POLICY BRIEF

HIV TREATMENT

# TRANSITION TO NEW ANTIRETROVIRALS IN HIV PROGRAMMES

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World Health Organization

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This policy brief provides advice on a phased approach to transitioning to new WHO-recommended HIV treatment regimens. The target audience includes country HIV programme managers, procurement agencies, implementing partners, and other relevant parties. The aim of this document is to ensure a continuous supply of antiretroviral (ARV) drugs, safely, rapidly and efficiently implement the 2016 WHO consolidated ARV guidelines and enable a smooth transition to optimized ARV regimens.

## Why transition to new antiretroviral drugs?

WHO HIV antiretroviral (ARV) drug guidelines have recommended adopting ARV regimens with high potency, high genetic barriers to HIV drug resistance (HIVDR), low toxicity and low cost. The adoption of better drug regimens could improve treatment adherence, viral suppression and quality of life of people living with HIV. These benefits could reduce pressures on health systems as lower rates of viral failure on new treatments could reduce the risk of HIVDR and HIV transmission. In addition, transition to new lower-cost ARV drugs could provide significant savings for national health budgets worldwide.

Introducing optimized drug regimens and formulations will promote more effective and durable ARV treatment, improve the quality of HIV care and could save costs.

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**Table 1 Summary of optimization profiles of the new ARV drugs recommended in the 2016 WHO consolidated ARV guidelines - comparative analysis**

| Optimization criteria | | DTG | EFV400 | DRV/r | RAL |
|---|---|---|---|---|---|
| Efficacy and safety | High antiretroviral potency | ✓ | ✓ | ✓ | ✓ |
| | Low toxicity | ✓ | ✓ | ✓ | ✓ |
| | High genetic barrier to resistance | ✓ | ✗ | ✓ | ✗ |
| Simplification | Available as generic fixed-dose combination | ✓ | ✓ | ✗ | ✗ |
| | Low pill burden | ✓ | ✓ | ✗ | ✗ |
| Harmonization | Use for pregnant women | ? | ? | ✓ | ✓ |
| | Use for children | ? | ✗ | ✓ | ✓ |
| | Use in HIV-associated TB | ? | ? | ✗ | ✓ |
| | Few drug interactions | ✓ | ✗ | ✗ | ✓ |
| Cost | Low price | ✓ | ✓ | ✗ | ✗ |

✓ yes ✗ no ? ongoing studies

DTG= dolutegravir; EFV400= low dose efavirenz; DRV/r= darunavir/ritonavir; RAL= raltegravir

## Clinical considerations for new ARV drugs: what are the knowledge gaps?

Since 2016, WHO has recommended adopting new alternative ARV drug options in HIV treatment regimens: dolutegravir (DTG) and efavirenz 400 mg (EFV400) for first-line therapy and darunavir/ritonavir (DRV/r) and raltegravir (RAL) for second- and third-line therapy.

## First-line treatment options: DTG and EFV400

DTG is associated with improved tolerability, higher antiretroviral efficacy, lower rates of treatment discontinuation, a higher genetic barrier to resistance and fewer drug interactions than other ARV drugs.

EFV400 has comparable efficacy and improved safety compared with EFV at the standard dose (EFV600).

These two new first-line options are becoming available in low- and middle-income countries as generic fixed-dose combinations at lower prices than the current preferred first-line regimens. EFV400 is now available as a single-pill fixed-dose combination (TDF + 3TC + EFV400). DTG is currently available as a single-strength formulation for once-daily use. Generic fixed-dose combinations of TDF + 3TC + DTG are expected to be available in early 2018.

## New and ongoing studies of DTG and EFV400 in various populations

Evidence for the safety and efficacy of DTG and EFV400 are still limited in specific populations, including young children, pregnant women and people with tuberculosis (TB) coinfection receiving rifampicin-based treatment. The ongoing clinical studies in these groups will provide results in two to three years. As the use of DTG and EFV400 expands in these populations, active drug toxicity monitoring and enhanced pregnancy safety surveillance should be implemented as part of pharmacovigilance policies. Emerging evidence suggests that DTG could also be a potential second-line ARV drug option in the future.

DTG- and EFV400-containing regimens have clinical and programmatic advantages compared with current standard first-line ART, but experience with their use in low- and middle-income countries is limited. More evidence is needed for specific populations.

