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INTERIM GUIDELINES



UPDATED RECOMMENDATIONS ON FIRST-LINE AND SECOND-LINE ANTIRETROVIRAL REGIMENS AND POST-EXPOSURE PROPHYLAXIS AND RECOMMENDATIONS ON EARLY INFANT DIAGNOSIS OF HIV

SUPPLEMENT TO THE 2016 CONSOLIDATED GUIDELINES
ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING
AND PREVENTING HIV INFECTION

DECEMBER 2018

HIV TREATMENT

**UPDATED RECOMMENDATIONS ON
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POST-EXPOSURE PROPHYLAXIS
AND RECOMMENDATIONS ON EARLY
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SUMMARY OF KEY TERMS

Age groups and populations	<p>The following definitions for adults, adolescents, children and infants are used in these guidelines for the purposes of implementing recommendations for specific age groups. It is acknowledged that countries may have other definitions under national laws:</p> <p>An adult is a person older than 19 years of age.</p> <p>An adolescent is a person aged 10–19 years of age.</p> <p>A child is a person 1–9 years of age.</p> <p>An infant is a child younger than one year of age.</p> <p>A neonate is an infant younger than four weeks of age.</p>
Adolescent girls and women of childbearing potential	Adolescent girls and women of childbearing potential are defined as premenopausal females capable of becoming pregnant.
Nucleoside Reverse Transcriptase Inhibitor (NRTI)	Antiretroviral drug that binds to and blocks reverse transcriptase, an HIV enzyme. Antiretroviral drugs from this class include abacavir, emtricitabine, lamivudine, tenofovir and zidovudine.
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Antiretroviral drug that binds to and blocks reverse transcriptase, an HIV enzyme. Antiretroviral drugs from this class include nevirapine and efavirenz.
Indeterminate range	A range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infection.
Integrase inhibitor	Antiretroviral drug that binds to and blocks integrase, an HIV enzyme. Antiretroviral drugs from this class include dolutegravir and raltegravir.
Optimized NRTI backbone	A combination of two nucleos(t)ide reverse-transcriptase inhibitor ARV drugs with known or presumed activity against HIV when combined with a third ARV drug (DTG, EFV or PI/r).
Periconception period	The period from before conception to early pregnancy (up to the end of the first trimester).
Protease inhibitor	Antiretroviral drug that blocks protease, an HIV enzyme. Antiretroviral drugs from this class include atazanavir, davunavir and lopinavir.
Signal of drug safety	<p>Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.</p> <p>A signal is a hypothesis together with data and arguments, and note that a signal is not only uncertain but also preliminary in nature.</p>

ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
Ct	cycle threshold
DTG	dolutegravir
EFV	efavirenz
EID	early infant diagnosis
FTC	emtricitabine
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
LPV	lopinavir
NAT	nucleic acid test
NRTI	nucleoside reverse-transcriptase inhibitor
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PI	protease inhibitor
PICO	population, intervention, comparator and outcome
RAL	raltegravir
RTV	ritonavir
/r	low-dose ritonavir
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLD	tenofovir, lamivudine and dolutegravir
TLE	tenofovir, lamivudine and efavirenz
XTC	3TC or FTC

EXECUTIVE SUMMARY

In 2016, WHO published updated consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. These guidelines included recommendations on the choice of ARV drugs for first- and second-line antiretroviral therapy (ART). An efavirenz (EFV 600 mg)-based regimen was recommended as the preferred first-line regimen, with a dolutegravir (DTG)- or efavirenz (400 mg)-based regimen recommended as alternative options because of limited efficacy and safety data in pregnancy and when taken concomitantly with tuberculosis (TB) treatment. ART recommendations for children remained unchanged in 2016 compared with 2013 because of lack of approved DTG dosing for use in children.

Since that time, evidence and experience have accumulated on the use of DTG in both first- and second-line ART, including during pregnancy and tuberculosis co-treatment, and for children. These guidelines provide updated recommendations on using DTG for these populations and updated recommendations on using ARV drugs for HIV post-exposure prophylaxis. A new recommendation is also provided on the interpretation of early infant diagnosis test results to improve the accuracy of diagnosis.

Recommendations were formulated following WHO standards for guideline development and based on up-to-date systematic reviews of the evidence, complemented with additional information regarding values and preferences, feasibility and acceptability and cost.

During the process of reviewing evidence in support of these guidelines, an important potential safety concern was reported suggesting that DTG may be associated with an increased risk of neural tube defects among infants born to women receiving the drug during the periconception period. In response, WHO issued a drug safety alert on 18 May 2018 indicating that consideration should be given to avoiding DTG use during the periconception period until more evidence is available.

These guidelines provide a more complete assessment of the use of DTG across all populations, including women of childbearing potential, considering the full range of known benefits and potential harms, and emphasizing the importance of a woman-centred approach to health care that respect women's autonomy in decision-making and provision of information and options to enable women to make informed choices. WHO is working actively with national health ministries, academic institutions and implementing partners to undertake an ongoing assessment of this potential risk of using DTG for women of childbearing potential. These guidelines are therefore Interim guidelines, and the recommendations on DTG use will be updated as soon as there are sufficient data to justify a change.

The table that follows outlines the updated new recommendations and brings forward relevant recommendations from the 2016 WHO consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

Table of recommendations

First-line ARV drug regimens

1. A dolutegravir (DTG)-based regimen is recommended as the preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- Adults and adolescents (*moderate-certainty evidence*)
- Women and adolescent girls of childbearing potential (*very-low-certainty evidence*)
- Infants and children with approved DTG dosing (*low-certainty evidence*)

Note of caution on using DTG during the periconception period among women and adolescent girls of childbearing potential

- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects and after the first trimester.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; hormonal contraception and DTG have no reported or expected drug–drug interactions although data are limited.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to the end of first trimester).^a
- Key considerations for national programmes when selecting the optimal ARV drug regimen for women and adolescent girls of childbearing potential include fertility levels, availability and coverage of contraceptives, pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors at the population level, drug availability and the maternal and infant toxicity profile.
- A woman-centred approach to health care should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making. Services must provide information and options to enable women to make informed choices.

Other remarks

- This recommendation applies to all infants and children for whom an approved DTG dosing is available.
- Because of limited long-term experience with DTG among both children and adults, active toxicity monitoring should be considered. WHO has developed specific guidance and tools (*WHO implementation tool for monitoring the toxicity of new antiretroviral and antiviral medicines in HIV and viral hepatitis programmes*. WHO, 2018 & http://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en/).

2. A raltegravir (RAL)-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence).

3. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendation, very-low-certainty evidence)

^aWHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.



Second-line ARV drug regimens

NEW DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for people living with HIV^a for whom non-DTG-based regimens are failing (*conditional recommendation, moderate-certainty evidence*)

NEW DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for children with approved DTG dosing for whom non-DTG-based regimens are failing (*conditional recommendation, low-certainty evidence*)

^a See Box 1 on women and adolescent girls of childbearing potential using DTG.

ARV drug regimens for HIV post-exposure prophylaxis

An HIV post-exposure prophylaxis regimen with two ARV drugs is effective, but three drugs are preferred (*conditional recommendation, low-certainty evidence*)^a

Adults and adolescents

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis (*strong recommendation, low-certainty evidence*)^a

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis for children for whom an approved DTG dosing is available (*strong recommendation, low-certainty evidence*)^b

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis (*conditional recommendation, low-certainty evidence*)

Children^c

AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens (*strong recommendation, low-certainty evidence*)^a

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis for children for whom an approved DTG dosing is available (*strong recommendation, low-certainty evidence*)

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis (*conditional recommendation, low-certainty evidence*)

^a WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

^b See Box 1 on women and adolescent girls of childbearing potential using DTG.

^c The choice of ARV drugs for children will depend on the availability of approved dosing and age-appropriate formulations for children. Use of DTG applies to all infants and children for whom an approved DTG dosing is available.

Early infant diagnosis of HIV

NEW An indeterminate range^a should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays (*strong recommendation, moderate-certainty evidence*)

^a **Indeterminate range:** a range of viral copy equivalents that would be too low to be accurately diagnosed as positive. The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 on the Roche COBAS[®] Ampliprep/COBAS[®] TaqMan[®] HIV-1 Qualitative Test v2.0 assay.

1. OBJECTIVES AND TARGET AUDIENCE OF THE GUIDELINES

1.1 Objectives

The objective of these guidelines is to provide updated evidence-based recommendations on the following:

- the choice of first- and second-line antiretroviral (ARV) agents for treating HIV (antiretroviral therapy (ART)), including among women of childbearing potential and people with concomitant tuberculosis infection;
- the choice of ARV agents for preventing HIV infection (post-exposure prophylaxis); and
- the use of an indeterminate range for the virological tests used in early infant diagnosis of HIV.

1.2 Target audience

These guidelines are primarily intended for use by national HIV programme managers. It will also be of value to the following audiences:

- people living with HIV and community-based organizations;
- national HIV treatment and prevention advisory boards;
- clinicians and other health workers;
- managers of national laboratory services; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in low- and middle-income countries.

1.3 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

- The guidelines should contribute to realizing the Sustainable Development Goals by achieving key global and national HIV goals.
- These guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, care and treatment.
- Implementation of these guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need HIV services, including ensuring informed, non-judgemental confidential consent, preventing stigma and discrimination in the provision of services and promoting gender equity.
- These guidelines promote a woman-centred approach to health care that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making about their health, and services provide information and options to enable women to make informed choices.
- Implementation of the recommendations in these guidelines should be informed by a rights-based approach, and consideration of local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.

Annex 1 describes the methods for developing these guidelines.

2. ARV DRUG REGIMENS FOR PEOPLE INITIATING ART

Good practice statements (1,2)

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote engagement and support of people and families to play an active role in their own care through informed decision-making. People should not be coerced to start ART immediately and should be supported in making an informed choice regarding when to start ART and what ARV drug regimen to use.

Recommendations

1. A dolutegravir (DTG)-based regimen is recommended as the preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)

- **Adults and adolescents (moderate-certainty evidence)**
- **Women and adolescent girls of childbearing potential (very-low-certainty evidence)**
- **Infants and children with approved DTG dosing (low-certainty evidence)**



Note of caution on using DTG during the periconception period among women and adolescent girls of childbearing potential

- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects, after the first trimester.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; hormonal contraception and DTG have no reported or expected drug–drug interactions although data are limited.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube defects (at conception and up to the end of the first trimester).³
- Key considerations for national programmes when selecting the optimal ARV drug regimen for women and adolescent girls of childbearing potential include fertility levels, availability and coverage of contraceptives, pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors at the population level, drug availability and the maternal and infant toxicity profile.
- A woman-centred approach to health care should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making and services provide information and options to enable women to make informed choices.

Other remarks

- This recommendation applies to all infants and children for whom an approved DTG dosing is available.
- Because of limited long-term experience with DTG among both children and adults, active toxicity monitoring should be considered. WHO has developed specific guidance and tools (*WHO implementation tool for monitoring the toxicity of new antiretroviral and antiviral medicines in HIV and viral hepatitis programmes*. WHO, 2018 & http://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en/).

2. A raltegravir (RAL)-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available (*conditional recommendation, low-certainty evidence*).

3. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (*conditional recommendation, very-low-certainty evidence*).

^aWHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

NEW

NEW

2.1 Background

The WHO 2016 consolidated ARV guidelines recommended TDF + 3TC (or FTC) + EFV at the standard dose of 600 mg (EFV 600) as the preferred first-line ART regimen for adults and adolescents to better harmonize across the majority of subpopulations and because of its known safety and efficacy profile (2). DTG was recommended as an alternative option for first-line ART because data on the safety and efficacy of DTG had not been established during pregnancy or among people with both HIV and TB using rifampicin. Higher cost and lack of generic fixed-dose combinations were also important limiting factors for recommending DTG as the preferred first-line therapy.

Since 2016, several studies have evaluated the safety and efficacy of DTG initiated during pregnancy, among people with both HIV and TB and children older than six years (3). In addition, increasing levels of pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTI) documented in low- and middle-income countries are creating demand for access to alternative ARV drugs. In 2017, WHO issued guidelines recommending that countries with pretreatment resistance to EFV or nevirapine (NVP) of 10% or greater should urgently consider using a non-NNRTI regimen as the preferred choice in first-line ART (4). Finally, generic single formulations and fixed-dose combination tablets of DTG are now available.

Studies investigating the use of low-dose EFV 400 mg (EFV 400) are underway and will be considered for future revision of these guidelines. For the purpose of this guidance, EFV 400 should remain an alternative first-line regimen for adults and adolescents, as the 2016 WHO guidelines indicate.

A key principle of WHO guidelines has been to harmonize ART regimens across all populations by promoting options that are suited to children, adolescents, pregnant women, adults and people with coinfections, including TB (5). Although there have been major advances in developing ARV drugs for adults, treatment for children is still often provided with suboptimal drug regimens and formulations. Suboptimal adherence as a result of lack of child-friendly formulations and the continued use of NVP-based regimens despite the high levels of pretreatment HIV drug resistance to NNRTIs contribute to lower viral suppression among children than among adults (6,7). National surveys in multiple countries in sub-Saharan Africa have reported very high levels of NNRTI resistance (up to 60%) among infants and children younger than 18 months (8).

In 2016, WHO recommendations for first-line regimens for infants and children remained unchanged from 2013 because of the lack of newer, more robust and tolerable options. Since then, DTG has been approved for children older than six years, and RAL has been approved for use from birth, providing additional options for neonates, infants and children living with HIV (2).

2.2 Supporting evidence

Adults and adolescents

An updated systematic review conducted in 2018 assessed the efficacy and safety of DTG among people living with HIV starting first-line therapy (Web Annex B). The review included 70 trials involving 33 148 people randomized to 161 treatment arms. The analysis showed high- to moderate-quality evidence that a regimen with two nucleoside reverse-transcriptase inhibitors (NRTIs) plus DTG was generally more effective (with higher viral suppression and CD4 cell count recovery rates and lower risk of treatment discontinuation) than two NRTIs plus EFV 600 for ART-naïve adults. DTG also had better viral suppression efficacy than other integrase inhibitors. Regimens containing DTG and EFV 600 were comparable with respect to mortality, AIDS-defining illnesses and occurrence of serious adverse events.

DTG has other advantages compared with EFV 600 mg, including lower potential for drug interactions (9), a shorter median time to viral suppression (10) and a higher genetic barrier to developing drug resistance (11). Its long half-life, low cost and low dose mean that including this drug in a once-daily fixed-dose combination is feasible (5). DTG has also documented in vitro and clinical activity against HIV-2 infection, which is naturally resistant to EFV (12–14). The availability of this drug as a generic fixed-dose formulation and the potential price reductions applicable to most low- and middle-income countries also support the recommended use of DTG as the preferred option for initiating ART (15). DTG has been associated with increased risk of insomnia and other neuropsychiatric adverse reactions, which merits further investigation. Compared with other ARV drugs, evidence to date does not suggest an increased occurrence of other serious adverse events in the short term, including cardiovascular events, immune reconstitution inflammatory syndrome or suicidal behaviour (16).

