the optimal indeterminate range for further testing. This represented a balance between the proportion of infants living with HIV that would be incorrectly identified as indeterminate (about 8–13%) and the proportion of HIV-uninfected infants that would potentially start treatment unnecessarily (about 2–7%).

South Africa has already implemented an indeterminate range and developed a standard operating procedure (SOP) for managing positive and indeterminate test results. Similarly, WHO technical consultation developed a new SOP that will help to ensure higher quality infant testing (Annex 1). Current evidence suggests that no specific requirements are necessary with regard to the type of assay (conventional or point-of-care (POC)) used to retest specimens with indeterminate test results.

Most countries already apply a national SOP when testing errors are encountered (for example, device malfunction, insufficient or rejected specimen, etc.). In most countries the health-care facility concerned is contacted and asked to ensure that the infant returns to the facility in order to provide a new specimen for testing. Due to the delay caused by the testing error, these samples are generally considered urgent and prioritized for testing once received by the laboratory. A new study suggests that repeating an indeterminate test result using the same sample, if available, will resolve the majority (>95%) of indeterminate results. Therefore, prior to contacting the healthcare facility to request the infant return to the facility for collection of a new sample, a repeat test should be conducted on the same sample using additional available dried blood spots or remaining whole blood.

### 3.1.2 Confirmatory testing of positive test results

A cost-effectiveness analysis undertaken to assess the value of confirmatory testing in different scenarios highlighted that confirmatory testing is indeed cost-effective. Without confirmatory testing, this analysis showed that in settings with MTCT rates similar to those of South Africa, more than 10% of infants initiated on ART may in fact be HIV-uninfected. Confirmatory testing of positive test results using a new sample, as per WHO guidelines, may avoid this occurrence, although this policy is not consistently implemented (Box 2).

It remains critical that programs ensure all HIV-exposed infants are retained and tested appropriately throughout the entire exposure
Box 2. Prioritizing confirmatory testing of positive and indeterminate tests

- Decreasing MTCT rates globally have led to concerns about false-positive and indeterminate tests.
- Patients with indeterminate results need immediate repeat testing and the patient should be managed according to the SOP presented in Annex 1.
- Patients with repeated indeterminate results need a multidisciplinary team of health-care providers to support retention, tracking and status resolution.
- In ART programs, there is a need to prioritize confirmatory testing of all positive test results using a new sample.
- Clinical monitoring and further testing based on the national infant testing schedule need to be done until a definitive HIV status is established.

Period and all infants with a positive result receive a confirmatory test. Furthermore, those with repeatedly indeterminate test results should be actively tracked, retained, retested and their status resolved.

Finally, POC EID testing is being implemented in several countries and settings (see 3.1.3). Previously there was limited evidence on how to conduct confirmatory testing of POC EID positive test results, but since publication of the 2016 WHO ARV Consolidated Guidelines several studies have been published on its performance. Two POC EID technologies are now included on the WHO list of prequalified in vitro diagnostic products. Results from both laboratory and field studies have shown performance comparable to that of laboratory-based technologies. Furthermore, two patient impact studies have been published which highlight the significantly improved patient outcomes when using POC EID technologies. Based on this updated evidence, POC EID testing can be used to confirm positive test results.

3.1.2 Managing discordant results and treatment interruption

Since 2010, WHO has recommended initiating infants on ART after an initial positive NAT, while simultaneously collecting a confirmatory sample. The 2016 WHO ARV Consolidated Guidelines suggest that if the second (confirmatory) NAT is negative, a third NAT, either EID (qualitative) or viral load (VL), should be performed before considering ART interruption. The introduction of an indeterminate range should potentially reduce the number and proportion of infants with discordant test results (different NAT results on separate samples); however, guidance on how to conduct treatment interruptions is needed.

Several factors should be considered when assessing patients for ART interruption after discordant test results (positive then a negative result) are followed by a third test with a negative result:

- the infant ought to have no clinical signs or symptoms suggestive of HIV infection;
- a follow-up plan should be agreed upon with family, caregiver(s) and health-care staff;
- tracking information (phone, address, etc.) of the family/caregiver(s) should be collected and confirmed.

