TECHNICAL UPDATE

TRANSITION TO NEW ANTIRETROVIRAL DRUGS IN HIV PROGRAMMES: CLINICAL AND PROGRAMMATIC CONSIDERATIONS

JULY 2017

HIV TREATMENT

World Health Organization

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CONTENTS

EXECUTIVE SUMMARY

WHO has recommended adopting drug regimens with high potency, lower toxicity, high genetic barriers to resistance, usefulness across different populations and lower cost. The use of optimized drug regimens can improve the durability of the treatment and quality of care of people living with HIV.

Adopting optimized antiretroviral (ARV) drug regimens can significantly affect the speed at which the 90–90–90 targets are achieved, enhancing access to treatment and improving treatment outcomes with impact on treatment adherence, viral suppression and the quality of life of people living with HIV, reducing pressures on health systems and the risk of HIV transmission.

A major transition to new lower-cost ARV drugs in antiretroviral therapy (ART) programmes in low- and middle-income countries could save more than US$ 3 billion in health budgets by the end of 2025.

The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection include dolutegravir (DTG) and efavirenz 400 mg (EFV400) as new alternative options in first-line ART regimens and are better tolerated than EFV at standard doses (EFV600). The 2016 WHO consolidated ARV guidelines also include darunavir/ritonavir (DRV/r) and raltegravir (RAL) as new alternative ARV drugs for second-line treatment.

As of June 2017, more than 20 low- and middle-income countries have included or are planning to include DTG as a first-line option in their national guidelines. This technical update summarizes the recent evidence and provides programme considerations to support countries on how to transition to new ARV drugs for use in first- and second-line ARV in low and middle- income countries.

WHO recently launched a new recommendation that countries in which the national prevalence of resistance to the non-nucleoside reverse-transcriptase inhibitors (NNRTIs) EFV or nevirapine (NVP) in populations initiating first-line ART exceeds 10% should consider transitioning to an alternative ARV drug such as DTG; this recommendation is expected to prompt countries to consider accelerating the transition to DTG away from NNRTI-based first-line therapy. EFV400 would remain a first-line option for countries without documented high levels of resistance to EFV or NVP and where access to DTG is limited because of regulatory issues and high cost. On an individual basis, EFV400 would also remain an option for adults who are virally suppressed on EFV600-containing regimens and have central nervous system side-effects.

There will be various options for phasing in the introduction of DTG. Some countries may initially target people using EFV with central nervous system side-effects, newly initiating ART individuals or populations with documented or higher risk for poor adherence and/or HIV drug resistance such as adolescents or reinitiators. Emerging evidence suggests that DTG could also be a potential second-line ARV drug option in the future.

Evidence of the safety and efficacy of DTG and EFV400 is limited among young children, pregnant women, people with HIV-associated tuberculosis (TB) receiving rifampicin-based treatment and people with advanced HIV disease. Ongoing clinical studies in these groups will provide results in two to three years, during which active drug toxicity monitoring and pregnancy safety surveillance should be implemented as part of pharmacovigilance policies, as the use of DTG and EFV400 expands in these populations.

To address the gaps in safety data, enhancing toxicity monitoring and pregnancy safety surveillance is recommended to safely introduce new drugs and formulations across populations. Safe and strategic sequencing of these drugs requires further evidence and programmatic experience, which the WHO drug optimization research agenda will address.

Nevertheless, to date, no major new safety issues have been detected with DTG use among people living with HIV, but surveillance for potential drug-associated adverse reactions such as immune reconstitution inflammatory syndrome, cardiovascular risk and central nervous system adverse drug reactions is recommended while the use of DTG is scaled up.

DRV/r is a boosted protease inhibitor (PI) used in second-line therapy, with no significant differences observed compared with other PIs in terms of serious adverse reactions and risk of treatment discontinuation, supporting its use as an alternative option in second-line ART regimens.

Similarly, RAL is approved for use for children, adults and pregnant women and is effective and well tolerated in both second- and third-line use after treatment failure with PI-based regimens among adults, adolescents and children.

The availability of DTG and EFV400 will increase as cheaper generic formulations of fixed-dose combinations containing these new drugs are expected to be available in 2017 and 2018. The current high prices of formulations from originator companies, pill burden and the lack of affordable generic fixed-dose combinations limit the large-scale use of RAL and DRV/r in low- and middle-income countries.

A switch from the use of current preferred second-line regimen options to DRV/r or RAL needs to be reassessed in the context of the increased availability of adequate formulations and reduced prices.

Integrase inhibitors, especially DTG, have been noted as the strategically preferred choice based on the longer-term vision for drug optimization and harmonization that many experts on ART for both children and adults share.

WHO has an essential role in supporting countries in transitioning to new ARV drugs and will continue monitoring clinical studies with new drugs and treatment strategies and develop the necessary normative and operational tools to support the rolling out of new treatment regimens in countries.

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1. CONTEXT

Countries are making progress towards achieving the 90–90–90 treatment targets, and optimizing current antiretroviral (ARV) drug regimens is a critical component of achieving these targets. Currently, 19.5 million people are receiving antiretroviral therapy (ART): treatment coverage of 54% among people living with HIV (*1*).

The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (*2*) promote earlier treatment initiation and better tolerated regimens to be used for people living with HIV, including adults, pregnant and breastfeeding women, adolescents and children. New first-line treatment options include dolutegravir (DTG) and efavirenz at the lower dose of 400 mg (EFV400). Darunavir/ritonavir (DRV/r) and raltegravir (RAL) are included as additional new options for second-line ART. Table 1 shows the current role of new ARV drugs in the 2016 WHO consolidated ARV guidelines and the major gaps in efficacy and safety data, especially for pregnant women, children and people with HIV-associated tuberculosis (TB).

As experienced during the introduction of previous ART regimens recommended in the 2006 and 2013 WHO guidelines, adopting optimized ARV drug regimens can improve access to treatment and treatment outcomes, leading to better treatment adherence, viral suppression and quality of life of people living with HIV, reducing the risk of

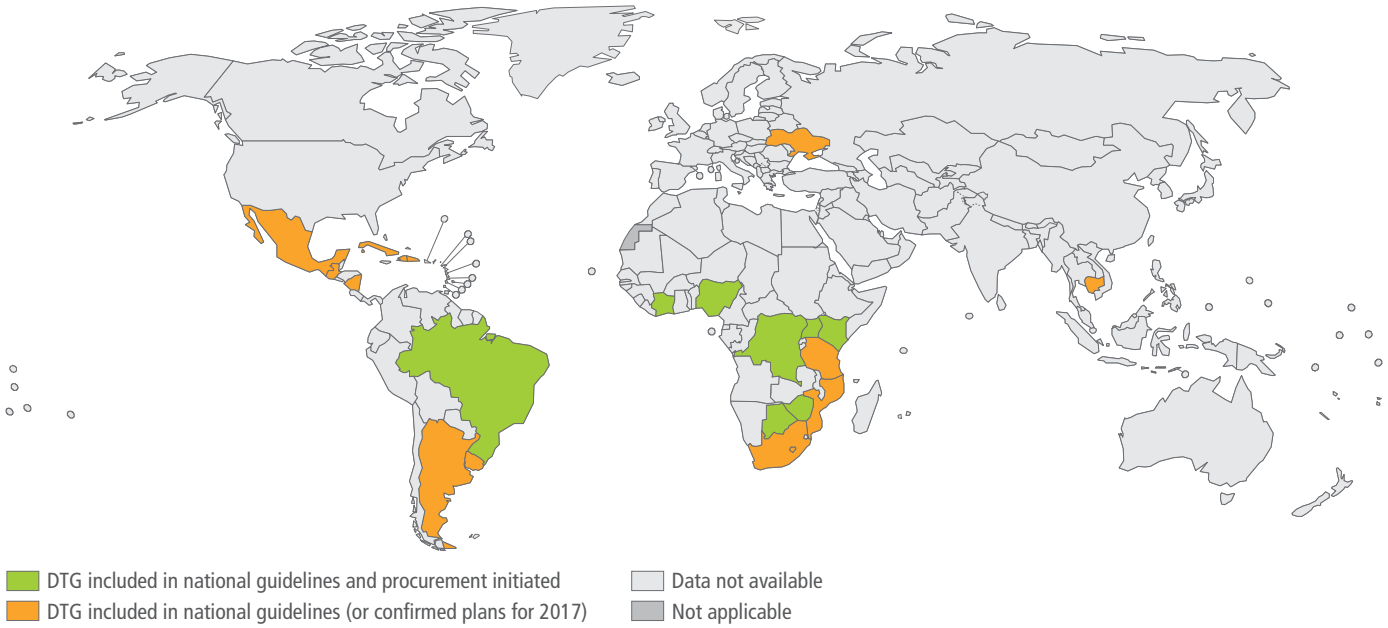
Table 1. Information and guidance on new ARV drugs according to the 2016 WHO consolidated ARV guidelines

New ARV option	Adults and adolescents	Pregnant women	Children	HIV-associated TB
Efavirenz, 400 mg (EFV400)	Recommended as alternative first-line option	Limited efficacy data (ongoing pharmacokinetic studies)	Dose reduction in children not needed (already pharmacokinetically adjusted)	No clinical data (ongoing pharmacokinetic studies)
Dolutegravir (DTG)	Recommended as alternative first- and third-line option	Used only if benefits outweigh the risk Limited efficacy and safety data (ongoing pharmacokinetic and clinical studies)	Recommended as third-line (approved for children >6 years old)	No clinical data (ongoing pharmacokinetic studies) Increased dose may be needed with use of rifampicin
Darunavir/ritonavir (DRV/r)	Recommended as alternative second- and third-line option (dose adjustment needed in third-line ART)	As recommended for adults but limited use in low- and middle-income countries	Recommended as third-line ART (approved for children >3 years old)	Not recommended with concomitant use of rifampicin
Raltegravir (RAL)	Recommended as alternative second- and third-line option	As recommended for adults but limited use in low- and middle-income countries	Recommended as second- and third-line option	Increased dose needed with concomitant use of rifampicin
Tenofovir alafenamide fumarate (TAF)*	Not recommended	No data available	No data available	No data available

Source: adapted from *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition* (*2*).

* Tenofovir alafenamide fumarate (TAF) is not currently recommended for treatment of HIV by WHO. This is because of the lack of safety data in pregnant women and the concern over the likely drug interaction between TAF and rifampicin, which could limit its use in HIV-associated TB. This recommendation may be reviewed, if new safety and pharmacokinetic data become available.

Figure 1. Adoption of DTG as a first-line option in low- and middle-income countries, June 2017



Source: Global AIDS Monitoring [online database] (*6*).

HIV transmission at the population level and alleviating the pressures on health systems.

Despite remaining evidence gaps, the new ARV drug options reviewed in this technical update are quickly becoming available as low-cost generic drugs and are being considered for nationwide scale-up in low-and middle-income countries. Further, introducing new ARV drugs into ART programmes in low- and middle-income countries could produce more than US$ 3 billion in savings by the end of 2025 (*3*).

However, transitioning to new ARV drugs requires careful clinical and programmatic considerations. Evidence for the safety and efficacy of these new options is still needed for some important subpopulations, and programmatic experience with these drugs is still very limited in low- and middle-income countries (*4*). Further, the longer-term complications of ART can be underestimated because most clinical trials enrol a select group of people based on highly specific inclusion criteria, and the duration of participant follow-up is relatively short, which requires that programmes closely monitor the introduction of these new ARV drugs. This publication summarizes the current evidence available, provides key considerations for transitioning and shares the initial programme experiences from early adopters of these new ARV drugs.