Identifying the most suitable regimens for adolescents is critically important given the demonstrated risk of suboptimal adherence compared with adults in some settings, which places them at high risk for treatment failure and developing drug resistance. In this context, a high value has been placed on more acceptable, tolerable and forgiving regimens for adolescents (17). There is limited evidence on the effectiveness of DTG versus EFV among adolescents; the Guideline Development Group endorsed the validity of extrapolating efficacy data from trials involving adults when direct comparative efficacy evidence for adolescents is not available (18).

Clinical and programmatic experience with DTG in low- and middle-income countries is limited, and the long-term safety of DTG is still unknown (19). A potential safety issue related to neural tube defects among infants born to women who were taking DTG at the time of conception has been identified from an analysis of an ongoing observational study in Botswana (20) *Web Annex C*. More data are needed on the safety and efficacy of taking DTG at conception and among individuals receiving rifampicin for HIV-associated TB treatment. Programmatic assessments and clinical trials that may inform future policies are underway (Box 1).

Neonates and children

The safety, tolerability, efficacy and favourable pharmacokinetics of DTG for children older than six years have been demonstrated in the short term (21–24). However, there is limited experience with DTG use for children younger than six years. Preliminary pharmacokinetic data from an ongoing trial involving children (25) support using a simplified dosing approach of 50-mg adult dosage for children weighing 25 kg or more. Similarly to lopinavir/ritonavir (LPV/r), DTG overcomes the high level of pretreatment NNRTI resistance, and a recent

cohort study (26) shows that DTG can achieve good viral suppression for children older than six years and weighing more than 15 kg and is safe and tolerable outside of a randomized controlled trial setting. Appropriate weight-based dosing for children younger than six years and weighing less than 15 kg is being identified, with approved dosing expected in late 2019. Dosing for HIV-associated TB treatment for children is still being investigated.

The Paediatric Antiretroviral Drug Optimization group, an advisory group to WHO, has endorsed the validity of extrapolating efficacy data from trials involving adults when direct comparative efficacy evidence for children is not available. Unless a specific rationale exists, safety and pharmacokinetic data for children should remain the basis for considering any new ARV drugs for treatment guidelines for infants and children living with HIV (18). Because comparative evidence is lacking between DTG and the current standard of care in children (EFV for children older than three years and LPV/r for children younger than three years), data were extrapolated from studies involving adults. In the adult data analysis, DTG was superior to a LPV/r-based regimen in terms of viral suppression at 48 and 96 weeks, discontinuation and emergent serious adverse events and adverse events indirect comparison; (Web Annex B).

For these reasons, the Guideline Development Group agreed that DTG should be recommended as the preferred first-line regimen for children for whom an approved DTG dosing exists (with the certainty of the evidence rated as low because of extrapolation from studies involving adults). As of mid-2018, DTG can be used for children older than six years weighing at least 15 kg; approved dosing down to four weeks is expected by the end of 2019. Because of the limited experience with DTG among children, the Guideline Development Group also advised that steps be taken to implement routine active toxicity monitoring (2).

For children for whom DTG approved dosing is not available, RAL is the only integrase inhibitor that can be used from birth. Approval of RAL was based on data from trials involving children that demonstrated appropriate pharmacokinetics, safety, tolerability and efficacy of RAL for infants, children and adolescents between four weeks and 18 years of age and pharmacokinetics and safety data for neonates (27–30). RAL successfully reduces viral load among infants with high viral load (31) and is safe and well tolerated for neonates and infants at high risk of infection (30). Its ability to rapidly reduce viral load makes it an appropriate candidate for first-line use among infants and young children for whom DTG dosing is not yet available (28,31). Recent data support using RAL for children with HIV-associated TB infection and receiving rifampicin-containing TB treatment (RAL dosed at 12 mg/kg given twice daily as an oral chewable formulation) (32).

There is currently no direct evidence assessing the efficacy of RAL-based ART versus LPV/r- or EFV-based ART among children living with HIV initiating treatment. Similar to DTG, the Guideline Development Group extrapolated evidence from studies involving adults (Web Annex B) showing that RAL is superior to EFV and LPV/r in terms of viral suppression, with fewer people discontinuing because of adverse events and fewer serious adverse events. The certainty of the evidence was low, because data were extrapolated from adults.

RAL and NVP are currently the only treatment option for neonates. Because comparative evidence between RAL and NVP is lacking for neonates, extrapolation from efficacy studies involving adults is necessary. Based on data for adults, RAL in combination with an age-appropriate NRTI backbone is superior to an NVP-based regimen in terms of viral suppression and change in CD4 cell count (Web Annex B). The differences were not statistically significant for any other outcomes. The certainty of the evidence was rated as very low because data were extrapolated from adults.

Despite its overall higher efficacy compared with the standard of care, RAL is known to have a lower genetic barrier to developing resistance compared with other integrase inhibitors (11,33). The Guideline Development Group raised concerns regarding the potential for suboptimal viral suppression and the potential risk of selection for resistance to integrase inhibitors in the context of a partly active NRTI backbone resulting from the presence of pretreatment resistance to NRTIs, which has been documented in up to 20% of ART-naïve infants and young children (8). In addition, the WHO 2016 recommendation for using twice-daily administration of DTG after failure of RAL-containing regimens makes using RAL less optimal in first-line ART unless no other effective options exist. For neonates, the lack of robust alternative options supports using RAL in first-line ART as the risk–benefit balance differs from that for its use for older infants and children, who can use LPV/r solid formulations.

For these reasons, the Guideline Development Group concluded that RAL for neonates should be preferred, whereas RAL can only be considered an alternative first-line regimen for infants and children until data for appropriate DTG dosing become available. The Guideline Development Group noted that neonates starting ART with a RAL-based regimen should stay on this regimen for no longer than three months – since this is when they can transition to LPV/r solid formulations – to minimize selection for resistance to integrase inhibitors.

Pregnant and breastfeeding women and adolescent girls and women of childbearing potential

Pharmacokinetic data from two studies (23,34) suggest that pregnant and non-pregnant women have relatively similar DTG levels, although they are lower during pregnancy than postpartum; however, DTG levels appear to remain within therapeutic ranges during pregnancy. DTG has also been shown to transfer into breast-milk, resulting in significant plasma concentrations among infants (35).

The Guideline Development Group reflected on different sources of evidence for the possible teratogenicity of DTG. Preclinical animal studies and early human clinical data on DTG found no association with birth defects. However, the preliminary results from an observational study on women using DTG at the time of conception in Botswana found four cases of children born with neural tube defects among 426 women compared with 14 in 11 300 women on a non-DTG regimen and 3 in 5787 on EFV-based regimens exposed before conception (36). This results in an incidence of 0.94% (95% confidence interval 0.37–2.40) among women taking DTG compared with a 0.12% (95% confidence interval 0.07–0.21) risk of neural tube defects in infants born to women taking other ARV medicines at the time of conception (20). This translates into a neural tube defect risk of 10 per 1000 women using DTG compared with 1 per 1000 using other ARV drugs. These data suggest that the potential safety issue might arise from a woman's exposure to DTG in the periconception period rather than during pregnancy. The same study had no other reports of infants with neural tube defects among women who started DTG later in pregnancy (after the period of risk of developing neural tube defects, 6–8 weeks after conception) (37). To better understand this signal of potential risk, active research and surveillance are ongoing for additional pregnant women in Botswana and other countries where women have been exposed to DTG at the time of conception (20).

The incidence of other adverse birth outcomes associated with DTG exposure during pregnancy – stillbirths, spontaneous abortions, preterm and very preterm delivery, small for gestational age and very small for gestational age – are comparable to or lower than those reported for exposure to non-DTG ART during pregnancy. Neonatal mortality does not differ significantly between infants born to mothers starting DTG-based ART during pregnancy versus those starting EFV-based ART (37).

Box 1. Potential safety issue affecting women living with HIV using DTG at conception (20)

The neural tube is the foundation of the spinal cord, brain and the bone and tissues that surround it. Neural tube defects occur when the neural tube fails to completely form; this formation takes place between 0 and 28 days after conception (38). The causes of neural tube defects are multifactorial and may be related to folate deficiency, use of certain medications or an underlying family history (39).

This signal for potential safety concern has been identified from an analysis of an ongoing observational study in Botswana that has found four cases of neural tube defects among 426 women who became pregnant while taking DTG-based ART (36). Surveillance is ongoing for additional pregnant women who were exposed to DTG at time of conception in Botswana and other countries. These data will provide more information about the safety of DTG for women of childbearing potential. Notably, the same observational study shows that DTG when administered later in pregnancy – after the neural tube defect is formed – has comparable pregnancy outcomes for women receiving EFV-based ART started during pregnancy.

The strength of the Botswana study was that the team established a prospective surveillance system with trained health-care workers in maternity services. The lack of reports of neural tube defects associated with DTG exposure in prospective reports from other countries could result from smaller numbers (since fewer women taking DTG have become pregnant compared with other ARV drugs), cases not being reported or because the safety signal seen in Botswana is a chance finding or associated with other factors.

WHO is taking this potential safety issue seriously and is working closely with relevant stakeholders, including health ministries, the study investigators, the originator company and partner organizations to investigate these preliminary findings. Regulatory authorities are also reviewing this matter. WHO will update these data and provide additional information as it becomes available.

The Guideline Development Group discussed at length the issues that this safety signal raises for women and adolescent girls who are of childbearing potential. Every effort was made to ensure that a woman-centred approach and women's choices and preferences were respected when formulating the recommendations (Box 2).

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 (with no coercion). 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 and 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 gender equality.

A human rights-based approach to ART

All ART should be prescribed using a human rights-based approach. This means that the pregnant or breastfeeding woman receives full information and medical guidance that is appropriate to her situation and is supported in making voluntary choices around medical therapy initiation, continuation and adherence/retention in care, as applicable. Health workers must help women to appropriately address their health-care needs and those of their children.

Source: *Consolidated guideline on sexual and reproductive health and rights of women living with HIV*. Geneva: World Health Organization; 2017.

HIV-associated TB infection

Clinical data on the efficacy and safety of DTG co-administered with rifampicin among people coinfecting with HIV and TB are based on pharmacokinetic studies involving healthy adult volunteers and the results of a single trial among adults with HIV and TB (40). These studies showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin, and this was well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV.

Additional research is underway to further inform the use of DTG among people with HIV-associated TB infection, including assessing the effectiveness of 100 mg of DTG once daily to overcome the drug–drug interaction with rifampicin (41). Pharmacokinetic studies are also in progress analysing the drug–drug interaction between DTG and other TB drugs in people with both HIV and TB. Rifabutin and DTG can be safely co-administered at standard doses (41).

For treatment of latent TB, a pharmacokinetic study of DTG with rifapentine involving healthy adult volunteers was stopped prematurely because unexpected and serious systemic toxicity occurred among two of the four participants enrolled (42). Preliminary findings from an ongoing study suggest that rifapentine and DTG can be safely used among people living with HIV (43), but the dosing schedule is still unclear, and further dosing and efficacy studies are underway.

Table 1. Preferred and alternative first-line regimens in adults and adolescents

Populations			Preferred first line regimen	Alternative first line regimen(s)	Special situations
Adult men and adolescent boys			TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + EFV 600mg	AZT + 3TC + EFV 600mg
Adult women and adolescent girls	Pregnant or breastfeeding ^a				
	Not of childbearing potential				
	of child-bearing potential	Offered and using effective contraception			
		Offered but not using effective contraception or without access to contraception or want to become pregnant ^g	Choose to use DTG after informed choice		
	Choose to use EFV after informed choice	TDF + 3TC (or FTC) + EFV 600mg	TDF + 3TC (or FTC) + ATV/r ^b	AZT + 3TC + EFV 600mg TDF + 3TC (or FTC) + RAL	
Children			ABC + 3TC + DTG ^c	ABC + 3TC + LPV	ABC + 3TC + EFV ^e (or NVP)
				ABC + 3TC + RAL ^d	AZT + 3TC + EFV ^e (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates			AZT + 3TC + RAL	AZT + 3TC + NVP	AZT + 3TC + LPV/r ^f

^a Based on programmatic practicality and uncertainty surrounding possible DTG effects after the neural tube closes at 28 days of gestation as noted by the originator and FDA, previous safe period after 8 weeks is now extended to after the first trimester. In practice, the majority of women will not yet know that they are pregnant during the first 8-12 weeks of pregnancy.

^b If the national prevalence of pre-treatment resistance to EFV or NVP is 10% or higher or if no other alternatives are available.

^c For age and weight groups with approved DTG dosing.[§]

^d RAL can be used as an alternative regimen if LPV/r solid formulations are not available.

^e EFV should not be used for children younger than three years of age.

^f If starting after 2 weeks of age.

^g Women of childbearing potential who intend to become pregnant or who are not otherwise using or accessing effective contraception can receive DTG based regimens if they have been informed of the potential increase in the risk of neural tube defects (at conception and up to the end of first trimester) (See tables on page 24-25). However, many vulnerable and at-risk adolescent girls and women may not be able to negotiate when they want to become pregnant and/or might not be aware they are pregnant.

2.3 Rationale for the recommendation

Cost and cost–effectiveness

DTG is now available as a fixed-dose combination and offers substantial potential cost savings, especially in low- and middle-income countries. The median prices of generic DTG-containing and EFV-containing fixed-dose formulations are comparable (US\$ 75–80 per person per year), but with economies of scale it is expected that the price of DTG could be US\$ 17–21 per person per year, lower than the current first-line regimen prices (44).

A review of 12 studies (44–55) assessing the cost–effectiveness, cost utility or cost savings of DTG as first-line ART for adults concluded that DTG-based regimens are highly cost-effective compared with the standard of care. None of the models evaluated the potential effects of neural tube defects with DTG exposure at conception and potential exclusion of women and adolescent girls of childbearing potential from the population to receive DTG-based regimens.

For children, cost and cost–effectiveness are less clear. Formulations of RAL and DTG for children are not widely available and are still being registered nationally. Although only the originator company currently manufactures the DTG and RAL formulations for children, access prices have been negotiated that appear to be comparable to other recommended ARV drugs and represent good value for money given the fairly small demand (18).

Equity and acceptability

The Guideline Development Group, supported by a contribution from a representative of the WHO Department of Global Health Ethics, discussed at length the potential impact of the recommendation on equity. The Group agreed that providing DTG to everyone who can safely use the drug is the most equitable approach. They also noted that, given the DTG safety signal, providing an alternative effective regimen such as EFV 600 would remain equitable.

WHO conducted structured online surveys with people living with HIV, health-care workers and HIV country programme managers to assess the acceptability, feasibility, values and preferences regarding the large-scale implementation of DTG-containing regimens (Web Annex D). The results of these surveys showed that most people living with HIV, health-care workers and programme managers preferred a DTG-containing regimen as first-line ART for ART-naive people initiating treatment (63%, 79% and 75%, respectively). However, an important limitation of this work was that the recent data on potential safety concerns when DTG is used in the periconception period were not known at the time of the surveys.

The survey also sought values and preferences regarding the preferred ARV regimen while taking rifampicin. One third of the people living with HIV would prefer to take once-daily EFV if taking rifampicin for TB treatment and 42% preferred a twice-daily DTG-containing regimen. More than half the health-care workers (58%) and 40% of programme managers would select the DTG twice-daily option as the preferred approach for people coinfecting with TB and HIV.

