Optimization of second-line and third-line antiretroviral therapy for people living with HIV

meeting report

27–28 November 2023

World Health Organization

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Abbreviations

3TC	lamivudine
ABC	abacavir
ARV	antiretroviral
ART	antiretroviral therapy
ATV/r	atazanavir/ritonavir
AZT	zidovudine
DRV/r	darunavir/ritonavir
DTG	dolutegravir
FTC	emtricitabine
INSTI	integrase strand-transfer inhibitor
LPV/r	lopinavir/ritonavir
NRTI	nucleoside reverse-transcriptase inhibitors
NNRTI	non-nucleoside reverse-transcriptase inhibitors
PI	protease inhibitor
TAF	tenofovir alafenamide
TAF–ED	tenofovir alafenamide + emtricitabine + dolutegravir
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLE	tenofovir + lamivudine + efavirenz
TLD	tenofovir + lamivudine + dolutegravir

Chapter 1

Introduction

1.1 Objectives

This meeting aimed to discuss clinical evidence, key challenges and research gaps for optimizing second-line and third-line antiretroviral therapy (ART) regimens included in current WHO treatment guidelines as well as the advances in the management of adverse drug reactions and emerging drug resistance to these ART regimens from a public health perspective.

The following key points were addressed:

- reviewing the recent evidence on efficacy and safety, including programmatic data;
- identifying research gaps;
- aligning the needs for different populations (adults, children and pregnant women);
- assessing the potential of darunavir/ritonavir (DRV/r) as a preferred protease inhibitor (PI) option in second-line and third-line ART for adults, pregnant women and children;
- discussing the efficacy and safety of recycling tenofovir in second-line regimens;
- discussing the safety of regimens containing tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), with considerations raised regarding their different side-effect profiles and use with boosted and unboosted ART regimens; and
- plans for updating WHO guidelines on preferred ART regimens.

1.2 Participants

Meeting participants included academic experts, HIV programme managers, principal investigators of key research studies, civil society representatives, implementation partners and donors. WHO was represented by staff members and consultants from the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes and the Regional Office for the Americas. Participants were from Botswana, Canada, Côte d'Ivoire, France, India, Kenya, Malawi, Mozambique, Netherlands (Kingdom of the), Portugal, Singapore, South Africa, Spain, Switzerland, Thailand, Togo, Tunisia, United Kingdom, United States of America, Zambia and Zimbabwe (see the full list of participants and affiliations in Annex 2).

1.3 Background

Globally, almost 40 million people are estimated to be living with HIV, and approximately 30 million were receiving treatment by mid-2022 *(1)*.
The optimal use of antiretroviral (ARV) drugs, including through simplifying and harmonizing treatment guidelines remain critical principles to support and sustain effective scale-up. Providing safe, effective and well-tolerated across all affected populations remains critical to ensuring the scale-up of treatment globally.

To end AIDS as a public health threat by 2030, ARV drug regimens and therapeutic strategies need to be innovated and optimized. Since 2013, WHO consolidated ART guidelines have promoted treatment optimization by standardizing and simplifying ART strategies across populations, by promoting the use of one-tablet-a-day regimens for first-line ART with less toxic and more efficient drugs *(2)*. More recently, the development of long-acting ARV drug formulations has the potential to improve treatment adherence and bring other therapeutic and preventive benefits *(3)*. At the same time, the introduction of new drug classes and the emerging evidence of the clinical and programmatic benefits of optimized doses of existing drugs justify periodic assessment of the WHO drugs selection and sequencing treatment strategies for the future normative revisions *(4)*.

To ensure that advances in HIV treatment strategies can be used across populations, generating evidence to support optimal ARV drug choices is a public health imperative. Innovation will be key to achieving equity in access to treatment across children, adolescents, adults and pregnant women. The success of ART means that more infants and children with previous exposure to an array of ARV drugs will survive into adulthood and require effective treatment options that are effective in the face of multi-drug resistance. As the cohort of people living with HIV age, challenges related to polypharmacy and adverse events of concern to ageing populations are anticipated to become more important.

In recent iterations of the consolidated WHO HIV guidelines, the most important change has been the shift from tenofovir + lamivudine + efavirenz (TLE) to tenofovir + lamivudine + dolutegravir (TLD) as the preferred first-line ART regimen. Two other important changes are the alignment of dolutegravir (DTG)-based regimens across all populations, including pregnant women and children; and the shift based on regimens from ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r) as the preferred second-line regimens to TLD (5). Since the last major guideline update, there have been several studies among people receiving second-line ART providing new evidence on the use of TLD in second-line ART as well as further evidence on the use of DRV/r and on the recycling of tenofovir in second-line regimens.

WHO recommends that third-line regimens include new drugs with minimal risk of cross-resistance to previously used ART regimens, such as integrase strand-transfer inhibitors (INSTIs) and second-generation non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). For individuals for whom DTG-based first-line regimen and an ATV/r or LPV/r second-line regimen have failed, DRV/r in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs) with the possible addition of DTG is a suitable option for third-line ART *(5)*.

Chapter 2

Summary of key discussions

2.1 Use of dolutegravir in second-line and switching studies

A Technical Working Group convened virtually by WHO on 27–28 November 2023. The meeting included plenary presentations and discussions moderated by a facilitator. (agenda in Annex 1).

To evaluate current evidence, WHO commissioned two systematic reviews and network meta-analyses to address the following key questions.

1. Should DRV/r be preferred over ATV/r and LPV/r in second-line regimens for pregnant women, children and adults?
2. Should zidovudine (AZT) replace TDF (or TAF) in second-line NRTI backbone, or should TDF (or TAF) be recycled regardless of NRTI resistance?

Complementary analyses of specific clinical studies and programmatic data were also presented and discussed by the group.

The Technical Working Group discussed the results of these evidence reviews and identified critical gaps in clinical knowledge, research, monitoring and surveillance related to optimizing second-line and third-line ART. At the end of the meeting, a list of priority future research was established by consensus.

A questionnaire on key aspects of these topics was given to all participants, with the main results included in Annex 3.

2.2. Use of darunavir/ritonavir in managing HIV

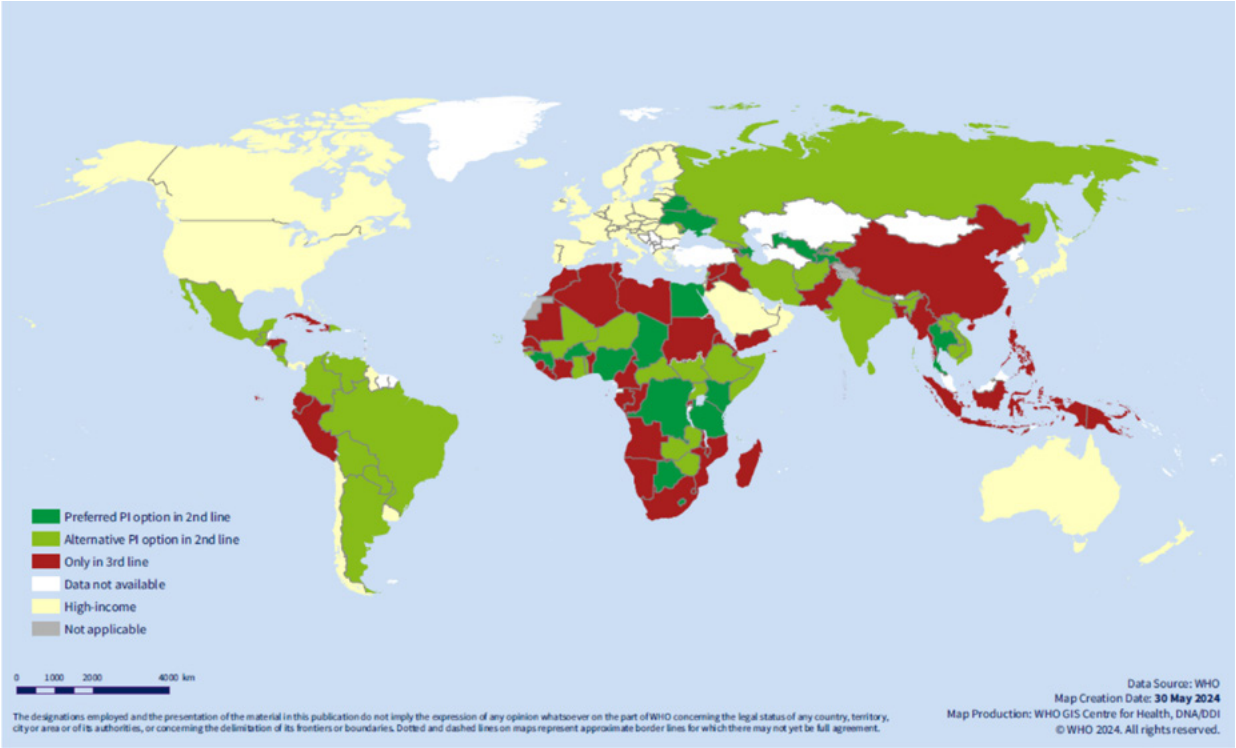
2.2.1. Background

The current WHO recommendations on using DRV/r were established in 2013: DRV/r stands as an alternative PI option in second-line ART and as a preferred PI option in third-line ART regimens *(5)*. A systematic review and network metanalysis conducted in 2016 could not show clear differences between DRV/r with ATV/r and LPV/r because of limited comparative effectiveness data. Additionally, several programmatic challenges, including the non-availability of generic boosted co-formulations, pill size and high comparative cost, made DRV/r a less feasible option in many low- to middle-income countries *(6)*.

Since these WHO recommendations were published, there has been a large programmatic transition to DTG both as first-line and second-line options *(7)*. New data from large clinical studies such as NADIA (DTG versus DRV/r), VISEND (DTG versus ATV/r versus LPV/r) and D2EFT (DTG versus DRV/r) were published, presenting direct comparisons between DRV/r and other PIs *(8–10)*. More recently, generic co-formulations of DRV/r became available at reduced cost *(11)*.

According to a WHO country survey conducted for this Technical Working Group meeting, the current adoption of DRV/r for HIV treatment in national guidelines has increased in low- and middle-income countries (Fig. 1). Although most countries (n = 48) with available data still recommend DRV/r as a third-line regimen, there is a trend towards recommending it as an alternative (n = 40) or even preferred (n = 23) PI option in second-line ART.

Fig. 1. Adoption of darunavir/ritonavir in antiretroviral regimens according to national guidelines in low- and middle-income countries (2023)



PI = protease inhibitors

In terms of drug demand forecasting, the number of people living with HIV accessing ART is increasing progressively and is expected to grow by 5 to 7 million over the next five years in low- and middle-income countries. The strongest growth in ART volumes is expected to be for first-line regimens, including TDF, lamivudine (3TC) and DTG. However, approximately 7–8% of the people receiving ART are currently using a second-line regimen, and projections show that the use of LPV/r is expected to decrease progressively, as the use of DRV/r increases over the next years (12).