In addition, several reports from low- and middle-income countries have documented increased levels of pretreatment HIVDR to the non-nucleoside reverse-transcriptase inhibitors (NNRTIs) EFV and NVP among people starting ART (*5*).

People with pretreatment HIVDR to NNRTIs are less likely to achieve viral suppression and more likely to experience viral failure, to discontinue treatment and to acquire new resistance mutations. Given these increasing levels of HIVDR, countries need to consider the possible introduction of new classes of ARV drugs in national guidelines (Boxes 4 and 5).

As of June 2017, more than 20 low- and middle-income countries have included or are planning to include DTG as a first-line option in their national guidelines (Fig. 1). Botswana and Brazil have started providing DTG nationwide, while Kenya, Nigeria and Uganda are initiating pilot programmes for a phased introduction (see Section 4 on country experiences). Cambodia, China, Kenya, Nigeria, the United Republic of Tanzania and Zimbabwe, among others, are also considering introducing an EFV400-containing regimen as a first-line option in their national programmes. DRV and RAL are still expensive ARV drug options, not currently available as generic formulations and frequently reserved for use in third-line therapy in low- and middle-income countries as new products, including generic fixed-dose combinations of DRV/r, become available. Boosted DRV formulations are currently made available to children and adolescents in 35 countries through a donation programme, and introducing RAL is being considered alongside DRV/r as protease inhibitor (PI)-based first-line regimens fail more children. Section 3 on programmatic considerations: challenges and opportunities provides additional details.

2. CLINICAL CONSIDERATIONS

2.1 Efficacy and overall safety profile of new ARV drugs among people living with HIV

2.1.1 DTG and RAL

A systematic review and network meta-analysis showed that DTG and RAL are more effective and better tolerated and protective against treatment discontinuation from adverse drug reactions than EFV600 and boosted PIs (*7*). Further, DTG is associated with fewer drug interactions and higher genetic barriers to resistance and is being launched as a low-cost, once-daily generic formulation for low- and middle-income countries.

However, clinical trial development programmes frequently exclude pregnant women and people with HIV-associated TB or with advanced HIV disease, leaving evidence gaps in the ability to recommend these ARV drugs across all populations. In addition, detecting rare adverse drug reactions requires evaluating many people, and such data can often only be accumulated through strengthened ARV drug toxicity monitoring and pregnancy registry or congenital anomaly surveillance programmes (see subsection 3.8.1 on enhancing monitoring for toxicity and pregnancy safety surveillance).

Trial data are emerging on the use of DTG in second-line treatment, in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs), compared with lopinavir/ritonavir (LPV/r) + two NRTIs, after failure of initial NNRTI-based first-line treatment (*8*). Interim results from this trial show that combinations of two NRTIs with DTG could be used as an alternative to standard second-line treatment with two NRTIs + LPV/r. However in this study, many people were genotyped and their NRTI backbones optimized before switching. Further research is needed to determine whether DTG + two NRTIs or DTG + boosted PIs are viable options for people for whom first-line NNRTI-based treatment has failed with high-level NRTI resistance but no access to resistance testing. Results from clinical trials with less restrictive inclusion criteria may also be needed.

Table 2 shows the key information on several new ongoing trials of DTG among treatment-naive and treatment-experienced people, which will enable more detailed assessment of safety and efficacy at the conclusion of the trials.

Table 2. Key ongoing randomized clinical trials evaluating DTG among treatment-naive and treatment-experienced people living with HIV

Clinical trial	Treatment arms	Sample size	Inclusion	When the first results are expected
ADVANZ-4	ABC + 3TC + DTG ABC + 3TC + DRV/r	108	Treatment naive Spain	2017, fourth quarter
NAMSAL	TDF + 3TC + EFV400 TDF + 3TC + DTG	606	Treatment naive Cameroon	2018, fourth quarter
ADVANCE	TDF + FTC + EFV600 TDF + FTC + DTG TAF + FTC + DTG	1100	Treatment naive South Africa	2020, first quarter
DAWNING	Two NRTIs + LPV/r Two NRTIs + DTG	624	First-line failures International	2017, third quarter
D2EFT	Two NRTIs + DRV/r DRV/r + DTG	610	First-line failures International	2019, first quarter

Source: adapted from Vitoria et al. (*4*).

2.1.2 Use of DTG and central nervous system side-effects

In the four major DTG clinical trials among treatment-naive people living with HIV, DTG showed better tolerability and low risk of severe adverse drug reactions. Across these four first-line studies, DTG was associated with an increased risk of insomnia but not with any increase in risk of other central nervous system adverse drug reactions (*9*). In the clinical development programme of DTG, more severe central nervous system adverse drug reactions, including depression and suicide ideation, have been very rare. In randomized trials, DTG has not differed significantly in the risk of suicidality from other ARV drugs, including EFV. However, this analysis should be repeated when more clinical trial results become available.

Of the five observational studies assessing central nervous system side-effects for DTG, four found increased risks of central nervous system adverse drug reactions compared with the rates observed in randomized trials, but these studies are subject to bias and confounding factors that may have resulted in people at greater risk for central nervous system side-effects being offered DTG rather than EFV to avoid the known central nervous system side-effects associated with EFV (*10–13*). These potential confounding effects are difficult to measure post hoc.

2.1.3 Integrase inhibitors and the risk of immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome occurs most often among people with low CD4 cell counts who are initiating ART and may require hospitalization and/or corticosteroid treatment. Since integrase inhibitors suppress HIV RNA levels more quickly than other ARV drug classes (*14,15*), there is concern that using DTG and other integrase inhibitors would result in more frequent occurrence of immune reconstitution inflammatory syndrome compared with current treatment, because immune function more rapidly recovers during first-line ART.

Most randomized clinical trials comparing first-line treatment with integrase inhibitors and other treatment classes have excluded people with the highest risk of immune reconstitution inflammatory syndrome (people with low CD4 cell counts or active TB or other active opportunistic infections), so data are limited (*16,17*).

A recent randomized trial assessing the benefit of providing additional RAL to people with advanced HIV disease (*18*) found no increased risk of immune reconstitution inflammatory syndrome among people receiving additional RAL for 12 weeks compared with standard NNRTI-based first-line regimens alone (9.9% versus 9.5%). In this study, people who received enhanced prophylaxis for opportunistic infections had a significantly lower risk of immune reconstitution inflammatory syndrome (*18*).

Data from two recent observational cohort studies in France and the Netherlands reported an association between the use of integrase inhibitors and an increased risk of immune reconstitution inflammatory syndrome; however, as with all observational studies, the certainty of the evidence is low because of high risk of bias (*10,11*).

Therefore, until more evidence becomes available, careful clinical monitoring may be required for people starting first-line, integrase-based treatment with known risk factors for immune reconstitution inflammatory syndrome. People living with HIV who have low CD4 cell counts should be offered appropriate prophylaxis for opportunistic infections to further reduce the risk of immune reconstitution inflammatory syndrome (*19*).

2.1.4 DTG and the risk of cardiovascular adverse drug reactions

An analysis of adverse drug reactions in nine randomized trials showed that the frequency of cardiovascular events overall among people taking DTG were comparable with that of other ARV drugs (*20*).

2.1.5 EFV400

The ENCORE-1 study demonstrated non-inferior efficacy for EFV400 compared with EFV600 as first-line treatment in combination with TDF + FTC among adults (*21*). There were significantly fewer EFV-related adverse drug reactions for EFV400 (38%) compared with EFV600 (48%), and significantly fewer people taking EFV400 discontinued treatment because of adverse drug reactions (2% versus 6%). Viral efficacy was comparable between the two doses.

2.1.6 DRV/r

A systematic review and network meta-analysis with six clinical studies on using boosted PIs in second-line ART found no significant differences between any of the treatment arms for serious adverse drug reactions and risk of treatment discontinuation, supporting the use of DRV/r as an alternative second-line option (*22*).

2.2 Considerations for specific populations: pregnant women, children and adolescents and people living with HIV and receiving TB co-treatment using rifampicin

2.2.1 DTG

2.2.1.1 Use of DTG during pregnancy and breastfeeding

The risks of adverse outcomes among pregnant women or adverse reactions to the fetus exposed in utero,

including congenital anomalies, need to be considered when introducing new ARV drugs into national programmes that include women of childbearing age. WHO currently lists DTG as an alternative, rather than a preferred option for first-line HIV treatment, partly because of the limited safety and effectiveness data available for pregnant women. Likewise, the United States Department of Health and Human Services guidelines note that there are insufficient data to recommend routine use of DTG-containing regimens for ART-naive pregnant women (*23*). The United States Food and Drug Administration and European Medicines Agency both recommend that DTG be used in pregnancy only if the potential benefits justify the potential risk.

Limited data from two studies (IMPAACT P1026 study and PANNA study) suggest that DTG drug levels are similar in pregnant and non-pregnant adults, albeit lower during pregnancy than postpartum (*24*,*25*). Ex vivo animal studies provide evidence that DTG penetrates the placenta (*26*), and as has been reported for other integrase inhibitors, two case reports of infants exposed to DTG in utero have demonstrated cord blood concentrations higher than maternal plasma concentrations, suggesting significant fetal exposure (*27*,*28*). Further, the plasma half-life of DTG appears to be around twice as long among neonates as among adults (*24*,*28*,*29*). DTG has also been shown to transfer into breast-milk, resulting in significant plasma concentrations in infants (*30*). Calcium or iron supplements taken routinely in pregnancy may reduce DTG concentrations if concomitantly taken (*31*). No toxicity was reported in preclinical studies in animals (*32*).

Congenital anomalies were observed in 6 of 97 births in Phase 3 studies or post-marketing surveillance, but reporting bias may be an issue (*4*). Five of 15 infants in the IMPAACT P1026 study had abnormalities, but a possible association with DTG was ruled out in all but two abnormalities, both minor. Congenital anomalies among infants exposed to DTG are being monitored in the Antiretroviral Pregnancy Registry (*32*); to date, 77 pregnancies with first-trimester exposure to DTG have been reported, with two congenital anomalies (2.7%), consistent with rates in the overall Antiretroviral Pregnancy Registry (32). The normal threshold for ruling out a two-fold increase in the rate of congenital anomalies (n = 200) has not yet been reached. The European Pregnancy and Paediatric HIV Cohort Collaboration has also assessed pregnancy and neonatal outcomes, with one birth defect reported among 33 infants with first-trimester in utero exposure to DTG (*33*). Across these studies, no clear pattern of abnormalities has emerged.

