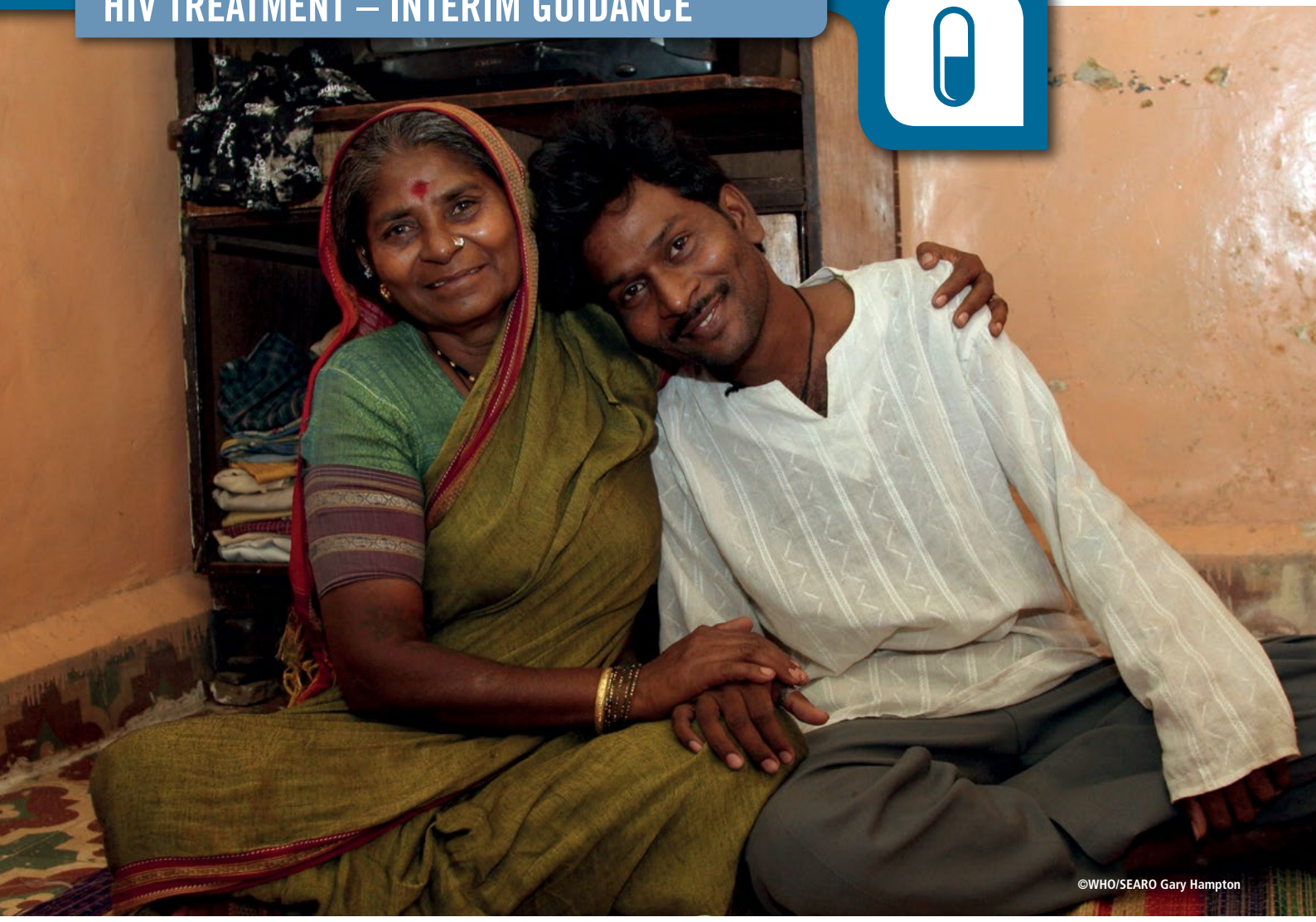
POLICY BRIEF

UPDATE ON ANTIRETROVIRAL REGIMENS FOR TREATING AND PREVENTING HIV INFECTION AND UPDATE ON EARLY INFANT DIAGNOSIS OF HIV

JULY 2018

HIV TREATMENT – INTERIM GUIDANCE



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UPDATE ON ANTIRETROVIRAL REGIMENS

Background

Since 2016, WHO has recommended tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) (or emtricitabine, FTC) + efavirenz (EFV) 600 mg as the preferred first-line antiretroviral therapy (ART) regimen for adults and adolescents. WHO recommended dolutegravir (DTG) as an alternative option to EFV for first-line ART because of the uncertainty regarding the safety and efficacy of DTG during pregnancy and among people living with HIV receiving rifampicin-based tuberculosis (TB) treatment.

