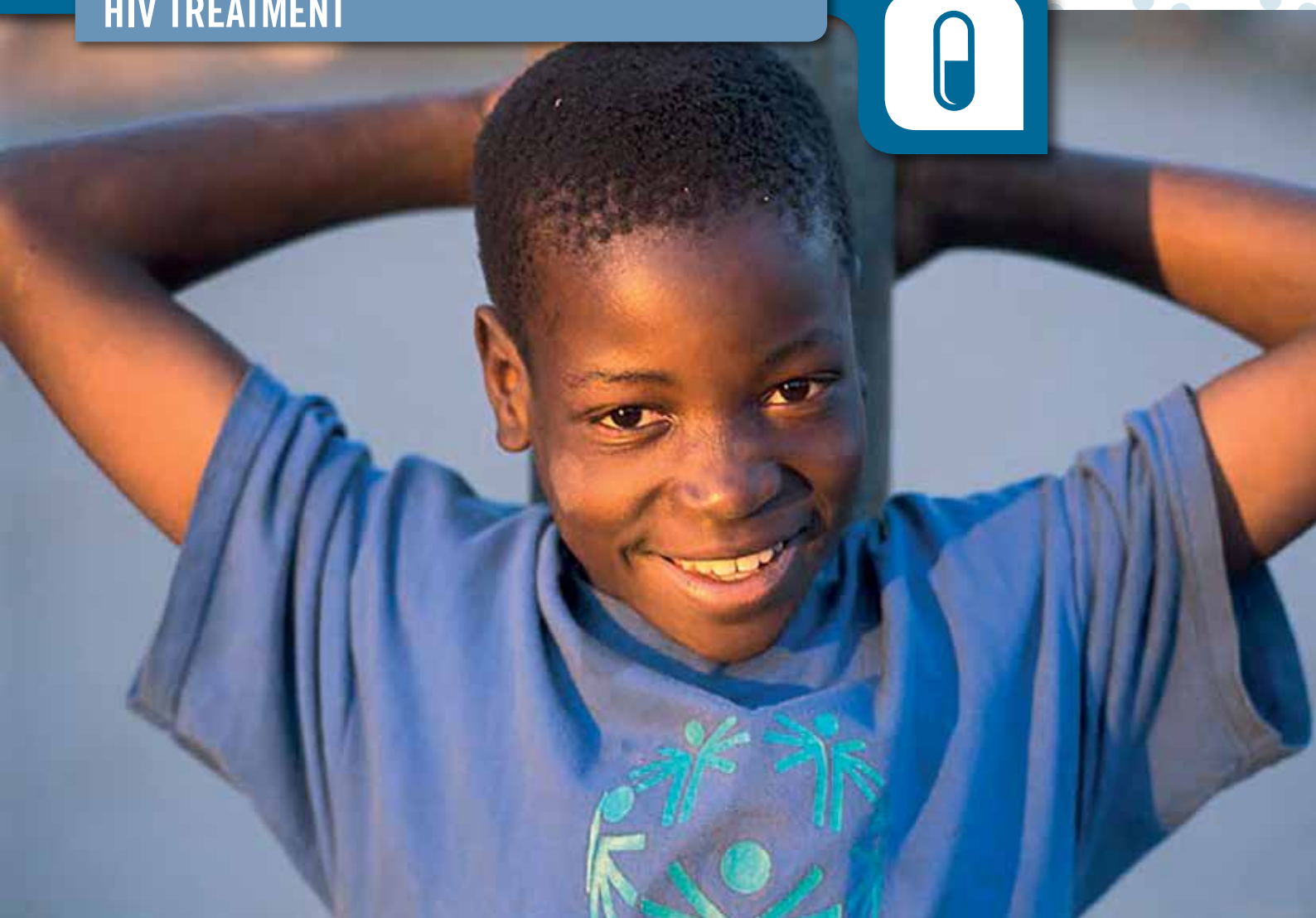


TECHNICAL UPDATE

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

JULY 2017

HIV TREATMENT





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

JULY 2017

WHO/HIV/2017.23

© World Health Organization 2017

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

**Suggested citation.** Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. Geneva: World Health Organization; 2017 (WHO/HIV/2017.23). Licence: CC BY-NC-SA 3.0 IGO.

