World Health Organization

GUIDELINES

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THE PUBLIC HEALTH RESPONSE TO PRETREATMENT HIV DRUG RESISTANCE

JULY 2017

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SUPPLEMENT TO THE 2016 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION: SECOND EDITION JUNE 2016

Guidelines on the public health response to pretreatment HIV drug resistance: July 2017

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CONTENTS

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV/r	ritonavir-boosted atazanavir
AZT	azidothymidine (also known as zidovudine)
CI	confidence interval
d4T	stavudine
D: A: D	Data Collection on Adverse Events of Anti-HIV Drugs (study)
DALY	disability-adjusted life-year
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
FPV	fosamprenavir
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HIVDR	HIV drug resistance
HR	hazard ratio
IDV	indinavir
INSTI	integrase strand transfer inhibitor (also known as integrase inhibitor)
LPV/r	ritonavir-boosted lopinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OR	odds ratio
PEP	post-exposure prophylaxis
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitors
PICO	population, intervention, comparator, outcome
PMTCT	prevention of mother-to-child transmission of HIV
PrEP	pre-exposure prophylaxis
QALY	quality-adjusted life-year
RAL	raltegravir
RTV	ritonavir
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
XTC	3TC (lamivudine) or FTC (emtricitabine)

DEFINITIONS

HIV drug resistance (HIVDR) is caused by a change (mutation) in the genetic structure of HIV that affects the ability of a particular drug or combination of drugs to block the replication of the virus. All current antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. Broadly speaking, there are three main categories of HIVDR.

- **Acquired HIVDR** develops when HIV mutations emerge from viral replication among individuals receiving ARV drugs.
- **Transmitted HIVDR** is detected among ARV drug–naive people with no history of ARV drug exposure. Transmitted HIVDR occurs when previously uninfected individuals are infected with virus that has drug-resistance mutations.
- **Pretreatment HIVDR** is detected among ARV drug–naive people initiating ART or people with prior ARV drug exposure initiating or reinitiating first-line ART. It can result from either transmitted or acquired HIV drug resistance, or both. Pretreatment HIVDR may have been transmitted at the time of infection (transmitted HIVDR) or may be acquired from previous ARV drug exposure (such as among women exposed to ARV drugs for the prevention of mother-to-child transmission (PMTCT) of HIV, among individuals reinitiating first-line ART after a period of treatment interruption without documented viral failure or among people who have received pre-exposure prophylaxis (PrEP)).

Age groups – consistent with the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, these guidelines use the following definitions for adults, adolescents, children and infants for implementing recommendations for specific age groups. Countries may have other definitions under national laws.

- An **adult** is a person older than 19 years of age.
- An **adolescent** is a person 10 to 19 years of age inclusive.
- A **child** is a person 1 to younger than 10 years of age.
- An **infant** is a child younger than 1 year of age.

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Guideline Development Group

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Santiago Avila (Centre for Research in Infectious Diseases, National Institute of Respiratory Diseases, Mexico), **Geoffrey Barrow** (University of the West Indies, Jamaica), **Rosa Bologna** (Hospital de Pediatría Dr J.P.Garrahan, Argentina), **Francesca Ceccherini-Silberstein** (University of Rome Tor Vergata, Italy), **Mohamed Chakroun** (Fattouma Bourguiba Teaching Hospital**,** Tunisia), **Martin Choo** (Kuala Lumpur AIDS Support Services Society, Malaysia), **Francesca Conradie** (Wits Health Consortium, South Africa), **Simone de Barros Tenore** (STD/AIDS Reference and Training Center, Brazil), **Mukesh Dheda** (Department of Health, South Africa), **Bui Duc Duong** (Viet Nam Authority of HIV/AIDS Control, Viet Nam), **Lisa Frenkel** (University of Washington, USA), **Zhang Fujie** (Beijing Ditan Hospital, China), **Tendani Gaolathe** (Botswana Harvard AIDS Institute, Botswana), **Eric Goemaere** (Médecins Sans Frontières, South Africa), **Huldrych Günthard** (University Hospital Zurich and Institute of Medical Virology, University of Zurich, Switzerland), **Mina Hosseinipour** (University of North Carolina at Chapel Hill and UNC project Malawi, USA/Malawi), **Emily Hyle** (Massachusetts General Hospital, USA), **Corinna Klingler** (Institute for Ethics, History and Theory of Medicine, Germany), **Nagalingeswaran Kumarasamy** (YRGCARE Medical Centre, VHS, India), **Othoman Mellouk** (International Treatment Preparedness Coalition (Middle East & North Africa), Morocco), **Morolake Odetoyinbo** (International Community of Women living with HIV, Kenya), **Mar Pujades-Rodriguez** (University of Leeds, United Kingdom), **Elliot Raizes** (United States Centers for Disease Control and Prevention, USA), **Steven Reynolds** (Johns Hopkins Bloomberg School of Public Health, USA and NIAID International Center for Excellence in Research, Uganda), **Kim Sigaloff** (Leiden University Medical Center, Netherlands), **Kenly Sikwese** (African Community Advisory Board (AFROCAB), Zambia), **Nazle Véras** (Ministry of Health, Brazil) and **Suwit Wibulpolprasert** (International Health Policy Program Foundation, Thailand).

Systematic Review Team and contributors

Lawrence Mbuagbaw led the systematic review with support from **Theresa Aves, Sayem Borhan** and **Alvin Leenus** (McMasters University, Hamilton Ontario, Canada), **Michael R. Jordan** (Tufts University School of Medicine, Boston, Massachusetts, USA) and **Neil Parkin** (Data First Consulting, Menlo Park, California, USA).

GRADE methodologist

Nandi Siegfried (independent clinical epidemiologist, South Africa).

External contributors to supporting evidence

Ravindra Gupta (University College London, United Kingdom) provided results of a systematic review on the global prevalence of pretreatment HIV drug resistance (HIVDR), and **Andrew Phillips** (University College London, United Kingdom) presented findings from modelling work carried out to inform the guidelines.

We also thank the following individuals for presenting at the Guideline Development Group meeting: **Daniel Kuritzkes** (Division of Infectious Diseases, Brigham and Women's Hospital, USA) presented the considerations and decision-making process for recommending pretreatment HIVDR testing of the United States and European treatment guidelines panels; **Deenan Pillay** (Africa Centre for Population Health, South Africa) presented unpublished data of relevance from the Treatment as Prevention trial; and **Emiliano Bissio**[1] (Merck Sharp & Dohme Corp, Argentina S.R.L. and FUNCEI, Argentina) presented on Argentina's panel considerations during their decision-making process for considering pretreatment HIVDR testing in response to recent findings of elevated levels of pretreatment HIVDR.

External Guidelines Review Group

Avelin Aghokeng (Institut de recherche pour le développement (IRD) and Collaboration entre le centre de recherche sur les maladies émergentes et réémergentes (CREMER), Cameroon), **Chris Archibald** (Public Health Agency of Canada, Canada), **Sergio Carmona** (National Health Laboratory Services, WITS University, South Africa), **Andrea De Luca** (University of Siena, Italy), **Charles Holmes** (Centre for Infectious Disease Research in Zambia and Johns Hopkins University, USA), **Gillian Hunt** (National Institute for Communicable Diseases, South Africa), **Seth Inzaule** (Amsterdam Institute of Global Health & Development, The Netherlands), **Jessica Justman** (International Center for AIDS Care and Treatment Programs (ICAP) at Columbia University, USA), **Pontiano Kaleebu** (Uganda Virus Research Institute, Uganda), **Daniel Kuritzkes** (Division of Infectious Diseases, Brigham and Women's Hospital, USA), **Nomthandazo Lukhele** (Ministry of Health, Swaziland), **Tadesse Mekonen** (Avcare Global, Namibia), **Nicaise Ndembi** (Institute of Human Virology, Nigeria), **Lisa Nelson** (Office of the United States Global AIDS Coordinator, USA), **Roger Paredes** (irsiCaixa AIDS Research Institute, Spain), **Mike Podmore** (StopAIDS, United Kingdom), **Anton Pozniak** (Chelsea & Westminster Hospital NHS Foundation Trust, United Kingdom), **Jonathan Schapiro** (National Hemophilia Center, Israel), **Annette Sohn** (TREAT Asia/amfAR, Thailand), **Katayoun Tayeri** (Iranian Research Center for HIV/AIDS, Islamic Republic of Iran) and **Carole Wallis** (Lancet Laboratories and BARC-SA, South Africa).

WHO Steering Group

Silvia Bertagnolio, **Meg Doherty**, **Cheryl Johnson**, **Martina Penazzato** and **Marco Vitoria** (Department of HIV and Global Hepatitis Programme), **Ying Ru Lo** (HIV, Hepatitis and Sexually Transmitted Infections Unit, Division of Communicable Diseases, WHO Regional Office for the Western Pacific), **Giovanni Ravasi** (HIV, Hepatitis, TB & STI Unit, Pan American Health Organization), **Harilala Nirina Razakasoa** (Communicable Diseases Unit, WHO Regional Office for Africa) and **Matteo Zignol** (Global TB Programme). Special thanks to **Cadi Irvine**, **Michael R. Jordan**, **Chantal Migone**, **David Sunderland** and **Hiwot Teferra Haile-Selassie** (consultants, Department of HIV and Global Hepatitis Programme), who supported the Steering Group.

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WHO staff and consultants

Andrew Ball, Boniface Dongmo Nguimfack, Shaffiq Essajee, Nathan Ford, Vincent Habiyambere and **Lara Vojnov** (Department of HIV and Global Hepatitis Programme), **Naoko Ishikawa** (HIV, Hepatitis and Sexually Transmitted Infections Unit, WHO Regional Office for the Western Pacific) and **Elena Vovc** (Joint Tuberculosis, HIV/AIDS & Hepatitis Programme, WHO Regional Office for Europe).

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Overall coordination

Silvia Bertagnolio (Department of HIV and Global Hepatitis Programme) coordinated the overall guideline development with programme management undertaken by **Cadi Irvine** and support from **Michael R. Jordan, Chantal Migone, David Sunderland** (consultants, Department of HIV and Global Hepatitis Programme) under the leadership of **Meg Doherty** and **Gottfried Hirnschall** (Department of HIV and Global Hepatitis Programme).

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EXECUTIVE SUMMARY

This publication provides guidance on the public health response to pretreatment HIV drug resistance (HIVDR) to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) among people without prior antiretroviral (ARV) drug exposure or people with prior ARV exposure who are initiating or reinitiating first-line antiretroviral therapy (ART). It also provides the consensus prevalence or threshold of pretreatment HIVDR to NNRTIs at which specific public health actions are triggered. This publication is a supplement to Chapter 4 of the 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2016 WHO consolidated ARV guidelines).

High prevalence of pretreatment HIVDR to NNRTIs negatively affects the success of the public health response to the treatment of HIV and potentially endangers the attainment of the global targets to end AIDS epidemic as a global threat. These guidelines support countries in responding to pretreatment HIVDR to NNRTIs in order to: (1) attain and maintain the treatment target of 90% viral suppression among all people receiving first-line ART by 2020; and (2) address the first strategic objective of the WHO Global Action Plan on HIV drug resistance 2017–2021: on the prevention and response to HIVDR.