The following factors should be considered when following up any infant undergoing treatment interruption:

- there is a need for active follow-up to ensure that a potentially infected infant is retained and re-initiated on treatment if virological rebound occurs;
- virological rebound in HIV-infected infants starting treatment early is expected to happen within 8 months of interruption in >99% of HIV-infected infants;
- infants who develop signs and symptoms indicative of HIV infection should undergo immediate testing;
- breastfeeding and continued risk of transmission require follow-up and appropriate testing throughout the period of risk until final diagnosis;
- there is value in minimizing follow-up testing by leveraging existing opportunities for infant testing (based on the national infant testing schedule and immunization or well-child appointment schedules), until final diagnosis is ascertained.

Few countries have existing policies on how to conduct treatment interruptions in infants with discordant test results. South Africa, for one, has implemented policies with intensive laboratory and clinical follow-up of these infants for 18 months. Both EID (qualitative) and VL (quantitative) tests are performed at 4 weeks, 3 months, and every 3 months after treatment interruption. However, since the likelihood of these infants being HIV-infected is low, a less aggressive 8 month approach is also reasonable in order to simplify the follow-up procedure; this is supported by emerging evidence on the timing of viral rebound in HIV-infected infants treated early. In this case both EID (qualitative) and VL (quantitative) tests could be performed at 4 weeks, 4 months and 8 months after treatment interruption (Annex 2). Infants who test positive on any follow-up test in either protocol should be re-initiated on treatment as per current guidelines, and a confirmatory sample taken.

Any SOP for interruption should be implemented considering the continuous risk of transmission resulting from breastfeeding and, once the intensive follow up is completed (8 months after treatment interruption), the national infant testing schedule for HIV-exposed infants should be applied in order to ensure an appropriate final diagnosis. If breastfeeding has stopped prior to the end of the intensive follow up, final HIV status can be defined with NAT performed at least 6 weeks post cessation of breastfeeding, as indicated in Annex 2 Scenario b.
3.1.3 Implementation of POC EID testing

The 2016 WHO ARV Consolidated Guidelines recommend the use of NAT technologies for early infant HIV testing that have been developed and validated for use at or near the point-of-care. POC EID provides the opportunity to reduce test turnaround times, limit patient loss along the HIV testing cascade, reduce infant mortality and facilitate task shifting to lower cadres of health workers at healthcare facilities with decentralized services. Sufficient evidence has been generated on the performance of these assays in their intended field settings to support rapid national regulatory approval and initiation of scale-up (Box 3). A number of countries are currently implementing POC EID technologies. Implementation studies in Malawi and Mozambique have shown that using POC EID leads to significantly reduced test turnaround times, with a higher yield of results being returned to the health-care facility and caregivers, and earlier and higher rates of ART initiation among HIV-infected infants.

Key lessons learned during pilot implementation projects include:

- optimizing the use of POC EID through product and site selection;
- selecting health facilities with high prevalence and high volumes to maximize device utilization;
- considering placement within or in-facility referral from high-yield entry points (e.g. nutrition and pediatric wards);
- ensuring service continuity by establishing a service and maintenance strategy with suppliers and provide service engineer back-up;
- integrating services within health facilities by assessing the need for additional training and continuous mentoring of health-care workers (HCW);
- strengthening the linkage between services to ensure prompt linkage to care for identified HIV-infected infants;
- ensuring the availability of pediatric ARV formulations for neonates to guarantee earlier ART initiation.

Box 3. New POC EID technologies

- Two technologies have received WHO prequalification.
- National regulatory agencies are encouraged not to delay adoption by conducting further evaluations but instead to adopt a rapid and streamlined registration and national approval process for immediate implementation.

3.1.4 Introduction of NAT at birth to facilitate earlier treatment initiation

Adding NAT at birth to the existing national infant testing schedule may result in earlier identification of HIV-infected newborns and consequently lead to earlier treatment initiation and lower mortality among infants. Data suggest that infants testing positive at birth start ART approximately 2 months earlier than non-birth-tested infants (6 weeks vs 15 weeks). However, cost-effectiveness analyses have shown that the survival gains from adding NAT at birth to the standard 6-week test are lost if the loss-to-follow-up after a negative birth result exceeds 37%, underscoring the fact that a high-functioning 6-week program needs to already be in place. A number of countries have already started implementation of NAT at birth, and country experiences are outlined in Box 4. It should be noted, however, that strengthening existing EID systems remains the priority while programs consider adding birth testing.

Several implementation considerations can be summarized from these experiences.