Following the signal of a potential association between periconception use of DTG and neural tube defects, a pilot online survey of women living with HIV was developed and disseminated to women via a civil society organization that was carrying out consultations with women in sub-Saharan Africa on this issue. A total of 51 women responded to the survey, 75% of whom were younger than 45 years. When asked which ART regimen WHO should recommend as first-line ART, 53% said a DTG-containing regimen, and 20% preferred an EFV-containing regimen; the rest were uncertain.

Women were also asked whether women and adolescent girls starting ART should start on a DTG-containing regimen. The responses were divided, with 37% of the women answering no and 37% responding yes; the remaining 20% were uncertain or had other comments (6%). Similarly, when the respondents were asked whether women and adolescent girls who are pregnant and starting ART should start on a DTG-containing regimen, the responses were divided: 37% said yes and 31% said no; the rest were uncertain (24%) or had other comments (8%).

Women were also asked how they would feel if their health-care provider advised that they could only take DTG if they were on reliable contraception because of the possible link between DTG and neural tube defects. More than half (57%) responded that they would want their health-care provider to give them information, and then they could decide themselves whether to take DTG; 22% said they would follow the health-care provider's advice; and 20% said they would not take DTG. The remainder were uncertain.

Concerns about potential safety issues related to women and adolescent girls of childbearing potential using DTG might exclude much of the population from using regimens containing this drug in the absence of consistent contraceptive methods (Box 1). This is particularly relevant in settings with a high rate of unintended pregnancies and high prevalence of HIV, especially sub-Saharan Africa, where 60–70% of the people living with HIV are women or adolescent girls. In sub-Saharan Africa, only 36% of women of childbearing age have effective access to contraception (56). Surveys among women and adolescent girls living with HIV are underway to assess the implementation considerations of the potential risk of using DTG in the periconception period, which is a difficult period to identify precisely. Guideline Development Group members assessed the acceptability and feasibility of using DTG safely in the periconception period and concluded that programmes and women and adolescent girls of childbearing potential required information, choice and a person-centred approach to using DTG (Box 3). The current recommendation and note of caution regarding women and adolescent girls of childbearing potential using DTG reflects this assessment of values and preferences.

Box 3. Values and preferences regarding contraceptive choice

Women living with HIV responding to a global values and preferences survey articulated that health care for women and girls living with HIV should be accessible, affordable and available, with provision of integrated sexual and reproductive health services. Respondents reported negative experiences in contraceptive choice: many have been told by service providers that they may only use condoms; others have been coerced or forced into using long-acting or permanent contraceptive methods. In addition, these methods are sometimes provided as a condition for receiving other services, such as safe abortion and post-abortion care or ART. Further, only about half the women surveyed reported receiving practical support for safe conception or for realizing their fertility desires. Experiences of violence were also reported as barriers to optimal sexual and reproductive health outcomes.

Nearly 60% of the survey respondents had experienced an unplanned pregnancy. Only 40% said they had accessed family planning services. Participants in some settings revealed a very low level of understanding, awareness and education on sexuality, pregnancy and pregnancy prevention. This is true for many women, including young women and adolescents, and women from key populations, including sex workers. Gender dynamics play a key role in decision-making around accessing and using contraception and in decision-making about the number and spacing of children.

Women living with HIV stated that compassionate, holistic, unconditional care and support and informed choice should be provided to all women living with HIV in the context of services related to pregnancy and fertility desires and the enjoyment of healthy sexuality. Survey respondents expressed the need for pregnancy and childbirth among women living with HIV – and the right to enter into sexual relationships and marriage – to be “normalized” within health services and within the community at large. Women want to be able to choose whether and when to disclose their status to their partners and to be supported in doing so if and when they want to.

The respondents described a routine lack of inclusion or choice in decision-making about their own sexual and reproductive health-care pathways and recommended that principles of human rights need to be embedded in all health-care policies, practices and training. In particular, women should never be pressured or coerced into any course of action (especially terminating pregnancy), whether explicitly without consent or even unwittingly.

Source: *Consolidated guideline on sexual and reproductive health and rights of women living with HIV*. Geneva: World Health Organization; 2017.

After the DTG drug safety alert was issued, women living with HIV have voiced concern that they should be given the right to make their own choices, with safety at home and in clinics, to make their own individual decisions about if, what and when they take ART and/or contraception. This means having the right to fully informed, safe access to comprehensive non-judgemental sexual and reproductive health care, including support to navigate adherence and potential consequences and side-effects, whatever decisions they take (57). (Box 4).

Box 4. Considerations for adolescent girls of childbearing potential – critical enablers to the WHO DTG recommendation

It is estimated that 15% of the 252 million adolescent girls aged 15–19 years living in developing regions (Latin America and the Caribbean, Africa and Asia excluding Australia, Japan and New Zealand) are sexually active, and among these adolescents, 23 million have an unmet need for modern contraception. In 2016, an estimated 21 million girls aged 15–19 years and 2 million girls younger than 15 years in developing regions became pregnant. Approximately half of these pregnancies were unintended (58).

Member States have agreed, as part of their commitment to the Sustainable Development Goals, to ensuring universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes.

Policy decisions on the use of DTG for adolescent girls and women of childbearing potential should stimulate a review of access to sexual and reproductive health services for people living with HIV and assess the status of integration between HIV and sexual and reproductive services in low- and middle-income countries.

The provision of effective family planning by health-care providers is essential to ensuring that adolescent girls living with HIV are well informed of their options to prevent unintended pregnancies, to provide pre-pregnancy care to avoid exposure to DTG during the periconception period and to provide alternative ARV drug options for those wishing to conceive.

DTG-based regimens are of particular benefit for adolescents due to their higher risk of suboptimal adherence and known challenges in dealing with the central nervous system side-effects that are associated with EFV. DTG's high genetic barrier to resistance is of particular importance in a population in which the risk of triple class resistance and viral failure is higher than in any other age (59,60). Careful consideration should therefore be given to promoting the safe use of DTG in this population.

A differentiated approach for adolescent-friendly and integrated services for sexual and reproductive health and HIV is needed; these services should consider potential barriers and approaches to increasing demand, supply, uptake and adherence to both HIV treatment and contraception, with particular attention paid to social and economic barriers to access (61). In view of the gradual shift to non-facility-based service delivery models, community networks and community health workers need to provide HIV and sexual and reproductive health services using an adolescent-friendly approach.

Finally, programmes should engage and involve adolescents, directly and through health worker and community-based approaches, to improve the understanding of contraceptive methods and sexual and reproductive health and how this relates to the DTG safety concern.

The most common reported challenges to adopting DTG as the preferred first-line option were ensuring a system for active long-term toxicity monitoring, preventing stock-outs, maintaining the supply chain during the transition period and ensuring adherence to twice-daily DTG for people coinfecting with TB and HIV.

Fixed-dose combinations are desirable overall, but no fixed-dose combination containing DTG is currently available for children. This may only become available in two years (62); in the meantime, once-daily administration of a small pill or scored dispersible tablets (currently being developed) in combination with an age-appropriate NRTI backbone in a fixed-dose combination is expected to be acceptable. A feasibility and acceptability assessment was conducted in South Africa on the use of RAL granules for treating neonates. A preparation of RAL granules was found to be acceptable and feasible to most participants in this low-resource setting. Accuracy of administration depended on the level of training provided by the health-care worker. Ensuring adequate training of health-care workers and caregivers is vital to ensure that the medication is administered accurately (63).

Feasibility

In early 2018, about 500 000 people living with HIV were using DTG globally, two thirds of them in high-income countries. Among low- and middle-income countries, Botswana, Brazil and Kenya have started adopting DTG as a preferred first-line option using different eligibility criteria (64–66). Other countries, including Georgia, Myanmar, Nigeria, Uganda, Ukraine, United Republic of Tanzania and Zambia, have already received their first shipments of DTG formulations from generic manufacturers (62).

By the end of 2017, almost 70 low- and middle-income countries (49%) had informed WHO that they have included or are planning to include DTG in their plan and transition to DTG-based regimens in their national guidelines (5). Multiple suppliers are capable of manufacturing DTG as a single product and as part of a fixed-dose combination and have already begun building capacity to cope with potentially increased demand. No shortfalls in capacity are expected (62).

Introduction of a DTG-based regimen for children older than six years appears to be feasible, especially given the possibility of using a simplified dosing approach with a 50-mg generic DTG formulation from at least 25 kg.

Treating neonates requires early infant diagnosis and linkage to care in the first four weeks of life. In settings where this is possible, using RAL granules is expected to be feasible, as demonstrated in a rapid assessment undertaken in KwaZulu-Natal, South Africa (67).

Difficulties in introducing 25-mg chewable RAL tablets for first-line treatment for children four weeks to six years of age has raised concerns about procurement and supply. The Antiretroviral Procurement Working Group acknowledges challenges with countries introducing RAL for a time-limited period until DTG becomes available and has flagged potential high risk of overstock or stock-out situations.

2.4 Clinical and implementation considerations

Despite a lower risk of drug–drug interactions compared with NNRTIs and boosted PIs, DTG cannot be used with some anticonvulsants (such as carbamazepine) and should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medicines containing polyvalent cations (68). This guidance applies equally to all populations and is particularly relevant for pregnant women and children, who frequently receive vitamin supplementation (Annex 4). For adolescent girls

and women taking DTG in combination with hormonal contraception, there are no reported or expected drug-drug interactions, although data is limited. Web Annex E provides details of contraceptive options for women and adolescent girls with HIV, including those taking an integrase inhibitors. Annex B shows contraceptive options for women and adolescent girls taking raltegravir. This can be applied to dolutegravir.

People coinfectd with HIV and TB treated with rifampicin-containing regimens should receive an additional 50 mg of DTG 12 hours after taking their main ARV drug regimen.

Given the suboptimal viral suppression on NNRTI-based regimens as demonstrated by increasing evidence from programmatic and observational data, use of NNRTI-based regimens is discouraged if alternatives are available. LPV/r-based regimens can provide a more robust option that overcomes potential resistance to NNRTIs and provides the opportunity to harmonize regimens across paediatric age groups until DTG dosing information becomes available for children younger than six years. EFV-based regimens can be used as a first-line regimen for children 3–6 years old in special circumstances.

When RAL granules are used to start treatment among neonates diagnosed with HIV, careful consideration should be given to making the appropriate dose change after the first week of life and then again after four weeks (Annex 3) for ARV dosing for children and ensuring adequate training of health-care workers to instruct caregivers because of the challenges of correctly reconstituting and administering the granule formulation.

For infants older than four weeks, because of the administration challenges presented by the RAL granule formulation, the Paediatric Antiretroviral Working Group has recommended use of the 25-mg chewable tablets as dispersible tablets after reviewing *in vitro* data on solubility and bioequivalence between tablets and granules (67) and taking into account the lack of adequate alternatives for this age group.

HIV programmes should plan carefully to ensure that DTG supply is available to meet the anticipated demand; a phased approach to implementation is highly recommended. Several countries have adopted approaches to start transitioning to DTG among people initiating first-line ART and/or those already receiving first-line NNRTI-based ART and who have intolerance of or contraindication to NNRTIs. To ensure supply security during the transition of DTG-containing regimens, country programmes should plan orders 6–12 months in advance and stagger large orders into smaller deliveries to avoid overburdening the procurement system. Ensuring sufficient buffer stocks of existing and new regimens throughout the transition period is also important. Implementing partners have developed specific toolkits and checklists to guide countries (44).

Not all countries can transition at the same time or speed. Some countries have limited capacity to develop and manage multiple implementation polices. Several clinical, operational and programmatic factors need to be considered. For example, the availability of country-level information on pretreatment HIV drug resistance to EFV or NVP can accelerate the transition to DTG (Box 5), and the lack of access to generic fixed-dose combinations and large stocks of EFV-containing regimens can be a barrier to rapidly scaling up DTG in some countries (4). Given the above-mentioned safety signal for women and adolescent girls of childbearing potential, ensuring that EFV continues to be widely available as countries introduce DTG is critical.

Additional factors to be considered during transition include training of health-care workers, appropriate messaging to communities and revision of monitoring tools.

Box 5. Considerations for countries with national estimates of pretreatment HIV drug resistance to EFV or NVP $\geq 10\%$

Increasing pretreatment HIV drug resistance among people initiating or reinitiating first-line ART has been documented in many low- and middle-income countries (69). Pretreatment HIV drug resistance to EFV or NVP ranges from 4% to 19% and exceeds 10% in six of the 11 countries in Africa, Asia and Central and South America reporting nationally representative estimates (70).

A systematic review of 26 studies showed that adults and children with pretreatment HIV drug resistance to EFV or NVP initiating NNRTI-based regimens are more likely to experience failure of viral suppression, more likely to discontinue treatment and more likely to acquire new resistance mutations. This evidence informed WHO to recommend that NNRTIs not be used for first-line ART in countries with a national prevalence of pretreatment HIV drug resistance to EFV or NVP exceeding 10% (71).

Women represent a population at high risk for pretreatment resistance to EFV or NVP, about twice as high as men, probably because of previous use of ARV drugs for preventing mother-to-child transmission (70). Although TDF + 3TC + DTG is generally the preferred regimen, DTG should be offered to adolescents and women of childbearing potential only when consistent and reliable contraception can be assured. Atazanavir/ritonavir (ATV/r) appears to be a suitable alternative based on considerations around cost, availability, toxicity profile, pill burden and genetic barriers to resistance. However, the higher comparative cost and potential increased risk for low birth weight and prematurity with using PIs in pregnancy should be considered. Other PI/r may have similar risks among pregnant women; LPV/r may also be associated with potential higher risk of early infant death when given at higher dosing in association with TDF in the third trimester (71).

The choice of alternative options to EFV in this context therefore needs to be made by weighing drug availability and toxicity profile. In countries with high levels of pretreatment HIV drug resistance, the risk and benefit balance should be carefully evaluated, and DTG (with consistent and reliable contraception for adolescent girls and women of childbearing potential) or ATV/r are the drug options to be considered.

Among people starting NNRTI-based ART with reported previous use of ARV drugs (such as women exposed because of preventing mother-to-child transmission and people restarting ART after treatment interruption), pretreatment HIV drug resistance to EFV or NVP ranges from 10% to 33% and is significantly higher than in the treatment-naïve populations in all WHO regions (3). WHO recommends that people starting ART with reported previous ARV drug exposure use a non-NNRTI-containing regimen, regardless of the country's prevalence of pretreatment HIV drug resistance to NNRTIs (4).

If the use of a non-NNRTI-containing regimen cannot be implemented, countries may consider using HIV drug resistance testing to guide the selection of first-line ART regimens, provided that capacity and resources are available (4). To ensure high-quality HIV drug resistance information for national decision-making, WHO has developed standardized HIV drug resistance surveillance methods (72).

An important consideration is the issue of changing to a DTG-based regimen for people who are stable on a first-line NNRTI-containing regimen (Box 6).

Box 6. Considerations for substituting first-line regimens with DTG-based regimens while maintaining the same NRTI backbone

Among people who are stable (no signs of clinical or immune failure) on TDF + 3TC (or FTC) + NNRTI with documented suppression of viral loads, substitution to TDF + 3TC + DTG can be associated with clinical and programmatic benefits, including reducing central nervous system side-effects, simplifying supply chains, reducing the risk of stock-outs and potentially saving costs (15), as shown in several studies (73,74). This would also apply to children for whom an approved DTG dose is available and who are stable on NNRTI-based or PI-based regimens (18). However, this approach may not be optimal for people with evidence of failure of suppression of viral loads given the high levels of resistance to NRTIs and the unknown efficacy of DTG in combination with an inactive NRTI backbone (see Box 7).