The use of DRV/r for children is still very limited since no co-formulation is available. Unitaid and the Clinton Health Access Initiative have partnered with a generic producer to accelerate the development of a formulation of DRV/r for children (120 mg/20 mg tablet) that is expected to be available in 2024 (13).

2.2.2. Systematic review and network meta-analysis on the use of darunavir/ritonavir for adults and pregnant women

According to the updated systematic review commissioned by WHO for this Technical Working Group meeting, the primary network of trials has expanded considerably. Since current WHO recommendations for second-line regimens were established, notable additional trials were NADIA, VISEND and D2EFT.

The systematic review found moderate- to high-certainty evidence supporting the use of DTG as a preferred option in second-line regimens, with better viral suppression rates, CD4 cell count increase and overall tolerability. However, DTG use led to body weight gain, which was not associated with PI use; more data on the incidence of metabolic syndrome and hypertension are needed. The review also showed that among PI options, ATV/r and DRV/r tended to be more effective and tolerable than LPV/r, ATV/r had more favourable lipid outcomes than DRV/r, but DRV/r had better overall safety outcomes compared with other PIs (Table 1).

Table 1. Comparative efficacy and safety of regimens containing atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir

	DRV/r + NRTIs versus LPV/r + NRTIs			ATV/r + NRTIs versus LPV/r + NRTIs			DRV/r + NRTIs versus ATV/r + NRTIs		
Comparison	**Effect (95% CI)**	**Absolute effects**	**Overall quality of evidence**	**Effect (95% CI)**	**Absolute effects**	**Overall quality of evidence**	**Effect (95% CI)**	**Absolute effects**	**Overall quality of evidence**
Viral suppression <50 copies/mL at 24 weeks	1.26 (0.85, 1.89)	49 per 1000 (–38 to 122)	⊕⊕⊕ Moderate	1.21 (0.97, 1.49)	40 per 1000 (–6 to 78)	⊕ Very low	1.11 (0.90, 1.37)	22 per 1000 (–22 to 63)	⊕⊕ Low
Viral suppression <50 copies/mL at 48 weeks	1.27 (0.95, 1.71)	48 per 1000 (–10 to 101)	⊕⊕⊕ Moderate	1.33 (1.08, 1.61)	55 per 1000 (16 to 87)	⊕ Very low	1.23 (1.00, 1.50)	41 per 1000 (1 to 75)	⊕ Very low
Viral suppression <50 copies/mL at 96 weeks	2.45 (1.65, 3.64)	150 per 1000 (92 to 195)	⊕⊕⊕ Moderate	1.37 (1.08, 1.76)	62 per 1000 (16 to 104)	⊕⊕ Low	1.49 (1.14, 1.96)	76 per 1000 (26 to 121)	⊕⊕⊕ Moderate
CD4 24-week change	–	36.02 cells/mL (–63.27, –8.83)	⊕⊕ Low	–	4.87 cells/mL (–23.07, 13.56)	⊕⊕ Low	–	12.46 cells/mL (–31.2, 6.24)	⊕⊕ Low
CD4 48-week change	–	17.71 cells/mL (–34.98, –0.62)	⊕⊕ Moderate	–	1.83 cells/mL (–13.37, 9.34)	⊕ Very low	–	16.23 cells/mL (–29.29, –3.42)	⊕⊕ Low
CD4 96-week change	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low	–	4.29 cells/mL (–24.9, 16.49)	⊕⊕ Low	–	17.3 cells/mL (–41.66, 8.82)	⊕⊕ Low
Discontinuations	0.56 (0.29, 1.05)	59 per 1000 (–101 to 7)	⊕⊕⊕ Moderate	0.70 (0.55, 0.89)	46 per 1000 (–72 to –16)	⊕⊕ Low	0.73 (0.57, 0.93)	42 per 1000 (–68 to –10)	⊕⊕ Low
Discontinuations due to adverse events	0.63 (0.18, 2.04)	14 per 1000 (–35 to 39)	⊕⊕ Low	0.63 (0.40, 1.00)	19 per 1000 (–32 to 0)	⊕⊕ Low	0.58 (0.38, 0.89)	21 per 1000 (–34 to –5)	⊕⊕⊕ Moderate
Overall adverse event (any grade)	0.74 (0.55, 0.99)	50 per 1000 (–108 to –2)	⊕⊕⊕ Moderate	0.91 (0.71, 1.16)	14 per 1000 (–56 to 21)	⊕⊕ Low	0.39 (0.27, 0.55)	182 per 1000 (–267 to –105)	⊕⊕⊕ Moderate
Overall severe adverse events	0.82 (0.47, 1.42)	24 per 1000 (–74 to 51)	⊕⊕⊕ Moderate	1.07 (0.81, 1.41)	9 per 1000 (–24 to 48)	⊕⊕ Low	0.68 (0.41, 1.09)	41 per 1000 (–80 to 11)	⊕⊕ Low
Overall severe adverse events (treatment related)	1.15 (0.34, 4.25)	16 per 1000 (–81 to 257)	⊕⊕ Low	1.69 (0.33, 12.04)	70 per 1000 (–82 to 508)	⊕⊕ Low	0.59 (0.42, 0.82)	48 per 1000 (–71 to –21)	⊕⊕⊕ Moderate
Weight gain 48-week change	–	2.31 Kg (1.14, 3.52)	⊕⊕⊕ Moderate	–	2.02 Kg (1.17, 2.81)	⊕⊕⊕ Moderate	–	0.30 Kg (–1.09, 1.71)	⊕⊕ Low
Hypertension (any grade)	0.82 (0.36, 1.89)	4 per 1000 (–19 to 23)	⊕⊕⊕ Moderate	–	–	–	–	–	–
Total cholesterol 48-week change	–	1.13 mmol/L (–1.79, –0.46)	⊕⊕⊕ Moderate	–	0.51 mmol/L (–0.68, –0.34)	⊕⊕⊕ Moderate	–	0.56 mmol/L (–1.43, 0.17)	⊕ Very low
Fasting glucose 48-week change	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low	–	0.13 mmol/L (–0.01, 0.26)	⊕⊕ Low	–	0.12 mmol/L (–0.06, 0.29)	⊕⊕ Low
High-density lipoprotein 48-week change	–	0.28 mmol/L (–0.61, 0.06)	⊕⊕⊕ Moderate	–	0.07 mmol/L (–0.12, –0.01)	⊕⊕ Low	–	0.15 mmol/L (–0.38, 0.07)	⊕ Very low
Low-density lipoprotein 48-week change	–	0.46 mmol/L (–1.07, 0.17)	⊕⊕⊕ Moderate	–	0.36 mmol/L (–0.49, –0.23)	⊕⊕ Low	–	0 mmol/L (–0.01, 0.01)	⊕ Very low
Triglycerides 24-week change	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕⊕ Moderate	–	0.85 mmol/L (–1.11, –0.58)	⊕⊕⊕ Moderate	–	0.04 mmol/L (–0.05, –0.02)	⊕⊕ Low
Triglycerides 48-week change	–	1.55 mmol/L (–2.4, –0.71)	⊕⊕⊕ Moderate	–	0.72 mmol/L (–0.94, –0.49)	⊕⊕⊕ Moderate	–	1.19 mmol/L (–2.81, 0.31)	⊕ Very low
Mortality	1.64 (0.43, 6.41)	22 per 1000 (–22 to 164)	⊕⊕⊕ Moderate	0.80 (0.35, 1.80)	6 per 1000 (–22 to 25)	⊕ Very low	0.87 (0.39, 1.88)	4 per 1000 (–20 to 28)	⊕ Very low

ATV/r= atazanavir/ritonavir, DRV/r= darunavir/ritonavir, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse-transcriptase inhibitor.

second-line studies only combined first- and second-line studies

For pregnant women, despite an expanded network of studies, there was only low-certainty evidence because of risk of bias in observational study designs and imbalances in the NRTI backbone composition of regimens. There was a higher risk of negative pregnancy outcomes, preterm births and small-for-gestational-age births among women receiving LPV/r-based regimens. ATV/r and DRV/r were less distinguishable from one another; however, there was a trend towards improved viral suppression for women on DRV/r-based regimens.

The available evidence continues to indicate that DRV/r has good safety and viral efficacy in pregnancy, with some new comparative data suggesting superior viral efficacy of DRV/r (given in twice-daily dosing) compared to ATV/r. Once-daily DRV/r has greater decrease of both total and unbound plasma levels of darunavir in later pregnancy than twice-daily DRV/r, with DRV/r once daily giving trough levels lower than half the maximal effective concentration (EC50) for wild-type virus in 3% and resistant virus in 14% of pregnant women versus 0% on twice-daily DRV/r (Table 2).

Table 2. Comparative of pharmacokinetic parameters of darunavir/ritonavir at different doses during late pregnancy

DRV dosage	Area under the curve: total DRV	Area under the curve: unbound DRV	Trough: total DRV	Trough Unbound DRV	Trough level below: EC_{50} wild-type virus[a] EC_{50} resistant virus[b]	Viral load <50 copies/mL at delivery (pooled)	Mother-to-child transmission
DRV/r 600/100 mg twice daily *(14–16)*	17–26% ↓	7–8% ↓	11–28% ↓	11% ↓	0/40 (0%) 0/6 (0%)	26/44 (59%)	1/52 (2%)
DRV/r 800/100 mg four times daily *(15,16–18)*	31–39% ↓	20–24% ↓	42–57% ↓	24–38% ↓	3/99 (3%) 7/50 (14%)	81/100 (81%)	0/95 (0%)
DRV/r 800/100 mg twice daily (↑ dose) versus 600/100 mg twice daily postpartum *(19)*	36% ↓		53% ↓			80% (20/25)	0/24 (0%)
DRV/cobicistat 800/150 mg four times daily *(20,21)*	50–56% ↓	40% ↓	79–89% ↓	88%↓		86% (30/35)	

DRV = darunavir, DRV/r = darunavir/ritonavir, EC_{50} = half maximal effective concentration.
[a]EC_{50} wild-type virus = 0.055 ng/mL (55 mg/L). [b]EC_{50} resistant virus = 0.55 ng/mL (550 mg/L).

Based on the available data, the United States Food and Drug Administration recommends DRV/r twice-daily dosing, and the European Medicines Agency recommends DRV/r once-daily dosing in pregnancy *(22,23)*. However, major HIV clinical guidelines currently recommend DRV/r twice-daily dosing for most pregnant women, except if the woman becomes pregnant on DRV/r once-daily dosing and has suppressed viral loads *(24,25)*.