- Countries that are considering birth testing should critically review current performance and opportunities for strengthening their 6-week EID program and consider other indicators, (e.g. PENTA1 immunization visit coverage and attended delivery rate), so that the potential gains provided by birth testing can be investigated more fully. For example, in settings where the attended delivery rate is much lower than PENTA1 immunization visit coverage the added value of birth testing as a means of expanding EID is limited.
- Pilot projects are a good way to start gaining national experience on this innovative testing approach, but in order to measure impact fully programs need to collect data on the feasibility and impact of birth testing and linkage to ART initiation.
- Targeted approaches which provide birth testing only for high-risk infants are expected to have a higher yield compared to routine birth testing. This approach may be potentially less resource intensive and present a lower burden for HCW.
- Active tracking of infants with negative NAT results at birth is critical to ensure that they return at 6 weeks to be retested and start co-trimoxazole (CTX); establishing unique patient identifiers or other innovative mechanisms (e.g. bar codes) to track babies can be considered.
- It is crucial that the turnaround time for reporting test results to health facilities and caregivers be rapid in order to optimize the benefit from NAT at birth, and POC assays should be used where they are available.
• Birth testing is acceptable to mothers, but challenges arise from the increased human resources needed, the difficulty of collecting blood samples in newborns, the need to ensure sample collection outside of standard working hours and deliver results, linkage to ART and the nature of the EID system as a whole (stock-outs, referral mechanisms, delayed results).

• The key to effective implementation is to ensure that newborns who have been identified as HIV-infected are linked to treatment and that age-appropriate formulations are available to start them on treatment.

• Good leadership and coordination are needed to oversee service provision, support supervision, mentorship and the quality improvement cycle.

Box 4. Implementation of birth testing: country experiences

South Africa
South Africa introduced NAT at birth in 2015 with specific nurse training at postnatal and delivery services and health register updates to enable data acquisition. Implementation challenges met by South Africa include weak linkage of the identified HIV-infected infants to care with consequent delay in ART initiation, and a low return rate for future testing among infants with negative results at birth. A qualitative sub-study found that birth testing had a high acceptability. Refusals were rare and mothers did not indicate that birth testing affected their subsequent acceptance of infant testing or postnatal clinic attendance. Weak follow-up systems were detected for mothers who had home deliveries, and concerns were raised by laboratory staff about increased workloads associated with additional testing requirements.

Kenya
Kenya started a NAT at birth pilot project in 2015 (defined as testing within 72 hours of birth) and its results formed the basis of a revised EID algorithm in 2016 and national scale-up plan, due to start in mid-2018. Prior to implementation, a central point was designated within the health-care facility for birth testing, an innovative dispatch register was developed, mothers were offered mentoring to assist with linkage between hospitals and communities and a prevention of mother-to-child transmission (PMTCT) psychosocial support group was formed. Good leadership and coordination was identified as being important for seeing patients through service provision. Challenges included issues related to referral, demand creation, turnaround time for test results and mothers who failed to collect test results. In addition, ART formulations were lacking for neonates who tested positive during the initial implementation phase.

Zimbabwe
Zimbabwe started a POC NAT birth pilot in April 2017 in ten health facilities for high-risk HIV-exposed infants (< 48 hours after birth). Ninety-seven per cent of the results were transmitted to caregivers, and all HIV-infected infants started ART within 5 days of testing. This project is likely to provide critical experience on a different approach to tracking children after birth testing and will generate further information on the value of targeting birth testing for high-risk infants rather than all HIV-exposed infants.

Democratic Republic of Congo
NAT at birth was first implemented in December 2016, with samples sent to central laboratories for processing. Laboratory personnel were trained to prioritize birth samples and ensure prompt return of results to the health facility. Challenges included long turnaround times between specimen collection and receipt of results (8–12 weeks from the national laboratory), stock-outs due to limitations in supply chain management, and difficulties in specimen transportation. Uptake of birth testing was good, but yield was low with numerous missed opportunities due to early discharge of women from maternity wards. As a result, birth testing remains limited to this pilot project (now terminated) and efforts are being made to strengthen the existing 6-week EID program.