Many low- and middle-income countries have limited access to routine viral load monitoring and would not be able to identify individuals for whom ART is failing and who could be at potential risk of receiving suboptimal therapy if this strategy is adopted.

Programmatic advantages associated with large-scale substitution of TDF + 3TC (or FTC) + NNRTI with TDF + 3TC + DTG have led to consideration of using the latter regimen for everyone receiving NNRTI-based ART who is clinically stable, regardless of viral suppression. Among children, consolidating ARV drug regimens is particularly important to reduce market fragmentation, facilitate the procurement and supply of formulations for children, lower the risk of stock-outs and increase the availability of formulations for children. However, the potential programmatic benefits need to be weighed against the potential increased risks of adverse events for people who tolerate their existing treatments when substituting with a new regimen (75).

WHO conducted structured online surveys with people living with HIV, healthcare workers and HIV country programme managers to assess the acceptability, feasibility, values and preferences regarding the large-scale implementation of DTG-containing regimens (Web Annex 4). The survey sought the views of participants on the option of switching people who are stable on an EFV 600-containing regimen to a DTG-containing regimen. Almost 60% of the people living with HIV surveyed preferred to have the choice to remain on an EFV 600-containing regimen, while 25% would be happy to change to DTG; 43% of programme managers and 44% of health-care workers would prefer that people stable on EFV 600-containing regimens remain on their current regimen, and 45% of programme managers and 52% of health-care workers stated that they would want to switch to DTG even if people were stable on EFV.

Resistance to both TDF and 3TC is common and is estimated to be present in about 60% of the people for whom NNRTI-based regimens are failing and about 10% among all people receiving ART regardless of whether treatment is failing or not (76,77). Since the efficacy of DTG in the presence of an inactive NRTI backbone is unknown, substituting NVP or EFV with DTG without viral load testing may be associated with increased risk for selection of DTG resistance and transmission in the population. This may affect future DTG efficacy and preclude the future use of DTG in salvage therapy (78).

Although viral load monitoring before substituting from TDF + 3TC (or FTC) + NNRTI to TDF + 3TC + DTG is encouraged and considered good practice, if countries adopt this substitution in the absence of viral load testing, closely monitoring outcomes and assessing viral load levels and drug resistance using standardized prospective studies and cross-sectional national HIV drug resistance surveys are encouraged to generate data that can be more easily interpreted and compared across settings (15,68).

2.5 Research gaps

Active research and surveillance are urgently needed to assess the risk of neural tube defects among neonates born to mothers with exposure to DTG during the periconception period.

Further research is also required to determine the long-term safety of DTG in various subpopulations, including breastfeeding infants born to women receiving DTG. These studies should reflect the characteristics of the people in treatment programmes, such as pregnant women and women and adolescent girls of childbearing potential, children and adolescents and people with TB coinfection and other comorbidities.

Similarly, the association of DTG with central nervous system and cardiovascular events, immune reconstitution inflammatory syndrome and other adverse reactions, including fatigue and headache, requires further long-term investigation to ensure safe harmonization across populations. Toxicity surveillance systems implemented alongside ART can provide data to better understand the frequency and clinical relevance of various types of toxicity.

A better understanding of the pharmacokinetics and appropriate dosing of DTG in neonates and children younger than six years old – including those coinfecting with TB – is also needed. More evidence is also required to assess the risk of selecting resistance to integrase inhibitors by using RAL in first-line therapy and how that will affect the subsequent use of DTG.

Switching clinically stable people with viral suppression from TDF + 3TC (or FTC) + EFV to TDF + 3TC + DTG can maintain viral suppression, but more data are needed on the benefits in reducing adverse events (75). Evidence on the benefits and risks of this approach requires urgent investigation.

3. SECOND-LINE ARV DRUG REGIMENS

Recommendations

NEW

DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for people living with HIV^a for whom non-DTG-based regimens are failing (*conditional recommendation, moderate-certainty evidence*)

NEW

DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone is recommended as the preferred second-line regimen for children with approved DTG dosing for whom non-DTG-based regimens are failing (*conditional recommendation, low-certainty evidence*)

^a See Box 1 on women and adolescent girls of childbearing potential using DTG.

3.1 Background

The scaling up of ART has substantially reduced HIV-related morbidity and mortality worldwide (79). With more people living with HIV receiving ART and improved early detection of failure to suppress viral loads through monitoring in low- and middle-income countries, many people are anticipated to need to switch to second-line and subsequent ART regimens (80).

Estimates suggest that, by 2020, 2–3 million people living with HIV will be receiving second-line ART (58). However, estimates indicate that fewer than 1 million adults and 100 000 children living with HIV are currently receiving second-line treatment in low- and middle-income countries. Limited access to viral load monitoring and lack of simplified regimens and formulations – especially for children – are important challenges to improving timely switching to second-line regimens (81).

The 2016 WHO consolidated guidelines (2) recommended two NRTIs plus LPV/r or ATV/r as the preferred second-line regimen for individuals for whom EFV-based or DTG-based regimens are failing; two NRTIs + DRV/r and LPV/r + RAL were recommended as alternatives because of cost constraints and the fact that DRV/r is not yet available in a heat-stable co-formulation (5). The choice of NRTI backbone for second-line ART continued to depend on which NRTI was used in first-line ART (if ABC + 3TC or TDF + 3TC (or FTC) were used, AZT + 3TC should be used in second-line ART and vice versa) with the goal of optimizing sequencing in the context of lack of access to genotyping.

Since the WHO consolidated ARV guidelines were published in 2016, several studies exploring various strategies for second-line therapy have been conducted, including those focusing on using ART classes other than PIs and NRTIs, NRTI-sparing regimens and strategies for optimizing PI doses (19,82).

More robust second-line options are needed for children among whom rates of viral suppression on ART have been consistently lower than among adults, as recently reported by the Population-based HIV Impact Assessments undertaken in several African countries. These studies suggest that suppression of viral loads is lowest among children younger than five years (18,83), who are at high risk of treatment failure and likely to need second-line treatment.

Despite major advances in ARV drug development for adults, treatment for children often relies on suboptimal drug regimens and formulations. Except for LPV/r, co-formulated boosted PIs are still unavailable.

The 2016 WHO consolidated guidelines reviewed preferred regimens for second-line ART for children, and RAL was introduced as a preferred option for second-line regimens for infants and children for whom LPV/r-based regimens are failing. ATV/r was also considered equivalent to LPV/r as a second-line option for children for whom NNRTI-based regimens are failing. Because of the lack of dosing information and regulatory approval for use in these populations, DTG was only recommended for third-line ART (2).

WHO continues to promote the optimization of second-line regimens to lower toxicity and pill burden and once-daily dosing, minimal or no cross-class resistance and a preference for regimens that can be used across all populations (84,85).

3.2 Supporting evidence

Adults and adolescents

An updated systematic review conducted in 2018 assessed the efficacy and safety of DTG in combination with an optimized NRTI backbone among individuals with HIV for whom a NNRTI- or PI-based first-line regimen is failing (Web Annex F). All studies investigating the use of DTG in second-line ART typically choose the best available NRTI backbone based on history or genotyping results (Box 7).

The review included seven trials involving 3877 people randomized to 16 treatment arms. The analysis showed high- to moderate-quality evidence that two NRTIs + DTG is generally a more effective regimen, with higher viral suppression and lower risk of treatment discontinuation because of adverse events, compared with two NRTIs + LPV/r, as well as evidence that DTG has the strongest suppressive efficacy compared with other integrase inhibitors. No differences were found in terms of mortality, AIDS-defining illnesses and occurrence of serious adverse events.

As noted above, DTG has other advantages compared with other second-line options, including lower cost, better tolerability, less potential for drug–drug interactions, lower pill burden and availability in once-daily fixed-dose combinations (9,82).

Experience with DTG in low- and middle-income countries as a second-line option is very limited compared with LPV/r and other boosted PIs. More than 70% of the people in low- and middle-income countries taking second-line ART are receiving a LPV/r-based regimen (58). There are also concerns about DTG safety during conception and complexity related to the need to double dose in the presence of rifampicin.

Children

Since the 2016 WHO consolidated ARV guidelines were published, the Paediatric Antiretroviral Drug Optimization group has endorsed the rapid introduction of integrase inhibitors for infants and children, with a preference for DTG over RAL. The group has also supported the use of DTG in second-line treatment and promoted the extrapolation of efficacy data from trials involving adults when direct comparative evidence is not available for children (18).

Although the use of DTG as second-line ART for children is still under evaluation (with results expected in 2020), based on extrapolation from data for adults, the Guideline Development Group agreed that DTG in combination with an optimized backbone regimen should be recommended

as a preferred second-line regimen for all children for whom an approved DTG dosing is available. DTG can currently only be used for children older than six years and weighing at least 15 kg, with approved dosing down to four weeks expected by the end of 2019. Because experience with DTG among children is limited, the Guideline Development Group also recommended that routine toxicity monitoring be ensured when this recommendation is implemented.

For children for whom approved DTG dosing is not available, boosted PI- and RAL-based regimens continue to be preferred for children for whom an NNRTI- or PI-based first-line regimen is failing, respectively (2).

Table 2. Summary of sequencing options for first, second and third-line ART regimens for adults (including pregnant women and adolescent girls) and children

Population	Failing first-line regimen	Preferred second-line regimen ^b	Alternative second-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or are pregnant) ^a	Two NRTIs + DTG ^b	Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))	Darunavir/ritonavir (DRV/r) ^{g,h} ± DTG ^{i,b} + 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 effective contraception and who are fully informed of the benefits and risks can use DTG. Women beyond the first trimester of pregnancy are not at risk on NTD and DTG-based ART is a safe option for those starting ART or those switching to second-line. Women of childbearing potential who intend to become pregnant or who are not otherwise using contraception should be informed of the potential increase in the risk of neural tube defects (at conception and up to the end of first trimester) before being offered DTG.

^c If population-level pretreatment resistance to EFV or NVP is $\geq 10\%$, the choice of alternative options to EFV needs to be made weighing the drug availability and toxicity profile. Women of childbearing potential who intend to become pregnant or who are not otherwise using contraception should be informed of the potential increase in the risk of neural tube defects (at conception and up to the end of first trimester) before being offered DTG.

^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 (Annex 3).

^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.

3.3 Rationale for the recommendation

Cost and cost–effectiveness

The median price of DTG is significantly lower than that for the boosted PIs currently used for second-line ART, especially in low- and middle-income countries (58). However, some upper-middle-income countries have no access to generic DTG formulations at reduced prices as a result of patent and licensing restriction.

Four studies, including one from sub-Saharan Africa, have evaluated the cost–effectiveness of DTG as second-line ART (44–46,53). All studies concluded that using DTG-based regimens is highly cost-effective compared with the standard of care (either for a national treatment policy or compared with current WHO guidelines), had lower total costs, offered significant cost savings and improved clinical outcomes.

For children, cost and cost–effectiveness are less clear. Formulations of DTG for children are not widely available and are being registered nationally by the originator company. While paediatric formulations of DTG are currently only manufactured by the originator company, access prices have been negotiated and appear to be comparable to other recommended ARV drugs and represent good value for money (58).

Equity and acceptability

The selection of second-line ART has important public health and programmatic implications. Effectiveness, tolerability and safety of regimens remain key considerations; issues such as cost, monitoring and drug delivery and storage should also be considered to ensure an equitable and acceptable selection of second-line and salvage ART.

For first-line ART, the Guideline Development Group, supported by a contribution from a representative of the WHO Department of Global Health Ethics, discussed at length the potential impact of the recommendation on equity. The group agreed that providing DTG to everyone who can safely use it is the most equitable approach. They also noted that, given the DTG safety signal, providing an alternative effective regimen, such as a boosted PI-based regimen, would remain equitable. Using DTG instead of boosted PIs was therefore considered to increase equity across populations in low- and middle-income countries.

Among adolescents and children, fixed-dose combinations are typically more acceptable, but similar to other second-line regimens, no fixed-dose combination for children currently contains DTG (86). Meanwhile, once-daily administration of a small DTG tablet in combination with an age-appropriate NRTI backbone in a fixed-dose combination is expected to be acceptable, especially compared with an ATV/r regimen, which would require separate administration of ATV and ritonavir.

Feasibility

Among low- and middle-income countries, Botswana, Brazil and Kenya have been early adopters of DTG as a preferred first-line option and are implementing programmatic transition to DTG (5). Only Botswana is planning to use DTG in second-line ART.

Introducing DTG-based regimens for children older than six years appears to be feasible, especially given the possibility of adopting a simplified dosing approach using a 50-mg generic DTG formulation from at least 25 kg.

Box 7. Use of TDF + 3TC + DTG in second-line ART following failure of TDF + 3TC (or FTC) + EFV: HIV drug resistance considerations

The use of DTG in combination with an optimized NRTI backbone is preferable and recommended as good practice (AZT + 3TC should be used as the NRTI backbone in a second-line regimen if TDF + 3TC (or FTC) was used in the failing first-line regimen and vice versa). Indeed, using TDF + 3TC + DTG in second-line ART following failure of TDF + 3TC (or FTC) + EFV, although it may have programmatic advantages, also raises concerns about the potential use of a suboptimal therapy. Viral resistance to TDF and 3TC is common among people for whom NNRTI-based ART is failing; up to two thirds of individuals have viral resistance to TDF, and in the vast majority of these resistance to 3TC is also present (76).

There is currently no evidence on the efficacy of DTG when used in combination with an NRTI backbone whose activity is compromised by the presence of one or more major resistance-associated mutations; DTG in combination with an optimized backbone is therefore recommended.

The apparent high genetic barrier of DTG to HIV resistance has prompted the investigation of DTG as part of two-drug therapy or monotherapy and in regimens with a partly active NRTI backbone.

Although the efficacy of DTG in combination with 3TC appears to be promising among ART-naïve individuals and may potentially be highly effective as maintenance therapy in people with suppression of viral loads (87,88), limited evidence currently supports using it among people with failure to suppress viral loads and documented resistance to 3TC.

In the DAWNING study, people were switched from NNRTI to DTG-based ART with at least one active NRTI predicted by genotypic resistance testing. Although DTG seems to be effective with at least one active NRTI for people for whom NNRTI-based ART is failing, a retrospective analysis suggests that selecting NRTI backbone sequencing according to WHO guidelines achieved modest but significantly greater suppression of viral loads (85).

Further, there has been no direct evaluation of DTG with an NRTI backbone predicted to be inactive by genotypic resistance testing, but findings from DTG monotherapy studies have demonstrated the rapid accumulation of integrase inhibitor mutations (89,90).

Overall, insufficient evidence supports using DTG in combination with TDF and 3TC as second-line ART for people for whom TDF + 3TC (or FTC) + EFV is failing as a first-line regimen. More data are needed on the efficacy of DTG among people with resistance to 3TC and TDF (78).