Preliminary reports from HIV services in Botswana, which has been using DTG for pregnant women with HIV for over one year, suggest that birth outcomes (stillbirth, neonatal

Table 3. New and ongoing studies of DTG and EFV in pregnancy

Clinical trial	Treatment arms	Sample size	Inclusion	When the first results are expected
SSAT063	EFV400 (pharmacokinetic study)	25	Pregnant women United Kingdom and Uganda	2017, fourth quarter
DOLPHIN-1	TDF + FTC + EFV600 TDF + FTC + DTG	60	Pregnant women Uganda	2018, third quarter
DOLPHIN-2	TDF + 3TC + EFV600 TDF + 3TC + DTG	250	Pregnant women Uganda	2019, first quarter
VESTED	TDF + FTC + EFV600 TDF + FTC + DTG TAF + FTC + DTG	550	Pregnant women International	2020, first quarter
PANNA	Two NRTIs + LPV/r Two NRTIs + DTG	32	Pregnant women International	2020
ING200336	TDF + FTC + ATV/r TDF + FTC + DTG	25	Pregnant women International Substudy of ARIA	2020

Source: adapted from Vitoria et al. (*4*).

death, preterm birth and small for gestational age) do not differ between women receiving EFV-based therapy and those receiving DTG-based therapy. This observation is based on retrospectively collected data for over 5000 women, 16% of whom were receiving DTG regimens. There was also no excess of congenital anomalies among infants born to women taking DTG, but relatively few of these women started DTG in the first trimester (*34*).

More data are needed on maternal safety and tolerability and adverse outcomes to the fetus exposed in utero and on the safety of infants exposed during breastfeeding. Several clinical trials assessing the effectiveness, safety, tolerability and/or pharmacokinetics of DTG during pregnancy are either underway or about to start, with findings expected between 2018 and 2021 (Table 3).

2.2.1.2 DTG for children and adolescents

WHO currently recommends DTG as alternative first-line ART for adolescents with HIV, but DTG is not considered for use in children since, at the time the guidelines were revised, DTG was not approved for people younger than

Table 4. Key clinical trials investigating the use of DTG, RAL and DRV among infants, children and adolescents

Study name	Dosing and formulation	Participants	Results
DTG			
IMPAACT P1093 (*35,37,38*)	Dosing based on ~1 mg/kg/day for age 6+ years; 25-mg tablet for <30 kg, 35-mg tablet for 30–40 kg, 50-mg tablet for ≥40 kg. For 2–5 years old, granules in suspension, dosing based on ~0.8 mg/kg/day	Treatment-experienced, integrase inhibitor–naive children and adolescents 2–17 years old	Drug concentrations within study target range, good viral response over 48 weeks, no tolerability issues, no drug-related adverse drug reactions or discontinuations
IMPAACT P1093 (Cohorts IV and V)	Granules in suspension, dosing based on ~0.8 mg/kg/day	Infants 6 months to <2 years old (Cohort IV) and 4 weeks to <6 months old (Cohort V)	Expected mid- to late 2017
ODYSSEY (*39*)	Recommended weight-based dosing and formulations	Children ≥6 years old starting first-line ART (A) or switching to second-line ART (B)	Expected 2020 (250 participants recruited to date)
RAL			
IMPAACT P1066 (*40,41*)	Dosing based on 6 mg/kg twice daily; 25-mg chewable tablet or scored 100-mg tablet	Children and adolescents 4 weeks to 17 years old	Good viral response, few drug-related grade 3/4 or serious adverse drug reactions; in younger cohort (4 weeks to <2 years old), two drug-related grade 3+ adverse drug reactions, one discontinuation, one case of immune reconstitution inflammatory syndrome
IMPAACT P1110 (*42*)	Dosing of 1.5 mg/kg once daily for 0–7 days old, 3 mg/kg twice daily for 8–28 days old, 6 mg/kg twice daily for 4+ weeks old	HIV-exposed neonates <4 weeks old at high risk of HIV infection	Ongoing
DRV/r			
DELPHI trial (*43*)	Dosing based on 11–19 mg DRV/kg and 1.5–2.5 mg RTV/kg twice daily	Treatment-experienced children and adolescents 6–17 years old	Similar safety and efficacy profile as in adults
ARIEL trial (*44*)	DRV/RTV dosing of 25/3 mg for children weighing 10 to <15 kg and 375/50 mg for 15 to <20 kg, twice daily	Treatment-experienced children 3–5 years old	Good viral response and few adverse drug reactions (grades 1–2 only)
DIONE study (*45*)	Once daily DRV/RTV 800/100 mg	Treatment-naive adolescents 12–17 years old	Well tolerated, no new safety issues

12 years. As of June 2017, DTG has been approved for use among children six years and older (weighing at least 30 kg by the United States Food and Drug Administration and weighing more than 15 kg by the European Medicines Agency). The IMPAACT P1093 study demonstrated the safety, tolerability, pharmacokinetics and efficacy of DTG among children and adolescents (Table 4) (*35–38*). This study is currently enrolling younger children into two additional cohorts, assessing DTG use among infants and children from four weeks old to younger than two years, with preliminary results expected in mid- to late 2017 (Table 4). The ODYSSEY study will also evaluate DTG use among children and adolescents; this is a multicentre randomized clinical trial of DTG-based regimens versus standard of care for first- and second-line ART (Table 4) (*39*). It will include a pharmacokinetic substudy to validate WHO weight-band dosing established by the WHO Paediatric ARV Working Group and will also explore the pharmacokinetic of TB co-treatment.

In summary, initial reports of DTG use for children look reassuring in terms of efficacy, safety and tolerability. Further results are awaited and will be important for determining whether DTG can be approved and be used more widely among infants and children.

2.2.1.3 DTG and HIV-associated TB

In a pharmacokinetic study of health volunteers, rifampicin significantly lowered plasma concentrations of DTG (*46*). The current guidance, based on this data, is to use a double dose of DTG (50 mg twice daily) with rifampicin. However, very limited published clinical data show efficacy and safety outcomes with this combination of DTG and rifampicin among people living with HIV who have TB. The same study found no significant interaction between DTG and rifabutin. One pharmacokinetic study and one randomized clinical trial are underway, evaluating DTG with rifampicin among healthy volunteers and people living with HIV (Table 5). A pharmacokinetic study of DTG with rifapentine was stopped prematurely because of flu-like adverse events occurred in two out of four healthy HIV negative volunteers participants enrolled. The mechanisms behind these reactions is unknown. Further evidence on co-administration of rifamycins and DTG is urgently needed.

2.2.2 EFV400

2.2.2.1 EFV400 for pregnant women

There is extensive clinical experience with TDF + 3TC + EFV among pregnant and breastfeeding women, using the standard recommended dose of 600 mg once a day (*47,48*). EFV400 appears to be better tolerated than EFV600, but there are concerns that drug concentrations may be lower during the third trimester of pregnancy. One study (SSAT063) is underway to evaluate the pharmacokinetic profile of EFV400 during pregnancy, and the final results are expected at the end of 2017 (Table 3).

2.2.2.2 EFV400 for adolescents

The use of EFV400 for adolescents has not been formally investigated, but pharmacokinetic data and modelling suggest that exposure to EFV will be sufficient to achieve viral suppression while reducing central nervous system

Table 5. Key randomized clinical trials evaluating DTG and EFV in HIV- associated TB

Clinical trial	Treatment arms	Sample size	Inclusion	When the first results are expected
SSAT062	EFV400 + rifampicin	20	Healthy volunteers United Kingdom (phase 1) People living with HIV Uganda (phase 2)	2017, fourth quarter
RADIO	DTG (50 mg and 100 mg once daily) + rifampicin	20	Healthy volunteers United Kingdom	2017, fourth quarter
NCT02771249 (NIH)	DTG + rifapentine	20	Healthy volunteers United States	Suspended for toxicity reasons
INSPIRING	Two NRTIs + EFV600 Two NRTIs + DTG	125	HIV-associated TB International	2019

Source: adapted from Vitoria et al. (*4*).
ATV/r = atazanavir/ritonavir; DTG= dolutegravir; EFV= efavirenz; LPV/r = lopinavir/ritonavir; NIH= National Institutes of Health

side-effects, often reported by adolescents as a reason for lack of adherence (*49*). However, since EFV has a lower genetic barrier to drug resistance, the use at lower doses is not expected to be optimal for adolescents with known challenges with adherence.

2.2.2.3 EFV400 and HIV-associated TB

Rifampicin-based treatment leads to short-term reductions in EFV drug concentrations during the first 1–2 weeks of treatment but several studies have consistently observed increases in EFV drug concentrations after longer-term treatment in combination with rifampicin-based combinations (*50*). However, these overall trends could partly be explained by differences in ethnicity, and overall treatment efficacy does not differ for EFV used with or without rifampicin. One pharmacokinetic study (SSAT 062) is underway to evaluate the interaction between EFV400 and rifampicin, with the results expected at the end of 2017 (Table 5).

2.2.3 DRV/r

2.2.3.1 DRV in pregnancy

The WHO 2016 consolidated ART guidelines listed DRV/r as an alternative second-line option that may be considered for use for pregnant women. The perinatal guidelines of the United States Department of Health and Human Services (*23*) list DRV, boosted with low-dose RTV or cobicistat, as a preferred PI for use among treatment-naive pregnant women instead of LPV/r.

Pharmacokinetic studies of DRV in pregnancy have demonstrated that total DRV plasma concentrations are 20–50% lower in the third trimester of pregnancy compared with postpartum (*51*). This effect was more pronounced with once-daily DRV/r 800/100 mg than with twice-daily 600/100 mg (*52*,*53*). Because of the low trough levels reported, the perinatal guidelines of the United States Department of Health and Human Services generally recommend twice-daily dosing for all pregnant women (*23*). In contrast, guidelines in the United Kingdom suggest that once-daily dosing can be continued for women who conceive on DRV/r and have suppressed viral loads on once-daily 800/100 mg (*54*).

Although DRV crosses the placenta, the mean ratio of cord blood to maternal plasma concentration is about 0.11 to 0.18, suggesting low placental penetration (*51*). To date, no increases in the risk of congenital anomalies associated with DRV have been detected in the Antiretroviral Pregnancy Registry, with sufficient first-trimester exposure reported to rule out at least a two-fold increased risk of overall congenital anomalies (rate of 2.6%, 10 of 385, among pregnancies with first-trimester use of DRV) (*32*).

Despite reductions in DRV concentrations in pregnancy, DRV-based regimens have been effective in preventing mother-to-child transmission. In a recent review evaluating both once-daily 800/100 mg and twice-daily 600/100 mg, only one of 137 infants across five studies became infected, and poor adherence was a likely cause (*51*). Data are limited on other pregnancy outcomes for women receiving DRV-based regimens in pregnancy. An analysis from the Antiretroviral Pregnancy Registry reported that rates of live birth, stillbirth and premature birth for 550 women receiving DRV/r were similar to those receiving other regimens (*55*). The DRV/r group had higher rates of miscarriage and low birth weight, but the analyses were not adjusted for potential confounders.

Although no major adverse pregnancy outcomes have been reported to date, continued monitoring of maternal, pregnancy and neonatal outcomes following in utero exposure to DRV/r is desirable, and the need for using the twice-daily dose during pregnancy should be noted.

2.2.3.2 DRV for children and adolescents

DRV is approved for children 3 years and older and weighing at least 10 kg (United States Food and Drug Administration) or at least 15 kg (European Medicines Agency), based on the results of several clinical trials (Table 5). DRV must be boosted with low-dose ritonavir (RTV) while dosing information for cobicistat for children is awaited. RTV-boosted DRV is primarily recommended for use as a third-line regimen for children because evidence is lacking for second-line use, it is relatively expensive and a fixed-dose combination is lacking (*2*).