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

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Layout by DesignIsGood.info

Cover photo: WHO

Printed in France

# CONTENTS

<b>EXECUTIVE SUMMARY</b> .....	<b>2</b>
<b>ACKNOWLEDGMENTS</b> .....	<b>2</b>
<b>1. CONTEXT</b> .....	<b>4</b>
<b>2. CLINICAL CONSIDERATIONS</b> .....	<b>6</b>
<b>2.1 Efficacy and overall safety profile of new ARV drugs among people living with HIV</b> .....	<b>6</b>
2.1.1 DTG and RAL .....	6
2.1.2 Use of DTG and central nervous system side-effects .....	7
2.1.3 Integrase inhibitors and the risk of immune reconstitution inflammatory syndrome .....	7
2.1.4 DTG and the risk of cardiovascular adverse drug reactions .....	7
2.1.5 EFV400 .....	7
2.1.6 DRV/r .....	7
<b>2.2 Considerations for specific populations: pregnant women, children and adolescents and people living with HIV and receiving TB co-treatment using rifampicin</b> .....	<b>7</b>
2.2.1 DTG .....	7
2.2.2 EFV400 .....	10
2.2.3 DRV/r .....	11
2.2.4 RAL .....	11
<b>3. PROGRAMMATIC CONSIDERATIONS</b> .....	<b>13</b>
<b>3.1 Prequalification and stringent regulatory approval of new antiretroviral drugs</b> .....	<b>14</b>
3.2.1 Availability and supply of generic EFV400-containing fixed-dose combinations .....	16
<b>3.3 Availability of DTG, RAL and DRV/r</b> .....	<b>16</b>
<b>3.4 Price of new ARV drugs in low- and middle-income countries</b> .....	<b>16</b>
<b>3.5 Capacity to produce active pharmaceutical ingredients</b> .....	<b>17</b>
<b>3.6 Forecasting and procurement</b> .....	<b>17</b>
<b>3.7 Formulations for children</b> .....	<b>18</b>
<b>3.8 Programme monitoring</b> .....	<b>18</b>
3.8.1 Enhancing monitoring for toxicity and pregnancy safety surveillance .....	18
3.8.2 Main approaches to monitoring toxicity .....	19
<b>4. COUNTRY EXPERIENCES</b> .....	<b>22</b>
<b>4.1 Catalytic procurement of DTG and introduction in Kenya, Nigeria and Uganda</b> .....	<b>22</b>
<b>4.2 Nationwide transitioning to DTG: the initial experiences of Botswana and Brazil</b> .....	<b>23</b>
4.2.1 Botswana .....	23
4.2.2 Brazil .....	23
<b>5. CONCLUSIONS</b> .....	<b>25</b>
<b>REFERENCES</b> .....	<b>26</b>
<b>ANNEX 1</b> .....	<b>31</b>

# 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.



## ACKNOWLEDGMENTS

Development of this technical update has been led by Meg Doherty, Marco Vitoria, Martina Penazzato, Shaffiq Essajee, Françoise Renaud, Silvia Bertagnolio and Boniface Dongmo (WHO Department of HIV, Global Hepatitis Programme). WHO also thanks the writers who contributed to this document: Andrew Hill and Claire Townsend. Technical inputs and review were provided by Elaine Abrams (ICAP, Columbia University), Martin Auton (The Global Fund to fight AIDS, Tuberculosis and Malaria), Polly Clayden (HIV i-Base), Tim Cressey (Program for HIV Prevention and Treatment-Clinical Trial Unit in Thailand), John Crowley

(United States Agency for International Development), Laurent Ferradini (WHO Cambodia), Melba Gomes (WHO external consultant), Aastha Gupta (Medicines Patent Pool), Christine Halleux (WHO Special Programme for Research and Training in Tropical Diseases), Joseph Harwell (Clinton Health Access Initiative), Michael Jordan (Tufts University), Carmen Perez-Casas (Unitaid), George Siberry (Office of Global AIDS Coordination) and colleagues from the WHO Global TB Programme (Yohhey Hamada) and WHO HIV Department (Andrew Ball, Nathan Ford, and Gottfried Hirschall).

# 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

预览已结束，完整报告链接和二维码如下：

[https://www.yunbaogao.cn/report/index/report?reportId=5\\_26358](https://www.yunbaogao.cn/report/index/report?reportId=5_26358)