**Table 2 Estimated timelines for completing new clinical trials of DTG and EFV400**

| ARV drug | 2017 | 2018 | | 2019 | | 2020 | |
|---|---|---|---|---|---|---|---|
| | Q3–Q4 | Q1–Q2 | Q3–Q4 | Q1–Q2 | Q3–Q4 | Q1–Q2 | Q3–Q4 |
| DTG | RADIO<br>DAWNING<br>ADVANZ-4 | IMPAACT 1093 | DOLPHIN 1<br>NAMSAL | DOLPHIN 2<br>D2EFT | INSPIRING | VESTED<br>ODYSSEY<br>ADVANCE | PANNA<br>ING200336 |
| EFV400 | SSAT 062<br>SSAT 063 | | NAMSAL | | | | |

● Pregnant women ● Children ● TB ● Adults

## Second-line treatment options: DRV/r and RAL

DRV/r coformulation is comparable to other boosted protease inhibitors in second-line therapy, with no significant differences in terms of serious adverse reactions and risk of treatment discontinuation, supporting its use as an alternative option in second-line regimens. It is also approved for children older than three years and recommended for use in third-line regimens.

RAL has been approved for children, adults and pregnant women and is effective and well tolerated for second- and third-line use after protease inhibitor (PI)–based regimens fail among adults, adolescents and children.

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.

Each country needs to decide whether to introduce DRV/r or RAL based on the availability of adequate formulations and reduced prices.

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## Enhanced monitoring for HIVDR

The prevalence of pretreatment HIVDR to EFV and nevirapine (NVP) is progressively increasing among people starting ART. People with pretreatment HIVDR are less likely to achieve viral suppression and more likely to experience viral failure, discontinue treatment and acquire new resistance mutations if they are treated with non-nucleoside reverse-transcriptase inhibitors (NNRTIs). Given these increasing levels of HIVDR, countries may want to consider introducing new classes of ARV drugs based on their country context and the prevalence of pretreatment HIVDR.

Countries with national pretreatment HIV drug resistance to EFV or NVP greater than or equal to 10% should consider a transition to DTG

## Enhanced monitoring for toxicity and pregnancy safety surveillance

Low- and middle-income countries have limited clinical and programmatic experience with DTG and EFV400-containing ART regimens. So far, no major new safety issues have been detected, but pregnancy safety surveillance and enhanced monitoring for unexpected or long-term drug-associated adverse reactions is recommended while the use of DTG is scaled up.

WHO recommends that, in addition to routine toxicity monitoring, countries consider implementing a combination of active toxicity surveillance approaches to address the specific needs of HIV treatment and prevention programmes while transitioning to new ARV drugs.

WHO and the Special Programme for Research and Training in Tropical Diseases (TDR) recently established a global central database for the surveillance of drug safety during pregnancy at antenatal clinics. 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.