The 2017 WHO report on HIV drug resistance shows that pretreatment HIVDR to NNRTIs is increasing and is higher in more recent studies across all WHO regions; yearly increases in NNRTI resistance were greatest in eastern Africa and smallest in Asia. Nationally representative surveys from 11 low- and middle-income countries conducted in 2014–2016 among people initiating first-line ART show high prevalence of pretreatment HIVDR to efavirenz (EFV) or nevirapine (NVP), the ARV drugs most commonly used in low- and middle-income countries, reaching 10% or above in six countries (Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe). In Africa, the prevalence of NNRTI resistance was greater than 10% in three of four countries reporting data to WHO, with pretreatment HIVDR to EFV/NVP ranging from 8.1% in Cameroon to 15.4% in Uganda. In Central and South America, pretreatment NNRTI resistance exceeded 10% in three of six countries and ranged from 6.3% in Colombia to 19.3% in Nicaragua.

The prevalence of NNRTI resistance from the national HIVDR surveys is broadly consistent with other available information, including HIVDR findings from a small sample of recently infected people enrolled in the Population-based HIV Impact Assessments surveys. In addition, a recent systematic review assessing the prevalence of pretreatment HIVDR from 56 044 individuals across 63 low- and middle-income countries showed a significant ($P < 0.05$) increase in NNRTI resistance in more recent studies across all WHO regions. A subanalysis, restricted to studies sampling people from 2014 to 2016, showed prevalence of NNRTI resistance close to or above 10% in eastern Africa, southern Africa and Latin America.

This review also found pretreatment HIVDR to NNRTIs to be significantly higher among individuals initiating first-line ART with previous ARV drug exposure (such as PMTCT-exposed women and people restarting ART after a period of treatment interruption) compared with ARV drug–naive ART initiators in all WHO regions. The seven national representative surveys of pretreatment HIVDR in Africa, South America and Asia that monitored resistance in these two groups noted similar findings. Across all WHO national pretreatment HIVDR surveys, NNRTI HIVDR was considerably higher among previously exposed ART initiators (22%) than among ARV drug-naive people (8%) ($P < 0.0001$).

To address concerns around the recently observed high prevalence of pretreatment HIVDR to NNRTI and its impact on treatment outcomes, WHO is strengthening its response to HIVDR through these guidelines and broader efforts described in the Global Action Plan on HIV drug resistance.

The 2016 WHO consolidated ARV guidelines recommend an NNRTI-based regimen for populations initiating (or reinitiating) first-line ART, except for children younger than three years. In this group, regimens containing ritonavir-boosted protease inhibitors (PI/r) are recommended as the preferred first-line ART because of the high rates of resistance associated with exposure to NNRTIs for PMTCT and other considerations. The vast majority of low- and middle-income countries do not differentiate between people initiating (or reinitiating) first-line ART and thus provide an NNRTI-based first-line regimen regardless of whether a person is starting ART for the first time or is restarting treatment.

The 2016 WHO consolidated ARV guidelines define the alternative non-NNRTI-containing first-line regimens for adults and subpopulations (children, pregnant women and people living with HIV with tuberculosis (TB) coinfection) (see table below). The HIVDR guidelines therefore refer to the alternative non-NNRTI first-line regimens that are already recommended and do not consider additional evidence on efficacy, toxicity or safety to inform the selection of a specific non-NNRTI regimen.

Recommended preferred first-line regimens and alternative first-line regimens for adults, adolescents, children and subpopulations in accordance with the 2016 WHO consolidated ARV guidelines

WHO preferred first-line ART regimens
Adults: tenofovir disoproxil fumarate (TDF) + lamivudine or emtricitabine (XTC) + efavirenz (EFV) as a fixed-dose combination (*strong recommendation, moderate certainty of the evidence*).
Adolescents 10–19 years old: TDF + XTC + EFV as a fixed-dose combination (*strong recommendation, low certainty of the evidence*).
Pregnant women: TDF + XTC + EFV as a fixed-dose combination (*strong recommendation, moderate certainty of the evidence*).
Children 3–10 years old: abacavir (ABC) + lamivudine (3TC) (*conditional recommendation, moderate certainty of the evidence*) + EFV (*strong recommendation, low certainty of the evidence*).
Children <3 years old: ABC (or zidovudine (AZT)) + 3TC (*strong recommendation, moderate certainty of the evidence*) + boosted lopinavir (LPV/r) (*strong recommendation, moderate certainty of the evidence*).
WHO alternative non-NNRTI-containing first-line ART regimens
Adults and adolescents 10–19 years old: TDF + XTC + dolutegravir (DTG) is the preferred alternative option (*conditional recommendation, moderate certainty of the evidence*).
Regimens containing co-formulated PI/r including boosted atazanavir (ATV/r), LPV/r and darunavir (DRV/r) are alternative options in special circumstances.
Pregnant women: regimens containing PI/r: ATV/r, LPV/r and DRV/r.
People with HIV-associated TB infection: DTG, LPV/r and RAL require dose adjustment during TB treatment with rifampicin. Because of potential significant interactions with rifampicin, ATV and DRV cannot be used.
Children 3–9 years old: the alternative first-line regimen remains ABC (or AZT) + 3TC (*strong recommendation, moderate certainty of the evidence*) + LPV/r (*strong recommendation, moderate certainty of the evidence*).
Children <3 years old: the alternative first-line regimen for those unable to tolerate an LPV/r-based regimen is ABC (or AZT) + 3TC + RAL.

Consistent with previous WHO guidelines, this supplement is based on a public health approach that considers feasibility and effectiveness across a variety of settings. In producing the recommendations, the key principles of availability, affordability, acceptability, accessibility and quality have been considered. These recommendations also endorse a people-centred approach to HIV treatment and care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity, equity, respect and autonomy.

Guideline development methods

In response to increasing prevalence of pretreatment HIVDR to NNRTIs observed in several low- and middle-income countries, WHO, advised by external experts and stakeholders, convened a guideline process to review the weight of the evidence for an effective response. From November 2016 to April 2017, three groups were formed to analyse and review the evidence: (1) the WHO Steering Group, consisting of WHO experts; (2) the independent Guideline Development Group; and (3) the External Review Group. The Guideline Development Group and External Review Group comprised geographically and gender-balanced external experts, including academics, researchers, programme managers, implementers and representatives of community networks and organizations. All contributors to the development of these guidelines were required to complete a WHO declaration of interests form before engaging in the guideline development process. The declaration of interests forms were extensively reviewed in consultation with the Office of Compliance, Risk Management and Ethics Department. For Guideline Development Group members who attended the meeting, no significant conflicts of interest were identified.

Recommendations were made based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to evidence review. Modelling, expert consultations and country case studies have informed the guidelines. The process has identified gaps in knowledge that will help guide future HIV drug resistance research. In addition, to indicate to countries the level of urgency of action, the Guideline Development Group formulated a consensus statement specifying the threshold for pretreatment HIVDR to NNRTIs that should trigger a public health response. The consensus statement was formulated in a transparent process following a framework developed by the methodologist and the WHO Steering Group that considered the current and historical pretreatment HIVDR prevalence data, results from the systematic review showing the impact of pretreatment HIVDR on treatment outcomes, modelling data and acceptability and feasibility.

Target audience

The primary audience for these guidelines is national HIV programme managers in low- and middle-income countries. These guidelines will also be a useful resource for clinicians and should help shape the priorities of policy-makers in development agencies, international organizations, nongovernmental organizations and other implementing partners. These guidelines will also be of value to people living with HIV, communities and civil society organizations that need to be engaged meaningfully to support their successful implementation.

Public health response to pretreatment HIV drug resistance to NNRTI

The boxes below summarize the recommendation and consensus statement made by the Guideline Development Group on the public health response to pretreatment HIVDR to NNRTIs.

Recommendation on managing pretreatment HIVDR to NNRTIs

Recommendation

For people initiating first-line ART with pretreatment HIVDR to NNRTIs,[a] a non-NNRTI-containing regimen may be preferable (conditional recommendation, low certainty of the evidence).

[a] Since individual-level HIVDR testing is largely unavailable in low- and middle-income countries, nationally representative pretreatment HIVDR data can be used to inform when public health actions should be taken at the population level (see consensus statement and figure on page 5).

Considerations on the recommendation for subpopulations

- Among people at high risk of pretreatment HIVDR to NNRTIs because of prior exposure to NNRTIs or from other risks, a non-NNRTI-containing regimen may be preferable, regardless of the country's prevalence of NNRTI pretreatment HIVDR and without the need to document the presence of NNRTI resistance by using an HIVDR test.
- For children, pregnant women and individuals receiving rifampicin for treating TB, the choice of a non-NNRTI-based regimen should be carefully considered based on the limited options available, existing age-appropriate formulations, safety and potential drug interactions as well as overall principles for optimizing drugs in ART programmes.

One of the key conditions to the recommendation was related to the availability of and feasibility of implementing HIVDR testing. Since HIVDR testing is costly and largely unavailable in low- and middle-income countries, the group decided that nationally representative data on the frequency of pretreatment HIVDR to NNRTIs could be used to guide whether countries should transition to a non-NNRTI-containing first-line ART regimen (see table on page 2 and figure on page 5).

Consensus statement on the public health response to pretreatment HIVDR

Consensus statement

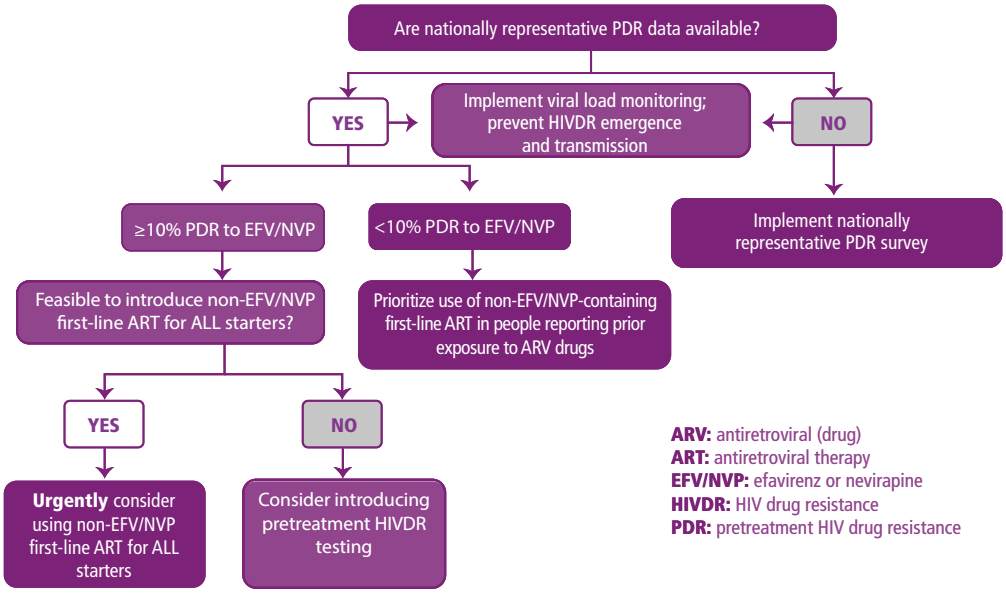
Countries in which the prevalence of pretreatment HIVDR to NNRTIs among people initiating first-line ART, regardless of previous ARV drug exposure, is ≥10% should urgently consider an alternative first-line ART regimen that does not contain NNRTIs (as defined in the 2016 WHO consolidated ARV guidelines).

Considerations on the consensus statement

- Where the national prevalence of pretreatment HIVDR to NNRTIs is ≥10% and the use of a non-NNRTI-containing regimen in first-line ART cannot be implemented at the population level, countries may consider using HIVDR testing to guide first-line ART regimen selection and continued viral load monitoring (see figure on page 5).
- Individuals at high risk of pretreatment HIVDR to NNRTIs as a result of previous exposure to NNRTI drugs should be considered for pretreatment HIVDR testing where the test is considered feasible and alternative non-NNRTI-containing regimens cannot be used at a large scale because of cost and other considerations.

