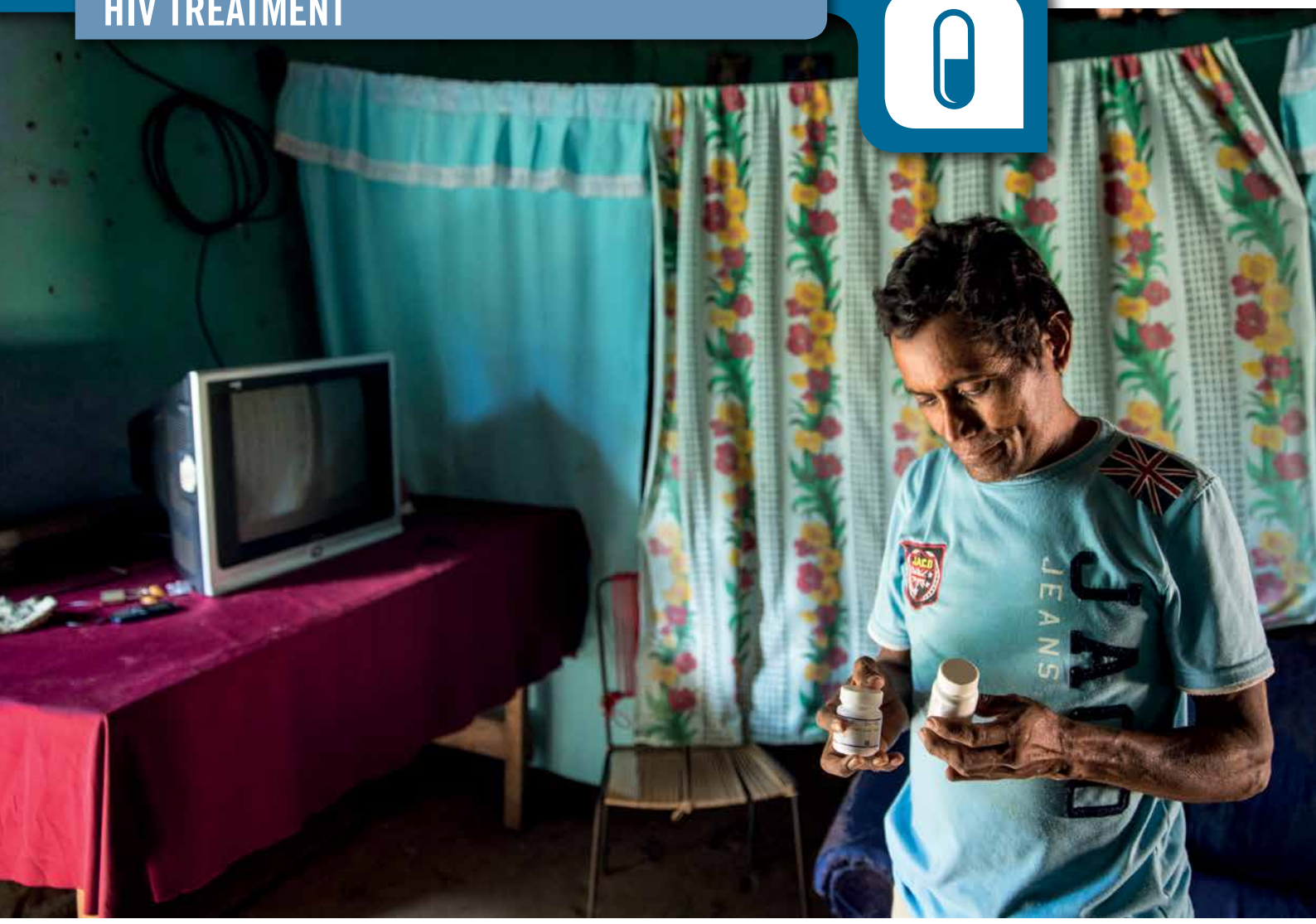
POLICY BRIEF

UPDATE OF RECOMMENDATIONS ON FIRST- AND SECOND-LINE ANTIRETROVIRAL REGIMENS

JULY 2019

HIV TREATMENT



World Health Organization

WHO/CDS/HIV/19.15

Suggested citation. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.15). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Printed in Switzerland.