DRV/r has been used successfully outside clinical trial settings among small numbers of adolescents (*56*,*57*). The rates of adverse drug reactions were low among 431 children and adolescents receiving DRV-based regimens in Europe and Thailand, with only five discontinuing related to toxicity or side-effects (*33*). Experience with using DRV/r as a third-line treatment option for children in Africa is growing after the New Horizons Advancing Pediatric HIV Care programme began providing DRV/r; about 40 children have received the drug so far. WHO and the WHO Paediatric ARV Working Group have developed weight-band dosing using pharmacokinetic modelling (*58*), both for single-strength DRV and for the DRV/r fixed-dose combinations being developed.

2.2.3.3 DRV and HIV-associated TB

Drug interaction studies of DRV/r and rifampicin-based treatment for TB have not been completed. The 2016 WHO consolidated ARV guidelines (*2*) contraindicate the use of DRV with rifampicin-based treatment.

2.2.4 RAL

2.2.4.1 RAL in pregnancy

The 2016 WHO consolidated ARV guidelines list RAL as an alternative second-line option that may be considered for use for pregnant women. The guidelines also note the general lack of data on the use of integrase inhibitors such

as DTG and RAL in pregnancy. Since 2015, the perinatal guidelines of the United States Department of Health and Human Services (*23*) have listed RAL as the preferred integrase inhibitor for ARV-naive pregnant women based on available pharmacokinetic and safety data. RAL shows high placental penetration, and limited data in newborns suggest high neonatal concentrations and a prolonged half-life compared with adults (*59*).

Similar to non-pregnant adults, the pharmacokinetics of RAL for pregnant women varies substantially (*60*). Plasma concentrations are generally lower in pregnancy than postpartum, especially in the second and third trimesters (*59–61*), although not sufficiently to adjust the dose (*23*). In terms of maternal safety and tolerability, there have been several reports of elevated liver transaminases among pregnant women receiving RAL, although most resolved without discontinuation (*59*). Frequent monitoring of liver transaminases among pregnant women receiving RAL is therefore advised (*23*).

No teratogenic effects have been detected in humans. Sufficient cases of first-trimester exposure to RAL have now been reported in the Antiretroviral Pregnancy Registry (*32*) to rule out a two-fold or higher risk of overall congenital anomalies. A recent review of 278 mother-infant pairs (*59*) found no adverse drug reactions associated with in utero exposure to RAL, although only two studies included in the review specifically recorded maternal and infant adverse drug reactions. Among women presenting late in pregnancy, most delivered with viral loads <400 copies/ml, despite highly variable viral loads at baseline (*59*).

Current data on the use of RAL among pregnant women do not suggest any major adverse effects except being associated with elevated liver transaminases. Guidelines suggest that women conceiving on RAL should be able to continue this drug in pregnancy. Nevertheless, the use of RAL in pregnancy should continue to be monitored.

2.2.4.2 RAL for children and adolescents

RAL is the only integrase inhibitor approved for infants and children as young as 4 weeks old and weighing at least 3 kg. Approval of RAL was based on the results of trial data on the pharmacokinetics, safety, tolerability and efficacy of RAL for infants, children and adolescents between 4 weeks and 18 years old (*40,41,62*). RAL has also been shown to be effective and well tolerated outside clinical trial settings, in treatment-experienced children and adolescents with viral failure (*56,63–65*). RAL is not currently approved for neonates, although the dosage for this age group is being investigated (Table 4).

The 2016 WHO consolidated ARV guidelines (*2*) recommend RAL for second- and third-line use when LPV/r-based regimens fail but endorse using RAL for treatment-naive infants and young children younger than three years if LPV/r pellets are not available or not tolerated when the risk of resistance to NNRTIs is high. Although RAL is not currently recommended for use in neonates, it remains the only integrase inhibitor used successfully to reduce viral load among highly viraemic infants (*66*). It was also reported to be safe and well tolerated among 25 HIV-exposed infants at high risk of infection (*42*).

Because of the administration challenges presented by the granule formulation (*2,67*), the WHO Paediatric ARV Working Group considered using the 25-mg chewable tablets as dispersible (*68*). After reviewing in vitro data on solubility and bioequivalence between tablets and granules (*69*) and considering the lack of adequate alternatives for this age group, the group endorsed using 25-mg tablets as dispersible tablets.

Overall, RAL has shown promising results across a range of studies. Its ability to rapidly reduce viral load makes it an appropriate candidate for first-line ART for infants and young children (*40,66*). Given the limited options available, randomized controlled trials to support using RAL in first-line treatment may not be necessary (*68*). However, additional data to confirm safe and effective first-line use for young children would greatly inform future versions of WHO guidelines and support broader use of this drug for children.

2.2.4.3 RAL and HIV-associated TB

The recommended dose of RAL in combination with rifampicin-based treatment is 800 mg twice daily (*70*). Clinical trials have evaluated the efficacy and safety of RAL at this higher dose and the efficacy and safety of the standard 400-mg twice-daily dose (*71*).

3. PROGRAMMATIC CONSIDERATIONS

Programmes should plan carefully and discuss the pace at which increased quantities of DTG and other ARV products can be made available. To ensure that supply is available to meet anticipated demand, a phased approach is highly recommended. Countries have adopted approaches to start with transitioning to DTG among people initiating first-line ART and/or those already receiving ART but with intolerance or contraindication to NNRTIs (see Section 4 on country experiences). Further, not all countries can transition at the same time or speed. Some countries have limited capacity to develop multiple implementation polices. Several clinical, operational and programmatic factors need to be considered. For example, the availability of country level information on pretreatment HIVDR to EFV or NVP can accelerate the transition to DTG, 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 countries. Box 1, Table 6 and Table 7 list some key programmatic considerations that can influence the transition to using new ARV drugs in first-line ART.

Box 1: Considerations on transition choices with new ARVs

WHO's principles of treatment optimization suggest five key principles for selection of an ART regimen: efficacy, safety, simplification of dosing and administration, harmonization across populations and cost. As countries think about transitioning to the newer ARVs highlighted in this document, it is important to consider how these 5 principles should be applied.

The 2016 ARV consolidated guidelines (*2*) introduced alternative drug options which are in general more efficacious, better tolerated and lower cost than those currently used. The main challenges for introducing these new drugs relate to the lack of fixed dose combinations and the lack of safety data across all populations which makes it difficult to achieve full harmonization and simplification.

For example, there are countries considering introducing EFV400 to reduce CNS side-effects and improve patient adherence. These countries may now face the dilemma of how best to use this drug while considering adoption of DTG. Both drugs are cheaper than EFV 600. A fixed-dose combination (FDC) containing TDF, 3TC and EFV400 is already available and there is emerging evidence that the lower dose of EFV does not result in sub-therapeutic levels in pregnancy or during co-treatment with rifampicin containing TB treatment. DTG is potentially even cheaper than EFV 400 but there is a lack of safety data in children and pregnant women, will need a dose adjustment if used with rifampicin. A generic FDC containing TDF, 3TC and DTG is expected in 2018.

For countries that are reporting increased levels of NNRTI resistance in PLHIV starting ART, adoption of DTG as a preferred first line would be a more appropriate choice and is recommended by WHO in the recently released HIV DR guidelines (*92*). In addition, integrase inhibitors, particularly DTG, have been noted as the strategically preferred choice in light of the longer term vision for drug optimization and harmonization that both paediatric and adult experts share (*4,68*) .Therefore, countries with high levels of NNRTI resistance or those that are planning to introduce DTG considering other programmatic advantages (Table 6), may consider initially targeting patients with CNS effects on EFV, those who are newly initiating ART or populations with higher risk for poor adherence and HIVDR such as adolescents or re-initiators.

However, EFV 400 may be an option for countries without high levels of NNRTI resistance and where access to DTG is limited due to regulatory issues and cost (Table 7). On an individual basis, a FDC containing EFV 400 could also be useful switch option for adults who are virologically suppressed on EFV 600 but who have CNS side effects.

When moving to consider use of new drugs in second-line, DRV/r and RAL, these are well tolerated and efficacious but both have important challenges in promoting simplification, harmonization and cost. Regulatory and intellectual property barriers as well as lack of age appropriate FDCs are potential barriers to enable drug optimization in second line. Finally, toxicity monitoring and surveillance is critical in order to safely introduce these drugs and formulations across populations. Safe and strategic sequencing of these drugs will require further evidence and programmatic experience which will be addressed in the WHO drug optimization agenda. As new ARV drugs are introduced in HIV treatment policies, policy makers should carefully consider these principles and develop national guidelines that take into account how those new drugs will be utilized in treatment regimens.

In the short term, it may be impossible to achieve fully optimized treatment approaches. As countries transition to newer ARVs, regimens may become temporarily less simple to administer because of lack of a FDC, and first line treatments may be less harmonized across all populations because of the inability to treat all with the same drug. This is an inevitable consequence of evolving drug development, and is not a reason not to adopt newer treatment options. Rather countries should actively track use of new drugs in order to gather evidence that ultimately can build towards more harmonized options.

3.1 Prequalification and stringent regulatory approval of new antiretroviral drugs

To improve and increase the number of manufacturer producing quality–assured formulations, three organizations have joined efforts: WHO through its Prequalification Programme; the United States Food and Drug Administration and PEPFAR (United States President's Emergency Plan for AIDS Relief); and the European Medicines Agency. The WHO Prequalification Programme has agreed that generic formulations approved or tentatively approved by the United States Food and Drug Administration and European Medicines Agency will be recognized as quality assured by WHO and added to the list of prequalified medicines (*72*). Increasing the availability of generic versions of assessed quality will stimulate price competition and support adequate supply.

The WHO prequalified list (*72*) currently includes two formulations of single-dose DTG. One is from the originator company prequalified by WHO in 2014 and the other is from a generic manufacturer recently tentatively approved by the United States Food and Drug Administration (*73*). The WHO Prequalification Programme is assessing a generic version of TDF + 3TC + DTG, with the results expected by the end of 2017. More submissions of DTG both single and fixed-dose generic formulations are expected in the next two years (*74*). For EFV400, the United States Food and Drug Administration has tentatively approved a generic version of TDF + 3TC + EFV400, and it is included in the WHO prequalified list. Another generic version is planned to be filed for approval in early 2018, with results expected in early 2019 (Fig. 2)

WHO has prequalified formulations of DRV as 75 mg, 150 mg and 600 mg single (without boosted RTV) from the originator company. There are also two generic 400-mg and 600-mg formulations from a generic manufacturer. There is no prequalified or tentatively approved coformulation of DRV/r yet, but two applications are expected to be filed in mid-2018 (*74*).