The Guideline Development Group expressed concern around the increasing prevalence of pretreatment HIVDR in low- and middle-income countries and agreed that urgent public health action is needed in countries with prevalence of pretreatment HIVDR to NNRTIs equal to or above 10% (see figure below).

WHO's recommended response to pretreatment HIVDR to NNRTIs



Implementation considerations for the guidelines

The Guideline Development Group made the following implementation considerations, in accordance with current WHO guidance, to be carried out regardless of the nationally observed prevalence of pretreatment HIVDR to NNRTIs, always ensuring people-centred care within HIV programmes:

- Identify and give priority to people at greater risk of pretreatment HIVDR to NNRTIs (people starting ART with prior exposure to NNRTIs, and potentially other groups, if identified[1]) for initiating a non-NNRTI-containing regimen in first-line ART without the need to perform pretreatment HIVDR testing (see figure above).
- Use fixed-dose combinations where possible and age-appropriate optimal ARV formulations to maximize adherence and minimize selection of HIVDR.
- Continue to expand viral load monitoring capacity, ensure that testing is done for everyone living with HIV and ensure that providers promptly switch individuals to second-line ART when virological failure (viral load >1000 copies/mL) is confirmed.
- Strengthen treatment literacy and adherence support[2] interventions, maximize retention in care, minimize loss to follow-up and ensure regular use of programme data.

[1] The systematic review did not identify any other group except the one with prior ARV drug exposure that was independently characterized by a high risk of NNRTI pretreatment HIVDR. However, the Guideline Development Group agreed that, if other subpopulations are identified to be at high risk of pretreatment HIVDR regardless of prior ART exposure, they should also be given priority for receiving appropriate public health intervention while minimizing any possible risk of stigma and discrimination.

[2] Adherence support interventions should be provided to people on ART (*strong recommendation, moderate certainty of the evidence*).

- Monitor the factors associated with the emergence of HIVDR at treatment sites using quality of care indicators that are predictive of HIVDR (such as early-warning indicators of HIVDR).
- Although all available data on HIVDR can be considered when preparing to make changes to public health and ART programme policies, countries should strive to use nationally representative pretreatment HIVDR data as a gold standard and should use these data to trigger national policy changes.
- The implementation considerations of transitioning to non-NNRTI-based first-line ART are further presented in a WHO technical update.[3]

[3] Technical update: transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. Geneva: World Health Organization; 2017.

INTRODUCTION

1

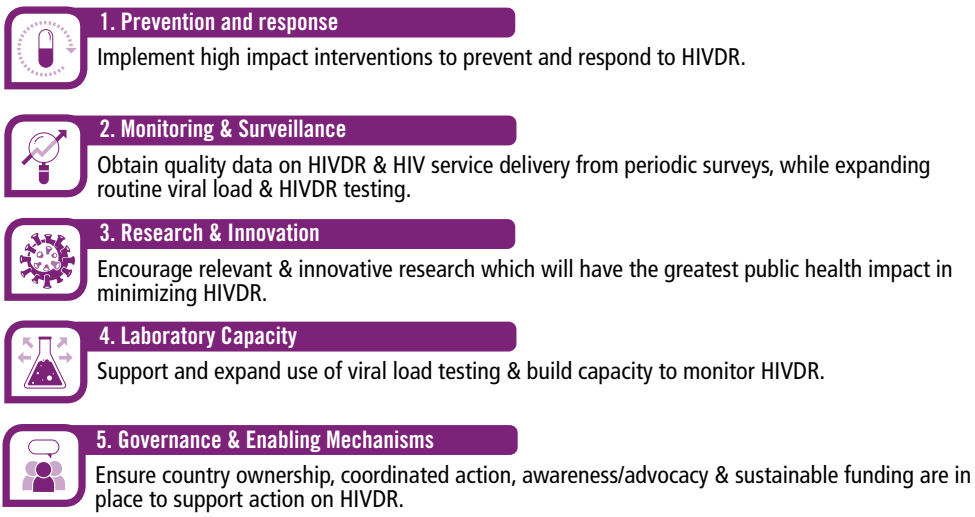
1. INTRODUCTION

1.1 Rationale

As of the end of 2016, the global response to HIV has brought more than 19.5 million people (*1*) into care and treatment at an annual investment exceeding US$ 11 billion (*2*), with 17.2 million more individuals anticipated to initiate antiretroviral therapy (ART) in the coming years and be successfully maintained on treatment for life.

These guidelines address the first strategic objective of the WHO Global Action Plan on HIV drug resistance 2017–2021: prevention and response to HIVDR. The Global Action Plan identifies critical areas for concerted and collective action on monitoring, prevention and response to HIVDR among national and international stakeholders (*3*) (Fig. 1.1).

Fig. 1.1. Strategic objectives of the Global Action Plan on HIV drug resistance, 2017–2021



Source: *Global Action Plan on HIV drug resistance, 2017-2021. Geneva: World Health Organization; 2017 (3).*

The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2016 WHO consolidated ARV guidelines) (*4*) recommend testing and treating everyone with diagnosed HIV, regardless of CD4 count. The preferred first-line ART regimen recommended for adults and adolescents, pregnant and breastfeeding women and children 3–10 years old is based on non-nucleoside reverse-transcriptase inhibitors (NNRTI). This recommendation is made regardless of: (*1*) the prevalence of resistance documented in the population starting ART; and (*2*) whether the person starting first-line ART reports having been previously exposed to NNRTIs or reports no prior exposure (*4*). In 2016, NNRTI-based first-line ART was recommended because of its safety, efficacy, tolerability and availability as a fixed-dose combination with tenofovir disoproxil fumarate (TDF) and lamivudine or emtricitabine (XTC). Alternative non-NNRTI-containing first-line ART regimens are also recommended (Table 1.1).

Table 1.1. Recommended preferred or alternative first-line regimens for adults, adolescents, children and subpopulations in accordance with the 2016 WHO consolidated ARV guidelines

WHO preferred first-line ART regimens
Adults: tenofovir disoproxil fumarate (TDF) + lamivudine or emtricitabine (XTC) + efavirenz (EFV) as a fixed-dose combination (*strong recommendation, moderate certainty of the evidence*).
Adolescents 10–19 years old: TDF + XTC + EFV as a fixed-dose combination (*strong recommendation, low certainty of the evidence*).
Pregnant women: TDF + XTC + EFV as a fixed-dose combination (*strong recommendation, moderate certainty of the evidence*).
Children 3–10 years old: abacavir (ABC) + lamivudine (3TC) (*conditional recommendation, moderate certainty of the evidence*) + EFV (*strong recommendation, low certainty of the evidence*).
Children <3 years old: ABC (or zidovudine (AZT)) + 3TC (*strong recommendation, moderate certainty of the evidence*) + boosted lopinavir (LPV/r) (*strong recommendation, moderate certainty of the evidence*).
WHO alternative non-NNRTI-containing first-line ART regimens
Adults and adolescents 10–19 years old: TDF + XTC + dolutegravir (DTG)[5] is the preferred alternative option (*conditional recommendation, moderate certainty of the evidence*).
Regimens containing co-formulated boosted protease inhibitors (PI/r) including boosted atazanavir (ATV/r), LPV/r and darunavir (DRV/r) are alternative options in special circumstances.[6]
Pregnant women: regimens containing PI/r: ATV/r, LPV/r[7] and DRV/r.
People with HIV-associated tuberculosis (TB) infection: DTG, LPV/r and RAL require dose adjustment during TB treatment with rifampicin. Because of potential significant interactions with rifampicin, atazanavir and DRV cannot be used.
Children 3–9 years old: the alternative first-line regimen remains ABC (or AZT) + 3TC (*strong recommendation, moderate certainty of the evidence*) + LPV/r (*strong recommendation, moderate certainty of the evidence*).
Children <3 years old: the alternative first-line regimen for those unable to tolerate an LPV/r-based regimen is ABC (or AZT) + 3TC + RAL.

Source: WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition* (4).

Recently, there have been key developments related to HIV drug resistance (HIVDR).

Modelling predicts that an increase in pretreatment HIVDR may be observed with the widespread use of ARV drugs for treating and preventing HIV infection. Paradoxically, as the number of people newly infected with HIV declines, the proportion of individuals infected with HIV from

[2] Experience is limited with using DTG in adolescents. The use of DTG is approved only for adolescents who are older than 12 years and weigh more than 40 kg.

[3] Special circumstances may include situations in which preferred or alternative regimens may not be available or suitable because of significant toxicity, anticipated drug–drug interactions, drug procurement and supply management issues or other reasons.

[4] A recent trial among pregnant women showed that, compared with AZT alone, ART containing TDF resulted in significantly lower rates of early HIV transmission. However, the data also suggested that the use of TDF (compared to AZT) in combination with elevated doses of LPV/r (as recommended by the United States Department of Health and Human Services) resulted in higher rates of preterm delivery before 34 weeks of gestation and early infant death, suggesting significant drug–drug interactions between TDF and LPV/r when administered at higher dose (see Box 3.4).

people on ART with unsuppressed viral load or people not currently receiving treatment but with prior exposure to ARV drugs, because of mother-to-child transmission (PMTCT) or previous treatment, will increase (5,6). This is predicted to result in a rise in the prevalence of pretreatment HIVDR. Should the prevalence of NNRTI pretreatment HIVDR exceed 10% and first-line ART continue to be NNRTI-based, modelling predicts that, over the next five years, pretreatment HIVDR would be responsible for cumulatively 150 000 people dying, 105 000 people newly infected with HIV and an additional US $ 650 million in treatment cost in sub-Saharan Africa alone (7).

WHO's global report on HIVDR from 2012 (8) documented that the prevalence of pretreatment HIVDR among ART initiators in low- and middle-income countries reached 6.8% in 2010 (8). Because the prevalence of pretreatment HIVDR was relatively contained, the 2016 WHO consolidated ARV guidelines (4) did not include a public health response to HIVDR among people starting ART. Recently, however, several studies from low- and middle-income countries have documented an increased prevalence of NNRTI pretreatment HIVDR at or above 10% among people starting first-line ART (9–14).

These results from published literature reporting high prevalence of pretreatment HIVDR have been confirmed by several nationally representative surveys from low- and middle-income countries among people initiating first-line ART. The prevalence of pretreatment HIVDR has reached 10% or above in seven of the 11 countries implementing national surveys in 2014–2016 and reporting findings to WHO: Argentina, Guatemala, Mexico, Namibia, Nicaragua, Uganda and Zimbabwe (15). The prevalence of pretreatment HIVDR is driven by resistance to NNRTIs, which exceeds 10% in six of the seven countries. In these surveys, the prevalence of NNRTI pretreatment HIVDR among people initiating first-line ART with reported prior exposure to ARV drugs[5] (21.6%, 95% confidence interval (CI) 13.8–32.2%) was consistently above 10% and the pooled prevalence significantly higher than among people who have no previous ARV drug exposure before starting first-line ART (8.3%, 95% CI 6.0–11.4%, $P < 0.0001$) (15).

Since NNRTI-containing regimens are the backbone of WHO's currently recommended preferred first-line regimen, and because HIVDR testing is not readily available in low- and middle-income countries, people with pretreatment HIVDR may not be identified and therefore may not receive a fully effective regimen – thereby inadvertently promoting further HIV transmission and transmission of drug-resistant HIV. With increasing prevalence of pretreatment HIVDR to NNRTIs observed among people starting ART in several countries, a public health response is warranted.