3.4 Research gaps

Further evidence is needed to inform the routine use of TDF + 3TC + DTG in second-line regimens following the failure of TDF + 3TC (or FTC) + EFV. Additional research is also required to better understand the choice and sequencing strategies in second- and third-line ART, especially for children and adolescents. Ongoing studies comparing the use of DTG and other integrase inhibitors combined with other ARV drug classes will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches. Finally, more data is needed to inform the recycling of the NRTI backbone in DTG-based second-line regimens following the failure of first-line TDF + 3TC (or FTC) + EFV. Several trials are underway to examine induction and maintenance using integrase inhibitors (including DTG), either in monotherapy or in combination with 3TC (or FTC).

Further studies are needed to assess the possible impact of resistance to the NRTI backbone on the long-term effectiveness and durability of second-line DTG-containing ART regimens. Residual NRTI activity (activity of TDF, 3TC and FTC) or reduced viral fitness is likely in the presence of certain resistance mutations, and could provide some protection against the selection of DTG resistance, but no clinical trials or observational studies have assessed their impact among people receiving this regimen.

4. WHAT TO USE IN HIV POST-EXPOSURE PROPHYLAXIS

Recommendations

Overall

An HIV post-exposure prophylaxis regimen with two ARV drugs is effective, but three drugs are preferred (*conditional recommendation, low-certainty evidence*)^a

Adults and adolescents

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis (*strong recommendation, low-certainty evidence*)^a

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis (*strong recommendation, low-certainty evidence*)^b

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis (*conditional recommendation, low-certainty evidence*)

Children^c

AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens (*strong recommendation, low-certainty evidence*)^a

NEW DTG is recommended as the preferred third drug for HIV post-exposure prophylaxis for children for whom an approved DTG dosing is available (*strong recommendation, low-certainty evidence*)

NEW When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for post-exposure prophylaxis (*conditional recommendation, low-certainty evidence*)

^a WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

^b See Box 1 on women and adolescent girls of childbearing potential using DTG.

^c The choice of ARV drugs for children will depend on the availability of approved dosing and age-appropriate formulations for children. Use of DTG applies to all infants and children for whom an approved DTG dosing is available.

4.1. Background

WHO guidelines for HIV post-exposure prophylaxis, formulated in 2014, aimed to provide a simplified approach to delivering post-exposure prophylaxis, given the suboptimal uptake and completion of post-exposure prophylaxis (PEP) (91–93). The guidelines aimed to align recommendations for HIV PEP with the ARV drugs available in low- and middle-income countries for treating and preventing HIV.

The 2014 guidelines recommended TDF + 3TC (or FTC) as the preferred backbone regimen for HIV PEP for adults and adolescents, and for children 10 years and younger, AZT + 3TC was the recommended backbone regimen. The recommended third drugs included ATV/r or LPV/r for adults and LPV/r for children, with several alternatives provided according to availability, including current age restrictions and the availability of age-appropriate formulations for

children. Since then, additional studies have been published that provide information about the tolerability and completion rates of the WHO-recommended HIV PEP regimens and data on newer ARV drugs, notably DTG.

These guidelines provide updated recommendations on ARV drugs for HIV PEP. The WHO 2016 consolidated ARV guidelines provide additional recommendations on eligibility, timing, prescribing and adherence support and clinical considerations (2). The WHO clinical guidelines on responding to children and adolescents who have been sexually abused describe further clinical considerations in providing appropriate care to children and adolescents who have been sexually abused (94).

4.2 Supporting evidence

An updated systematic review assessed the tolerability of HIV PEP and completion of different ARV regimens recommended by the 2016 WHO consolidated guidelines (Web Annex G). The systematic review identified 16 studies reporting the outcomes of different HIV PEP regimens using TDF + 3TC (or FTC) backbones. All studies involved adults, and no additional evidence was retrieved for post-exposure prophylaxis regimens for children or adolescents. Overall, the highest completion rates for HIV PEP were reported for TDF + 3TC (or FTC) in combination with DRV/r (93%, 95% confidence interval 89–97%) or DTG (90%, 95% confidence interval 84–96%). These regimens were also associated with the lowest rates of discontinuation or substitutions because of adverse events (1%, 95% confidence interval 0–2% for DRV/r; 1%, 95% confidence interval 1–4% for DTG).

For adults, the Guideline Development Group recommends that DTG may be used as the preferred third drug for HIV post-exposure prophylaxis. This recommendation considered the high rates of post-exposure prophylaxis completion and low rates of adverse events as well as the established high tolerability of DTG when used in ART (Web Annex B). This preference also considered cost, current and anticipated availability, low potential for drug–drug interactions and the desirability of aligning with recommendations for ART. Alternative third drug options include ATV/r, DRV/r, LPV/r and RAL, with the choice to be based on considerations of tolerability and completion rates as well as cost, availability and acceptability (Table 3).

The 2014 WHO guidelines on PEP noted that data on using EFV in HIV post-exposure prophylaxis were lacking and that there are concerns about giving a drug associated with early central nervous system and mental health adverse events to HIV-negative people who may have anxiety related to HIV exposure. Since then, data have been published suggesting that EFV is associated with high rates of discontinuing PEP because of central nervous system events (95). EFV should therefore only be used as a third drug option when no other options are available.

For children, no new evidence has been published since the review carried out for the 2014 guidelines. However, the recommendation to provide DTG as a preferred drug option for this population is now included, extrapolating from data for adults with the goal of aligning the recommendations for adults and adolescents. DTG is currently only recommended for children older than six years and weighing more than 15 kg. However, approval for use in younger age groups is anticipated, and the recommendation may extend further as dosing approval becomes available. Since other recommended ARV drugs for children also have age restrictions, the choice of ARV drugs for children depends on current age restrictions and the availability of age-appropriate formulations.

Considerations for adolescent girls and women of childbearing potential

The use of DTG in HIV PEP is conditional upon access to consistent and reliable contraception, considering concerns regarding the safety of DTG in the periconception period (see Box 1). As part of comprehensive PEP services, all women should be offered pregnancy testing at baseline and follow-up. Emergency contraception should be offered to girls and women as soon as possible and within five days of sexual exposure. For women not wishing to take emergency contraception, an alternative to DTG should be provided.

4.3. Implementation considerations

The uptake and completion rates for HIV PEP are suboptimal, and the recommendations for HIV PEP regimens should be considered together with existing WHO recommendations aimed at improving completion rates for HIV PEP, including adherence support and providing a full 28-day course of medication at the first clinic visit (2,91).

Choice of HIV PEP regimen should consider the ARV drugs already being procured within national HIV programmes. Additional considerations include the availability of heat-stable formulations, daily dosing, availability and affordability (Table 3).

People may be subject to ongoing high risk of exposure to HIV, leading to multiple prescriptions for PEP. In such situations, health providers should discuss with their clients the potential benefits of transitioning to HIV pre-exposure prophylaxis (PrEP) (96,97).

Table 3. Characteristics of third drug options for post-exposure prophylaxis

Choice criteria	ATV/r	DRV/r	DTG	LPV/r	RAL
Discontinuation rate in HIV post-exposure prophylaxis	9.3%	0.9%	1.4%	5.2%	2.7%
Dosing schedule	Once daily	Once daily	Once daily	Twice daily	Once or twice daily
Availability as a heat-stable formulation	No	No	Yes	Yes	Yes
Accessibility in countries (registration status)	Low	Low	Moderate	High	Low
Acceptability to health providers	High	High	High	High	High
Affordability	Moderate	Moderate	High	Moderate	Low
Age indication	>3 months	>3 years	>6 years	>14 days	Birth

4.4 Research gaps

Ongoing research is needed to document completion and drug-related discontinuation rates associated with different ARV drug regimens used in HIV PEP.

5. EARLY INFANT DIAGNOSIS

Recommendation

NEW

An indeterminate range^a should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays (*strong recommendation, moderate-certainty evidence*)

^a **Indeterminate range:** a range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infected. The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay.

5.1 Background

In 2016, WHO recommended that HIV nucleic acid-based testing (NAT) be used to diagnose HIV infection among infants and children younger than 18 months of age and that ART be started without delay while a second specimen is collected to confirm the initial positive NAT result (2). Confirmatory testing is critical because of the risk of false-positive results, potential contamination with maternal blood (and virus), specimen mislabelling or mix-up, laboratory or cross-sample contamination and an observed trend of low detection of HIV among both mothers and infants because of increased exposure to maternal treatment and enhanced infant prophylaxis (98). The potential for false-positive results is of particular concern in settings in which the mother-to-child transmission rate is less than 5%, since the positive predictive value of highly sensitive nucleic acid–based technologies may decrease to nearly 70% (99). However, in some countries in sub-Saharan Africa, less than 10% of infants with an initial positive test result receive a confirmatory test, potentially resulting in a significant proportion (12.5%) of infants starting lifelong treatment unnecessarily.

Although a variety of causes may result in a false-positive test result, most infants with false-positive test results have low levels of viraemia; however, guidance is limited on how to interpret low levels of viraemia detected in early infant diagnostic assays. All test results reported as detectable by the NAT technology are generally considered to be positive, relying on the thresholds of detection provided by the manufacturers. To ensure that infants do not start lifelong treatment unnecessarily, various approaches have been considered. Guidelines in the United States of America suggest that infants should not be considered HIV-positive unless they have the equivalent of at least 5000 viral copies/ml (100), and South Africa has introduced an indeterminate range that requires further testing before a definitive diagnosis is provided and treatment is initiated (101).

Previous WHO guidelines do not specifically address this growing concern about false-positive test results. Further, there is currently no specific recommendation on what level of viraemia should be considered a true positive result in infants.

5.2 Supporting evidence

A systematic review of 32 studies using an indeterminate range found 14 753 non-negative test results, of which 2436 (16.5%, 95% confidence interval 15.9–17.1%) were indeterminate (Web Annex H). One study reporting the final diagnoses of indeterminate cases found that 76% of

infants with an initial indeterminate test result were negative on repeat testing, suggesting that most infants were not HIV-infected despite the initial non-negative test result. These data indicate that, in countries not implementing an indeterminate range to manage early infant diagnosis test results, up to 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.

The optimal indeterminate range is considered to be the approximate equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay. 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%). The cycle threshold values vary by the assay used and cannot be directly applied between technologies or assays. Because true-positive infants with low levels of viraemia generally have less rapid disease progression and need to be followed up until final diagnosis is ascertained, the Guideline Development Group determined that it is more acceptable to have a higher proportion of true-positives incorrectly classified as indeterminate than false-positives, since all indeterminate test results should be followed up and repeat tested as soon as possible before lifelong treatment is administered.

Implementing an indeterminate range will support more accurate nucleic acid-based early infant diagnosis. Fewer HIV-negative infants will probably start unnecessary lifelong treatment, since most false-positives will fall within the indeterminate range rather than being identified as positive. This will limit confusion and challenges in interpreting potential subsequent discordant test results if the infant was classified as positive and already initiated treatment. Finally, in addition to reducing unnecessary treatment by limiting false-positive results, an indeterminate range will promote increased attention to confirmatory testing of all non-negative test results and trigger corrective action to minimize potential contamination at the point of collection or in the laboratory.

Possible harm identified includes the potential requirement for additional specimens, which could result in delays to treatment initiation, and the associated risk of loss to care for HIV-positive infants with indeterminate results on the first sample. However, infants with low levels of viraemia (a small proportion of HIV-positive infants who would fall within the indeterminate range) are expected to progress more slowly to morbidity and mortality (102). Further, implementing an indeterminate range may reduce the confidence of health-care workers in early infant diagnosis testing programmes if high rates of resampling and retesting are required.

5.3 Rationale for the recommendation

Cost and cost-effectiveness

Implementing an indeterminate range has been determined to save costs since minimum additional resources will be required to repeat test all non-negative specimens, especially those with an initial indeterminate test result, compared with the cost of unnecessary lifelong treatment.

A cost-effectiveness model compared the standard of care (no indeterminate range) to a variety of indeterminate range options and concluded that implementing an indeterminate range is far more effective than the standard of care across a variety of viral ranges (data unpublished). As the prevalence, positivity and mother-to-child transmission rate at each testing time point decrease, the cost-effectiveness of an indeterminate range increases and saves more costs than no indeterminate range.

Equity and acceptability

Implementing an indeterminate range may improve equity by ensuring that HIV-negative infants do not start lifelong treatment unnecessarily. This may also enable access to available treatment for infants correctly identified as HIV-positive.

A survey of values and preferences that included people living with HIV, health-care workers and programme managers found an indeterminate range to be highly acceptable. Most respondents preferred that the meaning of an indeterminate test result be clearly explained to mothers and other caregivers. The primary concern for all groups was the potential for confusion arising from inadequate explanations about the need to resample and retest the infant. However, as long as clear guidance on the meaning of an indeterminate test result is provided to mothers and other caregivers, there will be limited uncertainty about the acceptability of implementation.

Feasibility

Implementing an indeterminate range is expected to be feasible, especially if indeterminate test results are repeat tested using the same specimen. In the survey of programme managers, slightly more than half indicated that their country already has a written standard operating procedure for requesting a second specimen for invalid test results. However, there were some concerns regarding the additional time required for repeat testing all indeterminate test results and the need for storing specimens at the laboratory.

To ease the acceptability, feasibility and implementation of an indeterminate range, a standard operating procedure has been developed to support and guide countries based on expert opinion and values and preferences surveys (Annex 4 and Web Annex D). This standard operating procedure suggests that all indeterminate tests be repeat tested on the same specimen, if and when available. Most indeterminate test results are expected to be resolved with a repeated test on the same specimen, which would alleviate the need for and delay incurred in requesting a new specimen from the infant (98). If the same specimen cannot be repeat tested, then a new specimen should be requested and tested as quickly as possible. 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.

This recommendation to use an indeterminate range to support more accurate diagnosis of infants should be implemented for any nucleic acid–based test performed for infants younger than 18 months, including testing at birth and at six weeks of age. In addition, recent evidence indicates that using HIV serology assays to rule out HIV infection among asymptomatic HIV-exposed infants at nine months of age should be reconsidered. 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 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 concerns are supported by findings from Uganda and Kenya, where 15–40% of children under the age of two years and identified as HIV-infected had positive NAT but negative RDT (103,104). In this context, an expert group convened by WHO in May 2018 confirmed the importance of testing mothers to accurately assess infant exposure status and advocated undertaking nucleic acid–based testing instead of a serology test at nine months for all known symptomatic and asymptomatic HIV-exposed infants to determine HIV diagnosis before 18 months of age (Annex 5 shows the algorithm).

5.4 Implementation considerations

Generally, early infant diagnostic assays measure the presence of virus using real-time nucleic acid–based technologies that often report cycle thresholds. The cycle threshold – the polymerase chain reaction (PCR) cycle when amplification is observed – is inversely correlated with the amount of virus in a sample.

Based on the meta-analysis and cost–effectiveness modelling, the Guideline Development Group assessed that detecting an approximate equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay would be the most appropriate value to balance the risks and benefits of introducing an indeterminate range. Note that the cycle threshold values vary by assay used and cannot be directly applied between technologies or assays. Further, additional consideration 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 detected viral levels.

5.5 Research gaps

Research priorities regarding using an indeterminate range include the need for more detailed evidence on the impact of implementing an indeterminate range in populations with increased drug exposure and enhanced infant prophylaxis, the time of testing (earlier testing near birth), various sample types, differences in prevalence and different virus subtypes. More research would be valuable on the best messaging for health-care workers and mothers and other caregivers and on the optimal standard operating procedure for managing indeterminate test results. Further, understanding the feasibility of implementing an indeterminate range with all available nucleic acid–based technologies for early infant diagnosis and in various programmatic settings will be critical.