Since WHO published the 2016 ARV guidelines *(1)*, several studies have evaluated the safety and efficacy of DTG during pregnancy and the periconception period, among children and among people with HIV-associated TB infection. In addition, increasing levels of pretreatment antiretroviral (ARV) drug resistance documented in low- and middle-income countries prompted WHO to issue guidelines recommending that countries with pretreatment resistance to EFV or nevirapine (NVP) at or above 10% should urgently consider using an alternative regimen that does not contain non-nucleoside reverse-transcriptase inhibitors (NNRTIs) such as EFV *(2)*. DTG has been approved for children older than six years, and raltegravir (RAL) has now been approved for use from birth, providing additional options for neonates and children living with HIV.

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DTG in first-line ART

An updated systematic review conducted in 2018 showed that a regimen with two nucleoside reverse-transcriptase inhibitors (NRTIs) paired with DTG was more effective, with higher viral suppression and CD4 cell count recovery rates and lower risk of treatment discontinuation compared with EFV-based regimens among treatment-naive adults. DTG also had better efficacy at suppressing viral loads than other integrase inhibitors.

DTG has other advantages compared with EFV, including lower potential for drug–drug interactions, more rapid viral suppression and a higher genetic barrier to developing ARV drug resistance. DTG is also active against HIV-2 infection, which is naturally resistant to EFV. The availability of this drug as a generic fixed-dose formulation at a price comparable to current regimens in most low- and middle-income countries also supports the use of DTG as a better option for initiating ART. However, there are concerns regarding the safety of women and adolescent girls using DTG at conception (Box 1).

BOX 1. DTG SAFETY IN PREGNANCY

DTG has been found to be effective for pregnant women and is found in breast milk, resulting in significant plasma concentration in infants and thus a potential important tool to reduce the mother-to-child transmission of HIV infection. However, an ongoing observational study in Botswana recently identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. WHO is taking this potential safety issue seriously and is working closely with all relevant stakeholders, including health ministries, the study investigators, the manufacturer and partner organizations, to further investigate these preliminary findings. Regulatory authorities are also reviewing this matter. WHO will update these data and provide additional information as it becomes available.

Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; based on limited data, hormonal contraception and DTG have no reported or expected drug–drug interactions. The 2016 WHO ARV guidelines *(1)* recommended an EFV-based regimen as an alternative safe and effective first-line regimen that adolescent girls and women of childbearing potential can use during the period of potential risk for developing neural tube defects (at conception and up to eight weeks after conception).

The United States Food and Drug Administration and the European Medicines Agency approved paediatric dosing that supports the use of DTG for children older than six years and weighing more than 30 kg and 15 kg, respectively. The approved dosing for children younger than six years or weighing less than 15 kg is expected in late 2019. Among children for whom approved dosing of DTG is not available, RAL is considered an effective integrase inhibitor and is approved for use among infants starting at birth. RAL successfully reduces viral load among highly viraemic infants and is safe and well tolerated among neonates and infants at high risk of infection.

In summary, ample evidence supports using DTG as a preferred first-line ARV drug for everyone living with HIV older than six years and weighing more than 15 kg, including women and adolescent girls of childbearing potential who are using consistent and reliable contraception. Health-care providers should give women information and options to enable them to make informed choices about using lifelong ART regimens (Box 2).

Current concerns about using DTG during the periconception period are based on limited data. WHO is working actively with national health ministries, academic institutions and implementing partners to undertake ongoing assessment of this potential risk and will update the guidance on using DTG for women of childbearing potential as soon as there are sufficient data to justify a change.