WHO and the United States Food and Drug Administration under the PEPFAR initiative have not approved or tentatively approved or prequalified any RAL product. This means that no generic formulation of assessed quality is available and that the only available formulations approved by a stringent regulatory authority are from the originator manufacturer. Originator companies are encouraged to apply to the WHO Prequalification Programme since

Table 6. Summary of programmatic considerations on transitioning to DTG and EFV400 in low- and middle-income countries

Optimization criteria	DTG-containing regimens	EFV400-containing regimens	Comments
Efficacy	High efficacy, especially in the context of resistance to NNRTIs; efficacy data on HIV-associated TB still pending	Emerging data suggest adequate therapeutic levels in pregnancy and TB treatment with rifampicin but concerns on efficacy with rising resistance to NNRTIs in low- and middle-income countries	Favours DTG
Safety	No long-term safety data among people living with HIV. Limited safety data for young children, pregnancy, and HIV-associated TB	EFV has been used for decades in low- and middle-income countries and is safe for pregnant women and TB; lower doses are better tolerated	Favours EFV400
Simplification	Generic single formulation already available, but fixed-dose combinations expected only in 2018; dose adjustment needed for TB co-treatment (twice-daily dose)	Generic fixed-dose combinations already available; no dose adjustment needed and maintenance of once-daily dose	Favours EFV400
Harmonization	Strategically preferred choice in the long term	Limitations for use in all populations (not applicable to children)	Favours DTG
Cost	Cheaper than EFV600 but higher potential for further cost reduction (strong generic competition expected)	Cheaper than EFV600 but less potential for further cost reduction	Favours DTG

Fig. 2. Tentative timelines for approval by stringent regulatory authority of DTG and EFV400 formulations* (2016–2019)

ARV	2016	2017		2018		2019	
	Q3–Q4	Q1–Q2	Q3–Q4	Q1–Q2	Q3–Q4	Q1–Q2	Q3–Q4
DTG	●		● ● ●	● ●	● ● ● ●		
TDF/3TC/DTG			● ●		● ●	● ●	● ●
TDF/FTC/DTG				●		● ● ● ●	●
TDF/3TC/EFV400		●				●	

● Generic products approved by stringent regulatory authority ● Stringent regulatory authority expected to approve product by generic suppliers

Source: adapted from ARV market report: the state of the antiretroviral drug market in low- and middle-income countries, 2015–2020 (*74*).

* Assumes stringent regulatory authority approval received 12 months after filing date. Q1–Q2: first half; Q3–Q4: second half.

Table 7. Examples of scenarios and considerations for transition to new first-line ARV drugs

Potential country scenario	Factors that can influence the speed of uptake of new ARVs*	Country level actions needed to support introduction of new ARVs
Rapid transition to DTG-based first-line ART	Country with pretreatment HIVDR to NNRTIs ≥10%	Country has a policy for introducing DTG
	Availability of low-cost generic DTG in a fixed-dose combination	Supply chain system prepared for the transition
		DTG registered in the country
Phased transition to DTG-based first-line ART	Country with pretreatment HIVDR to NNRTIs <10%	Country has a policy on introducing DTG
	Low availability of low-cost generic DTG in a fixed-dose combination	Supply chain system not well prepared for the transition
	High burden of HIV-associated TB requiring rifampicin treatment	DTG registered in the country
	High burden of HIV in pregnant women	
Transition to DTG-based first-line ART could be **delayed**	Country with pretreatment HIVDR to NNRTIs <10%	Country has no policy on introducing DTG
	No availability of low-cost generic DTG in a fixed-dose combination	Supply chain system not prepared for the transition
		DTG not registered in the country
Transition to EFV400-based first-line ART can be **considered**	Country with pretreatment HIVDR to NNRTIs <10%	Country has no policy on introducing DTG
	Availability of low-cost generic EFV400 in a fixed-dose combination	Supply chain system prepared for the transition
	No availability of low-cost generic DTG in a fixed-dose combination	EFV400 in a fixed-dose combination registered in the country
		DTG not registered in the country
Transition to EFV400-based first-line ART should be **reconsidered**	Country with pretreatment HIVDR to NNRTIs ≥10%	

* Other programmatic factors such as patient and clinician readiness to accept the new drugs, viral load suppression rates among those on ART, ability to monitor drug toxicity and supervision and monitoring of programme quality should also be considered.

prequalifying the innovator products facilitates the review of the dossier for generic formulation and assessment process and contributes to reducing delays in introducing quality-assessed generic versions.

3.2 Registration status of DTG, RAL and DRV

The EFV600 formulation is widely available and registered in 89 countries, but EFV400 formulations have still not been registered in any country. As of July 2017, the WHO HIV drug regulatory status database showed that originator manufacturers have registered DTG, RAL and DRV in 63 (47%), 57 (42%) and 51 (38%), respectively, of the 135 low and middle-income countries (*75*). This percentage hides a great disparity between efforts made by originator companies to widely register their formulations and the generic manufacturers that have targeted registration for RAL and DRV, which the generic manufacturers have registered in 0 and 6 countries, respectively (Table 8). However, DTG as a single generic formulation (50 mg) has already been registered in 24 countries although it has only been filed for approval by a stringent regulatory authority very recently. By the end of 2017, DTG 50 mg is expected to be registered in 56 countries, and DTG-containing fixed-dose combinations in 38 countries. The time needed to obtain local registration (or a waiver) is likely to be one of most important factors determining the pace at which programmes can transition to new formulations.

3.2.1 Availability and supply of generic EFV400-containing fixed-dose combinations

Based on the list of ARV drug formulation priorities PEPFAR recently approved (*77*), TDF + FTC + EFV600 and TDF + 3TC + EFV400 have been added as primary priority ARV drugs (ARV drugs with improved packaging for enhanced service delivery, such as support of multi-month dispensing (including giving priority to 90-count bottles over 100-count bottles for once-daily medications) (*77*). This indicates that procurement of these formulations is expected to increase.

Some countries are already updating their national guidelines to add EFV400-containing regimens (*74*). Since these formulations replace existing EFV600-containing formulations in production chains, production capacity problems are not expected. There may be challenges with lead time during the transition period but otherwise no other challenges in pricing or sufficient capacity.

3.3 Availability of DTG, RAL and DRV/r

DTG could be widely available if the generic manufacturers register or get a waiver to sell their drugs in countries. The generic version of DTG is accessible to 131 countries through the Medicines Patent Pool direct licence agreement or an indirect licence coverage mechanism (*75*) (Fig. 3). The generic version of RAL has not been consistently available, although one generic manufacturer has obtained approval, so it continues to be supplied by the originator (*78*). In the past six years, the originators have supplied RAL to 32 countries and DRV to 36 countries (*75*). The price of generic DRV formulations is almost twice as high as the access price from originators, resulting in low demand of generic single DRV tablets. DRV is also best used with low-dose RTV in a heat-stable co-formulation, but no generic manufacturer has filed the product with the WHO Prequalification Programme so far.

3.4 Price of new ARV drugs in low- and middle-income countries

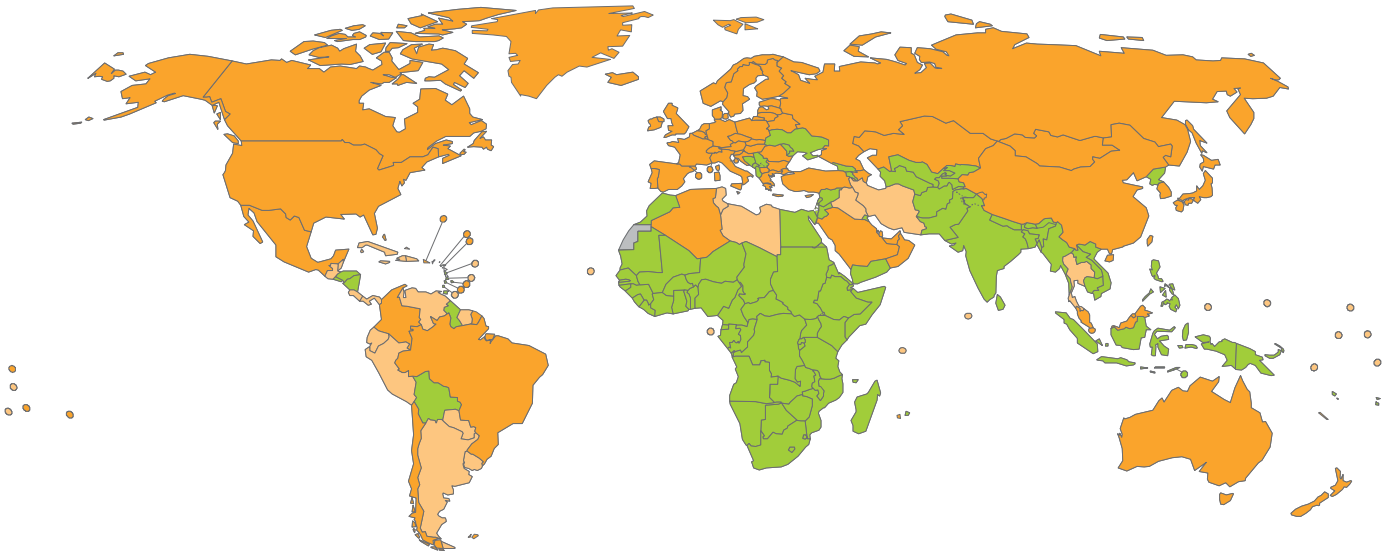
Pricing, compared with current types of treatment, should not be a barrier for uptake of DTG or EFV400 for most low- and middle-income countries. The expected average price for TDF + 3TC + EFV400 at launch was US$ 97–99 per person per year (*78*), but recent communication suggests that it has been reduced to US$ 78 per person per year as of June 2017 (*79*). In December 2015, a pricing agreement was developed between Unitaid, UNAIDS, the Clinton Health Access Initiative and Aurobindo Pharma to launch a DTG 50-mg single formulation at a price of US$ 44 per person per year, so that the effective cost of

Table 8. Registration status of DTG, DRV and RAL in low- and middle-income countries

Antiretroviral drug	Number of countries with market authorization by originator companies	Number of countries with market authorization by generic manufacturers
DTG	63	24
DRV	51	6
RAL	57	0

Source: Drug Regulatory Status Database [online database] (*76*).

Figure 3. Global status of DTG licensing



Voluntary licence (country included in the agreement list)
Outside licence (country can procure generic drug because it has no patent preventig from doing so, but it's not on the agreement list)
No licence (country cannot procure generic drug)
Not applicable

Source: Global AIDS Monitoring [online database] (*6*).

treatment with TDF + 3TC + DTG (~US$ 93–98 per person per year) in the low- and middle-income countries covered by this licence agreement is expected to be 10–15% lower than the current price of the TDF + 3TC + EFV600 formulation (*80*). With generic competition and increased purchased volumes, further price reductions are expected. Nevertheless, high prices and multiple pill regimens taken twice daily are important limiting issues for the uptake of RAL (US$ 580 per person per year) and DRV/r (US$ 900 per person per year) in second-line ART (*75*).

Voluntary licensing agreements for DTG are not in place in some upper-middle-income countries, and drugs are protected by patents in high-income countries. In these situations, DTG formulations could be too expensive to be cost-effective for first-line use compared with generic EFV formulations (*81*). In these settings, directly negotiating the DTG price, encouraging competition with other manufacturers of integrase inhibitors or compulsory licensing are potential strategies (Box 2).

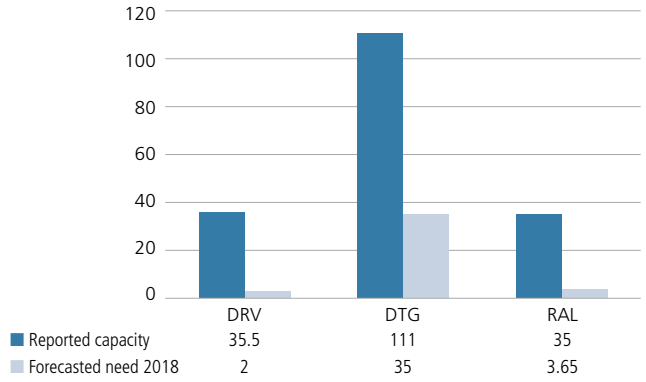
3.5 Capacity to produce active pharmaceutical ingredients

There is little or no risk of shortages of active pharmaceutical ingredients for DTG, DRV, EFV and RAL in the next 18 months. The available capacity versus predicted demand in 2018 is three times for DTG, 17 times for DRV and 10 times for RAL (*75*) (Fig. 4). This analysis may mask some risk during the next 6–8 months, as manufacturers and donors assess how quickly country programmes will transition and roll out their guideline changes. Managing the expectations of the potential speed of these transitions will be important, both for country programmes and the manufacturers.