6. PLANS FOR UPDATING, DISSEMINATION AND EVALUATION

These guidelines will be produced for dissemination as both printed hard-copy and web-based products and will be supported by peer-reviewed publication of the systematic reviews on which the recommendations are based. A policy brief will accompany the publication of the guidelines.

WHO will also incorporate these guidelines into the next full update of the WHO consolidated ARV guidelines planned for 2019. WHO will closely monitor data on the potential association between DTG and neural tube defects and regularly review emerging data. WHO will update recommendations related to DTG use as soon as relevant evidence becomes available.

WHO will work closely with WHO regional and country offices, national health ministries, implementing partners and networks of people living with HIV to plan for rapidly disseminating, adapting and implementing the new recommendations. Key steps in the dissemination include: presenting the recommendations at international conferences; holding workshops to support country adaptation; developing adaptation tools to assist countries in setting priorities; and ensuring briefings and joint planning with international and national implementing partners. The uptake of the recommendations in national guidelines will be assessed in 2020.

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ANNEX 1. METHODS FOR DEVELOPING THESE GUIDELINES

Methods for evidence synthesis

Key information sources

The WHO Guideline Steering Group formulated PICO (population, intervention, comparator and outcome) questions to guide the systematic reviews used in developing these guidelines (101). The following four PICO questions relevant to these guidelines were identified.

1. Should DTG (or RAL for children without approved DTG dosing) be recommended in combination with an age-appropriate NRTI backbone as the preferred first-line ARV agent for treating HIV infection?
2. Should DTG in combination with an optimized NRTI backbone be recommended as the preferred second-line ARV agent for treating HIV infection?
3. Should DTG be recommended as the preferred ARV agent in combination with tenofovir disoproxil fumarate (TDF) and 3TC or FTC (XTC) for HIV post-exposure prophylaxis?
4. Should an indeterminate range be implemented for more accurate molecular diagnosis of infants younger than 18 months?

A list of potential outcomes of interest for each question was circulated to all members of the Guideline Development Group, and members scored the importance on a scale of 1 (not important) to 9 (critical). The median score for each outcome was used to inform decision-making.

Systematic review teams developed protocols and conducted reviews in accordance with PRISMA reporting items for systematic reviews and meta-analyses.

Assessing the risk of neural tube defects associated with using DTG in the periconception period

As part of retrieving the evidence for these guidelines, a systematic review was carried out to assess the evidence for the safety of DTG in pregnancy. As part of this review, the investigators of an ongoing study in Botswana were requested to provide information on pregnancy and birth outcomes for women exposed to different ART regimens during the periconception period. The results of this analysis identified a potential association between DTG use at conception and neural tube defects discussed in these guidelines.

The reviewers then comprehensively reviewed other databases, surveillance systems and other data sources to determine whether any other cases of neural tube defects associated with DTG use had been identified. These included post-marketing surveillance data from the manufacturers, pregnancy registries (the Antiretroviral Pregnancy Registry) and birth outcomes registries (the National Study of HIV in Pregnancy and Childhood in the United Kingdom and Ireland and the European Pregnancy and Paediatric HIV Cohort Collaboration study group) and drug regulatory authorities.

The results of the review, which included the analysis from the Botswana study, were presented to the Guideline Development Group under a confidentiality agreement.

Values and preferences

To assess values and preferences, an online survey of people living with HIV was conducted to determine their views on recommendations that could be formulated. The survey was disseminated through networks of civil society organizations and organizations of people living with HIV. These surveys were carried out before a signal emerged of a potential risk of neural tube defects with DTG use in the periconception period. Following the dolutegravir drug safety alert, information regarding the values and preferences of women of reproductive age has been made available and has been integrated into these guidelines (2).

Web Annex D reports the results of the initial surveys. Web Annex D also reports on a pilot survey of women living with HIV carried out after the dolutegravir safety signal emerged (<http://www.who.int/hiv/pub/guidelines/ARV2018update/en/>).

Feasibility and acceptability

To explore the feasibility and acceptability of the possible recommendations, online surveys were conducted among health-care workers and of HIV programme managers. Health-care workers were contacted through existing networks of organizations of health-care workers. Programme managers were contacted through WHO regional advisers, who disseminated the surveys to country programme managers in their region. These surveys were carried out before a signal emerged of a potential risk of neural tube defects with DTG use in the periconception period. In addition, a specific acceptability and feasibility assessment was undertaken to inform deliberations on the use of RAL granules. This evaluation was undertaken in KwaZulu-Natal in collaboration with a local academic institution.

Web Annex D reports the results of this survey.

Certainty of the evidence and the strength of the recommendations

The GRADE method (3) was used to rate the certainty of the evidence and determine the strength of the recommendations. The GRADE approach to developing recommendations, which WHO has adopted, defines the certainty of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of a recommendation reflects the degree of confidence of the Guideline Development Group that the desirable effects of the recommendation outweigh the undesirable effects. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced morbidity and mortality), reducing the burden on the individual and/or health services and potential cost savings. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Additional burdens considered include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity).

The strength of a recommendation can be either strong or conditional.

A strong recommendation (for or against) is one for which there is confidence that the desirable effects of adhering to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation (for or against) is one for which the certainty of the evidence may be low or may apply only to specific groups or settings, Guideline Development Group concludes that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects or are closely balanced, but the Guideline Development Group is not confident about these trade-offs in all situations.

The certainty of the evidence, values and preferences of the end-users, feasibility, resource implications and considering the potential benefits and harm contribute to determining the strength of a recommendation.

Guideline Development Group meeting

The Guideline Development Group met for three days in Geneva, Switzerland on 16–18 May 2018. Three members of the group participated via videoconference. The systematic reviews and supportive evidence, including values and preferences, acceptability, feasibility and cost, were presented to the group. Evidence-to-decision-making tables were prepared in accordance with the GRADE process and presented to the group, and the methodologist facilitated discussions. The Group agreed at the start of the meeting that 70% of votes from members would be required for a decision. Voting was required for the recommendations on DTG as the preferred first-line regimen. All recommendations were formulated with the consensus of Group members.

Following the Guideline Development Group meeting in Geneva, a follow-up meeting was held via videoconference on 13 June 2018. The meeting was intended to confirm the recommendations of the Group, since drug regulatory authorities and other agencies had made several statements regarding the safety of DTG for women and adolescent girls of childbearing potential after the meeting in May. The Guideline Development Group confirmed the recommendations it made during the May meeting.

Peer review

A draft of the guidelines was circulated for review to members of the Guideline Development Group and the External Review Group. The Guideline Development Group reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest. Comments were interpreted in the light of any conflicts of interest declared (Web Annex A). Any conflicting or controversial comments were discussed with the WHO Guideline Steering Group. Disagreements were resolved through consensus of the WHO Guideline Steering Group.

Declarations of interest and biographies of Guideline Development Group members

All external contributors to the development of these guidelines completed a WHO declaration of interests form. This included systematic reviewers and contributors to the supporting evidence as well as all members of the Guideline Development Group and External Review Group. In accordance with the WHO declaration of interests policy for experts, a brief biography of each Guideline Development Group member was published on the WHO HIV website with a description of the objective of the meeting. No public comments or objections were received concerning any Group members.

The responsible technical officers reviewed all the declaration of interests forms completed by the Guideline Development Group members. Every effort was made to ensure that the representation of the Guideline Development Group minimized conflicts of interest. A management plan for each declared conflict was agreed. All declared interests and management strategies were discussed with the chairs and methodologist before the Guideline Development Group meeting. Conflicts of interest were shared with the Guideline Development Group at the start of the meeting, with participation closely monitored by the responsible technical officers and GRADE methodologist.

Review of declaration of interest forms identified two members who were principal investigators of two clinical trials of DTG-containing regimens (François Venter and Pablo Rojo). They were excluded from making recommendations on drug regimens but could make recommendations on early infant diagnosis of HIV.

Another member of the Guideline Development Group was excluded from making recommendations on ARV regimens because of a financial conflict of interest deemed significant (Mark Boyd). He declared being on the HIV advisory board of Gilead and had received US\$ 7500. He was also participating in the advisory board of ViiV (current) and had received US\$ 15 000. That member could make recommendations on early infant diagnosis of HIV. Web Annex A details the declared conflicts of interest and management plans.

Other declaration of interests were managed as follows. Thuy Le declared being a co-investigator of two trials that received funding from industry. However, she did not personally receive funding as funding went to the research institution. The WHO Guideline Steering Group and responsible technical officer reviewed the information and determined that full participation was appropriate. Thanyawee Puthanakit received funding through the PENTA foundation from industry. Research funding went to her institution and no personal funding was received. The WHO Guideline Steering Group and responsible technical officer reviewed the information and determined that full participation was appropriate. Wendy Stevens received funding for research relating to TB diagnostics (not directly relevant to the guidelines) from the Bill & Melinda Gates Foundation and MRC. This was not deemed a conflict of interest by the WHO Guideline Steering Group and responsible technical officer, and full participation was allowed.

The responsible technical officers assessed all completed declaration of interest forms for other external contributors to the guidelines, including the External Review Group. Individual participation was reviewed with regard to the interests declared.

External Review Group

Each member of the External Review Group was asked to complete and sign a declaration of interest form. This included members from partner organizations, including the United States Centers for Disease Control and Prevention and UNICEF. The responsible technical officers reviewed these to determine any conflicts of interests. Comments from the External Review Group were interpreted in the light of any conflicts of interest. Web Annex A details the declaration of interests and the management plan for External Review Group members.

All declaration of interest forms are on electronic file at the WHO Department of HIV and will be maintained for at least 10 years.

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ANNEX 2. DRUG TOXICITY AND DRUG–DRUG INTERACTIONS OF ARV DRUGS

Table 1 Types of toxicity associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of <i>HLA-B*5701</i> gene	Do not use ABC in presence of the <i>HLA-B*5701</i> gene. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are taking concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of UDP-glucuronosyltransferase 1-1 enzyme (<i>UGT1A1*28</i> gene)	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Anaemia, neutropaenia	Baseline anaemia or neutropaenia CD4 cell count of ≤ 200 cells/mm ³	Substitute with TDF or ABC. Consider using low-dose zidovudine.
	Lactic acidosis or severe hepatomegaly with steatosis lipoatrophy, lipodystrophy myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG ^a	Hepatotoxicity Hypersensitivity reactions	Coinfection with hepatitis B or C Liver disease	Substitute with another therapeutic class: EFV or boosted PIs.
	Insomnia	Older than 60 years Female	Consider morning dose or substitute with EFV, boosted PI or RAL.
DRV/r	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	

ARV drug	Major types of toxicity	Risk factors	Suggested management
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia and abnormal dreams) or mental symptoms (anxiety, depression and mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	For central nervous system symptoms, dosing at bedtime. Consider using EFV at a lower dose (400 mg/day or an integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms.
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Severe skin and hypersensitivity reactions	Risk factors unknown	
	Gynaecomastia	Risk factors unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
ETV	Severe skin and hypersensitivity reactions	Risk factors unknown	Substitute with another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution for people with pre-existing conduction disease or taking concomitant drugs that may prolong the PR or QRS intervals.
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with RAL or DTG if younger or older than 6 years respectively. If integrase inhibitors are not available EFV, NVP or boosted ATV can be used. If LPV/r is used in second-line ART for adults and the person has treatment failure with NNRTIs in first-line ART, consider integrase inhibitors.
	Pancreatitis	Advanced HIV disease, alcohol	Substitute with another therapeutic class (integrase inhibitors).
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea	Risk factors unknown	Substitute with atazanavir/r, darunavir/r or integrase inhibitors.

ARV drug	Major types of toxicity	Risk factors	Suggested management
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm ³ for women or >400 cells/mm ³ for men)	If hepatotoxicity is mild, consider substituting with EFV, including for children three years and older. For severe hepatotoxicity and hypersensitivity, and for children younger than three years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy and myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Stop ART. When symptoms are resolved, substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factor(s) unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years old BMI <18.5 or low body weight (<50 kg), notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute with AZT or ABC Do not initiate TDF at an estimated glomerular filtration rate of <50 mL/min, uncontrolled hypertension, untreated diabetes or kidney failure
	Decreases in bone mineral density	History of osteomalacia (adults) and rickets (children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

^a Potential signal of neural tube defect in neonates exposed to DTG during the first trimester of pregnancy. See Box 1 for clinical considerations for women and adolescent girls of childbearing potential.

Table 2 Key ARV drug interactions with DTG, EFV and boosted PIs and suggested management

ARV drug	Key interactions	Suggested management
Boosted PIs (ATV/r, DRV/r and LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the dose of LPV/r or substitute with three NRTIs (for children)
	Halofantrine	Use an alternative antimalarial agent
	Lovastatin and simvastatin	Use an alternative statin (such as pravastatin)
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Metformin	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use an alternative antihistamine agent
	TDF	Monitor renal function
	Simeprevir	Use an alternative direct-acting antiviral agent
	Ombitasvir + paritaprevir/ritonavir + dasabuvir	Use an alternative direct-acting antiviral agent
DTG	Dofetilide	Use an alternative antiarrhythmic agent
	Rifampicin	Adjust the dose of DTG or substitute rifampicin with rifabutin
	Carbamazepine, phenobarbital and phenytoin	Use an alternative anticonvulsant agent (such as valproic acid or gabapentin)
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least two hours before or at least six hours after supplements containing polyvalent cations, including but not limited to the following products: multivitamin supplements containing Fe, Ca, Mg or Zn; mineral supplements, cation-containing laxatives and antacids containing Al, Ca or Mg. Monitor for efficacy in suppressing viral load.
EFV	Amodiaquine	Use an alternative antimalarial agent
	Cisapride	Use an alternative gastrointestinal agent
	Methadone	Adjust the methadone dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Astemizole and terfenadine	Use an alternative antihistamine agent
	Ergotamine and dihydroergotamine	Use an alternative antimigraine agent
	Simeprevir	Use an alternative direct-acting antiviral agent
	Midazolam and triazolam	Use an alternative anxiolytic agent

^a This table was developed using the University of Liverpool's drug–drug interaction charts: www.hiv-druginteractions.org and www.hep-druginteractions.org. Web Annex 1 provides a more comprehensive table of ARV drug interactions.

ANNEX 3. DOSAGES OF ARV DRUGS

Dosages of ARV drugs for adults and adolescents

Adults and adolescents	
Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400–600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily (Please note that NVP based regimens are no longer recommended and should only be used in special circumstances).
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice daily
Lopinavir + ritonavir (LPV/r)	400 mg + 100 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of LPV/r (LPV 800 mg + ritonavir 200 mg twice daily or LPV 400 mg + ritonavir 400 mg twice daily), with close monitoring. In the presence of rifabutin, no dose adjustment required.
Integrase strand transfer inhibitors InSTI	
Dolutegravir (DTG)	50 mg once daily*
Raltegravir (RAL)	400 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of DTG (50 mg twice daily) and RAL (800 mg twice daily), with close monitoring. In the presence of rifabutin, no dose adjustment required.