BOX 2. A WOMAN-CENTRED APPROACH

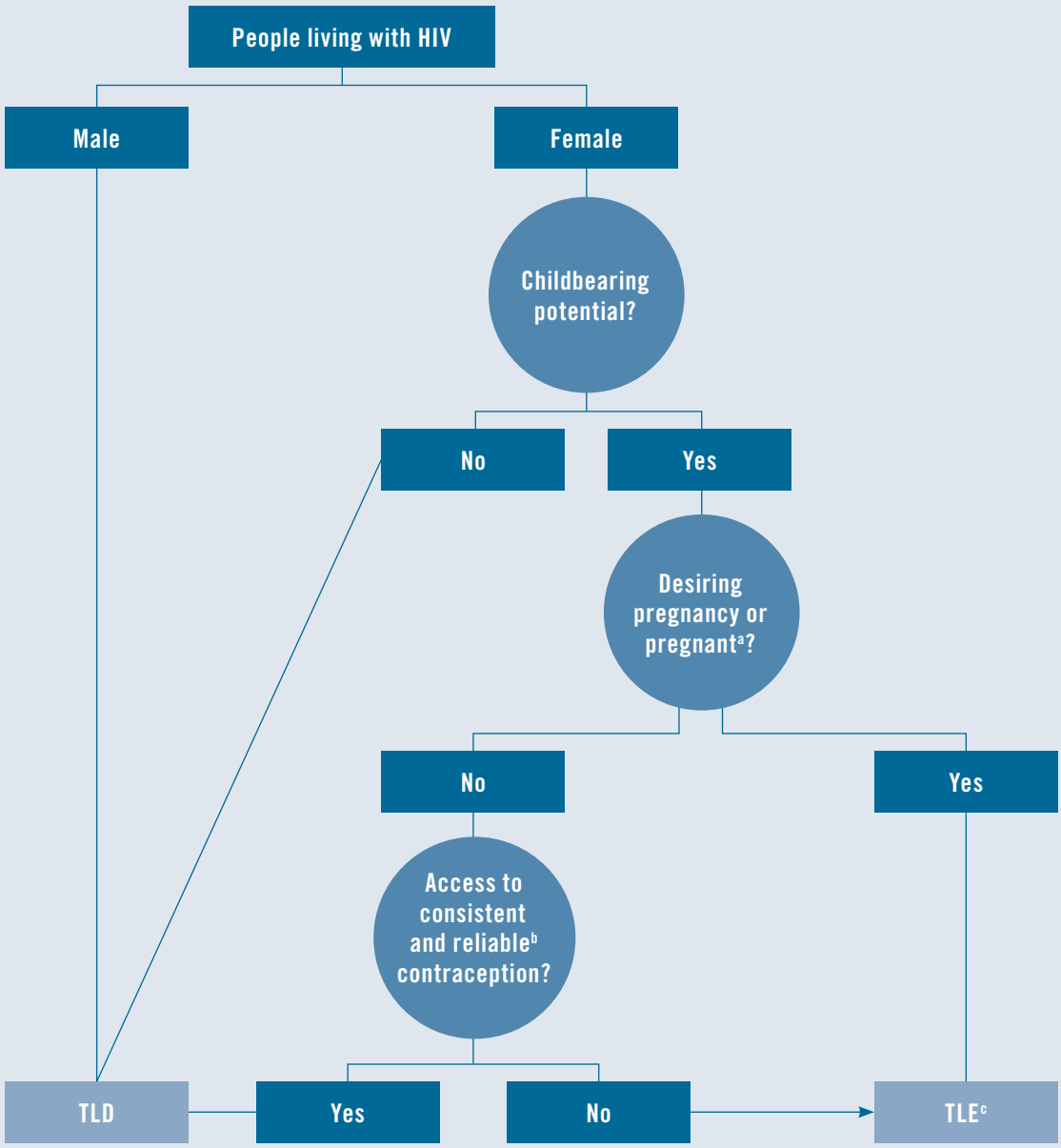
Woman-centred health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways. Care is provided in ways that respect women's autonomy in decision-making about their health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women, their families and communities are central to providing care and to designing and implementing programmes and services. A woman-centred approach is underpinned by two guiding principles: promoting human rights and promoting gender equality.