Eswatini (Swaziland)
Eswatini introduced two pilot projects to explore universal NAT at birth across five maternity sites in August 2017 using POC EID technologies in three sites (in partnership with EGPAF) and conventional testing in two sites (in partnership with ICAP). In the conventional test pilot, 93% of HIV-exposed newborns were tested before discharge from the maternity unit and six of the 1 548 tested were HIV-infected. In the POC testing pilot, 68% of HIV-exposed newborns were tested and 12 of the 1 314 tested were HIV-infected. Furthermore, 98% of results were returned to the caregiver. Of those HIV-infected, nine in the POC test pilot and four in the conventional test pilot were put on treatment. Both pilots confirmed that health-care facility staff face a heavier work burden when NAT at birth was added. Nurses often felt overwhelmed and failed to prioritize NAT at birth because many births occurred at night or on weekends when staffing was limited. Furthermore, although most mothers found birth testing to be acceptable, several were discharged or left the facility before getting tested, while others provided incorrect tracking information. Ensuring patient tracking and linkage proved to be a challenge.
3.1.5 Ensuring accurate interpretation of the 9-month test and simplifying the testing algorithm

The 2016 WHO ARV Consolidated Guidelines recommend that RDTs should be used to assess HIV exposure among infants younger than 4 months, while HIV exposure among infants 4–18 months old should be ascertained by testing the mother. When testing of the mother is not possible, current guidelines emphasize the importance of not considering a negative RDT result from an infant between 4–18 months as a definitive test of exposure. Implementation issues are highlighted in Box 5.

RDT at 9 months was initially recommended in the 2010 WHO recommendations on the diagnosis of HIV infection in infants and children21 with the goal of targeting NAT for those HIV-exposed infants most likely to be infected (e.g. those with a positive RDT) as a cost-saving measure. However, due to decreasing MTCT rates, increasing availability and lower costs of NAT, changing transmission and drug exposure dynamics, and the fact that RDTs are less effective at determining the need for NAT testing, such a targeted approach may be less compelling. Furthermore, the added programmatic complexity and potential for inappropriate interpretation of test results have additional unintended consequences.

In light of the challenges and data outlined above, consideration can now be given to replacing RDT at 9 months with NAT in the interests of minimizing the challenges of interpretation and simplifying the infant testing algorithm.

Annex 3 summarizes the new simplified algorithm, which is underscored by a number of key considerations:

- assessing HIV exposure status by performing RDT on the mother;
- at 9 months performing NAT for HIV-exposed infants, symptomatic and asymptomatic, and even where previous NAT results have been negative;
- ensuring indeterminate test results are repeat tested immediately and prioritized for rapid resolution;
- ensuring confirmatory testing is undertaken following any positive result; and
- ensuring all HIV-exposed infants are regularly followed up until final diagnosis, with the provision of CTX prophylaxis and clinical/nutritional assessment.

Finally, it remains critical that infant retention be continued until the end of the exposure period. More effort should be given to establishing a final diagnosis at 18 months of age or 3 months after cessation of breastfeeding, whichever occurs later. Although there is increasing coverage of the traditional 6-week infant test and more consideration is given to earlier time-points, the changing dynamics of transmission and increased drug exposure mean that increased efforts are needed to maintain follow-up throughout the entire exposure period. The aim is to ensure that all HIV-infected infants, including those infected in the postnatal period, are identified and receive treatment.

Box 5. Use of RDT: implementation considerations

- Priority should continue to be given to the testing of mothers at all entry points to determine exposure status for infants and children less than 18 months.
- If the mother is absent or unable to be tested, an RDT should be undertaken of the infant, but negative results of infants older than 4 months should not be considered as definitive exclusion of exposure and follow-up testing is required.
- If the mother is absent or unable to be tested and the infant presents with signs and symptoms of HIV infection, a NAT should be undertaken.
- NAT should be undertaken following any positive RDT in the mother or the infant and a confirmatory NAT undertaken following any positive NAT result.

Based on the 2016 WHO ARV Consolidated Guidelines10, RDTs are serological assays that can also be used to exclude established infection among healthy, HIV-exposed infants aged 9 months old and above. However, changes in transmission dynamics as well as in policy and practice have complicated RDT use for determining infection status. Substantial drug exposure for infants with implementation of the Treat All policy for mothers and enhanced postnatal prophylaxis of HIV-exposed infants may have resulted in viral load reduction and delayed antibody development in HIV-infected infants. Finally, the occurrence of maternal infection in late pregnancy or during the postnatal period may be responsible for a lack of passive HIV antibody transfer to the HIV-exposed infant. These factors increasingly jeopardize RDT accuracy at 9 months of age as a means of correctly ruling out established infection in HIV-exposed infants. These concerns are supported by findings from Uganda and Kenya,24, 25 where 15–40% of children under two years of age and identified as HIV-infected had a positive NAT but negative RDT.
3.2. ARV use for prevention and treatment of HIV in infants