Since pretreatment HIVDR testing is not routinely available in most low- and middle-income settings, the 2016 WHO consolidated ARV guidelines encourage countries to conduct surveys using nationally representative methods to generate pretreatment HIVDR prevalence (4). These results inform the choice of first- and second-line ART and pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis regimens (PEP) (16,17).

[5] First-line ART initiators with previous exposure to ARV drugs include PMTCT-exposed women and defaulters restarting ART after a period of ART interruption (without reported virological failure).

1.2 Scope of the guidelines

These guidelines inform on the public health response to pretreatment HIVDR to NNRTIs, which was not covered in the 2016 WHO consolidated ARV guidelines. These guidelines do not address resistance to other ARV drug classes or acquired drug resistance.

1.3 Objectives

These guidelines provide evidence-based recommendations to support the public health response to pretreatment HIVDR in countries in which a high prevalence of NNRTI pretreatment HIVDR has been documented among people initiating or reinitiating an NNRTI-containing first-line ART regimen.

These guidelines will review the evidence of policy options in the context of high prevalence of pretreatment HIVDR, which include:

1. using alternative first-line non-NNRTI-based regimens for individuals starting first-line ART; and
2. introducing pretreatment HIVDR testing to guide the selection of first-line ART regimens. The guidelines also specify the prevalence of pretreatment HIVDR to NNRTIs that should trigger a public health response at the country level. The guidelines are relevant for all populations, except children younger than three years, for whom a non-NNRTI-containing first-line regimen is already the preferred option.

1.4 Target audience

The guidelines are primarily intended for use by national HIV programme managers. They will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- national hepatitis programme managers;
- managers of sexually transmitted infection services;
- national strategic information teams responsible for monitoring and evaluation, research and surveillance;
- managers of ARV drug procurement and supply systems;
- managers of maternal, newborn and child health programmes and sexual and reproductive health programmes;
- clinicians and other health-care workers;
- managers of national laboratory services;
- people living with HIV, civil society, advocacy groups promoting HIV treatment and community-based organizations;
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in low- and middle-income countries; and
- ARV drug and diagnostic developers.

1.5 Guiding principles

The following principles have informed the development of these guidelines and should guide implementation of the recommendations.

- The guidelines should contribute to, and expedite, the achievement of important global HIV goals and other health goals and contribute to ending AIDS as a public health threat by 2030.
- The guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment and care.
- In addition to strengthening the continuum of HIV services, the recommendations in the guidelines should be implemented with a view to strengthening broader health systems, especially primary and chronic care.
- Implementation of the guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need HIV services by ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.
- Implementation of the recommendations should be informed by available pretreatment HIVDR national data, local HIV epidemiology, the availability of resources, the organization and capacity of the health system and, if possible, anticipated analysis of cost–effectiveness in the context of considering competing interventions with health benefits.
- The alternative non-NNRTI-containing regimens discussed in these guidelines are based on the regimen selection discussed and agreed on in the 2016 WHO consolidated ARV guidelines (Table 1.1). The Guideline Development Group did not formally review additional safety and efficacy evidence to compare the alternative options for different populations.
- Implementation of the guidelines should ensure people-centred care within HIV programmes. In particular, HIV programmes should:
    - provide a people-centred approach to HIV treatment and care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity, respecting autonomy (especially for vulnerable populations) and engaging and supporting people and families to play an active role in their own care through informed decision-making; and
    - offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general.

1.6 Organization of the guidelines

The guidelines are structured into five chapters. The key chapter on the public health response to NNRTI pretreatment HIVDR, Chapter 3, is divided into six sections.

- Chapter 1: Introduction
- Chapter 2: Methods
- Chapter 3: Public health response to pretreatment HIVDR
    - Section 3.1 describes relevant pretreatment HIVDR background information.

  - Section 3.2 describes the rationale and supporting evidence for the recommendation on the choice of first-line antiretroviral therapy in the context of pretreatment HIVDR, which serves as the primary public health response to pretreatment HIVDR to NNRTIs.
  - Section 3.3 describes the use of HIVDR testing. It details the rationale and process for the decision of the Guideline Development Group to make no recommendation but rather to incorporate HIVDR testing as a consideration within the consensus statement (see next point).
  - Section 3.4 describes the rationale and process for reaching a consensus statement on the threshold of pretreatment HIVDR to NNRTIs within a country that should trigger a public health action.
  - Section 3.5 describes implementation considerations for the guidelines.
  - Section 3.6 presents key research gaps identified by the Guideline Development Group.
- Chapter 4: Prevention of HIVDR
- Chapter 5: Dissemination and updating of the guidelines

Web Annexes 1–3 to this supplement are available at http://www.who.int/hiv/topics/drugresistance/en.

Web Annex 1 (*18*): Declaration of interests of Guideline Development Group members and conflict of interest management plan

Web Annex 2 (*19*): Systematic reviews and meta-analyses informing the guidelines on the public health response to pretreatment HIV drug resistance

Web Annex 3 (*20*): Public health actions to prevent HIVDR and respond to suboptimal performance of quality-of-care indicators

METHODS

2

2. METHODS

2.1 Methods of developing the guidelines

In response to increasing prevalence of pretreatment HIVDR to NNRTIs observed in several low- and middle-income countries, WHO, advised by external experts and stakeholders, convened a guideline process to review the weight of the evidence for an effective response. From November 2016 to April 2017, three groups were formed to analyse the evidence and review this guidance: (1) the WHO Steering Group, consisting of WHO experts; (2) the independent Guideline Development Group; and (3) the External Review Group. The Guideline Development Group and External Review Group comprised geographically and gender-balanced external experts, including academics, researchers, programme managers, implementers and representatives of community networks and organizations.

Using the PICO (population, intervention, comparator and outcome) format, the WHO Steering Group formulated the questions to guide the systematic reviews and assess the evidence to inform the new guidelines. Support was also provided by the Steering Group of HIVResNet, which is convened by the WHO Department of HIV and Global Hepatitis Programme. From November 2016 to March 2017, WHO convened three virtual meetings of the WHO Steering Group to develop, review and finalize the PICO questions, outcomes and stratifications for each systematic review.

In February 2017, a virtual meeting with the Guideline Development Group was held, during which the WHO Department of HIV provided an overview of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process. Using an electronic survey, the groups then ranked the importance of each systematic review outcome using the GRADE rating scale (*1–9*). The WHO Steering Group reviewed and provided input into the development of new evidence needed to inform the new guidelines and complete additional background work, including: systematic reviews of how pretreatment HIVDR affects treatment outcomes; cost–effectiveness analysis; cost considerations; reviews of the values and preferences of potential users; and consultations with key scientists, implementers and peer reviewers.

In March 2017, WHO organized an in-person meeting of the Guideline Development Group and WHO Steering Group to review the final results of the systematic reviews, the GRADE evidence profile tables and other background work. Based on the evidence provided, the Guideline Development Group made recommendations to WHO on the public health response to pretreatment HIVDR. The Guideline Development Group discussed cost, resource use, feasibility, acceptability, equity and implementation considerations related to the recommendations and proposed areas in which further research is required.

In April 2017, the External Review Group, the Guideline Development Group and WHO staff members from headquarters and regional offices reviewed and provided further input into these guidelines.

2.2 Evidence assessment

2.2.1 Evidence retrieved and reviewed

To inform the development of these guidelines, the following evidence was retrieved:

- systematic reviews on how pretreatment HIVDR affects outcomes, with standardized GRADE evidence tables to present quantitative summaries of the evidence and the assessment of its quality for each question by outcome (Web Annex 2 (*1*));
- cost–effectiveness analysis and cost considerations; and
- reviews of the values and preferences of end-users, including civil society members, health-care workers, HIV programme managers, scientists and implementers.

The Guideline Development Group reviewed evidence informing the following two key questions around the public health response to HIVDR.

1. What is the optimal public health response for individuals starting or restarting first-line ART (ARV-naive and ARV-exposed) with pretreatment HIVDR to NNRTIs?

To address this question, the Guideline Development Group reviewed:

- the association between NNRTI pretreatment HIVDR and increased risk of suboptimal treatment outcomes; and
- the evidence related to two possible responses to pretreatment HIVDR to NNRTIs:
    - using a non-NNRTI-containing regimen for people initiating first-line ART; and
    - using HIV resistance testing to inform the selection of first-line regimens.

2. What national prevalence (threshold) of pretreatment HIVDR to NNRTIs should trigger a public health response?

To address this question, the Guideline Development Group reviewed:

1. outputs from mathematical models;
2. surveys on values and preferences from programme managers, health-care workers and people living with HIV;
3. current global prevalence of NNRTI pretreatment HIVDR; and
4. the known impact of pretreatment HIVDR on treatment outcomes) to generate a consensus on a threshold of NNRTI pretreatment HIVDR above which public health actions should be triggered.

2.2.2 Methods used to inform possible recommendations

The standard GRADE approach was used to assess the certainty of the evidence provided by the systematic reviews, complemented by information from mathematical models; reviews of values and preferences from programme managers, health-care workers and people living with HIV; and cost and cost–effectiveness and feasibility considerations (Table 2.1).

Table 2.1. Criteria for consideration in evidence-to-decision-making tables

Certainty of the evidence	This is an assessment of the degree of confidence in the estimate of the effect: the likelihood that the effect will differ substantially from what the research found. "Differ substantially" means a large enough difference that it might affect a decision.
Benefits and risks	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or other alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely a strong recommendation will be made.
Values of outcomes	This is a judgement of how much the people affected by an intervention or option value each of the outcomes. How much people value outcomes in relation to each other needs to be considered when weighing the desirable effects of an intervention against its undesirable effects.
Costs and resource implications	This refers to the resource requirements for the intervention and the alternative. It includes: • costs: the value of the resources consumed (such as staff time, drugs and use of equipment) as a consequence of an intervention or option; and • cost–effectiveness: the cost of an intervention in relation to its effects. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness is more likely to support a strong recommendation.
Equity	The absence of avoidable or remediable health differences among groups of people that may be defined socially, economically, demographically or geographically.
Acceptability	This considers how much a recommendation is accepted by the people who are affected by it, or who are implementing it. If the recommendation is likely to be widely accepted or highly valued, it is likely that a strong recommendation will be made. A great deal of variability, or strong reasons why the recommended course of action is unlikely to be accepted, makes a conditional recommendation more likely.
Feasibility	Is it feasible to implement an intervention and sustain it? If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

The systematic reviews on the two possible responses to pretreatment HIVDR to NNRTIs were framed as described below and in Table 2.2.

1. The first systematic review and meta-analysis assessed treatment outcomes among people with pretreatment HIVDR to NNRTIs who are initiating (or reinitiating) an NNRTI-containing first-line ART compared with those with pretreatment HIVDR to NNRTIs who are initiating *non*-NNRTI-containing first-line ART.

To better capture all available relevant data, the review also included studies assessing treatment outcomes in people with pretreatment HIVDR (and pretreatment HIVDR to NNRTIs) initiating a NNRTI-containing first-line regimen compared with those with no pretreatment HIVDR (or pretreatment HIVDR to NNRTIs).

2. The second systematic review assessed treatment outcomes in people with pretreatment HIVDR to NNRTIs using HIVDR testing to guide the selection of first-line regimens compared with people with pretreatment HIVDR to NNRTIs initiating standard NNRTI-based first-line ART without using HIVDR testing.