Source: *Consolidated guideline on sexual and reproductive health and rights of women living with HIV (3).*

In countries with national pretreatment resistance at or above 10%, the choice of alternative options to EFV needs to be made by weighing ARV drug availability and the toxicity profile. In these settings, DTG (provided with consistent and reliable contraception for adolescent girls and women of childbearing potential) and atazanavir/ritonavir (ATV/r) are suitable ARV drug options to be considered (Fig. 1).

Recent data on the efficacy and safety of DTG co-administered with rifampicin among people coinfected with HIV and TB showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. This extra dose of DTG was well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV.

Fig. 1. Example of an algorithm for programmatic implementation of DTG



[a] TLD (fixed-dose combination of TDF + 3TC + DTG) could be considered for pregnant women identified as receiving or starting ART later in the pregnancy (second and third trimester), although the switch to TLE (fixed-dose combination of TDF + 3TC (or FTC) + EFV) should be ensured after delivery in case the woman does not have access to reliable contraception. TLD can be safely used in adolescents weighting more than 30 kg.

[b] Women should be advised on the possible effects of TLD on the pregnancy outcome and on the available contraceptive methods. Consistent and reliable contraception implies that contraceptive methods are widely available and easily accessible to the population, especially long-acting contraceptive methods and dual contraceptive methods with condoms.

[c] TLE is a safe and effective ART option for women desiring pregnancy or currently pregnant to use until the signal of potential risk of new tube defects associated with using DTG in the periconception period is confirmed or refuted.

DTG use in second-line ART

Several studies have shown that using DTG, in combination with an optimized NRTI backbone among people for whom a non-DTG-based first-line regimen has failed, is generally safer and more effective than using a protease inhibitor (PI)–based second-line regimen. Taken together with the other advantages, including lower cost, less potential for drug–drug interactions, lower pill burden and availability in once-daily fixed-dose combinations, the evidence to date suggests that DTG is a preferred ARV drug for second-line ART among adults and children for whom a NNRTI- or PI-based first-line regimen has failed, with the same restrictions for use among adolescent girls and women with childbearing potential as described for first-line treatment regimens (Table 1).

TABLE 1. SUMMARY OF SEQUENCING OPTIONS FOR FIRST-, SECOND- AND THIRD-LINE ART REGIMENS FOR ADULTS (INCLUDING PREGNANT WOMEN AND ADOLESCENTS) AND CHILDREN

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential women or pregnant)[a]	Two NRTIs + DTG[b]	Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))	Darunavir/ritonavir (DRV/r)[g,h] + DTG[i] + 1–2 NRTIs (if possible, consider optimization using genotyping)
	Two NRTIs + EFV[c]	Two NRTIs + DTG[b]	
Children	Two NRTIs + DTG	Two NRTIs + (ATV/r[d] or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG[e]	
	Two NRTIs + NNRTI	Two NRTIs + DTG[f]	

[a] An optimized NRTI backbone should be used such as zidovudine (AZT) following TDF or abacavir (ABC) failure and vice versa.

[b] Women and adolescent girls of childbearing potential with consistent and reliable contraception and who are fully informed of the benefits and risks can use DTG.

[c] If population-level pretreatment resistance to EFV or NVP is ≥10%, the choice of alternative options to EFV needs to be made weighing the drug availability and toxicity profile. DTG (with consistent and reliable contraception among adolescent girls and women of childbearing potential) or ATV/r are the drug options to be considered.

[d] ATV/r can be used as an alternative to LPV/r among children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of a ritonavir booster should be considered when choosing this regimen.

[e] This applies to children for whom approved DTG dosing is available. RAL should remain the preferred second-line regimen for the children for whom approved DTG dosing is not available.

[f] ATV/r or LPV/r should remain the preferred second-line treatment for the children for whom approved DTG dosing is not available. This applies to children for whom approved DTG dosing is available.

[g] For PI-experienced people, the recommended DRV/r dose should be 600 mg/100 mg twice daily.

[h] Children younger than three years should not use DRV/r.

[i] DTG-based third-line ART following the use of integrase inhibitors must be administered with DTG twice daily.