BACKGROUND

In 2018, WHO published interim guidelines recommending dolutegravir (DTG)-containing regimens as the preferred first- and second-line antiretroviral therapy (ART) regimens for people living with HIV *(1)*. However, a note of caution about women of childbearing potential using DTG was issued following a signal of a potential association of neural tube defects and women's use of DTG at the time of conception in an observational study from Botswana *(2,3)*. These 2018 guidelines also recommended 400 mg of efavirenz (EFV), in combination with tenofovir disoproxil fumarate (TDF) plus lamivudine (3TC) or emtricitabine (FTC), as an alternative first-line ART regimen. However, information on the efficacy of this regimen for pregnant women and people receiving rifampicin-containing tuberculosis (TB) treatment was lacking.

The 2019 updated guidelines provide the latest recommendations based on rapidly evolving evidence of safety and efficacy and programmatic experience using DTG and EFV 400 mg in pregnant women and people coinfected with TB *(4–6)*. These guidelines provide further reassurance of DTG as the preferred antiretroviral (ARV) drug in first- and second-line regimens due to the declining estimate of neural tube defect risk and observed efficacy. This reassurance comes at a time when pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTI) is increasing in low- and middle-income countries, creating demand for access to alternative non-NNRTI ARV drugs *(7)* (Box 1).

Box 1. Recommendations: first- and second-line ART regimens

First-line ART regimens[a]

1. **Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART** NEW
   - **Adults and adolescents**[b] *(strong recommendation, moderate-certainty evidence)*
   - **Infants and children with approved DTG dosing** *(conditional recommendation, low-certainty evidence)*
2. **Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART**[c] *(strong recommendation, moderate-certainty evidence)* NEW
3. **A raltegravir (RAL)-based regimen may be recommended as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available** *(conditional recommendation, low-certainty evidence)*
4. **A RAL-based regimen may be recommended as the preferred first-line regimen for neonates** *(conditional recommendation, very-low-certainty evidence)*

[a]See Table 1 for ARV drug selection.
[b]See Box 2 on women and adolescent girls of childbearing potential using DTG.
[c]Except in settings with pretreatment HIV drug resistance to EFV/nevirapine (NVP) exceeding 10%.

Second-line ART regimens[a]

1. **DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.**
   - **Adults and adolescents**[b] *(conditional recommendation, moderate-certainty evidence)*
   - **Children with approved DTG dosing** *(conditional recommendation, low-certainty evidence)*
2. **Boosted protease inhibitors in combination with an optimized NRTI backbone is recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing** *(strong recommendation, moderate-certainty evidence)*

[a]Table 2 for ARV drug selection.
[b]See Box 2 on women and adolescent girls of childbearing potential using DTG.

DTG IN FIRST-LINE ART

An updated systematic review conducted in 2019 to support the guidelines reaffirmed that a first-line regimen of DTG combined with two nucleoside reverse-transcriptase inhibitors (NRTIs) leads to higher viral suppression and lower risk of discontinuing treatment and developing HIV drug resistance compared with EFV-based regimens among treatment-naive adults. DTG has other advantages over EFV, including lower potential for drug–drug interactions, more rapid viral suppression and a higher genetic barrier to developing HIV drug resistance *(8,9)*. DTG is also active against HIV-2 infection, which is naturally resistant to EFV *(10,11)*. However, an increased risk for sleep disorders and weight gain (Box 4) has also been detected *(12,13)*.

The benefits and risks of using DTG at conception were assessed by reviewing the latest data from Botswana, other countries and modelling the population-level risks and benefits of DTG use among women of childbearing potential *(14,15)*. The risk of neural tube defects associated with using DTG at conception has declined since the initial report released in May 2018 yet remains statistically significantly higher than in other ARV drug exposure groups (Box 2). Continued surveillance is needed to more definitively confirm or refute the neural tube defect signal, and several studies are ongoing to address this. A woman-centred and a rights-based approach should be applied to antiretroviral delivery. Women should be provided with information about benefits and risks to make an informed choice regarding the use of DTG or other ART (Box 3).