Table 2.2. Systematic review framework to inform the impact of pretreatment HIVDR to NNRTIs on treatment outcomes and effective response

Populations	Intervention or group	Comparator
People with pretreatment HIVDR to NNRTIs	Initiating non-NNRTI-containing first-line ART	Initiating NNRTI-containing first-line ART
People or reinitiating NNRTI-based first-line ART	With pretreatment HIVDR to NNRTIs	Without pretreatment HIVDR to NNRTIs
	With pretreatment HIVDR to any first-line drug	Without pretreatment HIVDR to any first-line drug
People with pretreatment HIVDR to NNRTIs	HIVDR testing prior to ART initiation to select first-line ART regimen	Standard of care (NNRTI-based first-line ART) without HIVDR testing prior to ART initiation

The reviews included studies with available information on pretreatment HIVDR and people's treatment outcomes. The study population included people eligible to initiate first-line ART, including ARV drug naive people and people who had been exposed to ARV drugs through PMTCT or interrupted ART before restarting first-line ART. Studies using resistance testing methods other than the Sanger genotypic resistance test were excluded. Studies including people with documented treatment failure were also excluded.

The reviews defined relevant subpopulations by:

- age: children younger than 10 years, adolescents 10–19 years old inclusive and adults 20 years or older;
- key populations: people who inject drugs, sex workers, men who have sex with men, people who inject drugs and people living in prisons;
- sex; and
- previous exposure to ARV drugs and types of exposure: PMTCT-related exposure and previous interruption of ART.

2.2.3 Rating the values of outcomes

To rate the list of potential outcomes of interest, the members of the Guideline Development Group were asked to score the importance of the outcomes on a scale of 1 (not important) to 9 (critical) from the perspective of people living with HIV, to consider the importance of the values to end-users. The average of the scores and variability for each outcome were used to determine the outcomes critical for decision-making.

The studies were assessed for the following outcomes, ranked by the Guideline Development Group in order of importance.

- Virological suppression: the percentage of participants achieving undetectable plasma viral load over time (virological success). For this outcome, the lower limit of viral load detection and the time frames reported by the study authors were used.
- Progression to AIDS (clinical and immunological).
- Mortality.
- Incident resistance mutations: the acquisition of additional major resistance mutations as reported by the study authors.
- Discontinuation: defined as the proportion of study participants who either stopped their first-line ART for any reason or switched from first- to second-line because of HIVDR.
- Adverse events.

2.2.4 Methods used to inform a consensus statement

The Guideline Development Group developed and endorsed a consensus statement based on findings from: mathematical models; reviews of values and preferences from programme managers, health-care workers and people living with HIV; the current prevalence of NNRTI pretreatment HIVDR; and the known impact of pretreatment HIVDR on treatment outcomes from the systematic reviews mentioned above.

2.3 Interpretation of the certainty of the evidence

The GRADE method was used to rate the overall certainty of the evidence (Table 2.3). The certainty of the evidence is defined as the degree of confidence the Guideline Development Group has in the adequacy of the reported estimates of effect to inform a specific recommendation. The GRADE system classifies the certainty of the evidence as high, moderate, low and very low. For questions of effectiveness, randomized controlled trials are initially rated as high certainty of the evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low certainty of the evidence but can be downgraded for similar reasons to those of randomized controlled trials or upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose–response relationship or if all plausible residual confounding would reduce the demonstrated effect or increase the effect if no effect were observed.

Table 2.3. GRADE definition of the certainty of the evidence

Certainty of the evidence	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

2.4 Determining the direction and strength of a recommendation

The Guideline Development Group made a consensus decision on the direction and strength of each intervention being considered in a two-stage process. First, the Guideline Development Group considered all the domains included in the evidence-to-decision-making table – benefits versus risks, certainty of the evidence, values and preferences, acceptability, feasibility, resource use and equity issues, to determine whether to (1) make a recommendation in favour, (2) make a recommendation against or (3) make no recommendation. Second, the Guideline Development Group determined the strength of the recommendation as either strong or conditional.
The strength of a recommendation reflects the Guideline Development Group's degree of confidence that the desirable effects of the recommendation outweigh the undesirable effects (2). Desirable effects (potential benefits) include beneficial health outcomes (such as reduced incidence of HIV and reduced morbidity and mortality); reducing the burden on the individual and/or health services; and potential cost savings for the individual, communities, programme and/or health system. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services as well as resource use and cost implications.

A strong recommendation is one for which the Guideline Development Group is confident that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects.
A conditional recommendation is one for which the Guideline Development Group concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects or are closely balanced, but the Guideline Development Group is not confident about these trade-offs in all situations. In implementation, monitoring and rigorous evaluation is needed to address these uncertainties. This is likely to provide new evidence, which may change the calculation of the balance of trade-offs and may suggest ways to overcome any implementation challenges.

The Guideline Development Group decided the wording and strength of each recommendation by consensus (all members accepted the formulation of the recommendation and provided vocal approval during the meeting). At the beginning of the meeting, the Guideline Development Group agreed that, should a vote be required, a majority of two thirds would be required to pass a recommendation, but this was not necessary during the meeting.

2.5 Information sources

2.5.1 Systematic reviews of the evidence

The WHO Steering Group formulated PICO questions to guide the systematic reviews. A Systematic Review Team developed protocols and conducted reviews. PRISMA[6] guidelines for systematic reviews and meta-analysis were used for reporting of reviews (*3*). Data from the systematic reviews were summarized as evidence profiles using the GRADE approach. The systematic reviews are available in Web Annex 2 (*1*) and available on the Internet at http://www.who.int/hiv/topics/drugresistance/en/.

2.5.2 Modelling

The outputs reviewed by the Guideline Development Group were generated by an individual-based simulation model (HIV synthesis model) of HIV transmission, progression of HIV and the effect of ART, which includes the effects of acquiring and transmitting drug-resistant virus. This model has previously been used to address several questions related to HIV and ART programmes, including HIVDR (*4–7*), and was used to model the impact of HIVDR on mortality, HIV incidence and cost of the HIV programme. Parameters such as ART adherence profile, ART interruption rate and rate of switch to second-line ART after first-line failure vary randomly within the plausible bounds for settings in the specific geographical region. The model is based on heterosexually transmitted HIV in adult populations in sub-Saharan Africa; the model therefore does not explicitly include children and does not consider how HIVDR affects mother-to-child transmission. The outcomes for each policy option are generated every three months and averaged over a 20-year time perspective (2018–2038).

Key underlying model assumptions have been published previously (*4,5,8,9*); the assumptions on DTG were informed by data from randomized trials and other sources (*9–29*) and include:

- a 27-fold lower risk of acquiring resistance mutations with TDF + FTC + DTG compared with TDF + FTC + EFV (similar to PI/r-based regimens);
- half the risk of neurological toxicity with TDF + FTC + DTG compared with TDF + FTC + EFV and zero risk of rash with DTG (hence lower rate of discontinuation);
- 1.5 times potency for DTG compared with EFV (for PI/r, two times higher potency is assumed);
- a DTG cost of US$ 44 (US$ 106 for DTG + 3TC + TDF), EFV of US$ 38 (US$ 100 for EFV + 3TC + TDF), PI/r of US$ 213;
- a one-off country transition cost to change the first-line regimen of US$ 100 000; and
- an HIVDR resistance test costing US$ 100 per test.

2.5.3 Acceptability, values and preferences

The evidence relating to the acceptability and values and preferences of end-users (people living with HIV, programme managers and clinicians and other health-care workers) was reviewed using a combination of methods:

- three separate online surveys targeted at each end-user population described above, using the well-established SurveyMonkey Inc. (San Mateo, CA, USA, www.surveymonkey.com) platform (February and March 2017);

[6] PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

- surveys carried out using a questionnaire with closed and open questions during HIVDR expert meetings (February 2016); and
- surveys carried out using a questionnaire with closed and open questions during a series of consultations with health ministries, programme managers, implementing partners and donors, held in five WHO regions or subregions: African Region (lusophone, francophone and anglophone), European Region, South-East Asia Region, Western Pacific Region and Latin America (April and September 2017).

2.5.4 Cost and feasibility

The above-mentioned HIV synthesis model (section 2.5.2) was used to assess the cost and cost-effectiveness of policy options considered by the Guideline Development Group. Since this model is less relevant for countries with concentrated epidemics and high rates of non-heterosexual transmission of HIV, all other available models assessing DTG as a first-line agent and use of pretreatment HIVDR testing were systematically evaluated. The Guideline Development Group reviewed and discussed data from other cost–effectiveness models, some of them relevant for middle-income countries with concentrated HIV epidemics. In addition, the Guideline Development Group considered and assessed laboratory capacity and infrastructure for HIVDR testing in low- and middle-income countries.

Programmatic data from country implementation experience were used to support decision-making and assess feasibility. Programme data from Botswana and Brazil were presented to the Guideline Development Group, and an online WHO survey was used to ascertain the views of HIV programme managers in all WHO regions. The conclusions from the HIV programme manager surveys supported discussions on the feasibility of proposed interventions.

2.6 Process of formulating recommendations and consensus statement

The Guideline Development Group met in Geneva, Switzerland in March 2017 to review the evidence and to formulate recommendations and a consensus statement.

2.6.1 Recommendations

The Guideline Development Group considered the systematic reviews addressing the PICO questions and evidence-to-decision-making tables prepared in accordance with the GRADE process (Table 2.3) in making recommendations. The methodologist facilitated discussions. The systematic review results included GRADE evidence profile tables for outcome data (*1*).

For one of the possible public health responses (using HIVDR testing), based on the review of the evidence, the Guideline Development Group decided not to make a formal recommendation but included this intervention as a consideration within the consensus statement.

2.6.2 Consensus statement

When reaching consensus on the threshold of pretreatment HIVDR to NNRTIs at which a public health response should be triggered, the Guideline Development Group was asked to discuss the following three areas:

- whether a consensus statement was necessary to guide country-level decisions;
- agreement on the public health response(s) that would be triggered; and
- consensus on the quantitative threshold(s) of pretreatment HIVDR to trigger the response.

In establishing the threshold for pretreatment HIVDR to NNRTIs for public health and ART programme action, the methodologist facilitated the process below:

- consideration and discussion among the Guideline Development Group on the current and historical prevalence data, the systematic review showing how HIVDR affects treatment outcomes, modelling data and the acceptability and feasibility of the interventions;
- agreement that a consensus statement was necessary to guide country-level decisions;
- discussion regarding WHO-proposed options for the format of the threshold (staggered thresholds, one overarching threshold or others in accordance with suggestions from the group); and
- formulation of the consensus statement.

The group reached consensus without the need to vote.

2.7 External review

Members of the External Review Group were selected to ensure geographical and gender balance, ensuring broad expertise in public health, programme management and community representation. They reviewed a draft of the guidelines to comment. An online format was used to compile comments and suggested revisions. The online document allowed for increased consensus in the peer-review process, enabling transparent and real-time commenting and the possibility for individuals to respond (agree, disagree or expand) to other reviewers' feedback. The WHO Steering Group then reviewed all comments and resolved disagreements. All comments received were reviewed with subsequent action, indicating whether specific changes had been made to the guidelines in response to the comments. The members of the Guideline Development Group, people who had provided supporting evidence and the WHO Steering Group also reviewed the draft guidelines.

2.8 Declaration of interests

Conflicts of interests were managed as follows.