DTG use in HIV post-exposure prophylaxis

An updated review of the tolerability and completion rates of various ARV regimens for HIV post-exposure prophylaxis also supports the use of DTG together with TDF + 3TC (or FTC) for HIV post-exposure prophylaxis, with 90% of individuals receiving this regimen completing post-exposure prophylaxis. This evidence also supports the use of DTG-based post-exposure prophylaxis among children older than six years and weighing more than 15 kg. As part of comprehensive post-exposure prophylaxis services, all adolescent girls and women should be offered pregnancy testing at baseline and during follow-up. Emergency contraception should be offered to girls and women as soon as possible within five days of the sexual exposure and information provided on the risks (including the potential risks of neural tube defects) and benefits of DTG. For women and adolescent girls who do not want to take emergency contraception or DTG, an alternative ARV drug (such as a boosted PI) to DTG should be provided.

Introducing DTG in national HIV programmes

About 500 000 people living with HIV are currently using DTG globally, two thirds of them in high-income settings. Among lower- and middle-income countries, Botswana, Brazil and Kenya have started adopting DTG as a preferred first-line option using different eligibility criteria. Other countries, including Congo, Georgia, Myanmar, Nigeria, Uganda, Ukraine, United Republic of Tanzania and Zambia, have already received their first shipments of DTG formulations from generic manufacturers.

By the end 2017, almost 70 lower- and middle-income countries had included or were planning to include DTG in their national guidelines and to shift to a DTG-based first-line regimen. Multiple generic suppliers are capable of manufacturing DTG as a single product as well as part of a fixed-dose combination and have already begun building capacity to cope with potentially increased demand. No shortfalls in capacity are currently expected.

Programmes should plan carefully to ensure that DTG supply is adequate to meet anticipated demand, and a phased approach to introduction is recommended. Countries have adopted approaches to starting the transitioning to DTG among people initiating first-line ART and/or those already receiving ART but with intolerance or contraindication to NNRTIs. As this ARV drug transition occurs, buffer stocks of older and newer ARV drug regimens need to be secured to promote the continuity of supply. Some implementing partners have developed specific toolkits and checklists *(4)* to guide countries in planning procurement.

Programmes should strengthen the integration of sexual and reproductive health services within HIV treatment programmes to ensure reliable and consistent access to contraception for women and adolescent girls living with HIV. This is especially important for women and adolescent girls of childbearing potential who may decide, when all risk has been explained and understood, to take DTG-based regimens.

Transition to DTG and other optimal formulations for use among children is supported by the Optimal ARV Formulary and Limited Use List. Guidance on how to best transition to optimal formulations is also provided by partners of the ARV Procurement Working Group (APWG), which continue to facilitate pooled procurement and supply of ARV drugs for children in low- and middle-income countries.

WHO also recommends active toxicity surveillance of emerging toxicity issues as DTG and other new ARV drugs are being introduced. WHO developed a technical guidance tool that includes several adverse drug reaction reporting forms for DTG for use by health workers at ART sites and a dictionary for a database to match the adverse drug reaction reporting form for DTG. This tool will be part of the updated ARV guidelines to be published in 2018 and is part of *Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations* (WHO, July 2017, http://www.who.int/hiv/pub/toolkits/transition-to-new-arv-technical-update/en).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UPDATE ON EARLY INFANT DIAGNOSIS

In 2016, WHO recommended that HIV virological testing be used to diagnose HIV infection among infants and children younger than 18 months and that ART be started without delay while a second specimen is collected to confirm the initial positive virological test result.

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With increased access to HIV treatment for all and enhanced postnatal prophylaxis, mother-to-child transmission rates have declined considerably. Confirmatory testing of initial positive early infant test results is critical due to the risk of low level viremia, potential contamination with maternal blood, specimen mislabeling, and laboratory contamination. Also, as mother-to-child transmission rates decline, so does the positive predictive value of early infant diagnosis assays. A recent systematic review of testing approaches using an indeterminate range found that 16.5% of detectable test results were classified as indeterminate; this translates into more than 12% of detectable results classified as falsely positive leading to a large proportion of infants who may start lifelong treatment unnecessarily.

Implementing an indeterminate range has been determined to save costs, since minimum additional resources are required to implement repeat testing of all indeterminate specimens compared with the cost of unnecessary lifelong treatment.

