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TECHNICAL REPORT

HIV DIAGNOSIS AND ARV USE IN HIV-EXPOSED INFANTS: A PROGRAMMATIC UPDATE

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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

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

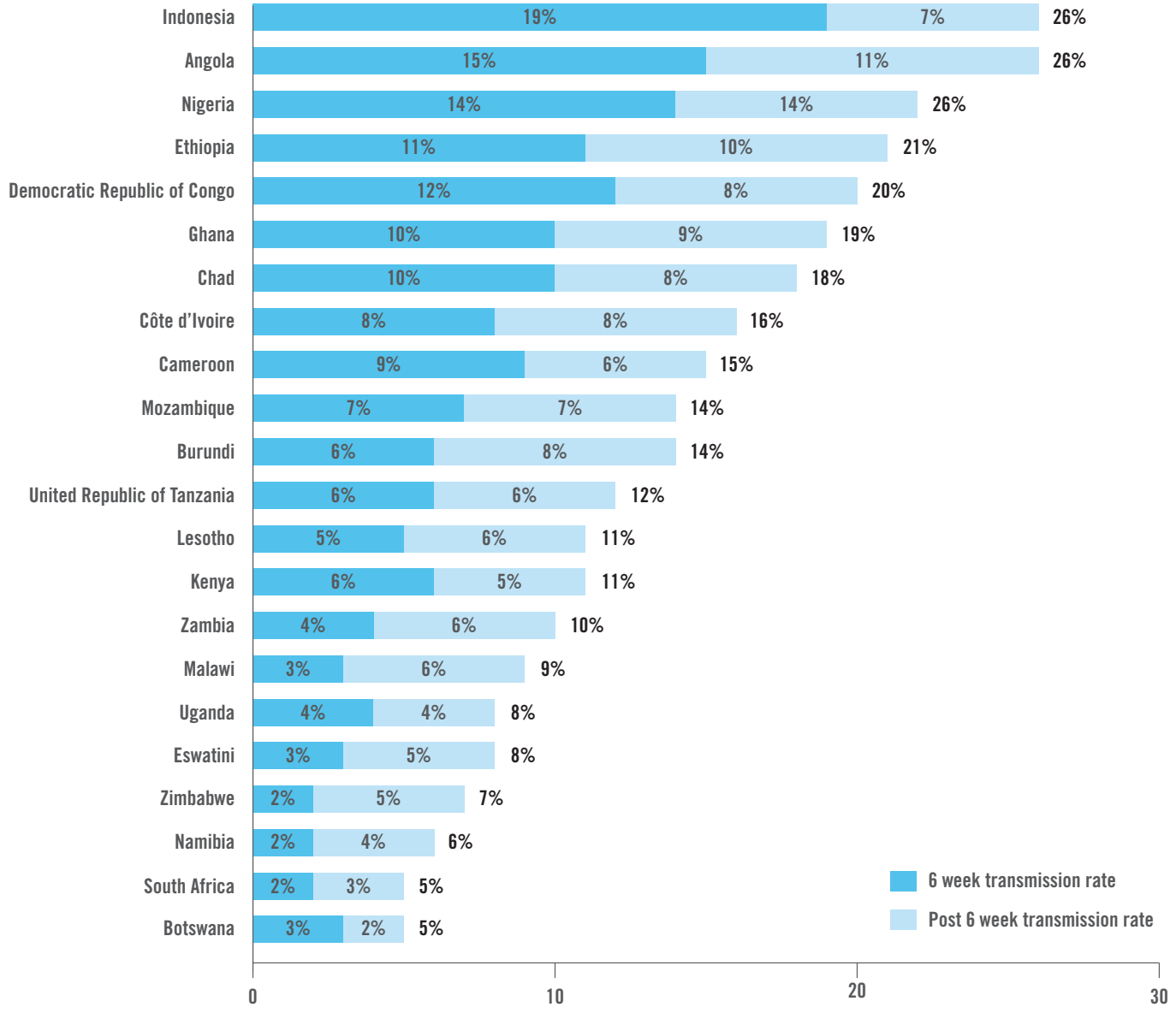
2.1 BACKGROUND

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 health-care 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.[3] 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.[9] 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*[10] 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 rrapid 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)[11], 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*.[10]

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[12] and low viremia observed in infants found to be infected with HIV[13] 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).

Box 1. Definition of terms for diagnostic results

- Indeterminate range: a range of viral copy equivalents that would be too low to accurately diagnose as positive.
- False-positive result: HIV-uninfected infants incorrectly identified as HIV-infected and potentially started unnecessarily on ART.
- False-negative result: HIV-infected infants incorrectly identified as HIV-uninfected.
- Non-negative result: any positive or indeterminate result. Polmyerase chain reaction (PCR) instrument reports a detectable result, which may be subsequently classified as "indeterminate" based on other data (e.g. assay-reported cycle threshold). May also be referred to as "not confirmed", "equivocal" or "irreproducible positive".
- Discordant result: positive/detectable first test; negative second test.
- Cycle threshold: the point at which virus amplification is first observed during the course of repeated PCR cycles. The cycle threshold is inversely correlated to the amount of virus in the sample.

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[14] that 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.[15] 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.[14] **Therefore, prior to contacting the health-care 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.[16] 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*[10] 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.[17] Results from both laboratory and field studies have shown performance comparable to that of laboratory-based technologies.[18] Furthermore, two patient impact studies have been published which highlight the significantly improved patient outcomes when using POC EID technologies.[19,20] **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*[10] 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;[21]
- 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;[22]
- 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.[15] 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.[22] 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,[10] 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*[10] 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 health-care 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.[18] Implementation studies in Malawi[20] and Mozambique[19] 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.

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).[23] 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