1. All external contributors to the development of these guidelines, including members of the Guideline Development Group and External Review Group, were required to complete a WHO declaration of interests form before engaging in the guideline development process and participating in the Guideline Development Group meeting. All contributors were requested to promptly notify WHO if any of the disclosed information changed during the course of this work.
2. In accordance with the WHO declaration of interests policy for experts, brief biographies of all members of the Guideline Development Group were published on the WHO HIV website for a period of 14 days, including a description of the objectives of the Guideline Development Group meetings. No public comments or objections were received concerning the Group's members.
3. The WHO Steering Group reviewed the completed declaration of interests forms and carried out online searches for potential conflicts, focusing on results from the last four years, with a view to managing disclosed interests in the use of ARV drugs for treating HIV infection and for interests in the use of laboratory assays to detect HIVDR. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts could affect the expert's objective judgement on the guideline development process and recommendations. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflict of interests outlined in the WHO *Handbook for guideline development (30)*.
4. Based on extensive review of the declaration of interests forms and consultation with the Ethics Officer (Office of Compliance, Risk Management and Ethics Department), it was deemed that two candidates for the Guideline Development Group declared significant possible conflicts of interest relevant to the subject matter of the meeting. They were therefore excluded from the Guideline Development Group ahead of the meeting.
5. No significant conflicts of interest were identified for Guideline Development Group members who attended the meeting. All relevant declared interests are summarized, with the agreed level of participation during the formulation of recommendations *(31)*. All Guideline Development Group members participated fully during the meeting.
6. Declared interests were shared with all participants at the Guideline Development Group meeting, so that the group was aware of any existing interests, non-financial and financial, among the members. The co-chairs and WHO Steering Group managed Guideline Development Group interventions with an eye to eliminating conflicts of interest by ensuring that all members were able to express their views and ensuring that no one member pursued their viewpoint exhaustively.
7. Comments on the guidelines received from the External Review Group were reviewed in relation to the interests declared by the individual members.
8. All declaration of interests forms are on electronic file at WHO's Department of HIV and will be maintained for 10 years.

Declaration of interests of Guideline Development Group members and conflict of interest management plan are provided in Web Annex 1 (18).

PUBLIC HEALTH RESPONSE TO PRETREATMENT HIV DRUG RESISTANCE

3

3. PUBLIC HEALTH RESPONSE TO PRETREATMENT HIV DRUG RESISTANCE

3.1 Background

A recent systematic review assessing the prevalence of pretreatment HIVDR between 1993 and 2016 from 56 044 ARV drug–naive initiators or initiators with prior exposure to ARV drugs across 63 low-and middle-income countries showed an increase in pretreatment HIVDR for any drug class over time (*1*).

NNRTI resistance was higher in more recent studies across all regions ($P < 0.05$). The estimated annual incremental increase of pretreatment HIVDR to NNRTIs was 29% (95% CI 17–42%) in eastern Africa, 23% (95% CI 16–29%) in southern Africa, 17% (95% CI 6–29%) in western and central Africa, 15% (95% CI 10–20%) in Latin America and 11% (95% CI 2–20%) in Asia.

Subanalyses, restricted to studies sampling people from 2014 to 2016, showed prevalence of NNRTI resistance close to 10% in each region: 10.1% in eastern Africa (95% CI 8.1–12.2%), 10.7% in southern Africa (95% CI 8.4–13.7%), 8.8% in Latin America (95% CI 6.2–12.4%) and a lower prevalence of HIVDR in western and central Africa (5%, 95% CI 2.7–7.9%) and Asia (4%, 95% CI 2.1–6.7%).

The results from this systematic review, published in WHO's 2017 report on HIVDR (*1*), are broadly consistent with findings from recent nationally representative surveys of pretreatment HIVDR in Africa, Latin America and Asia (Box 3.1).

Box 3.1 Target populations of pretreatment HIVDR survey

In WHO surveys, pretreatment HIVDR is typically measured among all individuals starting first-line ART. This population includes the following subpopulations: (1) ARV drug–naive first-line ART initiators; (2) first-line ART initiators reporting prior ARV drug exposure (such as women exposed to ARV drugs for PMTCT); and (3) first-line ART reinitiators with a previous history of treatment. In the first case, pretreatment HIVDR reflects transmitted HIVDR; in the second and third cases, it can reflect acquired HIVDR from ARV drug exposure. Regarding groups 2 and 3, in most low- and middle-income countries, ARV drug exposure refers to NNRTI drug exposure, since this drug class is included in WHO PMTCT regimens and first-line ART regimens for adults and children older than three years.

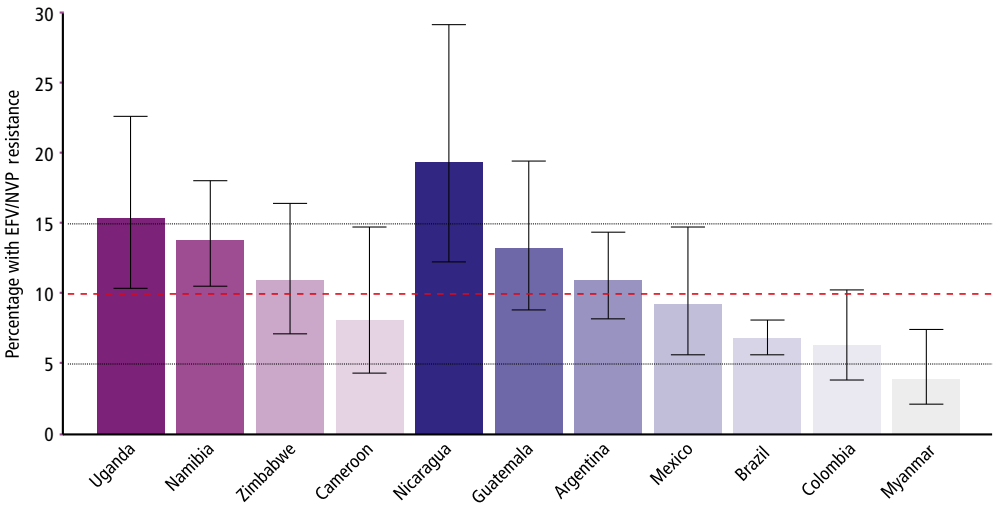
In the vast majority of low- and middle-income countries, NNRTI-based first-line ART is administered regardless of reported prior exposure to ARV drugs in the absence of documented treatment failure. Therefore, to reflect this programmatic reality in most countries, the population included in WHO surveys of pretreatment HIVDR includes all first-line ART starters (groups 1–3 above), regardless of reported history of prior ARV drug exposure.

Of the 11 countries reporting nationally representative survey data in populations initiating first-line ART between 2014 and 2016, six (Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe) had prevalence estimates of pretreatment HIVDR to NNRTIs[7] exceeding 10% and two (Nicaragua and Uganda) greater than 15% (Fig. 3.1).

Countries reporting the prevalence of pretreatment HIVDR to NNRTIs of less than 10% were Brazil, Cameroon, Colombia, Mexico and Myanmar. Brazil, Colombia and Mexico, however, monitored pretreatment HIVDR only in ARV drug–naive individuals, and this may explain the lower prevalence estimates in these countries.

In particular, pretreatment HIVDR to NNRTIs exceeded 10% in three of the four countries surveyed in Africa and ranged from 8.1% (95% CI 4.3–14.7%) in Cameroon to 15.4% (95% CI 10.3–22.5%) in Uganda. Pretreatment HIVDR to NNRTIs ranged from 6.3% (95% CI 3.8–10.2%) in Colombia to 19.3% (95% CI 12.2–29.1%) in Nicaragua (*1*).

Fig. 3.1. Pretreatment HIV drug resistance to EFV or NVP in first-line ART initiators (Pretreatment HIV drug resistance national surveys, 2014–2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3); sequences with predicted low-, intermediate- or high-level resistance are considered as resistant.

Source: *HIV drug resistance report 2017*. Geneva: World Health Organization; 2017 (*1*).

Both in a systematic review and across seven countries with national pretreatment HIVDR data for ART initiators with and without reported prior ARV drug exposure, pretreatment HIVDR to NNRTIs was significantly higher among previously exposed ART initiators than among ARV drug-naive people. Despite the increased risk of pretreatment HIVDR, people reporting prior ARV drug exposure in the absence of documented virological failure are typically reinitiated on an NNRTI-containing regimen in most countries. This is concerning, since this group can represent a significant proportion of first-line initiators (*2,3*) (Box 3.2; Fig. 3.2).

Box 3.2 describes in greater detail the populations at greatest risk of pretreatment HIVDR.

[7] Defined as resistance to EFV and/or NVP.

Box 3.2. Subpopulations at high risk of pretreatment HIVDR

Adults

A recent systematic review and meta-analysis *(1)* including 28 cohorts from low- and middle-income countries shows that pretreatment HIVDR to NNRTIs is significantly higher among individuals initiating first-line ART with prior ARV drug exposure compared with ARV drug–naive ART initiators in Asia (26% versus 3%, $P < 0.0001$), Latin America (36% versus 9%, $P < 0.0001$) and southern Africa (31% versus 4% ($P < 0.0001$). NRTI resistance was also significantly higher among individuals with previous ARV exposure in all regions.

The remarkable difference between pretreatment HIVDR to NNRTIs in drug-naive versus prior exposed first-line starters was also observed across the seven WHO recent national surveys of pretreatment HIVDR in low- and middle-income countries with pretreatment HIVDR data in ART initiators with and without prior ARV drug exposure. Pretreatment HIVDR to NNRTIs was significantly higher among previously ARV drug–exposed ART initiators (22%, 95% CI 14–32) than among ARV drug–naive people (8%, 95% CI 6–11%, $P < 0.0001$) *(1)*. The difference between the two groups was most pronounced in Namibia (9% in the ARV drug–naive group versus 35% in the ARV-exposed group), in Nicaragua (11% versus 76%, respectively), in Myanmar (3% versus 16%, respectively) and in Cameroon (8% versus 20%, respectively) *(1)* (Fig. 3.2).

Children

NNRTI resistance is also higher among children with prior PMTCT-related exposure than among ARV drug–naive children, suggesting that previous ARV drug exposure is a risk factor for pretreatment HIVDR across geographical locations, age groups and individual characteristics. A systematic review (2014–2017) documented high pretreatment HIVDR to NNRTIs among children starting ART (median pretreatment HIVDR to NNRTIs: 49%; range 7–100%) and especially in PMTCT-exposed children (four of seven studies found pretreatment HIVDR to NNRTIs among >50% of PMTCT-exposed children) *(1)*.

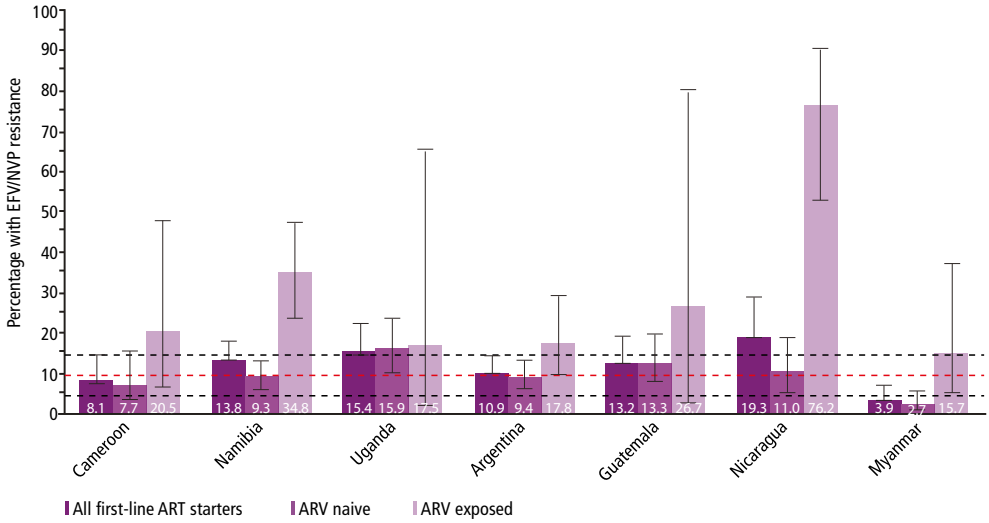
Self-reported previous use of ARV drug

Previous use of ARV drugs among people about to start first-line ART might be underreported to health-care providers because of fear of stigma and discrimination. In some national pretreatment HIVDR surveys, however, the proportion of people self-reporting prior use of ARV at the time of ART initiation was high, representing, for example, 18% of ART starters in Namibia, 12% of starters in Nicaragua and 19% of starters in Argentina *(1)*.