Countries, laboratories and manufacturers should consider use of an indeterminate range to improve the accuracy of all nucleic acid–based early infant diagnosis assays. The indeterminate range is defined as a range of viral copy equivalents that would be too low to be accurately diagnosed as clinically positive.

Based on available information, the optimal indeterminate range is considered to be the equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay. This value represents the best trade-off between the proportion of infants living with HIV that would be incorrectly identified as indeterminate and the proportion of HIV-uninfected infants that would potentially start treatment unnecessarily.

Note that the cycle threshold values vary by the assay used and cannot be directly applied between technologies or assays. Further, additional considerations may be necessary for countries using plasma as a sample type for infant testing rather than whole blood or dried blood spots, since the latter sample types typically capture and amplify intracellular nucleic acids that may increase the detected levels of virus. Finally, the age at which the child is tested and the timing of transmission may also affect the viral loads, since infants diagnosed at birth can have lower viral loads *(5)*. However, no evidence informs and justifies differences in indeterminate range values based on the time of sample collection, and further research is needed.

Laboratory considerations for optimizing high-quality early infant diagnosis

The complexity of early infant diagnosis testing is now growing because of the significant scaling up of the "treat all" policy, implementation of enhanced prophylaxis, reduced mother-to-child transmission rates and the increased relative contribution of postnatal transmission. Early infant diagnosis can no longer be a one-test process but now requires additional testing over the duration of exposure. Several additional key considerations are therefore required to strengthen the early infant diagnosis testing cascade.

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Repeat testing of indeterminate results in the laboratory

Most countries already apply a national standard operating procedure when testing errors are encountered (such as device malfunction or insufficient or rejected specimen) (Fig. 2). A new study suggests that repeating an infant test on the same sample, if and when available, will resolve most (>95%) indeterminate test results *(6)*.

Therefore, before the health-care facility is contacted to request that the mother and baby return to the facility for collecting a new sample, any indeterminate test should be repeat tested on the same sample using additional available dried blood spots or remaining whole blood.

Repeat testing of the same sample may not be possible with point-of-care or near point-of-care technologies when the sample is directly applied from the heel to the cartridge; however, in such instances a new sample should be taken and immediately tested to confirm a positive test result.

Confirmatory testing of all positive test results

An analysis of the cost–effectiveness of confirmatory testing in various scenarios highlighted that confirmatory testing is indeed cost-effective *(7)*. Without confirmatory testing, this analysis showed that, in settings with mother-to-child transmission rates similar to that of South Africa, more than 10% of infants who initiated treatment may potentially have false-positive diagnoses.

All positive test results should therefore be confirmatory tested using a new sample at the time treatment is initiated or before. Any nucleic acid–based assay can be used for confirmatory testing of children younger than 18 months, and programmes should consider using whichever platform is available, including point-of-care technologies.