* TLD (Tenofovir 300 mg, Lamivudine 300 mg, Dolutegravir 50 mg fixed dose combination) can be used once daily in adolescents living with HIV weighting at least 30 kg.

WEIGHT-BASED DOSING FOR ARV FORMULATIONS FOR INFANTS AND CHILDREN

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on ARV drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing in infants, children and adolescents less than 18 years of age. The work to develop and update simplified guidance on ARV drugs for use in children has been undertaken by WHO through the Paediatric Antiretroviral Working Group.¹

For simplification and ease of implementation, doses are expressed per weight-band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, careful consideration was given to the expected body surface area of children from low- and middle-income countries in each weight band. The primary source of information for the guidance provided is the manufacturer's package insert. This was supplemented with data from other clinical studies as well as expert paediatric pharmacology consultations. For fixed-dose combinations, a dose-modelling tool (<http://www.who.int/hiv/paediatric/generictool/en/index.html>) was used to predict the dose delivered for each component drug against the recommended dosing schedule. In some cases the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to ensure that in no case would a child receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. PK efficacy and safety studies have also confirmed the overall safety of this dosing approach. For simplification, ARV drugs no longer considered preferred or alternative options for children have been removed from the dosing guidance.

In the context of increasing implementation of virological testing at birth, and the shift towards treating infants earlier in an effort to reduce early mortality, these guidelines include weight-based dosing for term infants aged <4 weeks, including those weighing less than 3 kg. However, there is limited experience with initiating treatment in HIV-infected newborns aged <2 weeks, and a paucity of PK data to fully inform accurate dosing for most drugs in neonates, who are undergoing rapid growth and maturation in renal and liver function. PK data in preterm infants are available only for AZT; there is considerable uncertainty of appropriate dosing for NVP, RAL and 3TC in preterm and low birth weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects that may occur in this population. The management of HIV treatment in preterm neonates extremely is challenging because of the lack of appropriate pharmacokinetic, safety, and dosing information as well as suitable formulations. Dosing for postnatal prophylaxis for HIV-exposed infants is not provided here but can be found at <http://www.who.int/hiv/pub/arv/annexes-5Sep2016.pdf?ua=1>.

In this 2018 ARV guidelines revision, integrase inhibitors have been included more prominently among the preferred regimens recommended by WHO. At the time of this guidelines update, DTG was only approved for children above 6 years and 15 kg in Europe and above 30 kg in the United States. The registration trial is anticipated to generate data for dosing DTG in children down to age 4 weeks in early 2019, with potential regulatory approval in late 2019. This dosing

annex includes approved DTG dosing as well as simplified dosing based on pk and safety data from an ongoing multicounty study, which is also investigating the pharmacokinetics of DTG in TB co-treated children. In some weight bands (14-24.9 kg) the simplified dosing is based on preliminary findings, which are expected to be confirmed in early 2019. As the introduction of paediatric DTG will take time, programmes are encouraged to begin planning for the use of DTG in paediatric populations while the simplified dosing is being confirmed.

RAL granules were also added with the goal of providing a suitable formulation to deliver RAL to neonates. Due to concerns about the complexity of administration of the granule formulation, the 25 mg chewable tablets as dispersible tablets have been endorsed by the PAWG for infants and children older than 4 weeks of age and weighting at least 3 kg. This decision was largely based on in vitro data on solubility and bioequivalence between RAL tablets and granules as well as considering the limited availability of adequate alternative formulations for this age group.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as additional data and new formulations become available.

Antiretroviral drugs and formulations are available from several manufacturers, and available dosage strengths of tablets, capsules and liquid formulations may vary from the information provided here. Several optimal paediatric dosage forms are currently in development but have not yet received regulatory approval at the time of writing these updated guidelines. National programme managers should ensure that products planned for use have received stringent regulatory approval and of appropriate quality and stability. For guidance on the quality assurance of medicines, see the WHO medicines web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/about/en/index.html) and the Access to HIV/AIDS drugs and diagnostics of acceptable quality, which is available and updated at <http://www.who.int/hiv/amds/selection/en/index.html>. The current list of WHO prequalified drugs is available at <http://apps.who.int/prequal>. For the current list of ARV drugs approved and tentatively approved by the United States Food and Drug Administration, see <https://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm>. For the policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance, see <https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/>.

General principles

The principles followed in developing the WHO simplified tables include the following:

- Use of an age-appropriate fixed dose combination is preferred for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided where possible. Dispersible tablets (or granules for oral solution) are the preferred solid oral dosage forms, since each tablet can be made into liquid at the point of use.
- If suitable dispersible FDC's are not available and oral liquids must be used, it is recommended that children be switched to a solid oral dosage form as soon as possible
- While dosing neonates generally necessitates use of oral liquid formulations for administering precise dosing, switching to solid oral dosage form as soon as possible is recommended
- Where children have to use adult formulations, care must be taken to avoid under-dosing and overdosing. Use of scored tablets are preferred to ensure accurate dosing is provided, particularly if adult dosage forms are used. Splitting of unscored tablets should be avoided as uniform distribution of active drug product cannot be assured in tablet fragments.
- Some tablets such as LPV/r or ATV heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split, dissolved, chewed or crushed, since bioavailability is seriously reduced when not swallowed whole.
- At each clinic visit, children should be weighed and doses should be adjusted based on observed growth and change in body weight.
- Country programs should consider the national regulatory status and local availability status of specific dosage forms when developing national paediatric treatment recommendations.
- Research is ongoing for several antiretroviral medications to establish dosing guidance in neonates, infants and young children. The age indications for each drug mentioned in the drug pages are based on current evidence and will be updated as new recommendations become available.

Table 1 Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing in infants and children 4 weeks of age and older^a

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening												Strength of adult tablet		Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg					
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	2.5	3	3	300 mg/150 mg	1	1
AZT/3TC/ NVP ^b	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	2.5	3	3	300 mg/150 mg/ 200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 mg	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	1.5	1.5	600 mg/300 mg	0.5	0.5

^a For infants younger than 4 weeks of age refer to table 4 for more accurate dosing which is reduced due to the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the appropriate dosing of ARVs in preterm and low birth weight infants.

^b Please note that this regimen and formulation is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

Table 2 Simplified dosing of child-friendly solid formulations for once-daily dosing in infants and children 4 weeks of age and older^a

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily						Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg		
EFV ^b	Tablet (scored) 200 mg	–	–	1	1.5	1.5	–	2	
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/300 mg	1	
ABC/3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/300 mg	1	
ATV ^c	Capsules 100 mg	–	–	2	2	2	300 mg	1 ^d	
	Capsules 200 mg	–	–	1	1	1	–	–	
DRV ^e	Tablet 600 mg	–	–	–	1	1	600 mg	1	
	Tablet 150 mg	–	–	–	4	4	–	–	
RTV ^f	Tablet 25 mg	–	–	–	4	4	100 mg	1	
	Tablet 50 mg	–	–	–	2	2	–	–	
DTG ^g	Tablet 50 mg	–	–	–	–	TBC ^h	50 mg	1	

^aSee table 4 for dosing recommendations for infants younger than 4 weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the appropriate dosing of ARVs in preterm and low birth weight infants.

^bEFV is not recommended for children younger than 3 years and weighing less than 10 kg.

^cATV is only approved for use in children 3 months and older. ATV single strength capsules should be administered with RTV 100 mg for all weight bands. ATV powder formulation has limited availability in LMIC, but enables administration of ATV to infants and children as young as 3 months. Infants and children 5–15 kg should be administered 200 mg of ATV powder (4 packets, 50 mg/ packet) with 80 mg of RTV oral solution (1 ml). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042,206352s007/bl.pdf

^dA 300 mg dose for 25–29.9 kg is recommended on the basis of findings from the PRINCE-2 studyⁱⁱⁱ.

*DRV in combination with RTV should be used, in children older than 3 years, once daily when this is used without previous exposure to PI. While approved dosing for 30-35 kg is 675 mg, preliminary data from adult studies suggest that even lower DRV doses may be effective, therefore use of 600 mg dose was extended to the entire 25-35 kg weight band.

[†]RTV should only be use as a boosting agent in combination with ATV or DRV.

[‡]At the time of this update, DTG film coated tablets were approved for children above 6 years by the FDA (35mg for weight ≥ 40 kg, 50 mg for weight ≥ 40 kg)ⁱⁱⁱ and by the EMA (20 mg 15 to < 20, 25 mg for 20 to < 30, and 35 for 30 to < 40, 50 mg for weight ≥ 40 kg)^{iv} based on data from the IMPAACT 1093 trial^v. Simplified weight band dosing is being investigated in the Odyssey trial which supports the use of 50 mg dose for all children ≥ 25 kg, as proposed here. An anticipated dose of 50 mg in children 20-25kg is based on predicted exposure derived from PK results on DTG 25mg (FCT) in this weight band, more data to confirm this and further inform optimal dosing in the 14 to 25 kg weight bands is expected at the beginning of 2019 and will be included in an updated version of this annex. For adolescents living with HIV weighting more than 30 Kg a fixed dose formulation of TDF 300mg/3TC 300mg/DTG 50mg (TLD) can be used and is preferred.

Table 3 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing in infants and children 4 weeks of age and older^a

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening (PM)												Strength of adult tablet		Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg		AM	PM	AM	PM
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM						
Solid formulations																	
AZT	Tablet (dispersible) 60 mg	1	1	1.5	2	2	2.5	2.5	2.5	3	3	3	3	300 mg	1	1	
ABC	Tablet (dispersible) 60 mg	1	1	1.5	2	2	2.5	2.5	2.5	3	3	3	3	300 mg	1	1	
NVP ^b	Tablet (dispersible) 50 mg	1	1	1.5	2	2	2.5	2.5	2.5	3	3	3	3	200 mg	1	1	
LPV/r ^c	Tablet 100 mg/25 mg	–	–	–	2	1	2	2	2	2	2	2	–	–	3	3	
	Pellets 40 mg/10 mg	2	2	3	4	4	5	5	5	6	6	6	–	–	–	–	
DRV ^d	Tablet 75 mg	–	–	–	–	–	5	5	5	5	5	5	400 mg	1	1		
RTV ^e	Tablet 25 mg	–	–	–	–	–	2	2	2	2	2	2	100 mg	1	1		
	Tablet 50 mg	–	–	–	–	–	1	1	1	1	1	1	–	–	–	–	
RAL ^f	Chewable tablets 25 mg	1	1	2	2	3	3	4	4	6	6	6	400 mg	1	1		
	Chewable tablets 100 mg	–	–	–	–	–	1	1	1	1.5	1.5	1.5	400 mg	1	1		

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening (PM)								Strength of adult tablet	Number of tablets by weight band			
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg				20–24.9 kg		25–34.9 kg
		AM	PM	AM	PM	AM	PM	AM	PM			AM	PM	
Liquid formulations														
AZT	10 mg/ml	6 ml	9 ml	9 ml	12 ml	12 ml	12 ml	–	–	–	–	–		
ABC	20 mg/ml	3 ml	4 ml	4 ml	6 ml	6 ml	6 ml	–	–	–	–	–		
3TC	10 mg/ml	3 ml	4 ml	4 ml	6 ml	6 ml	6 ml	–	–	–	–	–		
NVP ^b	10 mg/ml	5 ml	8 ml	8 ml	10 ml	10 ml	10 ml	–	–	–	–	–		
LPV/r ^c	80/20 mg/ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–		
DRV ^d	100 mg/ml	–	–	–	2.5 ml	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–	–		
RTV	80 mg/ml	–	–	–	0.5 ml	0.5 ml	0.6 ml	0.6 ml	–	–	–	–		
RAL ^e	10 mg/mL (Oral granules for suspension: 100 mg/sachet)	3 mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–		

^a See table 4 for dosing recommendations for infants younger than 4 weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the dosing of ARVs in preterm and low birth weight infants.

^b NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial INVP levels. However, secondary analysis from the (CHAPAS)-1 trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose⁶⁸. More definitive evidence is expected from an ongoing trial. Please note that this regimen and formulation is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

^c LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 tablet could be used for patients 14–24.9kg (1 tab qam and 1 tab qpm) and for patients 25–34.9 kg (2 tab qam and 1 tab qpm). LPVr pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPVr pellets can be found at http://apps.who.int/iris/bitstream/handle/10665/193543/FactsheetIATT_WHO_UNICEF_lopinavir_eng.pdf?sequence=1. This dosing schedule applies to equivalent solid dosage forms that may become available in the near future (ie granules).

^d DRV, to be used in children older than 3 years, must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if less than 15 kg and with RTV 25 or 50 mg solid formulation in children 15 to 30 kg. ^e RTV should only be use as a boosting agent in combination with ATV or DRV.

^f RAL granules are approved from birth. Feasibility and acceptability of such formulations has not been widely investigated and concerns have been raised regarding administration in resource limited settings. Due to the administration challenges presented by the granule formulation the use of the 25 mg chewable tablets as dispersible has been endorsed by the PAWG for infants and children older than 4 weeks and weighting at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules⁶⁹ as well as considering the limited availability of adequate alternatives for this age group. However, findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administration of RAL granules in rural settings is feasible as long as supported with adequate training and counselling.

Table 4 Drug dosing of liquid formulations in infants less than 4 weeks of age^a

Drug	Strength of oral liquid	2-3 kg		3-4 kg		4-5 kg	
		AM	PM	AM	PM	AM	PM
AZT	10 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
NVP	10 mg/mL	1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL	0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r ^b	80/20 mg/mL	0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
RAL	10 mg/mL	0.4 mL (once daily) ^c		0.5 mL (once daily) ^c		0.7 mL (once daily) ^c	
	(Oral granules for suspension: 100 mg/sachet) ^c	0.8 mL		0.8 mL		1 mL	
				1 mL		1.5 mL	

^a PK data in preterm infants are available only for AZT; there is considerable uncertainty of appropriate dosing for NVP, RAL and 3TC in preterm and low birth weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects that may occur in this population. This guidance will be updated when more evidence is available from ongoing trials.

^b Do not use LPV/r solution in infants aged <2 weeks of age. LPV/r pellets should not be used in infants younger than 3 months. More details on the administration of LPV/r pellets can be found at <http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf>

^c RAL granules for oral suspension should use in neonates of at least 2 kg and be administered in once a day during the first week of life (http://www.merck.com/product/usa/pi_circulars/i/isenpress/isentress_pi.pdf)

Table 5 Dosing for RTV super-boosting of LPV/r for children receiving rifampicin-containing TB treatment^a

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening (PM)						Strength of adult tablet	Number of tablets by weight band					
		3–5.9 kg		6–9.9 kg		10–13.9 kg			14–19.9 kg		20–24.9 kg			
		AM	PM	AM	PM	AM	PM		AM	PM	AM	PM		
For children able to swallow tablets														
LPV/r ^b	Tablet 100/25 mg	-	-	-	2	1	2	2	2	2	2	-	3	3
RTV	Tablet 100 mg	-	-	-	1	1	1	2	1	2				
	Tablet 50 mg	-	-	-	2	2	3	3	3	3	3	100 mg	2	2
	Tablet 25 mg	-	-	-	4	4	6	6	6	6	6			
For children unable to swallow tablets														
LPV/r	Oral solution ^c 80/20 mg/ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml	3 ml	3 ml	-	-
	Pellets ^d 40 mg/10 mg	2	3	3	4	4	5	5	5	6	6	6	-	-
RTV ^e	Oral solution 80 mg/ml	0.8 ml	1.2 ml	1.2 ml	1.5 ml	1.5 ml	2 ml	2 ml	2 ml	2 ml	2.3 ml	2.3 ml	-	-
RTV	Powder 100 mg/packet	-	-	1	1	1	1	1	1	2	1	2	-	-

^a Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study which explored this approach in young children receiving LPV/r.