2.2.3. Systematic review of the safety of darunavir/ritonavir for children and adolescents living with HIV

For children and adolescents aged 3–18 years, the updated systematic review identified 14 studies, including two randomized clinical trials, five single-arm trials and seven observational studies that informed comparisons between ATV/r, DRV/r, DTG and LPV/r. As for adults, DTG had the best efficacy (viral suppression) and overall safety, while DRV/r had the best efficacy and safety among the boosted PI options; DTG was the preferred second-line regimen for children.

The randomized clinical trials included in this systematic review were CHAPAS-4 and SMILE: CHAPAS-4 is an open-label randomized trial including more than 900 children aged 3–15 years (232 children receiving DRV/r) comparing second-line regimens (26); SMILE is an open-label randomized trial including more than 300 children aged 6–18 years (158 children receiving DRV/r) comparing once-daily INSTI + DRV/r with standard regimens *(27)*.

The results from this systematic review showed that, across the studies of children and adolescents receiving DRV/r-containing regimens, no deaths were attributed to DRV/r and there were few drug-related severe adverse events and discontinuations. Small increases in total and LDL cholesterol and borderline significant differences between study arms in randomized clinical trials suggest the need for longer-term monitoring. The results for viral suppression (viral load <400 copies/mL) were satisfactory in both CHAPAS-4 and SMILE (>85% suppression rates). In CHAPAS-4, DRV/r-based regimens were reported to be as good as and trending towards being superior to ATV/r- and LPV/r-based regimens.

2.3. Recycling tenofovir and nucleoside reverse-transcriptase inhibitor resistance

2.3.1. Background

Since 2013, WHO has recommended AZT + 3TC as the NRTI backbone in a second-line regimen if TDF + 3TC was used in the failing first-line regimen and vice versa *(2)*. In an interim review conducted in 2018, some data emerged supporting using DTG in combination with TDF and 3TC as second-line ART for people for whom TLE failed as the first-line regimen *(28)*. However, despite some programmatic advantages of this approach, there are concerns about the potential use of suboptimal therapy, particularly regarding DTG drug resistance risk. Therefore, there is a need to better understand whether the use of TDF should be continued or AZT should be favoured in these conditions.

Since the last review, several trials and programmatic data have demonstrated clear widespread use of TLD with high suppression of viral loads *(7)*. Additionally, more clinical and observational data support switching from TLE to TLD without viral load testing or regardless of the viral load, with low levels of drug resistance *(9,29,30)*.

There was a change in the paradigm of ART sequencing: now there are several scenarios in a post-DTG transition, since most people are already receiving TLD but with differences in previous experience of ART regimens.

In mid-2023, WHO also optimized the HIV viral load monitoring algorithm, including the timing of the first viral load, the timing of repeat viral load after elevated viral load, treatment failure threshold and immediate (single viral load) switch to second-line ART if an NNRTI-based regimen fails *(31)*.

Finally, more safety data on TAF in specific populations – such as pregnant women, children and people with hepatitis B coinfection – and more information on body weight gain and cardiometabolic impact of TDF and TAF became available *(32–35)*.

According to the latest WHO estimates, about 200 000 people living with HIV used TAF in low- to middle-income countries in 2023, mainly in the African Region (98 702) and the Region of the Americas (95 153). As of the end of 2022, 14 low- and middle-income countries have procured TAF, including Botswana, the Islamic Republic of Iran, Mali, Mexico, Ukraine, Zambia and Zimbabwe, which account for almost 90% of all people living with HIV using TAF *(36)*.

There are certain considerations when using TDF or TAF with boosted PIs. If TDF is used with boosted ritonavir or cobicistat-containing regimens, it could worsen the safety profile, but there is no recommended dose adjustment; however, the dose of TAF must be reduced from 25 mg once daily to 10 mg once daily when taken with boosted PIs *(37)*. There is little evidence on how TDF or TAF work with boosted PI regimens in low- to middle-income countries, but now that the use of second-line regimens including boosted PIs are expected to increase, it is important to compare the safety of TDF and TAF in these situations.

2.3.2. Systematic review and network meta-analysis on maintenance of tenofovir in second-line nucleotide reverse-transcriptase inhibitor backbones

A systematic review of the benefits and harms of maintening TDF in second-line NRTI backbones was comissioned for this Technical Working Group meeting and was based on three types of evidence:

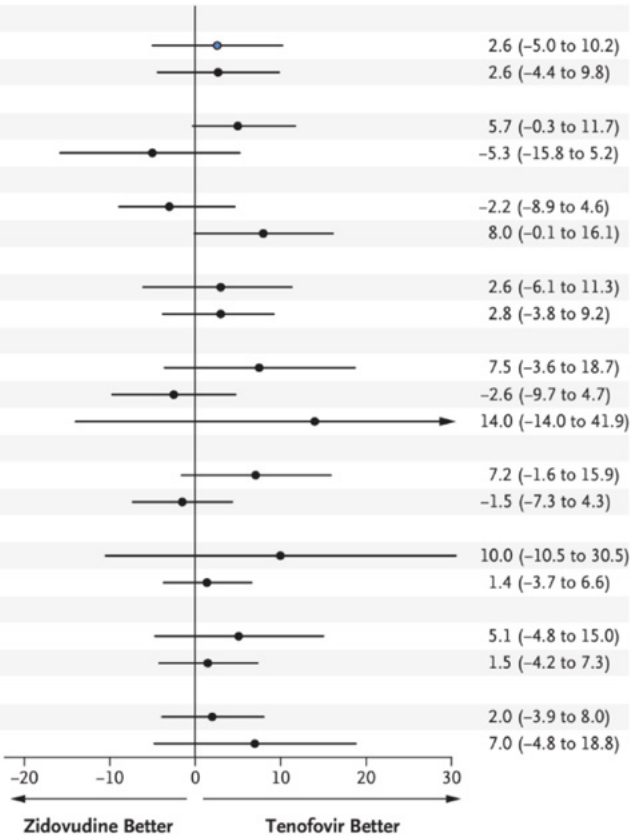
- direct evidence: studies comparing TDF recycling to AZT switch (mainly from the NADIA trial, GHESKIO cohort and EA-IeDEA cohort *(38–40)*);
- indirect evidence: comparing people with partly active versus fully active NRTIs (NADIA, EARNEST, SECOND-LINE, 2LADY and SELECT *(38,41–44)*); and
- supportive evidence: ARTIST is a single-arm, prospective, interventional study conducted in South Africa and was used as a proof of concept, and D^{2}EFT and VISEND are two randomized clinical trials that compared recycling to non-recycling strategies *(9,10,29)*.

The studies support recycling TDF in second-line NRTI backbones. The most direct evidence comes from the NADIA trial, a prospective, multicentre, two-by-two factorial, randomized, open-label, noninferiority, 96-week trial *(38)*. TDF and AZT did not differ significantly in terms of viral suppression at 48 weeks, but the results tended to be better for TDF. However, at 96 weeks and using a viral load threshold of <400 copies/mL, TDF was superior to AZT (+7.0%; 95% CI: 1.2–12.8%); these results were robust to a variety of subgroup analyses (Fig. 2). Of the seven people who developed DTG resistance, five were receiving AZT (Fig. 3).

The evidence favouring TDF recycling is further supported by observational studies (Table 3). The ARTIST study shows positive results despite the recycling of TDF: 74% of participants were virally suppressed at 48 weeks and close to 50% of unsuppressed participants re-suppressed with adherence counselling *(29)*. In the VISEND study, which included comparisons between TLD and tenofovir alafenamide + emtricitabine + dolutegravir (TAF-ED): at 48 weeks (in arm B) 82% of people receiving TAF-ED were suppressed, comparing to 72% of those receiving TLD, 71% of those receiving ATV/r patients and 56% of those receiving LPV/r *(9)*.

Fig. 2. NADIA trial: subgroup analysis of viral suppression in tenofovir and zidovudine groups at week 48