A large study from South Africa shows that 24% of 326 first-line ART initiators reported prior ARV drug exposure (17% prior PMTCT; 59% prior ART use; and 24% both PMTCT and prior ART use) and 42% of them had pretreatment HIVDR to NNRTIs (compared with 11% among ARV drug–naive people) (2) (personal communication, National Institute of Communicable Diseases, South Africa, May 2017). Other studies have reported high rates of first-line ART reinitiation after a period of disengagement from care. One quarter of the people receiving ART in a South African township disengaged from ART at least once during a recent two-year study period (2013–2014) *(3)*.

Prior exposure to ARV drugs is associated with poor response to ART. A subanalysis from the PASER African cohort showed that 83 people initiating first-line ART who self-reported previous NNRTI exposure had greater risk ofvirological failure at 12 months than ARV drug–naive people (n = 1944) (odds ratio (OR) 2.91; 95% CI: 1.48–5.72, P = 0.002) (6). In a study in Malawi, 24% of individuals with previous treatment interruption who reinitiated NNRTI-based ART experienced virological failure three months after reinitiation and had detected NNRTI resistance. All had to switch to second-line ART (7).

Fig. 3.2. Resistance to EFV or NVP in first-line ART initiators by reported prior ARV drug exposure (national pretreatment HIVDR surveys, 2014–2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3); sequences with predicted low-, intermediate- or high-level resistance are considered as resistant.

Source: *HIV drug resistance report 2017.* Geneva: World Health Organization; 2017 (1).

As the prevalence of pretreatment HIVDR increases, the financial and epidemic impact can be severe. Mathematical modelling predicts that, if the prevalence of pretreatment HIVDR exceeds 10% in sub-Saharan Africa and NNRTIs continue to be used in first-line ART regimens, over a 5-year period (2016–2020), pretreatment HIVDR is predicted to be responsible for cumulatively 135 000 AIDS-related deaths, 150 000 new HIV infections and US$ 650 million for ART cost in sub-Saharan Africa only (4) (Table 3.1).

Table 3.1. Projected impact of HIV drug resistance on AIDS deaths, new infections and ART costs in sub-Saharan Africa (pretreatment HIVDR >10%) during 2016–2020,[8] assuming the use of NNRTI-based regimens in first-line ART

	AIDS deaths	New HIV infections	ART costs
	2016–2020	2016–2020	2016–2020
Quantity attributable to HIVDR	135 000	105 000	US$ 650 million

Source: adapted from Phillips AN et al. J Infect Dis. 2017;215:1362–5.

[8] Using the Spectrum Goals Model, by applying the impact of drug resistance, as estimated using the HIV synthesis model. Estimating the current level of PDR in all ART initiators (including re-initiators) to be above 10%. Estimates based on adults only. Higher levels of drug resistance are seen in children, due to use of drugs aiming to prevent acquisition and higher levels of resistance acquisition on ART.

If not addressed, pretreatment HIVDR could jeopardize the anticipated durability and effectiveness of the currently recommended preferred first-line ART regimens for many people and have serious cost implications. In a recent publication from Aruba, an area in the Caribbean in which HIV is highly endemic, 54% of 104 individuals testing positive for HIV during 2010–2015 received pretreatment HIVDR testing; the prevalence of pretreatment HIVDR to NNRTIs was extremely elevated at 32% (95% CI: 23–41%). This instigated a change in local guidelines to reinforce baseline resistance testing and replace the WHO-recommended first-line regimen with an integrase inhibitor–based regimen (5).

3.2 Choice of first-line ART in the context of pretreatment HIVDR

Recommendation

For people initiating first-line ART with pretreatment HIVDR to NNRTIs,[a] a non-NNRTI-containing regimen may be preferable (*conditional recommendation, low certainty of the evidence*).

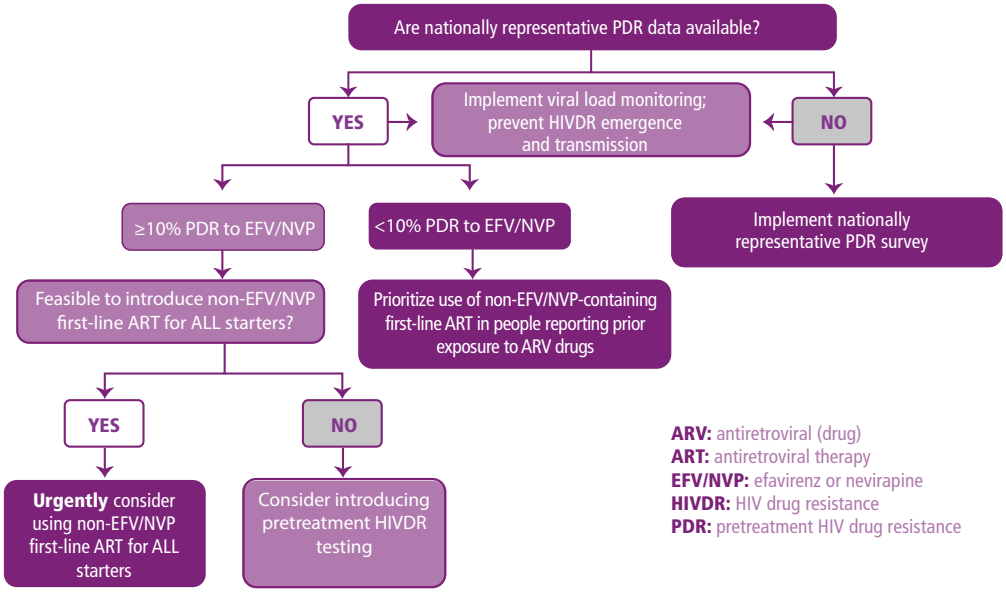
[a]Since individual-level HIVDR testing is largely unavailable in low- and middle-income countries, nationally representative pretreatment HIVDR data can be used to inform when public health actions should be taken at the population level (see section 3.4 and Fig. 3.3).

Considerations on the recomendation for subpopulations

- Among people at high risk of pretreatment HIVDR to NNRTIs as a result of prior exposure to NNRTIs or from other risks[12] (Box 3.2), a non-NNRTI-containing regimen may be preferable, regardless of the country prevalence of pretreatment HIVDR to NNRTIs and without the need to document the presence of NNRTI resistance by using an HIVDR test (Fig. 3.3).
- For children, pregnant women and individuals receiving rifampicin for the treatment of TB, the choice of a non-NNRTI-based regimen should be carefully considered in light of the limited options available, existing age-appropriate formulations, safety and potential drug interactions as well as the overall principles for drug optimization in ART programmes.

[9] The systematic review did not identify any other group except the one with prior ARV drug exposure that was independently characterized by a high risk of pretreatment HIVDR to NNRTIs. However, the Guideline Development Group agreed that, if other subpopulations are identified to be at high risk of pretreatment HIVDR regardless of prior ART exposure, they should also be given priority for receiving appropriate public health intervention while minimizing any possible risk of stigma and discrimination.

Fig. 3.3. Response to pretreatment HIV drug resistance



3.2.1 Rationale and supporting evidence for the recommendation

The Guideline Development Group made a conditional recommendation in favour of using an alternative non-NNRTI-based first-line regimen for people with detected pretreatment HIVDR to NNRTIs. This decision was based on the Guideline Development Group's assessment of the systematic review and GRADE evidence profiles that assessed the quality and certainty of the evidence, in addition to the supporting information presented to the Group. The Group decided that the benefits of implementing the recommendation probably outweighed its harm. The conditionality of the recommendation was primarily based on the low certainty of the evidence, in addition to some perceived challenges in introducing the currently recommended alternative first-line ART regimens (Table 1.1) for different populations, which is described in more detail below (Box 3.3).

The systematic review (*8*) included 26 studies (35 018 participants) focusing on children and/or adults: one randomized controlled trial (*9*), three case–control studies (*10*–*12*) and 22 cohort studies (*7*,*13*–*33*). Four of the cohort studies comprised children. One cohort study included both children and adults. Twenty-one cohort studies included adults only. The three case–control studies included adults.

The overall conclusions of the review were that, compared with people initiating a non-NNRTI-based regimen, people with pretreatment HIVDR to NNRTIs who initiated a NNRTI-based regimen are more than 30% less likely to achieve virological suppression, 23 times more likely to experience virological failure or death and nine times more likely to discontinue treatment.

Compared with those without NNRTI resistance mutations, people with pretreatment HIVDR to NNRTIs who use NNRTI-containing regimens are 13 times more likely to experience virological failure or death, almost five times more likely to experience virological failure as binary outcome or measured as a time to event (hazard ratio (HR) 3.04) and five times more likely to discontinue treatment. Pretreatment HIVDR and pretreatment HIVDR to NNRTIs had similar negative effects on treatment outcome among children compared with adults.

The values and preferences of people living with HIV varied slightly in support of using alternative non-NNRTI regimens, with most favouring it. The intervention was (highly) acceptable to programme managers and health-care providers, and equity was likely to increase with access to non-NNRTI regimens for those in greatest need (people for whom NNRTI treatment is more likely to fail because of pretreatment HIVDR). The intervention is feasible with widespread use in several countries; in most settings, cost would not be a barrier and the intervention is predicted to be cost-effective (34). However, if a change in first-line regimen is not feasible on a large scale, giving priority to individuals starting ART with prior exposure to NNRTIs and possibly further groups at increased risk of HIVDR was justified from an equity and acceptability perspective.

3.2.2 Comparing benefits and harm

Overall, based on review of the data presented from the systematic review, the Guideline Development Group deemed that the benefits of the intervention outweighed the harm.

Of the 26 studies included in the systematic review (8), nine were large multinational cohorts: three were based in Africa, one in Asia and five across two or more continents. One study included previously exposed women; four studies included treatment-naive children; one study included both treatment-naive children and adults; and the rest included treatment-naive adults. Four studies included mixed populations (exposed and naive to ART). One study included only people who had been previously exposed to single-dose nevirapine (NVP). All other studies included only treatment-naive people.

Seven studies compared treatment outcomes among children and adults with pretreatment HIVDR to NNRTIs initiating an NNRTI-containing regimen with people with pretreatment HIVDR to NNRTIs initiating a non-NNRTI-containing regimen (9–11,17,18,24,26).

Viral suppression was less likely among people with pretreatment HIVDR on NNRTI-containing regimens (OR 0.66, 95% CI: 0.45–0.97) (10) (*very low certainty of the evidence*).