3.6 Forecasting and procurement

The market size of DTG as a single formulation and from 2018 as a fixed-dose combination with TDF and 3TC or FTC is projected to grow exponentially from about 230 000 person-years (number of people treated per year

Figure 4. Capacity to produce active pharmaceutical ingredients for new ARV drugs in 2017 compared with forecasted demand in 2018



Source: adapted from a 2017 WHO technical report on sources and prices of active pharmaceutical ingredients (unpublished).

using this formulation) in 2017 to 8.3 million by 2021, whereas DRV is not projected to surpass 69 000 and RAL 16 000 by 2021 (Table 9) (*75*). Uptake may be even greater if other high burden countries as South Africa decide to make a rapid transition. The lessons learned from the TDF + FTC + EFV and TDF + 3TC + EFV transition show that the lead time could be up to 9–12 months from placing an order to getting the product into the country.

3.7 Formulations for children

DTG and RAL for children are registered in 17 low- and middle-income countries, but both are manufactured by originator companies. Generic versions being developed include 10-mg and 50-mg scored DTG tablets, DTG + ABC + 3TC 5 + 60 + 30 mg tablet and 5-mg and 50-mg scored dispersible RAL tablets (*83*). The availability of DRV is currently limited to countries that are part of the New Horizons Advancing Pediatric HIV Care Collaborative (*84*). A fixed-dose combination of DRV/r as a 120/20 mg dispersible tablet is being developed. Existing formulations of RAL and DRV are listed in the Interagency Task Team optimal formulary or limited-use list (*67*), and the WHO ARV Procurement Working Group coordinates procurement through the facilitated pooled mechanism. The price of these drugs in formulations for children remains expensive, with DRV costing US$ 250 per person per year for the 75-mg tablet. Forecasting formulations for children remains challenging; however, efforts are in place to improve tools to support better quantification, forecasting and estimation of future demand.

Overall, developing and introducing age-appropriate formulations for children continue to be slow, and urgent action is needed to ensure access to better drugs for children.

3.8 Programme monitoring

3.8.1 Enhancing monitoring for toxicity and pregnancy safety surveillance

To address the gaps in safety data and monitor toxicity issues as ARV drugs are used, WHO recommends that active toxicity surveillance and additional research be conducted (*2*).

Monitoring ARV drug toxicity is an integral part of the monitoring and evaluation framework within ART programmes and programmes for preventing mother-to-child transmission.

Box 2. WHO guidance on toxicity of ARV drugs

Based on the priority toxicity issues to be addressed, WHO recommends that, in addition to routine toxicity monitoring, countries consider implementing a combination of active toxicity surveillance approaches to address the particular needs of HIV treatment and prevention programmes while transitioning to new ARV drugs:

- actively monitoring ARV drug toxicity;
- ARV drug pregnancy registry and surveillance of congenital anomalies; and
- actively monitoring ARV toxicity in mother-infant pairs during breastfeeding.

Source: Consolidated guidelines on person-centred HIV patient monitoring and case surveillance (*85*).

Table 9. Volume of demand for EFV, DTG, DRV and RAL (in person-years), based on estimated average projections (2016–2021)

ARV drug	2016	2017	2018	2019	2020	2021
EFV	13 500 000	15 700 00	17 100 000	16 700 000	16 200 000	14 900 000
DTG	0	230 000	965 000	3 500 000	6 000 000	8 300 000
DRV	0	2 700	7 600	5 200	39 000	69 000
RAL	7 800	9 800	12 400	14 500	16 000	16 000

Source: Global Price Reporting Mechanism for HIV, tuberculosis and malaria [online database] (*75*).

Table 10 presents priority populations and areas that need strengthened toxicity surveillance and recommended approaches.

3.8.2 Main approaches to monitoring toxicity

3.8.2.1 Routine ARV drug toxicity monitoring as part of HIV patient monitoring

The 2017 WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance (*85*) provide updated guidance for monitoring and managing toxicity and instructions for measuring the prevalence of toxicity (Table 11) from routine ART management and clinical practice. Routine toxicity monitoring will provide data on the incidence and clinical significance of serious toxicity and how it affects treatment outcomes and attrition (Box 3).

Table 10. Populations, targeted types of toxicity for DTG, RAL and DRV/r and toxicity surveillance approaches

Population	ARV drugs and targeted types of toxicity	Surveillance approaches
Adults, adolescents and children	• DTG: central nervous system toxicity and immune reconstitution inflammatory syndrome, unexpected or long-term toxicity • RAL: central nervous system toxicity and immune reconstitution inflammatory syndrome myopathy and hepatotoxicity • DRV: hepatotoxicity	• Active ARV toxicity monitoring
Pregnant and breastfeeding women and infants	• Maternal health outcomes (DTG): central nervous system toxicity and immune reconstitution inflammatory syndrome; RAL: hepatotoxicity • Birth outcomes (all ARV drugs): miscarriages, preterm delivery, stillbirth, low birth weight, small for gestational age, major congenital anomalies • Infant and child outcomes (all ARV drugs): growth and development, unexpected toxicity	• ARV pregnancy registry and surveillance of congenital anomalies • Mother-infant pairs monitoring during breastfeeding

Table 11. Programme indicators for routine ARV toxicity monitoring

Indicators	Numerator and denominator	Disaggregation	Measurement method	Programme relevance and interpretation
National indicator				
Toxicity prevalence: % of people receiving ART with treatment-limiting toxicity	Numerator: number of people living with HIV and receiving ART within the past 12 months who have stopped treatment or substituted regimen because of toxicity Denominator: number of people living with HIV who were receiving ART in the past 12 months	Regimen, sex, age (<3, 3–9, 10–14 and 15+ years), pregnant and breastfeeding women, key population,* TB and HIV or hepatitis and HIV coinfections and toxicity categories as adapted from a patient card or ART register	Numerator and denominator: programme records, such as ART registers Numerator includes deaths	Measures how toxicity affects treatment outcomes. Helps to guide national policy on ART regimens, diagnosis, strategies for preventing toxicity, health-care worker training and retention in care

Source: Consolidated strategic information guidelines for HIV in the health sector (86).

* In many settings key population-specific data cannot be collected from routine programme monitoring; surveys are required (see section 3.8.2.2 on active ARV toxicity monitoring).

Box 3. What is new in routine monitoring of ARV drug toxicity as part of the 2017 WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance

- An ART patient card and ART register with an updated section on ARV toxicity monitoring and instructions for measuring the prevalence of toxicity.
- Countries are encouraged to update, simplify and standardize patient monitoring tools (cards, registers and reports) across facilities as transitioning to "treat all" and/or introducing new ARV drugs.
- WHO provides guidance and technical assistance for these transitions.

Source: Consolidated guidelines on person-centred HIV patient monitoring and case surveillance (85).

3.8.2.2 Active ARV toxicity monitoring

WHO recommends using this approach to monitor emerging toxicity issues and/or new ARV drugs that require strengthened monitoring of potential central nervous system and serious immune reconstitution inflammatory syndrome reactions associated with DTG. Active toxicity surveillance could be included in ART sites that already support a strong monitoring and evaluation or research programme, since these sites generally have a reliable system for capturing clinical and toxicity data. WHO has developed technical guidance on active ARV drug toxicity monitoring that includes a generic adverse drug reaction reporting form for DTG for use by health workers at ART sites (Annex 1) and a dictionary for a database to match the adverse drug reaction reporting form for DTG (Box 4).

3.8.2.3 ARV drug pregnancy registry and surveillance of congenital anomalies

A pregnancy registry actively records information on serious adverse drug reactions among women during pregnancy and monitors pregnancy and birth outcomes using a systematic and standardized data collection approach. At each of the visits at selected antenatal clinics, information is obtained from women on their medical and obstetric histories and the use of drugs – including ARV drugs – during the course of pregnancy (*85*). All babies are given a standard surface examination to establish whether any major external congenital anomalies are present. These data are recorded in a standard data collection sheet and entered into a central database. WHO and the Special Programme for Research and Training in Tropical Diseases (TDR) have developed a protocol (87,88), generic model forms and training materials for country adaptation. WHO and TDR established a global central registry for epidemiological surveillance of drug safety in pregnancy in mid-2016 with a data entry programme to help countries in pooling data from in-country pregnancy registries and birth outcome surveillance projects (Box 4).

Box 4. What is new in the ARV drug pregnancy registry and surveillance of congenital anomalies

- WHO and TDR recently established a global central database for the surveillance of drug safety during pregnancy at antenatal clinics (89). This database provides a list of variables for the surveillance of drug safety and a data dictionary to match the core variables to help countries in establishing surveillance projects with standardized variables and tools. Countries are encouraged to contribute and pool the data collected into this database established for the epidemiological surveillance of drug safety in pregnancy.
- There is a data entry programme that any country may use as data entry interface or they may export their data from a local electronic database. A user guide to facilitate its use by countries or projects is also available (89).
- A surface examination video is available for training caregivers to conduct a standardized baby examination at birth, including congenital anomalies and weight and length measurements (90).
- WHO and TDR provide guidance and technical assistance for planning and implementing these surveillance programmes.

3.8.2.4 Monitoring mother-infant pairs during breastfeeding

The data collected under this approach are analysed to determine whether any additional risk of adverse outcomes among infants can be attributed to the exposure to ARV drugs during breastfeeding (*91*). Standardized and simple assessments for growth and nervous system development need to be implemented at specific times at all facilities during the growth of the breastfeeding infant. All findings, including reports on HIV infection, growth parameters, fractures, seizures and hospitalization, are recorded. Separate guidance will be prepared to help national programmes collect, record and submit their data to the global database. WHO provides technical assistance for developing and implementing ARV toxicity surveillance and including it into the monitoring and evaluation effort of HIV treatment and prevention programmes. WHO works with health ministries and technical partners to adapt the minimum dataset, tools and protocols and piloting and

implementing surveillance projects as are being provided to Malawi or South Africa.