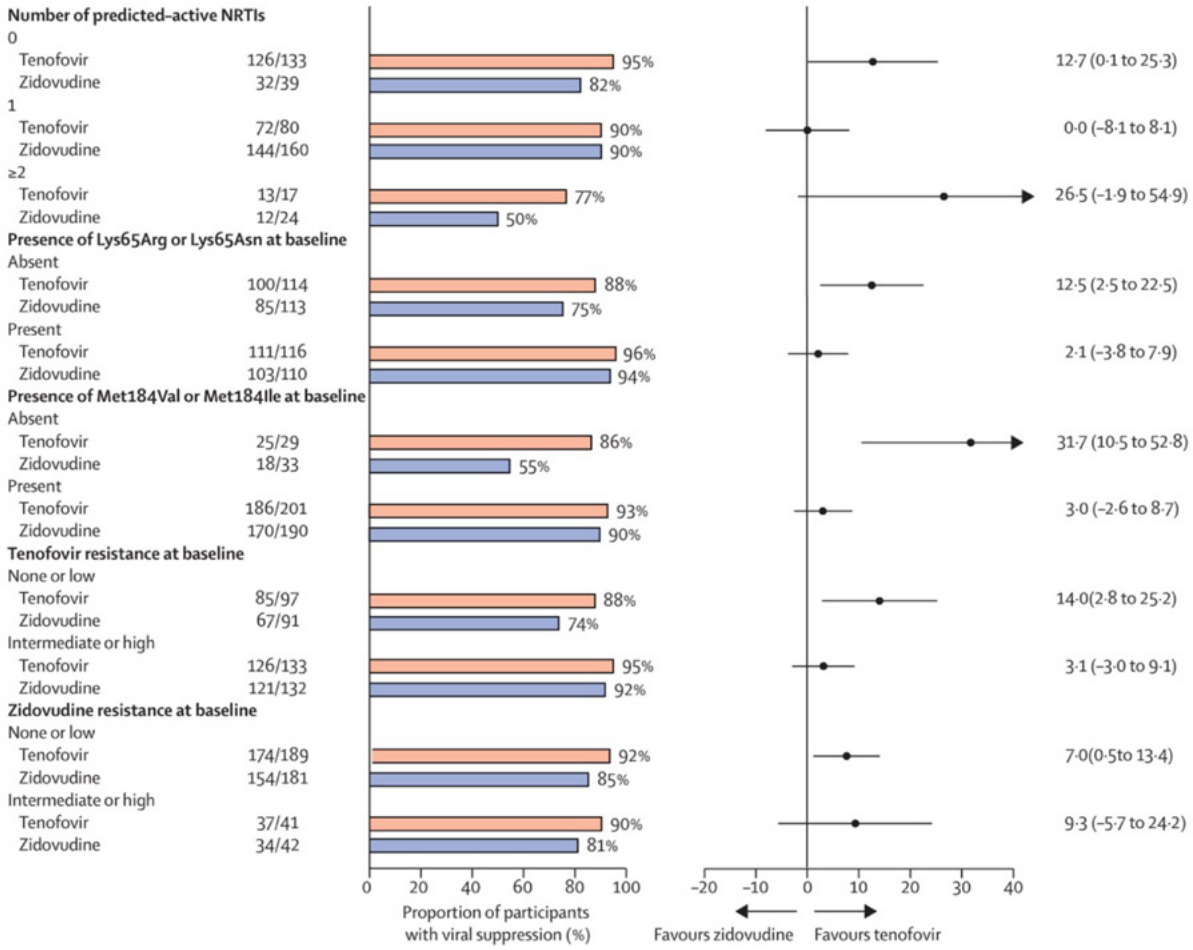
Subgroup	Tenofovir	Zidovudine	Difference in Percentage Points (95% CI)
	no. of patients/total no. (%)		
Randomization group			
Dolutegravir	108/118 (91.5)	104/117 (88.9)	2.6 (−5.0 to 10.2)
Darunavir	107/115 (93.0)	103/114 (90.4)	2.6 (−4.4 to 9.8)
Viral load at baseline			
<100,000 copies/ml	161/171 (94.2)	146/165 (88.5)	5.7 (−0.3 to 11.7)
≥100,000 copies/ml	54/62 (87.1)	61/66 (92.4)	−5.3 (−15.8 to 5.2)
CD4+ cell count at baseline			
<200 cell/mm^3	105/115 (91.3)	115/123 (93.5)	−2.2 (−8.9 to 4.6)
≥200 cell/mm^3	110/118 (93.2)	92/108 (85.2)	8.0 (−0.1 to 16.1)
Sex			
Male	85/93 (91.4)	79/89 (88.8)	2.6 (−6.1 to 11.3)
Female	130/140 (92.9)	128/142 (90.1)	2.8 (−3.8 to 9.2)
No. of predicted active NRTIs			
0	126/133 (94.7)	34/39 (87.2)	7.5 (−3.6 to 18.7)
1	73/80 (91.2)	150/160 (93.8)	−2.6 (−9.7 to 4.7)
≥2	13/17 (76.5)	15/24 (62.5)	14.0 (−14.0 to 41.9)
Presence of K65R/N at baseline			
No	103/114 (90.4)	94/113 (83.2)	7.2 (−1.6 to 15.9)
Yes	109/116 (94.0)	105/110 (95.5)	−1.5 (−7.3 to 4.3)
Presence of M184V/I at baseline			
No	24/29 (82.8)	24/33 (72.7)	10.0 (−10.5 to 30.5)
Yes	188/201 (93.5)	175/190 (92.1)	1.4 (−3.7 to 6.6)
Tenofovir resistance at baseline			
None or low level	86/97 (88.7)	76/91 (83.5)	5.1 (−4.8 to 15.0)
Intermediate or high level	126/133 (94.7)	123/132 (93.2)	1.5 (−4.2 to 7.3)
Zidovudine resistance at baseline			
None or low level	173/189 (91.5)	162/181 (89.5)	2.0 (−3.9 to 8.0)
Intermediate or high level	39/41 (95.1)	37/42 (88.1)	7.0 (−4.8 to 18.8)



Source: Paton et al. *(8)*.

The figure shown is the percentage of people with a viral load of less than 400 copies/mL at week 48, according to randomly assigned treatment group and prespecified subgroups. The first subgroups shown are the other factorial randomization groups (the DTG group and DRV group). The percentage of people with suppression is based on the United States Food and Drug Administration snapshot algorithm and includes everyone with data available for subgroup classification. The widths of the confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

Fig. 3. NADIA trial: subgroup analysis of viral suppression in tenofovir and zidovudine groups at week 96



NRTI = nucleoside reverse-transcriptase inhibitor.

Source: Paton et al. *(38)*.

Viral suppression analysis is based on the United States Food and Drug Administration snapshot outcome and includes all cases with baseline data available for subgroup classification. The left side of the figure shows the subgroups and the proportion of participants with viral suppression of less than 400 copies per mL at week 96. The right side of the figure shows the point estimate of the (unadjusted) difference in proportions between the treatment groups (DTG minus DRV/r or tenofovir minus AZT) and the 95% confidence interval within a specific stratum. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

Table 3. Comparison of the NADIA, GHESKIO and EA-IeDEA studies on viral suppression with tenofovir recycling and zidovudine switching groups

Study	Time	Threshold (copies/mL)	TDF recycled	AZT switch	TDF versus AZT relative risk (95% CI)
EA-IeDEA cohort *(38)*	48 weeks	<1000	127/212 (60%)	2089/3028 (69%)	0.95 (0.81–1.12)
NADIA *(8)*	48 weeks	<1000	219/233 (94%)	211/231 (91%)	
GHESKIO *(39)*	48 weeks	<200	244/434 (56%)	54/144 (38%)	1.22 (0.84–1.76)
NADIA *(38)*	48 weeks	<400	215/233 (92%)	207/231 (90%)	
GHESKIO *(39)*	96 weeks	<200	218/372 (59%)	70/218 (32%)	1.39 (0.83–2.32)
NADIA *(38)*	96 weeks	<400	214/233 (92%)	196/231 (85%)	

AZT = zidovudine, TDF = tenofovir disoproxil fumarate.

2.3.3. Use of tenofovir alafenamide versus tenofovir disoproxil fumarate in nucleoside reverse-transcriptase inhibitor backbones

One of the potential advantages of TAF over TDF is its lower impact on renal and bone health, which are common comorbidities for people living with HIV. However, these benefits have been demonstrated only in terms of laboratory determinant measurements and may be offset by the higher risk of weight gain and dyslipidaemia associated with TAF, especially when combined with DTG and boosted PIs, respectively *(35)*. Therefore, the choice between TDF and TAF in second-line regimens should consider the person's baseline characteristics, comorbidities, preferences and potential drug–drug interactions. Moreover, the availability and cost of TDF- and TAF-containing regimens may vary depending on the setting and access to generic formulations. In resource-limited settings, where TDF is widely available and affordable, it may still be a reasonable preferred option for second-line therapy; as long as renal and bone toxicity are monitored and managed appropriately. Conversely, in settings where TAF is accessible and affordable, it may offer a safer alternative for people with impaired renal function or osteoporosis or those who cannot tolerate TDF. However, cardiometabolic effects should also be monitored and managed.

Finally, the comparison of partly to fully active NRTIs show that the less active NRTIs, the better viral suppression is achieved (Table 4). Additional outcomes, also informed by the NADIA trial, show comparable tolerability between TDF and AZT, significantly better CD4 cell count gain with TDF, non-differentiable weight change and other metabolic outcomes, and better safety with TDF.

In conclusion, the systematic review and network meta-analysis showed that maintaining TDF may be superior to switching to AZT in second-line regimens, considering both viral suppression and increase in CD4 cell counts. The robustness of results across a variety of scenarios, including various NRTI resistance profiles, suggests that TDF recycling can lend itself to a public health approach.

2.3.4. Considerations on managing children and adolescents receiving nucleoside reverse-transcriptase inhibitor backbones

Results from CHAPAS-4 show that, for the primary endpoint (viral load <400 copies/mL), TAF + FTC performed better than the standard of care: 89% of children receiving TAF + FTC had suppressed viral loads at 24 months versus 83% receiving the standard of care *(26)*. Across all anchor drugs, TAF performed better than the standard of care, and the difference overall is 6.3 percentage points (95% CI: 2.0–10.6, P = 0.004). Across a number of predefined subgroup analyses TAF performed better than the standard of care (Fig. 4) and there were low rates of adverse events overall.

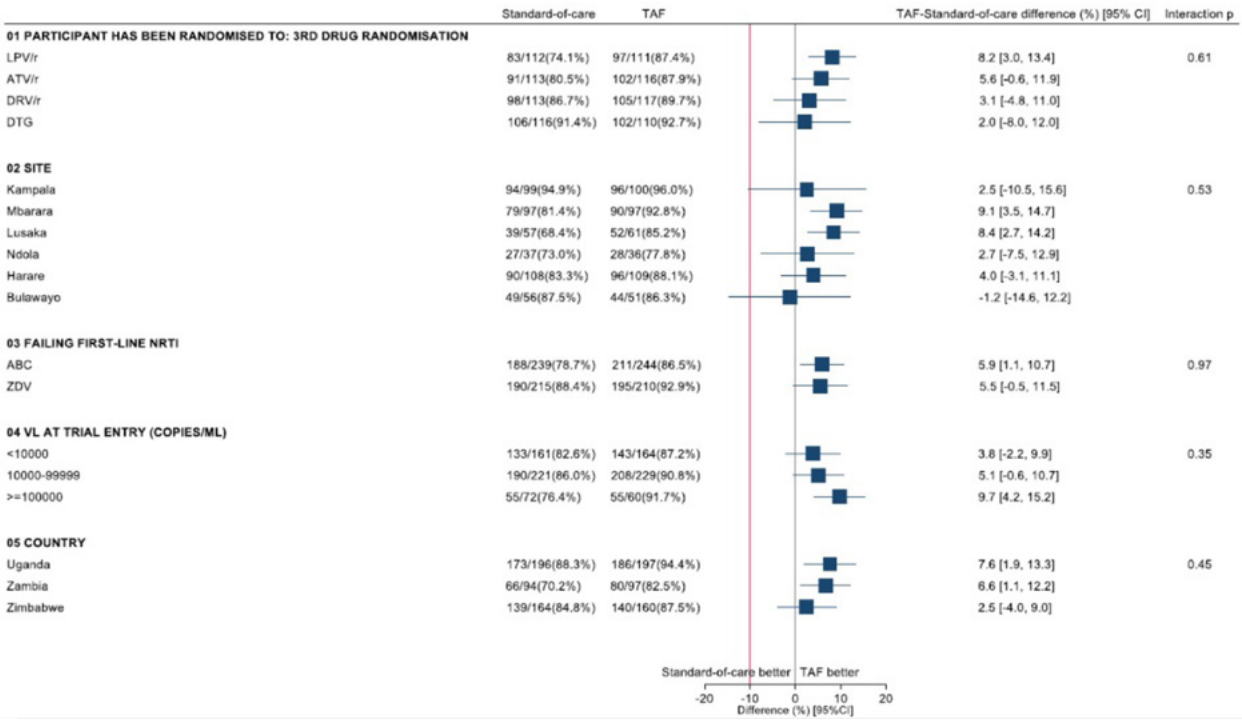
There was no evidence of any difference between TAF and abacavir (ABC) or AZT (the standard of care) in terms of serious adverse events, grade 3 and 4 adverse events or ART-modifying adverse events. Also, no evidence of difference between TAF and the standard of care for bone mineral density was found, except a greater increase in total body less head bone mineral

Table 4. Comparison of the DAWNING, EARNEST, NADIA and SECOND-LINE studies on viral suppression with partly and fully active nucleoside reverse-transcriptase inhibitors

	48 weeks			96 weeks		
Trials	**<two active NRTIs**	**≥two active NRTIs**	**<two NRTIs vs ≥two NRTIs relative risk (95% CI)**	**<two active NRTIs**	**≥two active NRTIs**	**<two NRTIs versus ≥two NRTIs relative risk (95% CI)**
DAWNING – DTG *(45)*	84%	84%	1.15 (0.94–1.41)	–	–	1.25 (1.01–1.57)
DAWNING – LPV/r *(45)*	73%	59%		–	–	
NADIA – DTG *(8,38)*	91%	72%		81%	61%	
NADIA – DRV/r *(8,38)*	95%	65%		79%	35%	
EARNEST – LPV/r *(41)*	76%	65%		74%	65%	
SECOND-LINE – LPV/r *(42)*	–	–		89%	81%	

DRV/r= darunavir/ritonavir, DTG = dolutegravir, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse-transcriptase inhibitor.