3.2.1 Implementation challenges to providing ePNP for high-risk infants

The 2016 WHO ARV Consolidated Guidelines recommend a dual regimen of AZT and NVP which can be extended for up to 12 weeks in breastfeeding infants deemed to be at high risk of MTCT. A high-risk infant is defined as an infant whose mother was first identified as HIV-infected at delivery or in the postpartum, infected during pregnancy or breastfeeding, started ART late in pregnancy, or did not achieve viral suppression by the time of delivery (Annex 4). All high-risk infants should receive dual drug prophylaxis (AZT plus NVP) for the first 6 weeks. In breastfeeding infants, this should be followed by either an extra 6 weeks of AZT plus NVP or an extra 6 weeks of NVP alone (see Box 6).

This recommendation is based on evidence from randomized clinical trials and takes into account the risk-benefit ratio of ePNP: potential for increased drug toxicity versus additional protection from HIV transmission. The rationale for the use of extended ePNP especially in high-risk breastfeeding infants rests on the assumption that mothers started promptly on ART achieve viral suppression within 12 weeks, thereby greatly reducing the risk of breast milk transmission and the need for ongoing infant prophylaxis.

Countries have adopted ePNP using a variety of different approaches. In Kenya, Eswatini (Swaziland), and Mozambique, ePNP has been adopted for all breastfeeding HIV-exposed infants, while nine countries (Botswana, Ghana, Namibia, Nigeria, South Africa, Tanzania, Uganda, Zambia and Zimbabwe) have adopted ePNP for high-risk infants identified primarily on the basis of maternal ART duration and, when available, maternal VL close to delivery. Most countries opted for at least 12 weeks of prophylaxis, usually AZT/NVP for the first 6 weeks followed by NVP alone. Three countries (Kenya, Namibia and South Africa) link the duration of ePNP to the maternal VL, and extend ePNP over the entire breastfeeding period when viral suppression is not achieved. Finally, in three countries (Botswana, Zambia and Tanzania), triple prophylaxis with a fixed-dose combination (FDC) of AZT/3TC/NVP has been adopted to address the challenges of procuring syrups.

Recent guidelines on infant feeding in relation to HIV re-affirm the position of WHO that the best way to prevent MTCT in the postpartum period and optimize infant survival is to ensure that mothers living with HIV are well controlled on ART and able to breastfeed their infants for up to two years, with the infant being exclusively breastfed in the first six months of life. If a mother on ART is virologically suppressed, the risk of breast milk transmission of HIV is very low and infant prophylaxis confers minimal additional benefit beyond 4–6 weeks of life.

Some program have adopted ePNP for all HIV-exposed infants. While this may simplify decision-making, it increases costs and exposes a large number of infants who may not need ePNP to added toxicity. This type of approach ought to be reserved for selected situations where a majority of mothers are at high risk of transmitting HIV. Data on the average duration of ART at delivery and, where available, the proportion of pregnant women with VL>1000 at the end of the third trimester might help policymakers to determine whether added costs and toxicity are outweighed by potential benefit. Even then, it should only be an interim measure while strategies to increase the coverage of maternal testing, early treatment and improved adherence are being implemented.

However, there are several situations where viral suppression throughout the breastfeeding period cannot be ensured in the mother, for example:

- if a mother refuses or is unable to start or continue ART and intends to breastfeed her infant;
- if the provider knows the mother is poorly adherent to ART while breastfeeding;
- if maternal VL is known to be high when the infant prophylaxis regimen is about to be stopped.