Testing throughout the exposure period

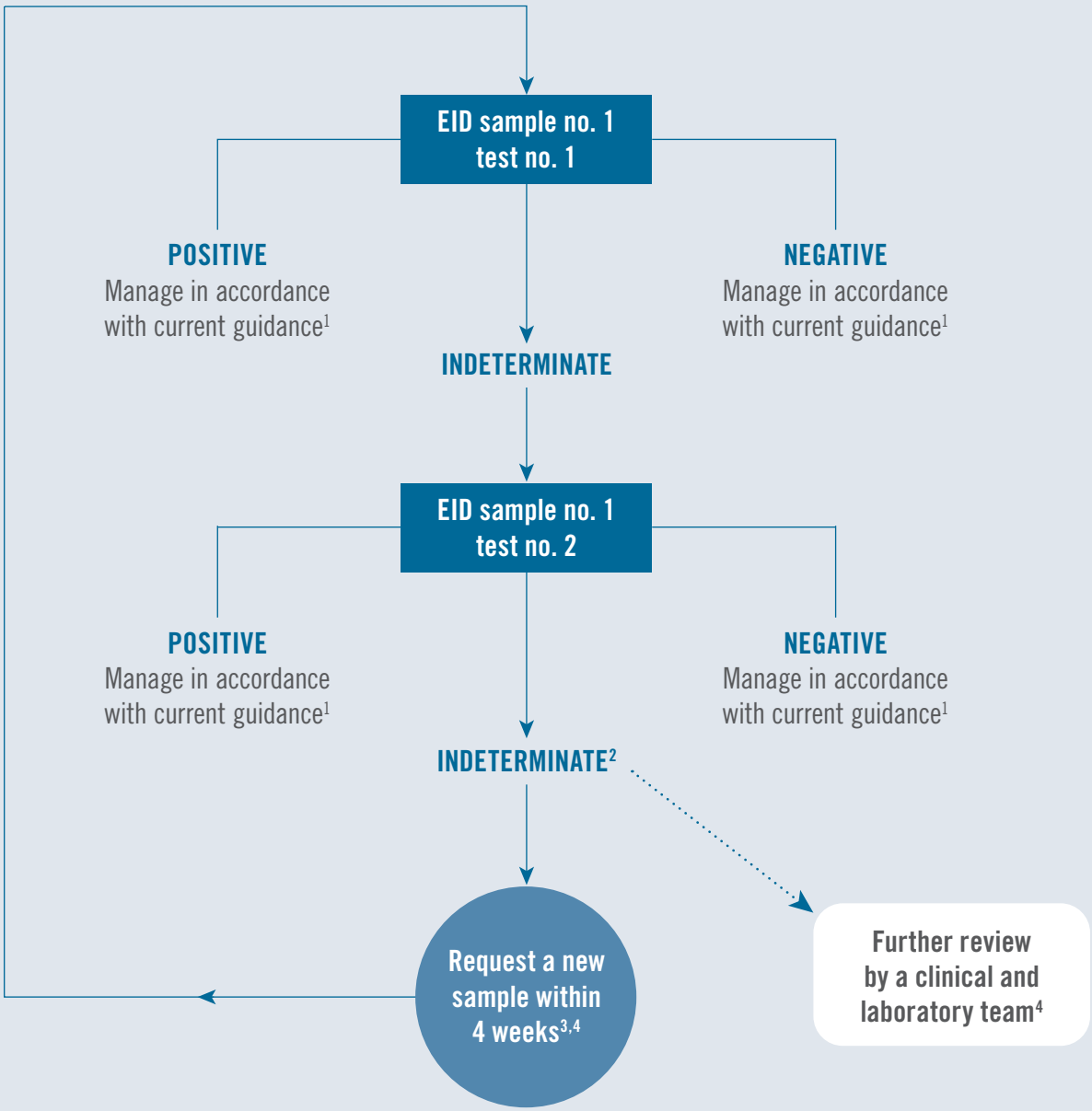
The indeterminate range, repeat testing of indeterminate test results and confirmatory testing of all positive test results should be implemented for all nucleic acid–based testing conducted throughout the early infant diagnosis cascade.

The dynamics of mother-to-child transmission have now shifted towards increased transmission during the postnatal period: about half the children acquiring HIV get it during breastfeeding *(8)*. Programmes should therefore strengthen the early infant diagnosis cascade to ensure that all HIV-exposed infants are tested throughout the entire exposure period. WHO guidelines recommend that the final diagnosis of HIV-exposed infants be conducted three months after breastfeeding ends or at 18 months of age, whichever is later.

Fig. 2. Standard operating procedure for early infant diagnosis testing

All indeterminate tests should be repeat tested on the same specimen, if and when available. If the same specimen cannot be repeat tested, then a new specimen should be requested and tested as quickly as possible.

For specimens with two indeterminate test results, a new specimen should be requested. For infants repeatedly testing indeterminate, it is suggested that a team of experts review clinical and test information to determine the best follow-up care.



EID: early infant diagnosis.

1. See the 2016 WHO consolidated ARV drug guidelines.
2. Do not report as positive or initiate ART but maintain prophylaxis in accordance with current guidance.
3. Repeat samples should be given priority in the laboratory.
4. A team of laboratories, clinicians or paediatricians, complex case experts (if possible) and caregivers should review repeated indeterminate results in two separate samples together with clinical information. Infants should be actively tracked to ensure follow-up and retention.

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For more information, contact:

World Health Organization
Department of HIV
20, avenue Appia
CH-1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv

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