Fig. 4. CHAPAS-4 study: subgroup analysis for viral suppression with tenofovir alafenamide by failing first-line nucleoside reverse-transcriptase inhibitors at week 96



ABC = abacavir, 3TC = lamivudine, AZT = zidovudine, DTG = dolutegravir, INSTI = LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse-transcriptase inhibitor, NNRTI = non-nucleoside reverse-transcriptase inhibitor, TDF = tenofovir disoproxil fumarate.

Source: Musiime et al. *(26)*.

density for TAF than the standard of care (P = 0.04). Finally, in terms of increase in weight to week 96, children receiving TAF had a higher weight gain (+7.0 kg) than those receiving the standard of care (+6.2 kg). The TAF doses used in the study were 15 mg for <25 kg and 25 mg for ≥25 kg. The TAF and TDF concentrations generated were those previously demonstrated to be well tolerated for adults.

The results from the ODYSSEY trial show that, among participants in arm B (second-line ART) including DTG, failure to suppress viral loads was similar for TDF versus ABC (hazard ratio 1.19, 95% CI 0.50–2.83, P = 0.70) and higher on AZT versus ABC (hazard ratio 2.22, 95% CI 1.01–4.88, P = 0.05) *(46)*. Failure to suppress viral loads was also numerically higher for children with no high-level resistance at baseline to AZT versus children receiving ABC with high-level resistance (hazard ratio 2.56, 95% CI 0.70–9.31, P = 0.15). The results among participants in arm B starting on ABC show that the failure rates by week 96 were comparable for children with high-level baseline ABC resistance versus no high-level ABC resistance (hazard ratio 0.90, 95% CI 0.23–3.61, P = 0.88).

2.3.5. Considerations on dolutegravir resistance risk in the context of tenofovir + lamivudine + dolutegravir transition

A rapid scoping review assessed the virologic efficacy and prevalence of DTG resistance for ART-experienced people with failure to suppress viral loads receiving DTG-containing regimens *(47)*. Data on these trials, in which individuals with predominantly failing NRTI-containing first-line regimens began second-line therapy with a regimen containing DTG plus two NRTIs, show low levels of drug resistance: overall, among 1428 people living with HIV with a median 13% (3.5–25.0%) failed to suppress viral loads (Table 5). Although the trials showed low levels of failure to suppress viral loads and emergent drug resistance, some individuals developed failure to suppress viral loads with drug resistance mutations later.

Data from 12 cohort studies, in which people living with HIV in sub-Saharan Africa underwent transitioned from a predominantly first-line dual NRTI + NNRTI regimen to a first-line dual NRTI + DTG regimen, show that viral suppression outcomes were comparable or improved after switching (Table 6). However, the studies varied in the number of individuals transitioning and the availability of viral load data; genotypic resistance testing was infrequently performed, creating difficulty in gathering information from these studies. Additional cohort surveillance data from the United States Centers for Disease Control show that the prevalence of DTG resistance ranged from 3.9% in Uganda to 19.6% in Mozambique *(58)*.

Available data on DTG resistance show the need for further investigation to determine whether there is more transmitted DTG resistance among infants born to women with viral non-suppression.

Current knowledge on adults receiving NNRTI-based regimens with unsuppressed viral load show very high levels of acquired resistance to both NNRTI and NRTI. Data from the 2021 WHO HIV drug resistance report show rates of TDF resistance ranging from 13% in South Sudan in 2018 to 84% in Uganda in 2016 among adults receiving ART for 12 months *(69)*; similar rates were observed at 48 months.

The primary outcome of the D2EFT trial (HIV-1 RNA <50 copies/mL at week 48), found that DTG treatment was non-inferior to a regimen containing ritonavir-boosted PI when people were switched to a ritonavir-boosted PI-based regimen *(10)*. The VISEND study also showed that recycling TDF with DTG was found to be non-inferior to optimizing the backbone to DRV/r *(9)*. No significant difference in viral suppression was observed between people switching to TLD with viral suppression less than 1000 copies/mL versus greater than 1000 copies/mL (Fig. 5).

Clinical trial data on the prevalence of DTG resistance among people living with HIV with failure to suppress viral loads while receiving DTG-based ART was divided into six scenarios:

- scenario 1: ART-naive people living with HIV who started DTG plus two NRTIs (15 trials, 4588 people living with HIV);
- scenario 2: ART-naive people living with HIV who started DTG-based dual therapy (three trials, 967 people living with HIV);
- scenario 3: ART-experienced people living with HIV with failure to suppress viral load on an NNRTI-containing regimen switching to DTG plus two NRTIs (six trials, 1428 people living with HIV);
- scenario 4: ART-experienced people living with HIV with suppressed viral load switching to DTG plus two NRTIs (four trials, 930 people living with HIV);
- scenario 5: ART-experienced people living with HIV with suppressed viral load switching to DTG-based dual therapy (10 trials, 1784 people living with HIV); and
- scenario 6: ART-experienced people living with HIV with suppressed viral load switching to DTG monotherapy (four trials, 276 people living with HIV).

The prevalence of acquired INSTI-associated drug resistance mutations was 1.6% by weeks 48 to 96 in scenario 3 and 2.9% by weeks 24 to 48 in scenario 6. In contrast, the prevalence of drug resistance in the other scenarios was ≤0.1%.

Table 5. Failure to suppress viral loads and prevalence of emergent HIV drug resistance in six clinical trials of ART-experienced people living with HIV with active virus replication receiving dolutegravir-containing regimens

Trial	Regions	Population	DTG-containing ART	Number of people living with HIV	Weeks	*n* (%) with failure to suppress viral loads	*n* (%) undergoing genotypic resistance typing	*n* (%) with INSTI drug resistance mutations
SAILING (48.49)	Europe, North America, South America, Asia, Oceania, Africa	Adults; viral load <400 copies/mL; INSTI-naive, two-class resistance	DTG + optimized background regimen	354	48	21 (5.9%)	9 (2.5%)	2 (0.6%)
DAWNING (45,50)	Europe, South America, Asia, Africa	Adults; viral load <400 copies/mL on a first-line NNRTI-containing regimen	DTG + two NRTIs (21 fully active)	312	48	11 (3.5%)	11 (3.5%)	3 (1.0%)
NADIA (8,38)	Kenya, Uganda, Zimbabwe	Adults and Zimbabwe adolescents; viralload <1000 copies/ml on a first-line NNRTI-containing regime	DTG + TDF + 3TC or AZT + 3TC	235	48	20 (8.5%)	11 (4.7%)	4 (1.7%)
					96	24 (10.2%)	21 (8.9%)	9 (3.8%)
ARTIST (29,51,52)	South Africa	Adults; viral load <400 copies/mL while on a first-line NNRTI-containing regimen	DTG + TDF + 3TC	135	24	21 (15.6%)	4 (3.0%)	0 (0%)
			DTG twice daily + TDF + 3TC	64	24	9 (14.1%)	3 (4.7%)	0 (0%)
IMPACT P1093 (53-55)	North America, South America, Asia, Africa	Infants, children and adolescents with viral load <1000 copies/mL; most ART-experienced	DTG + two NRTIs	142	48	36 (25.3%)	36 (25.3%)	5 (3.5%)
ODYSSEY (46.56)	Europe, Asia, Africa	Children and adolescents with viral load ≥500 copies/mL on a first- or second-line ART regimen	DTG + two NRTIs	196	96	31 (15.8%)	29 (14.7%)	4 (2.0%)

3TC = lamivudine, AZT= zidovudine, DTG = dolutegravir, INSTI = integrase strand-transfer inhibitor, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse-transcriptase inhibitor, NNRTI = non-nucleoside reverse-transcriptase inhibitor, TDF = tenofovir disoproxil fumarate.

Source: Chu et al. *(47)*.