There is no formal recommendation for these types of situations and no evidence to guide the best course of action. It is reasonable, however, to assume that infant prophylaxis serves as a “back-up” solution for preventing postnatal transmission of HIV, and national programs could consider the merits of giving clinical providers the option of continuing infant prophylaxis beyond the recommended 6- or 12-week period. If this option is introduced in the national guidelines, there ought to be clearly defined scenarios in which continuing prophylaxis is warranted. National guidelines should also emphasize that the best way to prevent breast milk transmission of HIV is by optimal maternal treatment for the entire duration of exposure. Continuing prophylaxis should therefore be seen as an interim measure while efforts are made to support and improve maternal treatment adherence. Deciding to continue prophylaxis should take into consideration the factors that led to poor maternal adherence as they may have an impact on adherence to infant prophylaxis. Once stopped, infant prophylaxis should not be re-started if there are new concerns about maternal adherence. There is no evidence to support such an approach; instead the focus should be on determining why the mother was unable to remain adherent. If the decision has been made to continue infant prophylaxis, mothers and infants should be evaluated at regular intervals to assess the need for ongoing infant prophylaxis.
As more effective treatments increasingly come to be used in pregnant women, we can expect decreasing MTCT rates. However, some women will still be diagnosed late or have incident infections and this group is likely to drive most new cases of HIV transmission to infants, owing to the high level of maternal virus in the absence of treatment. One possibility would be to provide "presumptive treatment" as postnatal ePNP, by administering a triple-drug regimen at therapeutic doses to this selected group of infants with the goal of minimizing transmission and drug-resistant HIV (HIVDR) selection in the event of established infection despite prophylaxis. Such approaches need to be paired with careful review of infant testing practices in order to determine the potential impact of triple ePNP on virological assay performance for infant diagnosis (i.e. at least one specimen must be collected prior to initiating any presumptive treatment so that a NAT can be performed as soon as possible).

3.2.2 Early infant treatment: limited options and complex administration

Early infant ART improves survival and reduces long-term morbidity but mortality remains substantial in the first months of life. Introducing NAT at birth could enable ART to be started before 2 weeks of age. However the only regimen available for this age group has for many years been one containing AZT, 3TC and NVP. This regimen could be continued with close clinical monitoring until 3 months of age and then switched to a LPV/r-based regimen, using LPV/r pellets, or LPV/r could be introduced at the end of the second week of life as syrup and then switched to a solid formulation at 3 months of age.

Raltegravir (RAL) granules have recently been approved by the US Food and Drug Administration for use in neonates at full term, except for low birthweight or premature babies. This is a considerable advance in increasing treatment options for neonates. Feasibility and acceptability of this formulation are currently being assessed in a study in South Africa. The 2016 WHO ARV Consolidated Guidelines already recommend the use of RAL as an alternative first-line treatment for children younger than 3 months where LPV/r pellets cannot be used. At present, RAL suitable for administration in the neonatal period is only available as a granule for oral suspension, but improved formulations are being developed for future use.

Countries considering whether to introduce birth testing will need to consider their ability to decentralize newborn treatment by strengthening HCW capacity, ensuring commodities are available at peripheral health facilities and/or extending the referral system to nearby facilities, as well as ensuring that HCW are fully trained and equipped to start newborn infants on treatment.
3.3. Improving service delivery and implementing a postnatal package of care

There are several barriers to the uptake of effective infant HIV services, and no single intervention can address all the barriers facing women and their infants at different times and places. Socio-economic and traditional factors that keep mother-infant pairs together are among the enabling circumstances that improve service uptake. Programs could benefit from combining effective interventions into “service packages” to support service provision and focus on the community engagement that supports uptake.

Interventions which have been proven to improve provision and uptake of infant HIV services and the retention of mother-infant pairs include:

- client-focused interventions that provide support to individual clients using reminder text messaging, conditional cash incentives and male partner involvement;
- and health system-focused interventions, including measures to enhance the program (POC testing technologies, provider training and support, enhanced counselling services and peer support), to strengthen the health system (quality improvement initiatives and mother and child health (MCH)/HIV service integration) and to support community-based services and HCWs.

Promoting integration to reduce fragmentation of care for mothers and infants and ensure that infants remain in the testing cascade until final diagnosis should be a priority. Strong antenatal and well-baby care systems provide opportunities to strengthen service delivery for HIV-exposed infants. Integration within a well established maternal, neonatal, and child services platform, which traditionally provides services closest to clients, facilitates mother-infant pair follow-up and reduces the cost and time-visit burden on clients. The integrated information systems that link mother and infant information improve client tracking and facilitate continuity of care provision. Examples include longitudinal follow-up registers and cohort analysis as well as linkage with information on communit-based services. Programs should however take into consideration the increasing burden on the MCH platform within the context of existing human resources and the challenges of changing services.

Community engagement and community-based services play an important role in supporting HIV-exposed infant care. These clear and highly context specific services play a “boosting” role in supporting facility-focused services and include community-based HIV testing. The engagement of networks of women living with HIV has been effective in several countries and has been used to improve community HIV literacy to create demand, form support groups at the facility and community levels, strengthen linkage to care by escorting newly diagnosed clients to treatment clinics, conduct defaulter tracking and provide active follow-up of mother-infant pairs. In several settings, these interventions led to reduced loss to follow-up among mother-infant pairs.