^b The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 tablet could be used for patients 14-24.9kg (1 tab qam and 1 tab qpm) and for patients 25-34.9kg (2 tab qam and 1 tab qpm).

^c RTV liquid requires a cold chain during transport and storage.

^d LPV/r pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPV/r pellets can be found at <http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf>. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPV/r granules.

^e RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super-boosting.

Table 6 Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX) prophylaxis for infants and children who are at least 4 weeks of age

Drug	Strength of paediatric tablet or oral liquid	Number of tablets or ml by weight band once daily						Strength of adult tablet	Number of tablets by weight band
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg		
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	1	
CTX	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–	
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–	
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2	
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	800 mg/160 mg	1	
INH/CTX/B6 ^a	Tablets (scored) 300 mg/960 mg/25 mg	–	–	–	0.5	0.5	960 mg/300 mg/25 mg	1	

^a A scored tablet (480mg/150mg/12.5 mg) is under development.

Optimal Paediatric ARV Formulary

In recent years, a number of improved ARV formulations have become available, such as dispersible, scored FDC tablets in place of the traditional liquid formulations. These products have greatly simplified the delivery of paediatric HIV care in low-income settings; however, the proliferation of options, has resulted in a multiplicity of formulations across regimens and weight-bands. Economies of scale are used by generic manufacturers to maintain affordable pricing but fragmentation of demand across too many duplicative products creates instability in the reliable supply of paediatric ARV dosage forms and complicates procurement and supply chain management.

Partners of the ARV procurement working group (APWG) and of the Global Accelerator for paediatric formulations (GAP-f)^{xi} provide formulary guidance to programmes on selection of optimal paediatric ARVs defined using a robust set of criteria. The Optimal formulary is currently a list of 8 products that delivery recommended and appropriate first and second line regimens across all paediatric weight bands. The formulary was first developed in 2011 but is routinely revised to correspond to current WHO guidelines and available products. Programs are encouraged to procure paediatric dosage forms that are included on the Optimal Paediatric ARV Formulary. During periods of transitions or in special circumstances (eg. Neonatal treatment, TB co treatment and third line), dosage forms included on the ARV Limited-use formulary provide appropriate coverage^{xvi}.

The need for new formulations

The work of the Paediatric Antiretroviral Working Group and the Paediatric ARV Drug Optimisation^{xii, xiii} groups continue to highlight the urgent need for better age appropriate formulations for infants and children living with HIV. A number of solid formulations are under final stage of development (ABC/3TC/LPVr granules as well as ABC/3TC/EFV and DTG 10 mg scored dispersible tablets). In addition, the availability of co-formulated DRV/r in heat-stable fixed-dose combination formulations is critical to facilitate treatment sequencing and uptake of future 2nd and 3rd line treatment. A number of formulations containing approved ARVs for paediatric use have been formally prioritised and are listed in table 6. Finally, additional formulations containing newer drugs for which there is currently no paediatric indication were considered and the central future role of DTG and TAF in optimizing dose, sequencing and harmonization across age groups was highlighted.

In moving towards promoting drug optimisation for children and adolescents, WHO will continue to work to simplify prescribing, dispensing and dosing guidance and work with the pharmaceutical industry (originator and generic) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate the scaling up of ART for children.

Table 7 Anticipated simplified dosing for formulations under development.

Drug	Strength of dosage form (mg)	Number of tablets or sprinkle capsules or sachets by weight band											
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC/LPV/r	30 mg/15 mg/40 mg/10 mg	2	2	3	3	4	4	4	5	5	5	6	6
DRV/r	120 mg/20 mg	–	–	–	–	2	2	3	3	3	3	4	4
ABC/3TC/EFV	150 mg/75 mg/150 mg	–	–	–	–	1.5	1.5	2	2	2.5	2.5	3	3
DTG ^a	Scored dispersible 10 mg	1	1.5	2	2	2.5	2.5	3	3	3	3	–	–
ABC/3TC/DTG ^b	60 mg/30 mg/5 mg	2	3	4	4	5	5	6	6	6	6	–	–

^a This dosing was outlined by the PADO group in December 2017^(iv) based on best available information. However, optimal dosing of DTG in children below 25 kg is still being investigated and this proposed dosing will be revised as soon as more evidence is gathered from ongoing studies.

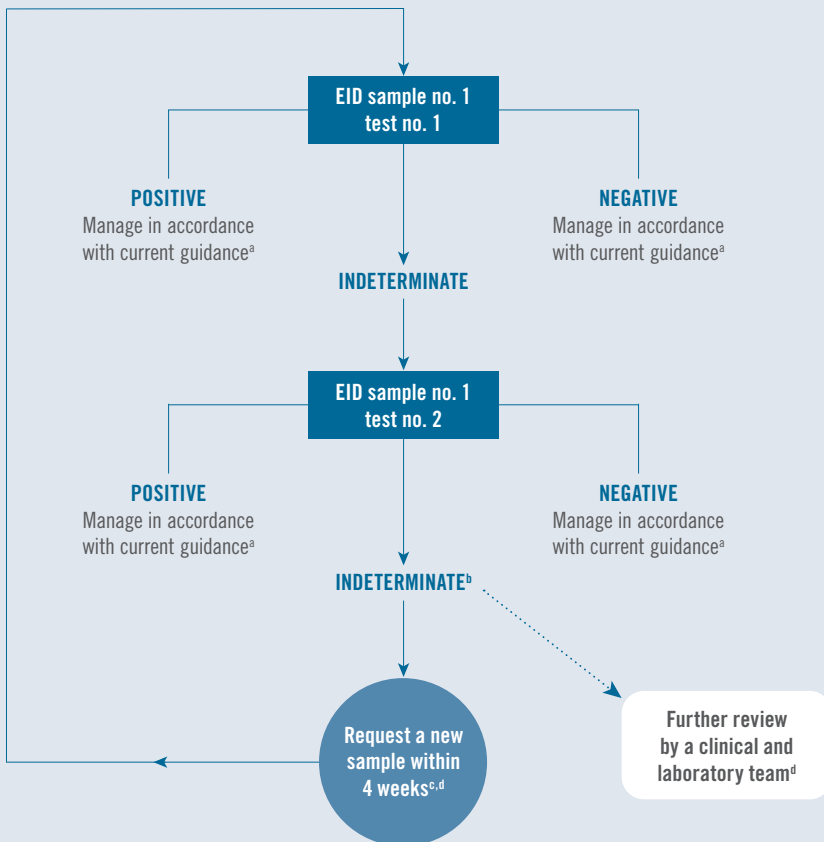
^b This dosage form is the one identified by the PADO group⁽ⁱⁱⁱ⁾ as the most likely to deliver appropriate dose based on the best available information. However, the group strongly emphasized the importance of validating this dosing and ratio as soon as final dosing for DTG is approved down to 4 weeks of age. Scored tablets with doubled- strength of each component drug (ABC/3TC/DTG 120/60/10 mg) would enable reduction of the pill burden for children, but difficulties with assuring accuracy of dosing when scoring a triple-drug FDC will need to be addressed. Importantly, **manufacturers interested in developing ABC/3TC/DTG could start development of a prototype, but will need to delay advancing their development plans until the dosing and the ratio are confirmed** (expected in early 2019).

- i PAWG members: Elaine Abrams (ICAP at Columbia University, USA); Mo Archary (University of Kwazulu-Natal, South Africa); Yodit Belew (US Food and drug administration HHS, USA); David Burger (Radboud University Nijmegen Medical Centre, The Netherlands); Edmund Capparelli (University of California San Diego, USA); Diana Clarke (Boston Medical Center, USA); Polly Clayden (HIV i-Base, UK); Timothy R. Cressey (Program for HIV Prevention and Treatment-IRD/Harvard T.H. Chan School of Public Health & Chang Mai University, Thailand); Angela Colbers (Radboud University Nijmegen Medical Centre, The Netherlands); Mutsa Dangarembizi (University of Zimbabwe, Zimbabwe); Paolo Denti (University of Cape Town, South Africa); Andrea Ecker (European Medicines Agency, The Netherlands); Shaffiq Essajee (UNICEF, USA); Carlo Giaquinto (University of Padova, Italy); Diana Gibb (MRC Clinical Trials Unit, United Kingdom); Rohan Hazra (National Institute of Child Health and Human Development, USA); Mansoor Khan (Texas A&M University Rangel College of Pharmacy, USA); Marc Lallemand (Drugs for Neglected Diseases initiative, Switzerland); Janice Lee (Drugs for Neglected Diseases initiative, Switzerland); Lana Lee (USAID, USA); Linda Lewis (Clinton Health Access Initiative, USA); Helen McIlleron (University of Cape Town, South Africa); Anita Mesic (Medicines Sans Frontiers, France); Mark H. Mirochnick (Boston Medical Center, USA); Lynne Mofenson (Elizabeth Glaser Pediatric AIDS Foundation, USA); Victor Musiime (Joint Clinical Research Center, Uganda); Elizabeth Obimbo (University of Nairobi, Kenya); Atieno Ojoo (UNICEF, Denmark); Fernando Pascual (Medicines Patent Pool, Switzerland); Jorge Pinto (Federal University of Minas Gerais Belo Horizonte, Brazil); Nande Putta (UNICEF, USA); Natella Rakhmanina (Elizabeth Glaser Paediatric AIDS Foundation, USA); Pablo Rojo (Hospital de 12 Octubre Madrid, Spain); Ted Ruel (University of California San Francisco, USA); Saint Raymond Agnes (European Medicine Agency, UK); George Siberry (Office of the U.S. Global AIDS Coordinator U.S. Department of State, USA); Nandita Sugandhi (ICAP at Columbia University, USA); Marissa Vicari (International AIDS Society, Switzerland); Melynda Watkins (Clinton Health Access Initiative, USA); Caroline Yonaba (Resau EVA, Burkina Faso).
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- vii Cotton MF, Liberty A, Torres-Escobar I, Gonzalez-Tome MI, Lissens J, Zaru L, et al. Safety and Efficacy of Atazanavir Powder and Ritonavir in HIV-1-Infected Infants and Children From 3 Months to <11 Years of Age: The PRINCE-2 Study. *Pediatr Infect Dis J.* 2018 Jun;37(6):e149–e156.
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- xv <http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en/>
- xvi The 2018 optimal formulary and limited-use list for paediatric ARVs. Policy brief <http://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/>

ANNEX 4. 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.



^a See the 2016 WHO consolidated ARV drug guidelines.

^b Do not report as positive or initiate ART but maintain prophylaxis in accordance with current guidance.

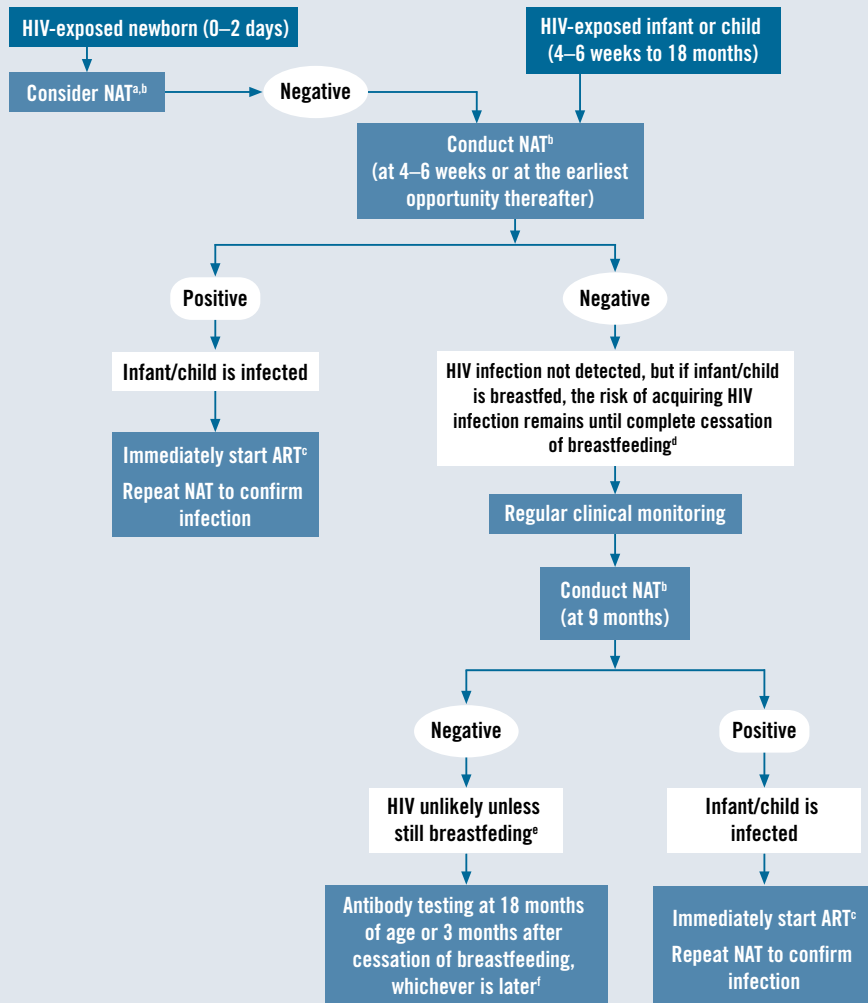
^c Repeat samples should be given priority in the laboratory.

^d 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.

ANNEX 5. REVISED SIMPLIFIED EARLY INFANT DIAGNOSIS 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 based on existing WHO recommendations.

- 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, regardless of previous NAT results after delivery.
- Ensure that confirmatory testing is undertaken following any positive result.
- Ensure that indeterminate test results are repeat tested immediately and given priority for rapid resolution.
- Ensure regular follow-up for all HIV-exposed infants until final diagnosis, including providing co-trimoxazole prophylaxis and clinical and nutritional assessment.



^a Based on the 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 and to confirm positive results.

^c Start ART, without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and mother-to-child 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 nine-month test is conducted earlier than three months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or three 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, final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least three 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 child is uninfected; positive antibody testing confirms that the infant is infected.

Web annexes

Web Annex A	Declarations of interests for the Guideline Development Group and External Review Group
Web Annex B	Systematic literature review and network meta-analysis assessing first-line ART treatments
Web Annex C	Report on the safety of dolutegravir in pregnancy and breast feeding
Web Annex D	Surveys of values and preferences
Web Annex E	Recommendations for use of hormonal contraception for women living with HIV using antiretroviral therapy
Web Annex F	Systematic review of which ART regimen to switch to when failing first-line treatment
Web Annex G	Systematic review of the safety and efficacy of antiretroviral drugs for post-exposure prophylaxis
Web Annex H	Meta-analysis and review of the literature of indeterminate results during HIV early infant diagnosis testing
Web Annex I	Report on the cost-effectiveness of implementing an indeterminate range for early infant diagnosis of HIV
Web Annex J	Table of drug interactions

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