Table 6. Viral suppression outcomes in 12 sub-Saharan African cohorts undergoing programmatic transition to tenofovir + lamivudine + dolutegravir

Cohort	Countries and years	*n*	Pre-switch treatment	Pre-switch viral load	Post-switch viral load
van Oosterhout et al. *(58)*	Malawi 2020-2021 (National Treatment Program)	>800 000	Naive; first-line ART; second-line ART	Not available	Not available 6462 noted to have failure to suppress viral load
Dorward et al. *(59)*	South Africa 2019-2022	121 174	Dual NRTI and NNRTI	95% <1000 copies/mL	30% had follow-up viral load 91% <50 copies/mL
Romo et al. *(60)*	Five countries 2017-2020 (IeDEA Consortium)	36 393	Dual NRTI and NNRTI	91% <200 copies/mL 99% <1000 copies/mL	Viral load ≥1000 copies/mL higher without recent viral load and with a pre-switch viral load 21000 copies/mL
Tschumi et al. *(61)*	Lesotho 2021 (VICONEL cohort)	14 242	Dual NRTI and NNRTI	83% <50 copies/mL 96% <1000	After 12 months: 94% <50 copies/mL; 99% <1000 copies/mL
Bacha et al. *(62)*	Six countries 2017-2020 Children and adolescents (BIPAD)	9 419	Naive (5%); NNRTI (75%); PI (20%)	91% <400 copies/mL 93% <1000 copies/mL	84% had follow-up viral load. 92% <400 copies/mL (80% <400 copies/mL if no pre-switch suppression of viral load)
Schramm et al. *(30)*	Malawi 2019 (MSF programme)	1 892	TLE (95%)	95% <50 copies/mL	98% <50 copies/mL (88% with baseline viraemia)
Esber et al. *(63)*	Four countries 2018-2021 (AFRICOS Study Group)	1576	Dual NRTI and NNRTI	94% <1000 copies/mL	At 23 months, 97% $1000 copies/mL
Esber et al. *(63)*	Four countries 2018-2021 (AFRICOS Study Group)	1576	Dual NRTI and NNRTI	94% <1000 copies/mL	At 23 months, 97% $1000 copies/mL
Brown et al. *(64)*	Lesotho 2020 (DO-REAL study)	1 225	Dual NRTI and NNRTI	96% <100 copies/mL 98% <1000 copies/mL	At 4 months, 95% viral load <100 copies/mL 98% < 1000 copies/mL
Mehari et al. *(65)*	Ethiopia 2018-2020	349	Dual NRTI and NNRTI	81% <50 copies/mL	92% had viral load <50 copies/mL
Kouamou et al. *(66)*	Zimbabwe 2018-2019 Children and adolescents	184	NNRTI: 63% PI: 37%	76% <1000 copies/mL	At 7 months, 95% had viral load <1000 copies/mL; of 10 with viral load 21000, 9 had baseline viral load ≥1000 copies/mL
Kingwara et al. *(67)*	Kenya 2017-2020 Children and adolescents	167	NNRTI and PI ART regimens	Not reported	AT 6 months, 93% <400 copies/mL
Semengue et al. *(68)*	Cameroon 2021	139	TLE	90% <1000 copies/mL	At 14 months, 95% viral load <400 copies/mL

ART= antiretroviral therapy, NRTI = nucleoside reverse-transcriptase inhibitor, NNRTI = non-nucleoside reverse-transcriptase inhibitor, PI = protease inhibitor, TLE = tenofovir + lamivudine + efavirenz.

Source: Chu et al. *(47)*.

Fig. 5. VISEND trial: subgroup analysis of HIV viral suppression efficacy at week 48

HIV-1 RNA result at week 48, %	HIV-1 RNA <1000 copies/mL		HIV-1 RNA ≥1000 copies/mL			
	DG + 3TC/TDE (*n* = 209)	DTG+ FTC/TAF (*n* = 209)	DTG+ 3TC/TDF (*n* = 208)	DTG+ FTC/TAF (*n*= 211)	LPV/r + 3TC/AZT (*n* = 167)	ATV/r+ 3TC/AZT (*n* = 197)
Intent to treat						
• <1000 copies/mL	88	85	83	86	69	81
• <50 copies/mL	80	74	72	80	56	70
Per-protocol (FDA snapshot)						
• <1000 copies/mL	98	98	93	95	83	90
• <50 copies/mL	90	86	82	88	68	78

3TC = lamivudine, AZT= zidovudine, DTG = dolutegravir, FTC = emtricitabine, LPV/r = lopinavir/ritonavir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate.

Source: Mulenga et al. *(9)*.

A nationwide study in the United Republic of Tanzania showed a 5.8% overall prevalence of DTG resistance, higher for children at 7.0%. For both adults and children, the risk of DTG resistance was only observed among ART-experienced people receiving long-term ART *(70)*. Unpublished data from Kenya show that the prevalence of DTG resistance was about 6.1% among people receiving first-line DTG-containing ART and higher at 15.6% among those for whom a second-line DTG-based regimen failed.

Finally, data from a cohort on HIV-1 drug resistance of people receiving DTG-based ART show that resistance to NRTIs was a major risk factor for DTG resistance, indicating that individuals receiving functional monotherapy are more likely to develop DTG resistance *(71)*. Resistance to NRTI may not affect treatment failure risk but could potentially increase the risk of acquiring resistance in case of failure.

In summary, the risk of viral failure in INSTI-associated drug resistance mutations for people receiving DTG-containing ART can be classified into three categories:

- ART-naive individuals receiving two NRTIs + DTG: an extremely low risk of about 0.1%;
- ART-experienced individuals with first-line viral failure on an NNRTI regimen: risk between 1% and 4% after one to two years of follow-up; and
- ART-experienced individuals undergoing transition to a first-line NNRTI: no study systematically assessed risk.

The low prevalence of viral failure with emergent INSTI resistance mutations reinforces the decision to switch from NNRTI- to DTG-based ART. The low prevalence of drug resistance suggests that non-adherence is the primary cause of failure, and more research on the best ways to sustain optimal adherence is therefore needed.

Chapter 3

Key points and conclusions

The Technical Working Group reviewed key clinical trials, observational studies and programmatic data in the proposed topics that could inform future reviews for updating HIV treatment policies; critical gaps in research, monitoring and surveillance on second-line and third-line regimens containing DRV/r, TAF and TDF were identified. The key points are summarized below.

3.1. Using darunavir/ritonavir in second-line and third-line regimens

DRV/r should be preferred as a boosted PI, for second- and third-line therapy, but there are concerns about the genetic barrier of resistance (although it is higher for DRV/r than for ATV/r), side-effects, drug–drug interactions and the need for research to address gaps in the guidelines.

The are challenges of administering DRV/r to people with tuberculosis (TB) considering interactions with rifampicin-based TB treatment. The possibility of using a non-DRV-based regimen during this period was discussed and the need for individualized treatment decisions. The positioning of DRV/r as an alternative option in second-line regimens was also discussed, with concerns raised about the availability and cost of third-line therapies.

There is a need for research to clarify the optimal dosing of DRV/r for pregnant women and optimizing the dosing and formulations of DRV/r for children.

3.2. Recycling tenofovir and the impact of nucleoside reverse-transcriptase inhibitor resistance

- Available data show that there should be a move towards TDF (or TAF) recycling in second-line regimens. The presence of NRTI resistance mutations in first-line regimens may not affect the treatment response to second-line regimens.
- There was a consensus on the need to reclassify risk, viral suppression failure and adherence definitions.
- No serious concerns were raised about the safety of using TDF with a boosted PI, although it may require frequent creatinine or renal function monitoring for some people. People using TAF with boosted PIs should have a lower TAF dose.
- There is a lack of clinical studies examining drug resistance testing and clinical outcomes. There is a potential future role of drug level testing in informing decisions; however there are challenges to conducting tests in routine practice in low- and middle-income settings.
- DTG resistance risk must be evaluated carefully, and alternative treatment strategies using newer drugs are needed. There is a need to consider switching regimens, and the concern about distinguishing people with DTG resistance and failure to suppress viral loads from those without DTG resistance and failure to suppress viral loads.
- The global transition of most people receiving ART to TLD raises concerns about reframing the sequencing paradigm of first-, second- and third-line regimens. The current WHO definition of failure to supress viral loads for people receiving TLD can lead to inappropriate switching and needs to be revisited.
- TLD became the anchor regimen in most low- to middle-income countries, but managing viraemia among people receiving TLD may be a concern, especially in cases of adherence problems and DTG resistance.

3.3. Conclusions

- The Technical Working Group agreed on the need to update the WHO recommendations on the preferred PI option in second-line regimens, considering the recent evidence presented at the meeting, including programmatic data. PI preferences should be aligned across different populations - adults, children, pregnant women, individuals co-infected with TB - as far as possible.
- The Technical Working Group recommended that DRV/r be used as the preferred PI option and ATV/r as an alternative, and LPV/r should be reserved for special circumstances (such as drug interactions and stock-outs) or phased out.
- The Technical Working Group had a divided position regarding the optimal dosing schedule of DRV/r for pregnant women and suggested that further information from ongoing pharmacokinetic studies during pregnancy are needed to inform the decision.
- The Technical Working Group supported keeping TDF (or TAF) in the NRTI backbone with intensified adherence support in all proposed scenarios and highlighted the importance of patient choice and impact on adherence when using ATV/r, which can cause indirect hyperbilirubinaemia.
- The Technical Working Group expressed low to moderate concerns on the safety outcomes of using TDF with boosted PIs, such as renal and bone toxicity, and concluded that the benefits of suppression of viral loads greatly outweigh the potential risks.
- The Technical Working Group discussed the trade-offs of using TAF instead of TDF, such as lower risk of renal and bone toxicity, but higher risk of body weight gain and cardiometabolic events and suggested to invest in cardiovascular primary prevention and monitoring of metabolic and renal parameters.

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Annex 1: Meeting agenda

Day 1: Should DRV/r be preferred over ATV/r and LPV/r as the preferred PI option in second-line regimens, including pregnant women and children?

Time	Topic	Presenters and facilitators
5 minutes	Welcome remarks and objectives of the meeting	Marco Vitoria and Françoise Renaud
10 minutes	Current WHO recommendations and what has changed in the ART landscape since the last review on this topic	Marco Vitoria
30 minutes	Update of systematic review and network meta-analysis on the use of DRV/r in adults and pregnant women	Steve Kanters and Lynne Mofenson
10 minutes	Comments and clarifications	Elaine Abrams and Alexandra Calmy
10 minutes	Coffee break	
30 minutes	Review on the safety of DRV/r in adults, adolescents and children	Clare Herd and Claire Townsend
10 minutes	Comments and clarifications	Elaine Abrams and Alexandra Calmy
40 minutes	Plenary discussion and questions for the Technical Working Group	Elaine Abrams and Alexandra Calmy
5 minutes	Conclusions and next steps	Marco Vitoria and Françoise Renaud

Day 2: Should AZT replace TDF (or TAF) in second-line NRTI backbones or should TDF (or TAF) be recycled regardless of NRTI resistance?