Ensuring provision of a comprehensive integrated postnatal package of HIV services will promote the delivery of a set of interventions that contributes not only to improved HIV outcomes but better early childhood development overall.
4. **SUMMARY AND WAY FORWARD**

Several novel innovations implemented by countries and partners have shown promise. While successful interventions are being scaled up, it remains imperative to focus on strengthening existing systems that support infant testing and early treatment initiation. Moreover, changing dynamics in transmission and treatment standards are adding to the complexity and interdependency of testing, prophylaxis and treatment. This will require an increasing need to tailor strategies to the epidemic and policy context. Finally, more programmatic evidence-driven experiences are needed to support and inform national policies, programmatic planning and implementation.

**Box 7: Key research questions**

**Infant diagnosis**

- Assess the impact of implementing an indeterminate range, particularly at different testing time points, sample types, and technologies.
- Acquire impact data to assess the added value of birth testing within the EID program.
- Assess the value of providing birth testing to high-risk infants only.
- Measure the impact of tracking tools (ie, bar codes) to ensure effective tracking and repeat testing at 6 weeks among infants testing negative at birth.
- Determine if there is added value in integrating birth testing with BCG vaccination.
- Assess the optimal timing and frequency of VL testing of pregnant and breastfeeding women.
- Assess the impact of maternal treatment and infant prophylaxis on infant diagnoses.
- Determine and evaluate the most effective approaches to retaining infants throughout the EID cascade until final definite diagnosis.

**Infant prophylaxis and treatment**

- Determine dosing and safety of new ARVs for the purpose of prophylaxis or treatment in neonates and infants.
- Develop optimal formulations and ensure timely uptake of newly recommended ARVs for newborns and infants.
- Document country experiences with ePNP.
- Understand the clinical relevance of maternal viremic episodes and their relative contribution to the overall transmission rate.
- Conduct studies to explore the additional benefit of ePNP in the context of well implemented effective maternal ART regimens.
- Assess adherence to ePNP and how to improve retention and support for mothers.
- Determine the feasibility of using triple therapy as prophylaxis for infants whose mothers are first identified as HIV-infected in the post-partum period.

**Service delivery and post-natal package of care**

- Consider combining interventions together into packages to support service delivery.
- Promote integration to ensure that infants remain in the testing cascade until final diagnosis.
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Meeting participants

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13. Avy Violari; Man Chan; Kennedy Otwombe; Ravindre Panchia; Patrick J-PD, Gibb; Mark, Cotton; Abdel, Babiker;. Time to viral rebound after stopping ART in children treated from infancy in CHER. Abstract #137, CROI; March 4-7, 2018; Boston, Massachusetts.


Annex 1: Managing indeterminate test results: standard operating procedure

1. Refer to 2016 WHO ARV Consolidated guidelines.
2. Do not report as positive nor initiate ART, but maintain prophylaxis per current guidance.
3. Repeat samples should be prioritized in the laboratory.
4. Repeated indeterminate results in two separate samples should, together with clinical information, be reviewed by a team of laboratories, clinicians pediatricians, complex case experts (if possible), and caregivers. Infants should be actively tracked to ensure follow-up and retention.
Annex 2: Managing discordant results and treatment interruption

This option provides follow-up care to the infant for a minimum of 8 months after interruption of ART. Where possible, both EID (qualitative) and VL (quantitative) tests should be performed at 4 weeks, 4 months, and 8 months after treatment interruption.

Further follow-up is needed to consider the exposure to breastfeeding and carry out the national infant testing schedule for HIV-exposed infants to ensure appropriate final diagnosis. If breastfeeding has stopped prior to the end of the intensive follow up, final HIV status can be defined with NAT performed at least 6 weeks post-cessation of breastfeeding.

EID and viral load at 4 weeks, 4 months, and 8 months after interruption

Scenario a: Cessation of breastfeeding occurs after completion of the follow up post ART interruption.

