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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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