Time	Topic	Presenters and facilitators
5 minutes	Welcome and objectives of day 2	Marco Vitoria and Françoise Renaud
10 minutes	Current WHO recommendations and what has changed in the ART landscape since the last review on this topic	Marco Vitoria
20 minutes	Update of systematic review and network meta-analysis on keeping TDF (or TAF) in second-line NRTI backbones	Steve Kanters
15 minutes	Considerations on management of NRTI backbone in children and adolescents	Elaine Abrams and Anna Turkova
10 minutes	Considerations on DTG resistance risk in the context of TLD transition	Michael Jordan
10 minutes	Comments and clarifications	Elaine Abrams and Alexandra Calmy
10 minutes	Coffee break	
40 minutes	Plenary discussion and questions for the Technical Working Group	Elaine Abrams and Alexandra Calmy
10 minutes	Conclusions and next steps	Marco Vitoria and Françoise Renaud

Annex 2: List of participants

External experts

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Mohammed Chakroun	Fattouma Bourguiba Teaching Hospital, Monastir, Tunisia
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Angela Colbers	Radboud University Medical Center, Nijmegen, Netherlands (Kingdom of the)
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Aleny Couto	Ministry of Health, Maputo, Mozambique
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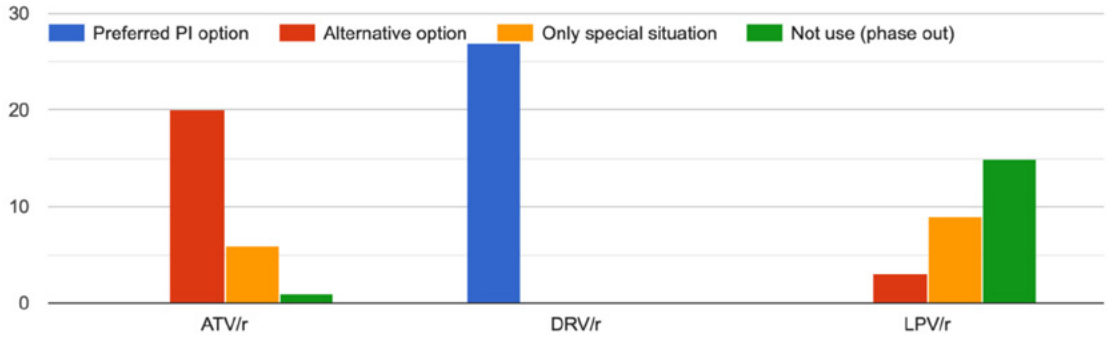
Annex 3: Summary of questionnaire results

The questionnaire was collaboratively developed by the facilitators and WHO staff. It considered the most relevant topics discussed in the meeting and aimed to offer guidance for future updates of WHO normative work. The external expert group was invited to complete the questionnaire.

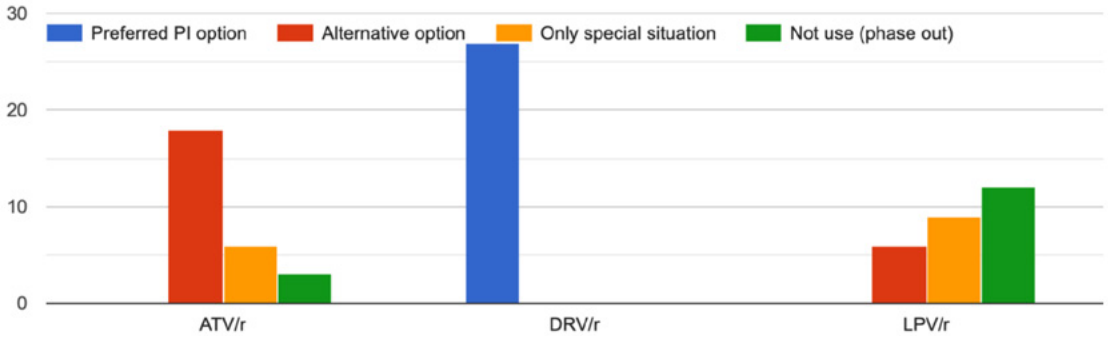
1. Ranking ATV/r versus DRV/r versus LPV/r as PI options

For adults in need of a boosted PI containing regimen, how would you rank the options below?



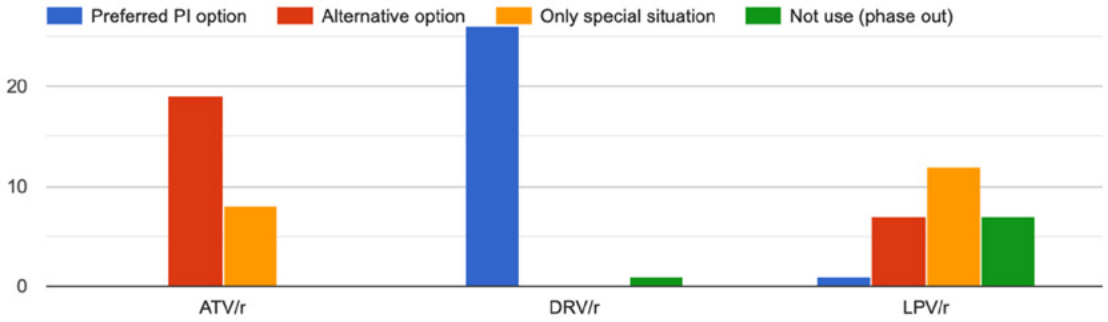
ATV/r = atazanavir/ritonavir, DRV/r= darunavir/ritonavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor.

For pregnant women in need of a boosted PI containing regimen, how would you rank the options below?



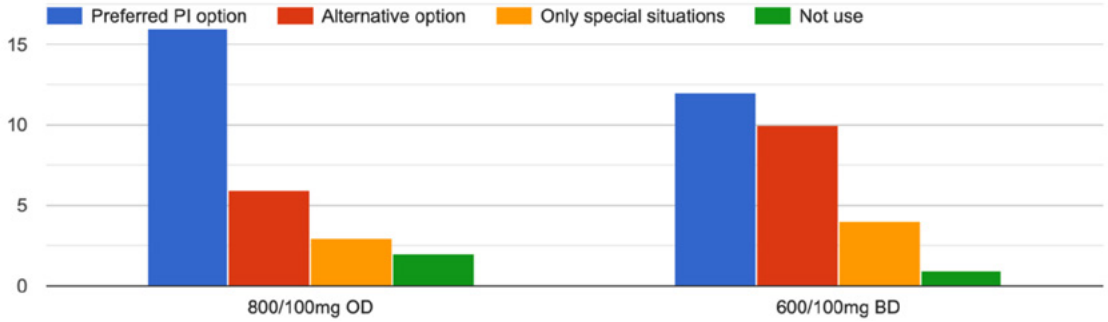
ATV/r = atazanavir/ritonavir, DRV/r= darunavir/ritonavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor.

For children > 3 years old in need of a boosted PI containing regimen, how would you rank the options below?



ATV/r = atazanavir/ritonavir, DRV/r= darunavir/ritonavir, LPV/r = lopinavir/ritonavir, PI = protease inhibitor.

How would you rank the dosing of DRV/r in pregnant women with HIV?

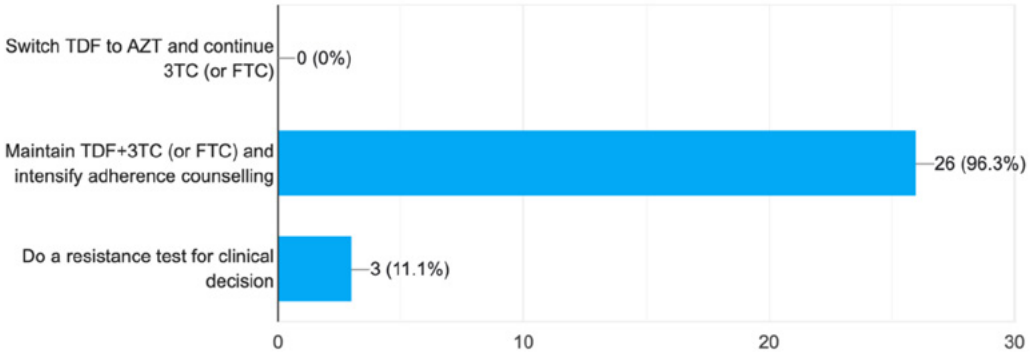


BD: twice daily, DRV/R = darunavir/ritonavir, OD: once daily, PI = protease inhibitor.

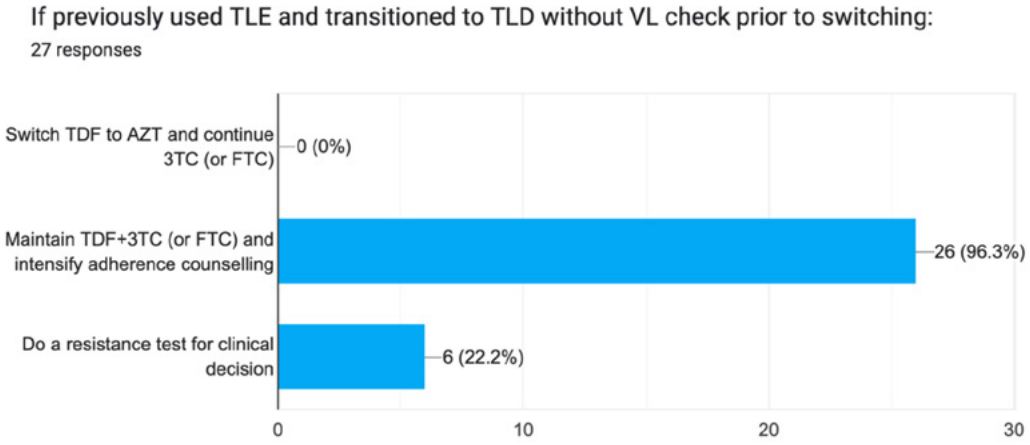
2. Management of NRTI backbone in the presence of viral load rebound when using TDF + 3TC + DTG

If previously used TLE and transitioned to TLD without evidence of virologic failure (ie: VL suppressed before switching):

27 responses



3TC = lamivudine, AZT = zidovudine, FTC = emtricitabine, TDF = tenofovir disoproxil fumarate, TLD = tenofovir + lamivudine + dolutegravir, TLE = tenofovir + lamivudine + efavirenz, VL: viral load.