Box 2: Updates on the risk of neural tube defects among infants born to women exposed to DTG before conception or early in pregnancy

Although the prevalence of neural tube defects associated with using DTG at conception in the Tsepamo study has declined from 0.94% (4 of 426 exposures) to 0.30% (5 of 1683 exposures), the prevalence difference remains statistically significantly higher than all other ARV drug exposure groups. A further study by the Botswana Ministry of Health and the United States Centers for Disease Control and Prevention (CDC) increased the number of birth outcome surveillance sites in Botswana, expanding the estimated coverage of births in Botswana from 72% in the Tsepamo study to 92% of all births. As of March 2019, this study had identified one additional neural tube defect with DTG ART at conception (1 of 152 exposures, 0.66%, 95% confidence interval (CI) 0.02–3.69%) versus 0 of 381 births to women receiving non-DTG ART at conception and 2 of 2328 births to women without HIV (0.09%, 95% CI 0.01–0.31%). A systematic review found only one other neural tube defect reported with DTG ART at conception, from the prospective international Antiretroviral Pregnancy Registry (1 neural tube defect in 247 DTG exposures at conception, 0.40%). However, outside Botswana, which has no national food folate fortification, most reports come from countries with national food folate fortification programmes, which significantly lower the prevalence of neural tube defects in the general population (16).

If the neural tube defect signal currently observed in Tsepamo study is confirmed, although it is three-times higher than the other populations, the absolute risk is very low, 0.30% – 1 in 1000 in the general population with potential increase to 3 in 1000, a risk difference of 2 excess neural tube defect per 1000 periconception exposures compared to EFV ART at conception. With recent data made available from expanded Minsitry of Health and CDC surveillance from Botswana, the weighted estimate risk remains low at 0.36% (95% CI 0.10 – 0.62).

Data on birth outcomes, including neural tube defects, among pregnant women exposed to other integrase inhibitors are reassuring so far, although the number of prospective periconception exposures is limited and most reports come from high-resource settings with national food folate fortification. Continued surveillance is needed to more definitively confirm or refute the neural tube defect signal, and several studies are ongoing to address this.

Box 3: 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 a woman's autonomy in decision-making about her 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 women of childbearing potential or any pregnant or breastfeeding woman receives full information about risks and benefits of ART 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.

The risk–benefit models suggest that the benefits of DTG for women of childbearing potential newly initiating ART, which include greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions and fewer mother-to-child transmissions, are likely to outweigh the risks, such as adult morbidity resulting from DTG-associated weight gain and neonatal deaths among the infants of pregnant women with DTG-associated weight gain. DTG is also predicted to be more cost-effective, resulting in more disability-adjusted life-years averted at a lower cost than EFV.

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Box 4: Weight Gain and new ARV use

The updated network meta-analysis for the 2019 guidelines found that there was potentially an absolute increase of between 3-5 kg in body weight in individuals receiving DTG-based regimens at 48 weeks, with low certainty evidence. The weight gain was greatest in those using TAF + FTC + DTG. Upon initiating DTG-treatments clinicians should therefore highlight the importance of a healthy diet, avoidance of tobacco, and regular exercise in attempt to manage weight.

More research is needed with patient communities and advocacy groups to understand the social implications of potential weight gain. The early response from community and women enrolled in studies who experienced weight gain while taking DTG, was that weight gain is largely a viewed as a favourable outcome, but that they desired further information on the potential health implications as this becomes more available. Adequate counselling and support on the potential weight gain was clearly emphasized by the groups.

DTG is approved for use among children older than six years and weighing more than 15 kg and is widely available for children weighing at least 20 kg who can take 50mg film-coated adult tablets. DTG dosing for children weighing less than 20 kg is expected in late 2019, and a dispersible tablet for children is being developed, with approval expected in mid-2020. Among children for whom approved dosing of DTG is not available, raltegravir (RAL) is considered an effective option and is approved for use from birth. RAL successfully reduces viral load among highly viraemic infants and is safe and well tolerated among neonates and infants at high risk of infection.