Scenario b: When cessation of breastfeeding occurs before completion of the follow up post ART interruption.
Annex 3: Simplified EID algorithm

The key principles for establishing whether HIV-exposed infants and children younger than 18 months are infected with HIV in low- and middle-income countries are as follows:

- Assess HIV exposure status by antibody testing the mother.
- Perform NAT test for any HIV exposed child that presents outside of national infant testing algorithm with clinical symptoms irrespective of previous NAT results.
- At 9 months perform NAT for HIV-exposed infants, symptomatic and asymptomatic, and even where previous NAT results have been negative.
- Ensure that indeterminate test results are repeat tested immediately and given priority for rapid resolution.
- Ensure that confirmatory testing is undertaken following any positive result.
- Ensure regular follow-up for all HIV-exposed infants until final diagnosis, including providing co-trimoxazole prophylaxis and clinical and nutritional assessment.

Notes:

a. Based on 2016 WHO Consolidated ARV Guidelines, addition of NAT at birth to the existing testing algorithm can be considered.

b. POC NAT can be used to diagnose HIV infection as well as to confirm positive results.

c. Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.

d. For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.

e. The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.

f. If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.
Annex 4: Algorithm for risk assessment

This algorithm was developed to support risk assessment at the time of delivery and to help identify infants at high and low risk:

Infants at low risk should be given standard prophylaxis (NVP or AZT alone for 4–6 weeks) while those at high risk should be given ePNP. In order to navigate this algorithm successfully, clinicians will need to know a number of parameters from the mother’s antenatal chart:

- HIV status and date of last HIV test (to identify status and need for testing or retesting at delivery);
- if known to be positive, and ART started, date of ART initiation;
- if VL collected, date of sample collection relative to delivery and VL result.

Programs should consider incorporating a VL test at or around 36 weeks’ gestation, ensuring that the turnaround time is short enough to have a result available by the expected delivery date.
### Annex 5: Dosing and formulation options for infant prophylaxis

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Dose 0-6 weeks AZT plus NVP</th>
<th>Dose 6-12 weeks AZT plus NVP</th>
<th>Dose 6-12 weeks NVP only</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Syrups</strong></td>
<td>AZT dose 1.5ml (15mg) twice daily</td>
<td>AZT dose 6ml (60mg) twice daily</td>
<td>NVP dose 2ml (20mg) once daily</td>
<td>– Accurate dosing for all drugs (included for low birth weight newborns) and one type of formulation for the whole 12-week period – Costly to procure and transport syrups – Difficult to hide in the home – Supplier availability may be limited – Might be acceptable where most women of childbearing age are well controlled on ART and numbers of high-risk infants is low, but would not be the best option for a program that chooses to treat all infants as high risk</td>
</tr>
<tr>
<td><strong>Syrups and single drug tablets</strong></td>
<td>AZT dose 1.5ml (15mg) twice daily</td>
<td>AZT dose 1 tab (60mg) twice daily</td>
<td>NVP dose ½ tab (25mg) once daily</td>
<td>– Combines accuracy of syrup dosing in the first 6 weeks and the ease of tablets from 6 to 12 weeks – Challenges of syrups as before – ½ a tab of NVP represents a slight overdose of NVP (25mg vs 20mg)</td>
</tr>
<tr>
<td><strong>FDC</strong></td>
<td>¼ tab (15mg AZT, 7.5mg 3TC, 12.5mg NVP) twice daily</td>
<td>Unsuitable</td>
<td>Not applicable</td>
<td>– Difficult to quarter a FDC accurately: caregivers should use the first quarter in the morning and the second quarter in the evening in order to keep daily dose accurate – 3TC not part of the recommended prophylaxis regimen – Cannot use FDC during weeks 6 to 12 without giving 5 times more than the recommended daily NVP dose</td>
</tr>
<tr>
<td><strong>FDCs and single drug tablets</strong></td>
<td>¼ tab (15mg AZT, 7.5mg 3TC, 12.5mg NVP) twice daily</td>
<td>AZT dose 1 tab (60mg) twice daily</td>
<td>NVP: ½ a 50mg tablet once daily</td>
<td>– Combines ease of FDC with single drug tablet for the second – Challenges of FDC as above</td>
</tr>
</tbody>
</table>

**Remarks:**
- It should be noted that unlike for NVP, there is no specific prophylaxis dose for AZT. The recommended dose is the same as that used for treatment - 15 mg twice daily for term infants in the first six weeks of life, increasing to 60mg twice daily from week 6 to week 12.
- When presumptive treatment is administered, age-appropriate regimens and dosing should be used as illustrated in current WHO treatment guidelines. 