**Figure 1 Pretreatment HIVDR to EFV or NVP among first-line ART initiators in selected countries**

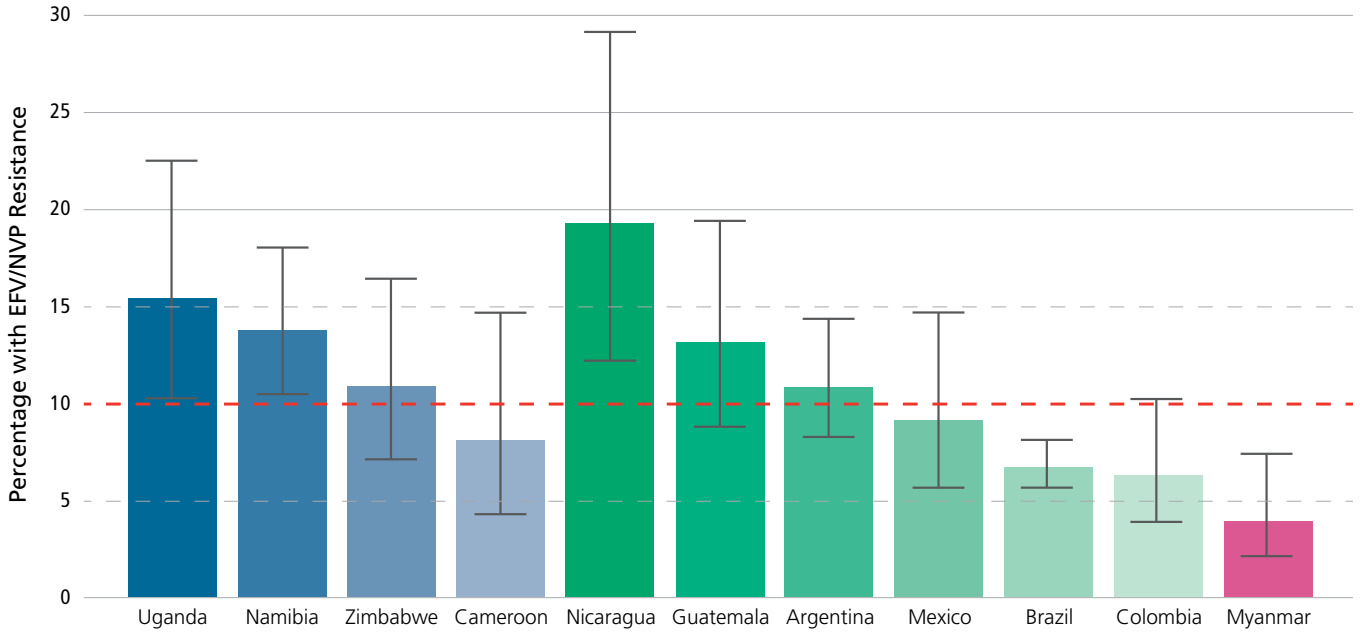

**Table 3 Toxicity and pregnancy safety surveillance approaches recommended for new ARV drugs**

| Populations | New ARV drugs and major toxicities | Surveillance approaches |
|---|---|---|
| Adults, adolescents and children | • DTG: central nervous system toxicity, immune reconstitution inflammatory syndrome, unexpected or long-term toxicity<br>• DRV/r: hepatotoxicity<br>• RAL: central nervous system toxicity, immune reconstitution inflammatory syndrome, myopathy, hepatotoxicity | • Active ARV toxicity monitoring |
| Pregnant and breastfeeding women and infants | • Maternal health outcomes:<br>  • DTG: central nervous system toxicity and immune reconstitution inflammatory syndrome<br>  • RAL: hepatotoxicity<br>• Birth outcomes (all new ARV drugs): miscarriages, preterm delivery, stillbirth, low birth weight, small for gestational age, major congenital anomalies<br>• Infant outcomes (all new ARV drugs): growth and development, unexpected toxicity | • ARV pregnancy registry and surveillance of congenital anomalies<br>• Monitoring mother-infant pairs during breastfeeding |

Long-term toxicity and safety monitoring of new ARV drugs need to be regularly reviewed until the evidence is sufficient to demonstrate that expanded use in public health programmes creates no excessive risk.

## Programmatic considerations for new ARV drugs: potential opportunities and challenges related to transitioning to new ARV drugs in low- and middle-income countries

Programmes should plan carefully and discuss the pace at which increased quantities of DTG and other new ARV drugs can be made available. This will require a gradual process of transition. To ensure that supply is available to meet the anticipated demand, a phased approach is highly recommended.

Several issues should be considered when planning the transition to new treatment options.

1. Countries should make accurate estimates of pretreatment HIVDR to EFV or NVP using the standardized surveillance methods proposed by WHO to help guide the transition to DTG.

2. The rate of transitioning to new ARV drugs will also depend on the availability of adequate supply of generic fixed-dose combinations and the need to properly use the current stocks of EFV600-containing formulations. People should not risk treatment interruption.

3. Health-care providers will need training on using these new products, including managing toxicity and how to adjust doses of DTG during rifampicin-based treatment for TB.


**Table 4 Key items programmes need to consider for a safe transition to new first-line ARV drugs**

| Optimization criteria | DTG-containing regimens | EFV400-containing regimens | Comments |
|---|---|---|---|
| Efficacy | High efficacy, especially in context of HIVDR to NNRTIs; efficacy data on HIV-associated TB are pending | Emerging data suggest adequate therapeutic levels in pregnancy and during TB treatment with rifampicin; concerns about efficacy with rising pretreatment HIVDR to NNRTIs in low- and middle-income countries | Favours DTG |
| Safety | No long-term safety data for people living with HIV. Limited safety data for young children, pregnant women and people with HIV-associated TB | Efavirenz has been used for many years in low- and middle-income countries and proved safe for people living with HIV, including pregnant women and people with TB. Lower doses are tolerated better | Favours EFV400 |
| Simplification | Generic single formulation is available, but fixed-dose combinations are expected in | Generic fixed-dose combination available; no dose adjustment needed | Favours EFV400 |