Among people coinfected with HIV and TB, the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. This extra dose of DTG is well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV *(17,18)*.

EFV 400 mg in first-line ART

The updated systematic review found that EFV 400 mg is better tolerated than EFV in standard dose (EFV 600 mg), with lower risk of treatment discontinuation and severe treatment-related adverse events. Regimens containing EFV 400 mg and EFV 600 mg were comparable for viral suppression, mortality and mental and nervous system adverse events.

EFV 400 mg is available in a smaller pill size and can potentially reduce treatment costs compared with EFV 600 mg; both are available as generic fixed-dose combinations.

EFV 400 mg is expected to be safe for pregnant women to use, like EFV 600 mg. Data from the Tsepamo study in Botswana show that EFV 600 mg is safer in pregnancy than lopinavir/ritonavir (LPV/r) or nevirapine (NVP)-based ART regimens at conception, with safety similar to that of DTG in terms of pregnancy outcomes and no elevated risk of neural tube defects *(19)*. Pharmacokinetic and pharmacodynamic studies suggest that drug concentrations decline slightly with EFV 400 mg but remain within the therapeutic range and are unlikely to result in reduced efficacy *(6)*. It is not advised to use EFV 400 mg and EFV 600 mg in settings with high levels of pretreatment HIV drug resistance.

EFV 400 mg can be co-administered with rifampicin-containing anti-TB treatment, with co-administration well tolerated and plasma concentrations maintained above the levels considered to be effective *(5)*.

In summary, the evidence supports using DTG as a preferred first-line ARV drug for everyone living with HIV with approved dosing, including adults, pregnant women, women and adolescent girls of childbearing potential, children and people coinfected with TB. EFV 400 mg is recommended as an alternative drug, with EFV 600 mg maintained as an option for special situations. RAL is recommended for neonates and can be considered an alternative if LPV/r solid formulations are not available for children weighing less than 20 kg (Table 1).

Health-care providers should provide women with accurate, relevant and age-appropriate information and options to enable them to make informed choices about using lifelong ART regimens (Box 3).

Table 1. Preferred and alternative first-line ART regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a]
Children	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r ABC + 3TC + RAL[e] TAF + 3TC (or FTC) + DTG[f]	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV[g] (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

[a]Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (Box 2).

[b]EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. DTG-based ART is preferred, and if DTG is unavailable, a boosted PI-based regimen should be used. The choice of PI/r depends on programmatic characteristics.

[c]TAF may be considered for people with established osteoporosis and/or impaired kidney function.

[d]For age and weight groups with approved DTG dosing.

[e]RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.

[f]For age and weight groups with approved TAF dosing.

[g]EFV should not be used for children younger than three years of age.

[h]Neonates starting ART with an RAL-based regimen should transition to an LPV/r solid formulation as soon as possible.

[i]LPV/r syrup or granules can be used if starting after two weeks of age.

DTG in second-line ART

The updated evidence reviews assessed the efficacy and safety of DTG in combination with an optimized NRTI backbone for people for whom a non-DTG-based first-line regimen has failed. The analysis confirmed the 2018 recommendations, showing that DTG is generally safer and more effective than protease inhibitor (PI)–based second-line regimens.

Taken together with other advantages, including lower cost, less potential for drug–drug interactions, lower pill burden and availability in once-daily fixed-dose combinations, DTG is recommended as the preferred ARV drug for second-line ART among adults, adolescents and children for whom a non-DTG-based first-line regimen has failed. For those taking a first-line regimen containing DTG that has failed, a boosted PI-containing regimen should be used (Table 2).

Table 2. Preferred and alternative second-line ART regimens

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC + EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/r[f])	AZT + 3TC + DRV/r[g]
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f] or DRV/r[g])

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir disoproxil fumarate.

[a]Sequencing if PIs are used in first-line ART: ATV/r (or LPV/r or DRV/r depending on programmatic considerations) + TDF + 3TC (or FTC) and then AZT + 3TC + DTG in second-line ART.

[b]Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy (Box 2).