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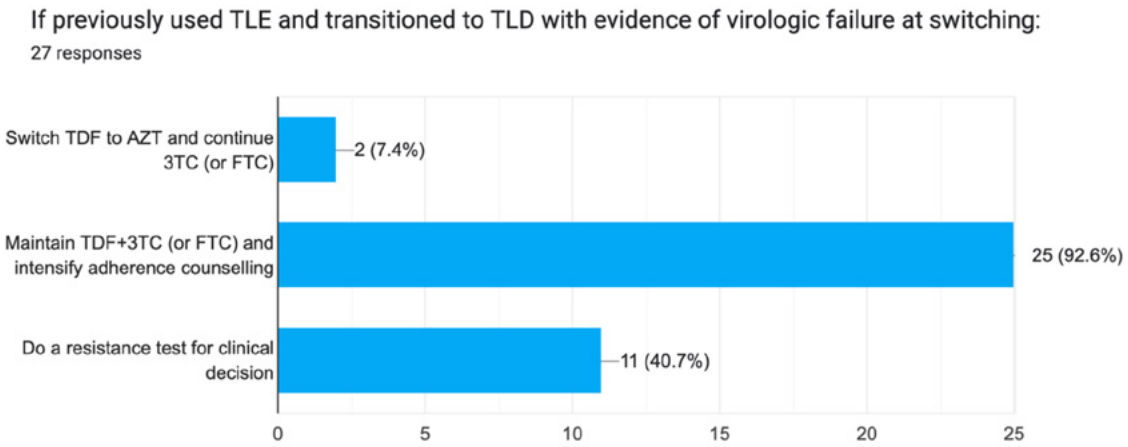
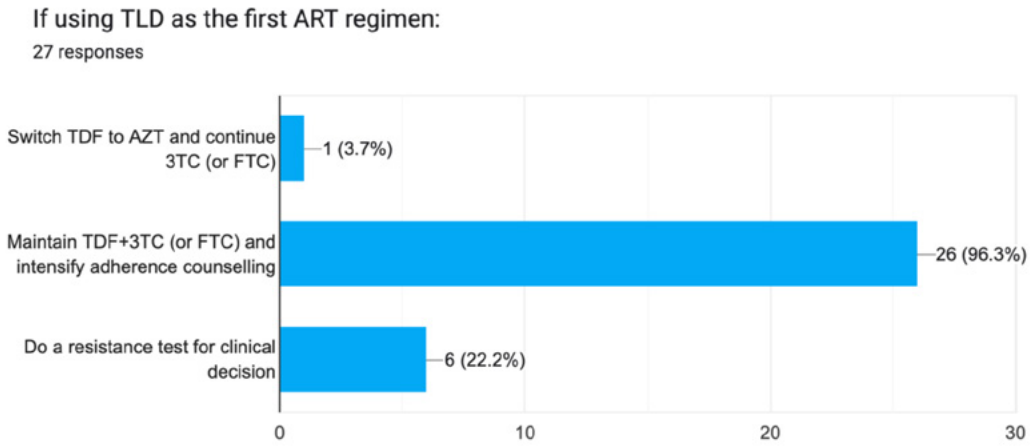


3TC = lamivudine, AZT = zidovudine, FTC = emtricitabine, TDF = tenofovir disoproxil fumarate, TLD = tenofovir + lamivudine + dolutegravir, TLE = tenofovir + lamivudine + efavirenz.

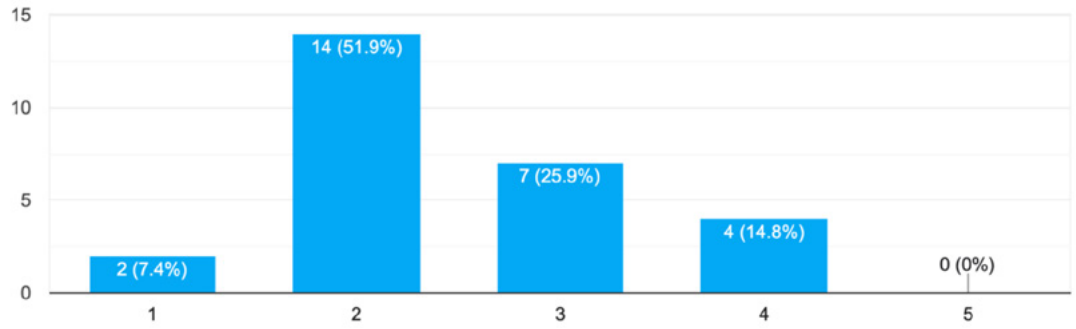


3TC = lamivudine, ART = antiretroviral therapy, AZT = zidovudine, FTC = emtricitabine, TDF = tenofovir disoproxil fumarate, TLD = tenofovir + lamivudine + dolutegravir.

3. Assessing safety issues with TAF and TDF in second-line regimens

How serious is the risk of renal toxicity associated with TDF when used with boosted PIs?

27 responses

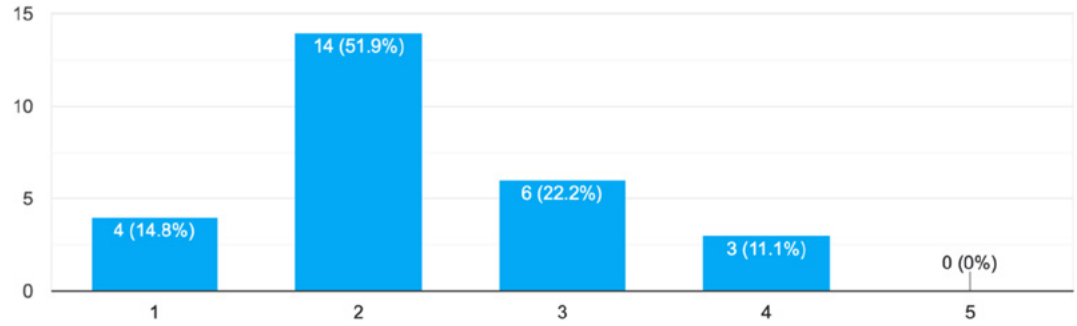


1 = very low 2 = low 3 = moderate 4 = high 5 = very high

PI = protease inhibitor, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate.

How serious is the risk of bone toxicity associated with TDF when used with boosted PIs?

27 responses

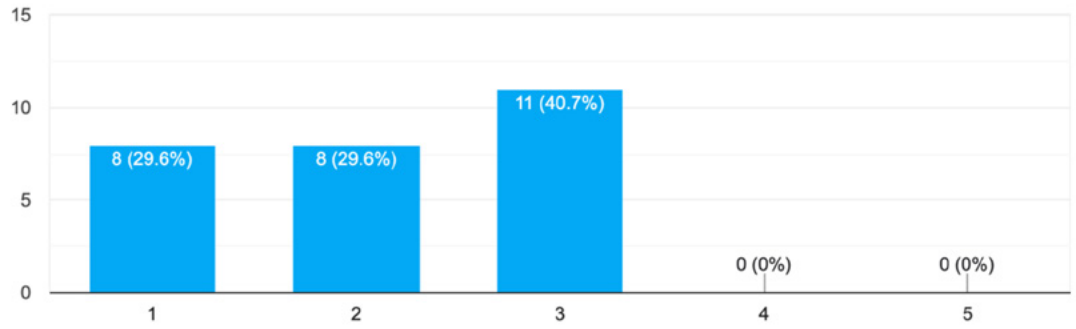


1 = very low 2 = low 3 = moderate 4 = high 5 = very high

PI = protease inhibitor, TDF = tenofovir disoproxil fumarate.

How serious is the risk of cardiometabolic disorders associated with TAF when used with boosted PIs?

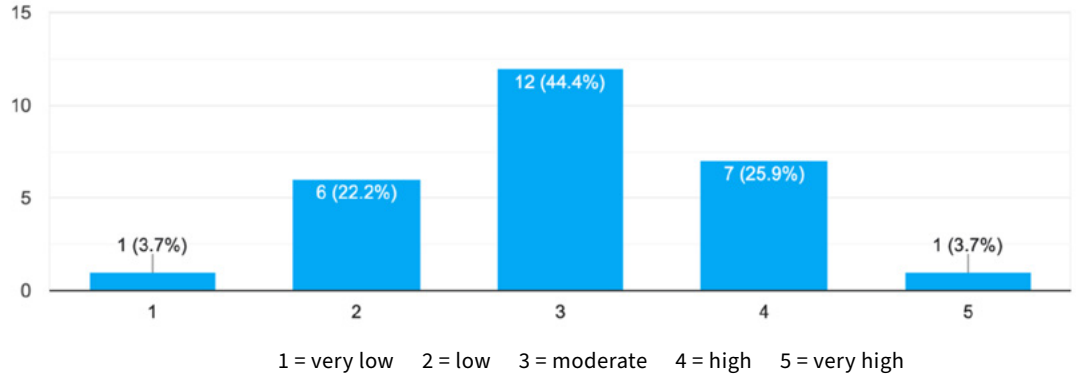
27 responses



1 = very low 2 = low 3 = moderate 4 = high 5 = very high

PI = protease inhibitor, TAF = tenofovir alafenamide.

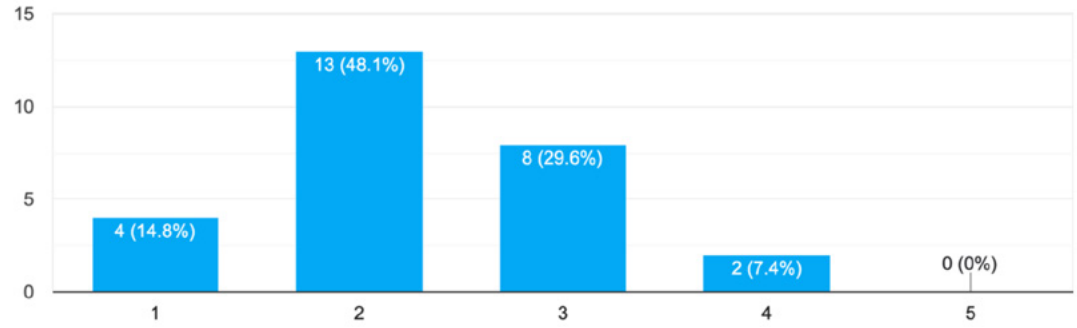
How serious is the risk of hyperbilirubinemia associated with the use of ATV/r use?
27 responses



1 = very low 2 = low 3 = moderate 4 = high 5 = very high

ATV/r = atazanavir/ritonavir

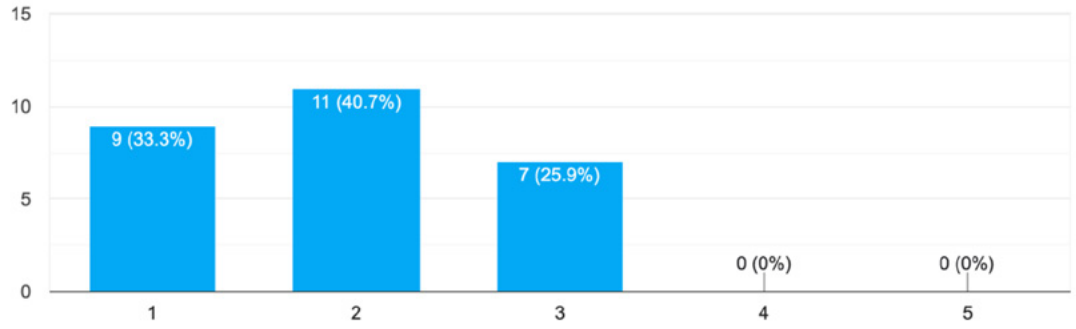
How serious is the risk of increased lipid level associated with the use of DRV/r?
27 responses



1 = very low 2 = low 3 = moderate 4 = high 5 = very high

DRV/r = darunavir/ritonavir

How serious is the risk of CVD associated with the use of DRV/r?
27 responses



1 = very low 2 = low 3 = moderate 4 = high 5 = very high

CVD: cardiovascular disease, DRV/r = darunavir/ritonavir.

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