3.8.2.5 Enhancing monitoring for HIV drug resistance

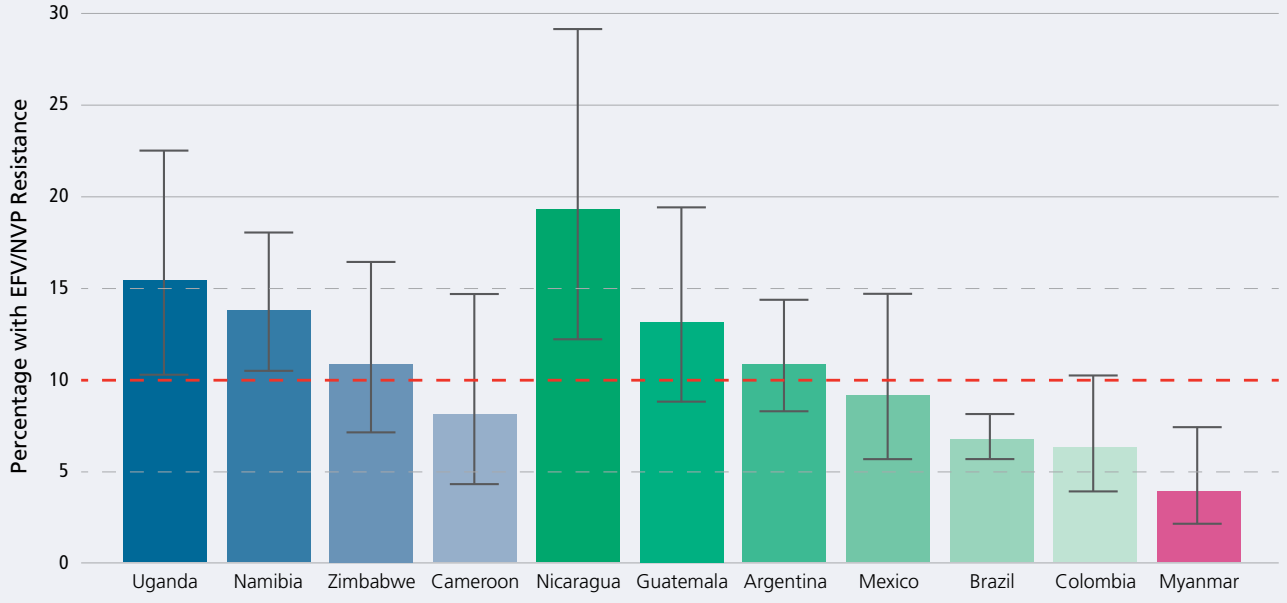
Given these increasing levels of HIVDR countries may want to consider the introduction of new classes of ARVs based on their country context and levels of PDR (Box 5).

Box 5. HIVDR considerations

A recent systematic review shows that levels of HIVDR to NNRTIs among people initiating first-line ART have increased significantly in all WHO regions (*5*). In recent nationally representative WHO surveys, pretreatment HIVDR to EFV and NVP among people initiating first-line ART ranges from 4% to 19% and exceeded 10% in six of the 11 countries in Africa, Asia and Central and South America that reported national data. For the people starting first-line ART with reported previous NNRTI drug exposure, pretreatment HIVDR to EFV and NVP ranges from 18% to 27% and is significantly higher than in the treatment-naive population (Fig. 5).

People with pretreatment HIVDR to NNRTIs initiating NNRTI-based ART are less likely to achieve viral suppression; more likely to experience viral failure; more likely to experience viral failure or death (composite outcome); more likely to discontinue treatment; and more likely to acquire new resistance mutations (*92*). To address this concern, WHO recently published guidelines on the public health response to pretreatment HIV drug resistance (*92*). These guidelines build on existing WHO recommendations on what to start among people initiating ART and recommend that, in countries in which the prevalence of pretreatment HIVDR to EFV or NVP among previously ARV drug–unexposed and –exposed people initiating first-line ART is ≥10% should urgently consider an alternative first-line ART regimen that does not contain NNRTIs. The guidelines also note that, for people at high risk of pretreatment HIVDR to NNRTIs as a result of previous exposure to NNRTIs or other risks, a non-NNRTI-containing regimen may be preferable, regardless of the country's prevalence of pretreatment HIVDR to NNRTIs and without the need to document the presence of resistance to NNRTIs by using an HIVDR test. To ensure high-quality HIV drug resistance information for national decision-making, WHO has developed standardized HIVDR surveillance methods available at http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-2015-update/en.

Figure 5. Pretreatment HIVDR to EFV or NVP among people initiating first-line ART (weighted surveys), 2014–2016



4. COUNTRY EXPERIENCES

4.1 Catalytic procurement of DTG and introduction in Kenya, Nigeria and Uganda

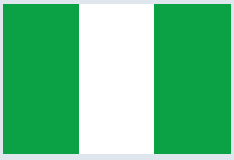
Many low- and middle-income countries are considering introducing DTG as part of a preferred or alternative first-line regimen. However, experience with DTG in low- and middle-income countries has been limited so far, with clinical trials and use largely restricted to high-income settings among highly selected people. Although the safety and efficacy of DTG have been well described in these contexts, health ministries are seeking to gain experience with DTG as part of the first-line regimens in populations more representative of the HIV epidemic in resource-limited settings.

A limited, catalytic procurement initiative through the Unitaid-funded Clinton Health Access Initiative Optimal ARV drug project is enabling several early-adopter countries to bring generic DTG into the country to rapidly initiate people on DTG and conduct enhanced monitoring to gain experience with single-tablet DTG and derive lessons for national scale-up (*93*). The single-tablet DTG will replace either NVP or EFV, and people can be easily transitioned to a triple fixed-dose combination of TDF + 3TC + DTG once available. Three countries have started pilot projects on procurement and rollout of DTG: Kenya, Nigeria and Uganda. The goal of these projects is to create learning and a platform for widespread adoption of DTG regimens when available in the near future.

Figure 6. Summary of DTG phase-in guidelines in early-adopter countries

Kenya

- Adopted DTG as alternative first-line ART; national roll-out begun in June 2017
- Eligibility: EFV intolerance; suboptimal regimens (such as TDF/3TC + NVP or PI); people who inject drugs
- National AIDS a STI Control programme analysing routinely collected data to monitor outcomes, uptake rates and facility-level characteristics
- ICAP at Columbia University supporting in Kenya through the Optimize Project of the United States Agency for International Development
- Procurement through the Unitaid-CHAI Optimal ARV drug project for 20 000 people



Nigeria

- Adopted DTG as alternative first-line ART
- Eligibility: NNRTI intolerance; discontinuing treatment: post-exposure prophylaxis, option B, lost to follow-up
- Operation research in three high-volume hospitals
- Study size: about 174
- Procurement through the Unitaid-CHAI Optimal ARV drug project for 6 500 people

Uganda

- Adopted DTG as alternative first-line ART
- Eligibility: all new initiators; NNRTI intolerance
- Operational research in six high-volume facilities in two districts
- Study size: about 385: 176 treatment naive, 209 treatment experienced
- Procurement through the Unitaid-CHAI Optimal ARV drug project for 6 500 people

Findings from operational research in Nigeria and Uganda and routine monitoring in Kenya will provide information on:

- Toxicity monitoring and side-effects
- User acceptability and preferences
- Knowledge gaps among prescribers and dispensers
- Training needs
- Viral suppression

These early-adoption efforts are seeking to understand user and provider experiences with DTG – including acceptability and preference, monitoring efficacy and safety and generating learning and evidence to inform effective roll-out strategies. Fig. 6 highlights the major aspects of each project.

4.2 Nationwide transitioning to DTG: the initial experiences of Botswana and Brazil

In 2016, Botswana and Brazil were the first two national treatment programmes to announce the large-scale introduction of DTG for first-line treatment.

4.2.1 Botswana

As part of the national treat all strategy, Botswana's Ministry of Health established a tender agreement with the manufacturer in June 2016, to provide TDF/FTC + DTG to everyone newly diagnosed with HIV (including pregnant women and those with HIV –associated TB) and those already receiving ART with intolerance to EFV. Their target is to treat 100 000 people until the end of 2018 (*94*). The national ART guidelines were also updated with this new treatment policy (*95*). Adopting DTG-containing regimens as preferred first-line choice could prevent 120 000 people from acquiring HIV and save 55 000 lives over the next 15 years (*96*). Currently, Botswana's Ministry of Health estimates that about 30 000 people living with HIV are using a DTG-containing regimen.

Since the data on the safety of DTG during pregnancy are still limited, Botswana has established a protocol to monitor the occurrence of congenital malformations and other adverse birth outcomes among women living with HIV using DTG-containing regimens during pregnancy. This approach has been previously adopted in the introduction of other drugs, such as co-trimoxazole and EFV among pregnant women living with HIV (*97–99*).

4.2.2 Brazil

In September 2016, Brazil's Ministry of Health negotiated a reduction of 70% of the original price of DTG, with savings of US$ 1.1 million (*100*). The Ministry of Health has also recently updated national treatment guidelines to recommend DTG as the preferred first-line therapy for treatment-naive people (except for pregnant women and those with TB) as well as third-line therapy for treatment-experienced people (*101*). DTG was acquired in sufficient quantities to serve about 100 000 people living with HIV in one year, and the first DTG distribution started

Table 12. Summary of the key characteristics of DTG transition protocols in five countries

Country	DTG eligibility criteria					Pregnancy during DTG use	TB during DTG use	Use viral load for DTG substitution	Follow up of DTG exposed pregnant women and foetuses until delivery and birth	Standard definition of immune reconstitution inflammatory syndrome
	ART naive	NNRTI intolerance	NNRTI exposure/ contra indication	Pregnant women	HIV-associated TB					
Botswana	✓	✓	✗	✓	✓	Stay on DTG	Stay on DTG (double dose)	✗	✓	✗
Brazil	✓	✓	✗	✗	✗	Switch to RAL	Switch to RAL	✗	✓*	✓
Kenya	✗	✓	✗	✗	✗	Switch to EFV	Stay on DTG, (double dose)	✓	✓	✗
Nigeria	✗	✓	✓	✗	✗	Switch to EFV or ATV/r	Switch to EFV or LPV/r	✓	✓	✓
Uganda	✓	✓	✗	✗	✓	Switch to EFV or ATV/r	Stay on DTG (double dose)	✓	✓	✓

* Also follow up DTG-exposed babies after birth.
ATV/r = atazanavir/ritonavir; DTG= dolutegravir; EFV= efavirenz; LPV/r= lopinavir/ritonavir; RAL= raltegravir

in January 2017 (*102*). In addition, the Ministry of Health has also optimized the national ARV drug list, removing obsolete drugs and adjusting the stocks of major first- and second-line options, and combined with the significant price reduction, enabling DTG to be included in the national drug portfolio with the same ARV budget as the previous year. As of June 2017, about 38 000 people living with HIV are using DTG-containing regimens, with 24 000 using DTG as initial ART and 14 000 individuals in third-line regimens.

Considering the number of people who will initiate the use of this drug for the first time, a targeted toxicity monitoring protocol was implemented in partnership with the national drug regulatory agency (Brazilian Health Regulatory Agency – Anvisa). Active toxicity monitoring has been introduced, using an electronic standardized questionnaire to be completed every month at the time of drug dispensing, to report possible adverse drug reactions related to DTG use. The questionnaire includes the type, duration and severity of a potential adverse reaction (WHO standard list with 5000 options), basic clinical and laboratory data before drug use, concomitant use of drugs other than ARV drugs (including herbal products and supplements) and occurrence of opportunistic diseases and other comorbidities (including immune reconstitution inflammatory syndrome) during DTG use. The doctor or pharmacist registers all these data online through the national Medication Logistics Control System (SICLOM) at the time of drug dispensing, but the questionnaire can also be printed for completion at home before collecting medicine.

The project started in April 2017 and was initially implemented in 10 major HIV treatment centres. A detailed preliminary analysis of the results of these questionnaires will be completed when the system reaches 10 000 questionnaires registered. The DTG toxicity monitoring system is planned to be expanded nationwide during the second half of 2017. With the availability of the questionnaire to all HIV services, the Brazil's AIDS programme expects that about 25 000 to 30 000 new people will be included in the toxicity monitoring system in the next three months.

In summary, several low- and middle-income countries have already started the transition to DTG in first-line ART using various approaches, and their implementation processes need to be closely monitored (Box 6). Enhanced monitoring of overall toxicity and of safety in specific populations such as pregnant women and people with coinfections is important. Table 12 summarizes the main characteristics of the current DTG protocols in five countries.

Box 6. Transition to DTG in the context of resistance to NNRTIs in Latin American and Caribbean countries

In a recent technical consultation convened by the Pan American Health Organization (PAHO) held in Brasilia, Brazil (*103*), representatives from national HIV programmes from 16 Latin American and Caribbean countries and civil society organizations gathered to discuss and identify opportunities, challenges and technical cooperation needs to advance the optimization of ART and access to DTG in the context of HIVDR and DTG regulatory status. There was a consensus that implementing nationally representative surveys of pretreatment HIVDR should be a priority to support decision-making on policy update and ART optimization in Latin America and the Caribbean. At the same time, there was very limited support for using genotyping for pretreatment regimen selection, since this was considered too expensive and not feasible for most countries. The Medicines Patent Pool licence on DTG and the MEDSPAL database (www.medspal.org) provide detailed information on the national ARV drug regulatory status and therefore on the opportunity to access low-price generic DTG. The PAHO Strategic Fund will continue to offer technical cooperation supporting the strengthening of supply chain management and pooled procurement mechanisms in the context of transition. Transition to DTG should be promoted even when resistance levels are low or unknown, but national levels of pretreatment HIVDR to NNRTIs ≥10% should accelerate this transition. The transition to DTG can be feasible in the short term in the low- and middle-income countries included in the Medicines Patent Pool licence (the Plurinational State of Bolivia, El Salvador, Guatemala, Guyana, Haiti, Honduras and Nicaragua) that can access generic formulations at low prices. For other countries with data exclusivity or patent protection (Chile, Colombia, Mexico, Peru and Trinidad and Tobago), negotiating DTG prices and promoting competition with other manufacturers of integrase inhibitors could be a viable option. All remaining countries, mostly upper-middle-income countries, could benefit from the functional coverage of the Medicines Patent Pool licence (patent not recognized), and some internal discussion on the procurement strategy to be adopted and transition timeline is warranted. In this context, several countries renewed their commitment to implementing HIVDR surveillance and to start planning the transition to DTG, and Brazil, which already started it in 2016 (see Section 4 on country experiences) will further expand DTG access to everyone living with HIV in 2017–2018.

5. CONCLUSIONS

There are many factors to consider when deciding to introduce new ARV drugs: efficacy, safety, drug interactions (e.g. TB drugs), price, affordability, population prevalence of HIVDR, regulatory approval and availability of quality-assured generic and fixed-dose formulations.

The transition from EFV600 to DTG as a first-line option in low- and middle-income countries could be cost-neutral, or even reduce costs, if DTG can be provided in the context of generic competition and reduced pricing. The current price for generic formulations of DTG has fallen to US$ 44 per person per year and could become even lower as more generic versions become available.

Countries with a prevalence of pretreatment HIVDR to EFV or NVP exceeding 10% should urgently consider introducing DTG in first-line treatment. This is because people with HIVDR to NNRTIs are less likely to achieve viral suppression and more likely to discontinue treatment, with an increased risk of viral transmission. In addition, DTG has an improved overall safety profile compared with EFV, bringing additional clinical and programmatic benefits.

RAL and DRV/r are effective and safe alternative ARV drugs in second-line therapy, especially for children and pregnant women, for whom alternative options are limited. However, the high cost and lack of affordable generic versions limits their potential for large-scale use.

However, evidence for the safety and efficacy of most of these new ARV drugs is still limited in important groups, since young children, pregnant women, people with HIV-associated TB receiving rifampicin-based treatment and people with advanced HIV disease are frequently excluded from initial ARV drug trials. This limits population-based use and requires age- and sex-specific roll-out plans. Specific ongoing studies will enable more detailed assessment of safety and efficacy in these groups, with results expected within the next years. In addition, active toxicity monitoring and safety surveillance in populations for which data are lacking are required given the use and expansion of DTG and other new ARV drugs.

Ongoing programmes in Botswana and Brazil, which include close adverse event monitoring tools, will provide important data in the coming years.

WHO has an essential role in supporting countries in transitioning to new antiretroviral drugs. WHO will continue monitoring ongoing and future clinical studies on new drugs and develop necessary normative and operational tools for countries to safely introduce and roll out new treatment regimens. Efficiently phasing in the new improved medicines can help countries to move faster towards achieving the global HIV targets by 2020.

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ANNEX 1

ADVERSE DRUG REACTION REPORTING FORM FOR DOLUTEGRAVIR (DTG)

(This form is to be adapted and used within the national HIV programme and targeted programme for monitoring ARV drug toxicity)

Information will be kept confidential

Name of HIV treatment facility:	Code of reporting site: Code of reporting form designed by adverse drug reaction centre:
Patient ID: ..... Date of birth: ..... / ...../ ..... Sex: ☐ Male ☐ Female ☐ Transgender Weight: ..... (kg) Height: ..... (cm) Case ID number:	Clinical status at time of DTG initiation: Symptomatic disease: ☐ Yes ☐ No Laboratory test results for ART monitoring (if available): CD4 cell count at DTG initiation: ..... Last CD4 cell count: ..... Last viral load (latest): .....
Indication for DTG use: ☐ ART initiation (first-line regimen) ☐ Substitution for EFV or NVP intolerance or toxicity ☐ Third-line regimen ☐ Other (specify):	Active TB: ☐ Yes (Date of diagnosis: ..... / ..... / .....) ☐ No Pregnancy: ☐ Yes ☐ No ☐ Don't know If pregnant: date of last menstrual period: ..... / ..... / ..... Gestation week at start of event: ..... (weeks)

ARV OR CONCOMITANT DRUGS AT THE TIME OF ADVERSE DRUG REACTION ONSET

Name of ARV drug	Dose	Start date	End date

Other medicines	Dose	Start date	End date

ADVERSE DRUG REACTIONS

Start date: ...../ ...../ ..... End date: ...../ ...../ ..... ☐ Ongoing

NEUROPSYCHIATRIC EVENTS:

- ☐ Abnormal dreams or nightmares
- ☐ Anxiety
- ☐ Confusion or abnormal thinking
- ☐ Depression or mood changes
- ☐ Dizziness, spinning sensation or vertigo
- ☐ Fatigue, tiredness or weakness
- ☐ Insomnia or sleep problems
- ☐ Poor concentration or memory problems
- ☐ Paraesthesia or painful neuropathy
- ☐ Suicide ideation
- ☐ Other (specify): .....

OTHER EVENTS:

- ☐ Skin rash/hypersensitivity reaction
- ☐ Elevated ALT/AST (hepatotoxicity)
- ☐ Other (specify): .....

.....

.....

Complementary laboratory test results at the time of adverse drug reaction (if available):

A: ..... (µmol/L)

AST: ..... (µmol/L)

- ☐ Other (specify): .....

.....

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (see definition on page 2)

Did any opportunistic disease occur after the onset of DTG?

☐ Yes ☐ No

If YES, check and/or describe:

- ☐ Tuberculosis (Date of diagnosis: ...../ ...../ .....)
- ☐ Cryptococcal meningitis (Date of diagnosis: ...../ ...../ .....)
- ☐ Cerebral toxoplasmosis (Date of diagnosis: ...../ ...../ .....)
- ☐ CMV retinitis (Date of diagnosis: ...../ ...../ .....)
- ☐ Kaposi's sarcoma (Date of diagnosis: ...../ ...../ .....)
- ☐ Other:

..... (Date of diagnosis: ...../ ...../ .....)

..... (Date of diagnosis: ...../ ...../ .....)

..... (Date of diagnosis: ...../ ...../ .....)

COMORBIDITIES

- ☐ Diabetes
- ☐ Cardiovascular disease
- ☐ Hepatitis B coinfection
- ☐ Hepatitis C coinfection
- ☐ Renal insufficiency (acute or chronic)
- ☐ Hepatic insufficiency
- ☐ Mental disorder

(specify): .....

- ☐ Other (specify): .....

Adverse drug reaction management:

- ☐ Dose adjustment
- ☐ Discontinue ARV drug
- ☐ Change regimen: New regimen: ..... / ..... / ..... Date of changin regimen: ..... / ..... / .....
- ☐ Other drug used to manage adverse drug reaction (specify) .....
- ☐ Other (specify) .....

Seriousness of the adverse drug reaction

☐ Death ☐ Requires or prolongs hospitalization ☐ Congenital anomaly or birth defect

☐ Life threatening ☐ Disability or permanent damage ☐ Not serious

Results after treating the adverse drug reaction

☐ Died due to adverse drug reaction ☐ Not yet recovering ☐ Recovered with sequelae

☐ Died not due to adverse drug reaction ☐ Recovering ☐ Recovered without sequelae

☐ Unknown

Completed by: .....

Email: .....

Signature: .....

Title: .....

Telephone: .....

ate of reporting: ...../...../.....

Please report even if:

You are not certain the product caused the event OR you do not have all the details

Person to report:

Doctor, pharmacist or nurse

Time to report:

All reporting forms should be completed as soon as possible and sent to XXX by day XX every month. The designated personnel will enter the data in the designed spreadsheet and send to xxxx by the xxth day of every month.

Who to send it to:

Name: .....

Tel.: ..... Fax: ..... Email: .....

For more information, contact:

Name: .....

Tel.: ..... Fax: ..... Email: .....

Important information

- A serious adverse drug reaction is an adverse reaction that can cause one of the following consequences: limiting treatment, death, life threatening, requires or prolongs hospitalization, disability or permanent damage, congenital anomaly/birth defect.
- A case that leads to treatment interruption or requires changing drug or regimen because of an adverse drug reaction is also considered a serious adverse drug reaction.

ARV drug	Common toxicity, adverse reaction	Management
DTG	• Central nervous system or mental symptoms (insomnia, sleep problems, anxiety, depression) • Skin hypersensitivity reactions • Immune reconstitution inflammatory syndrome	Central nervous system or mental symptoms are usually mild and subside within a few weeks after initiation. Skin hypersensitivity reactions or persistent central nervous system or mental adverse reactions: replace with another therapeutic class (EFV or boosted PIs). Managing immune reconstitution inflammatory syndrome includes treating the emergent infection, continuing ART and supportive measures as needed. Use of corticosteroids can be considered in some situations. Central nervous system immune reconstitution inflammatory syndrome can be a life-threatening condition and frequently needs urgent care and support.

Definition of immune reconstitution inflammatory syndrome
Immune reconstitution inflammatory syndrome describes a collection of infectious or inflammatory conditions associated with paradoxical clinical worsening of pre-existing infectious processes caused by the host's regained capacity to mount an inflammatory response after people living with HIV initiate antiretroviral therapy (ART). It usually occurs in the first two months after starting ART among people living with HIV with severe immunodeficiency and quick immune recovery (rapid increase in CD4 counts and viral load suppression). Immune reconstitution inflammatory syndrome can present clinically in two types. The first is called unmasked immune reconstitution inflammatory syndrome because of occult and subclinical opportunistic infection and a generally detectable pathogen. The second is called paradoxical immune reconstitution inflammatory syndrome and is characterized by recrudescence or relapse of infection successfully treated previously and marked antigen-induced immune activation with no or few detectable pathogens.

This reporting form by no mean implies that the health personnel or confirmed drug caused the adverse reaction or side-effect. This reporting form will be stored at the database of drug safety of the national AIDS programme.

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