Viral failure or death was more likely among people with pretreatment HIVDR on NNRTI-containing regimens when measured as a time-to-event (HR 3.6, 95% CI 1.7–7.5, *low certainty of the evidence* (9) or binary outcome (OR 22.9, 95% CI 4.74–110.3, *very low certainty of the evidence*) (17).

Discontinuation was more likely among people with pretreatment HIVDR on NNRTI-containing regimens (OR 8.70; 95% CI: 3.51–21.53) (9) (*low certainty of the evidence*).

There was no difference in time to virological failure (18,24), time to viological suppression (25) (OR 0.66; 95% CI: 0.45–0.97) or progression to AIDS (9) (OR 1.5; 95% CI: 0.40–5.63) (*very low certainty of the evidence*). Nor was there any difference in adverse events when measured as symptoms or as laboratory abnormalities (9) (*low certainty of the evidence).* No studies reported quality of life outcomes.

Although the overall study results were consistent in favouring the use of a non-NNRTI-containing regimen, the certainty of the evidence was downgraded because of indirectness (studies not directly addressing the participants, exposure, comparison or outcomes of interest), inconsistency (considerable statistical heterogeneity) and imprecision (wide confidence intervals).

One clinical trial showed higher risk of virological failure or death, increased discontinuation, no difference in adverse events (Grade 3+, laboratory abnormalities) and progression to higher WHO stage among people with pretreatment HIVDR on NNRTI regimens compared with non-NNRTI-based regimens (9). For these outcomes, the certainty of the evidence was graded as low because of: (1) indirectness, since the effect of pretreatment HIVDR was not based on a randomized comparison; (2) the population in this study being very specific: women previously exposed to single-dose NVP; and (3) the drugs compared in this study (NVP versus LPV/r) not fully reflecting the scope of evidence sought (EFV versus non-NNRTI).

The findings from 26 studies (6,9–33) comparing outcomes among children and adults initiating an NNRTI-containing first-line ART regimen with pretreatment HIVDR compared with people without pretreatment HIVDR are consistent with those presented above.

Virological failure was more likely among people who had pretreatment HIVDR compared with no pretreatment HIVDR when measured as a binary outcome (OR 2.96, 95% CI 1.89–4.65; 12 studies *(6,13,16,20,21,24,25,28–31,33); very low certainty of the evidence*) or time to event outcome (HR 2.49, 95% CI 1.92–3.25; seven studies *(10,12,18,19,22,27,32); very low certainty of the evidence)*.

The risk of virological failure or death (composite outcome) was greater among people who had pretreatment HIVDR compared with no pretreatment HIVDR when measured as a binary outcome (OR 8.23; CI 3.47–19.53; three studies *(11,17,23); very low certainty of the evidence*) or as time-to-event outcome (HR 8.70; CI 3.50–21.63; one study *(9); low certainty of the evidence*).

Time to virological suppression was longer for people with pretreatment HIVDR versus no pretreatment HIVDR (HR 0.64; CI 0.49–0.83; two studies *(14,26); very low certainty of the evidence*).

New resistance-associated mutations after treatment were more likely among people with pretreatment HIVDR compared with people without pretreatment HIVDR (OR 2.44; 95% CI: 1.69–3.51; *very low certainty of the evidence*) *(6,30)*.

Discontinuation of ART was more likely among people with pretreatment HIVDR when measured as a binary outcome (OR 3.18; 95% CI: 1.53–6.61; *very low certainty of the evidence*) *(11,13)* or time-to-event outcome (HR 3.80; 95% CI: 1.49–9.69) *(15)*.

There was no difference in new AIDS events when measured as a binary outcome (OR 1.74, CI 0.56–5.43, one study (11), very low certainty of the evidence) or time-to-event outcome (HR 1.06, 95% CI 0.68–1.65; one study (15), very low certainty of the evidence). There was no difference in death (OR 1.96; CI 0.17–22.46; one study (11), very low certainty of the evidence) or in time to death among people with pretreatment HIVDR compared with those without (HR 0.75, 95% CI 0.24–2.34; one study (15), very low certainty of the evidence). No studies reported quality-of-life outcomes or adverse event outcomes.

In a subset of nine studies assessing outcomes among children and adults initiating an NNRTI-based regimen with and without pretreatment HIVDR to NNRTIs (9,12,13,17,20,22–25), the negative effect of pretreatment HIVDR to NNRTIs on outcome was even stronger.

The risk of virological failure was higher among people who had pretreatment HIVDR to NNRTIs compared with people without pretreatment HIVDR to NNRTIs when measured as a binary outcome (OR 4.51; 95% CI: 2.76–7.36, low certainty of the evidence) (13,17,20,25) or as time-to-event outcome (HR 3.04; 95% CI: 1.88–4.89, low certainty of the evidence) (12,22).

Virological failure or death (composite outcome) was more likely among people who had pretreatment HIVDR to NNRTIs versus no pretreatment HIVDR to NNRTIs when measured as binary outcome (OR 12.98; 95% CI: 4.74–39.08) (17,23) or as time-to-event outcome (HR 8.70; 95% CI: 3.50–21.63, low certainty of the evidence) (9).

Discontinuation of ART was more likely among people with pretreatment HIVDR to NNRTIs than people without pretreatment HIVDR to NNRTIs (OR 5.00; 95% CI: 1.70–14.70, very low certainty of the evidence) (13).

Pretreatment HIVDR in children and adolescents

A subanalysis of the systematic review assessed how pretreatment HIVDR affected treatment outcomes among children younger than 10 years and adolescents 10–19 years old inclusive. The negative effect of pretreatment HIVDR was similar across age groups (adults versus children and adolescents) initiating an NNRTI-based regimen for the outcomes of virological failure and incident resistance mutations, with no subgroup effect. The systematic review identified a subset of four studies assessing pretreatment HIVDR and how it affected outcomes among individuals initiating a NNRTI-containing regimen <10 years old, <18 years old, <13 years old and <12 years old, respectively (17,18,23,30).

The risk of virological failure or death was greater among children with NNRTI mutations starting NNRTI-based ART versus non-NNRTI-based ART (OR 22.9; 95% CI 4.74–110.3) (17). The time to virological failure was similar in the two groups.

The risk of virological failure or death was higher among children with pretreatment HIVDR to NNRTIs compared with children without NNRTI mutations (OR 12.98; 95% CI: 4.74–39.08) (17,23).

Virological failure was more likely among children with pretreatment HIVDR than among children without pretreatment HIVDR (OR 15.25; 95% CI: 3.77–61.69) (30).

Acquisition of new HIVDR mutations was more likely to occur among children with pretreatment HIVDR than among children without pretreatment HIVDR (OR 3.47; 95% CI: 1.31–9.19) (30).

Conclusions from the systematic review in adults and children

In conclusion, adults and children with pretreatment HIVDR to NNRTIs initiating NNRTI-containing regimens showed worse outcomes than did people initiating or reinitiating non-NNRTI-containing regimens. Specifically, people with pretreatment HIVDR to NNRTIs initiating NNRTI-based regimens were less likely to achieve virological suppression, more likely to experience virological failure or death (measured as a binary and time-to-event outcome) and more likely to discontinue treatment than people initiating a non-NNRTI-based regimen; adverse events and progression to AIDS were similar in the two groups.

In addition, adults and children with NNRTI drug resistance mutations when starting an NNRTI-based ART regimen were more likely to experience virological failure or death (measured as a binary and time-to-event outcome), less likely to achieve viral suppression and more likely to discontinue

treatment than people without NNRTI resistance mutations; and similarly, were more likely to acquire new resistance mutations and discontinue treatment than people without any pretreatment HIVDR mutations. No studies comparing the outcomes of people with and without pretreatment HIVDR or with and without pretreatment HIVDR to NNRTIs reported quality-of-life or adverse-event outcomes.

The effect of pretreatment HIVDR on treatment outcome persisted in studies in which the treatment regimen was fully or mostly consistent with WHO's recommendation (TDF + XTC + EFV) *(10,13,14,24,27,28)*. The effect of pretreatment HIVDR did not differ based on whether the NNRTI used was NVP or EFV.

The overall benefit of using a non-NNRTI regimen in the face of pretreatment HIVDR is to avoid the risk of suboptimal outcomes, including new resistance-associated mutations, ART discontinuation, viral failure or the combined outcome of viral failure or death.

The systematic review did not identify any harm in using a non-NNRTI-containing regimen among people with pretreatment HIVDR. Possible harm may relate to the choice of an alternative non-NNRTI-containing regimen for certain populations in which the safety and toxicity evidence has not yet been fully determined. The 2016 WHO consolidated ARV guidelines describe this, and it is also summarized in Boxes 3.3 and 3.4 and under the considerations for different drug classes.

Considerations for using a DTG-containing regimen in first-line ART

The 2016 WHO consolidated ARV guidelines included DTG as an alternative option in first-line ART for adults and adolescents because it is associated with durable viral suppression, improved clinical outcomes, high tolerability and low toxicity *(35)*.

- A systematic review and network meta-analysis assessing the efficacy and safety of the integrase strand transfer inhibitors (INSTIs) among ART-naive adults in seven randomized controlled trials *(36–42)* showed that a regimen with two NRTIs + INSTI was generally more effective (with higher viral suppression and CD4 cell recovery rates and lower risk of ART discontinuation) than two NRTIs + EFV *(moderate certainty of the evidence) (43)*.
- DTG has clinical and programmatic advantages, including shorter median time to viral suppression, lower potential for drug interactions and a higher genetic resistance barrier compared with EFV and other ARV drugs *(35)*.
- In countries with an HIV-2 epidemic, DTG could bring important added value, since HIV-2 is inherently resistant to NNRTIs but seems to be sensitive to DTG *(34,44)*. However, all available data are in vitro *(45)*, and data from in vivo clinical studies are not yet available.

The 2016 WHO consolidated ARV guidelines (35) outline the considerations of the potential harm of and barriers to using DTG-based regimens as follows:

- There is limited availability of generic formulations and fixed-dose combinations as of mid-2017.
- Currently, there is only one approved producer of a generic DTG stand-alone formulation.
- ABC + 3TC + DTG is the only fixed-dose combination available on the market and mainly in high-income countries at very high prices (non-generic formulation). The alternative non-NNRTI first-line regimen (TDF + XTC + DTG) is not currently available as a fixed-dose combination but is anticipated to be in 2018.

- Information is limited on the safety and efficacy of DTG regimens when used during pregnancy or when used during the rifampicin phase of TB treatment.
- The long-term safety of DTG is unknown, since studies have only evaluated its safety and efficacy until 48–96 weeks. In addition, there is still an unknown risk of neurological side-effects when using an alternative DTG-containing regimen and an unknown risk of immune reconstitution inflammatory syndrome.

Box 3.3 Challenges of using DTG among children, pregnant women and people with active TB who are taking rifampicin (in accordance with the 2016 WHO consolidated ARV guidelines (35))

- Because suitable dosing and safety data are lacking for children, the 2016 WHO consolidated ARV guidelines did not consider a DTG-based regimen as an alternative first-line ART for children. However, in December 2016, the European Medicines Agency approved the use of DTG for children older than six years and weighing more than 15 kg (*46*). In addition, the IMPAACT 1093 trial investigating the dosing and safety of DTG from four weeks of age is expected to be completed by the end of 2017 (*47*). The WHO guidelines will take this new information into account in the next revision, planned for 2019.

- The efficacy of DTG in TB and HIV coinfection is not well established, and dose adjustments are needed with TB drugs. EFV is safe for people with active TB who are taking rifampicin, and no dose adjustment is needed. Pharmacokinetic modelling studies suggest that rifampicin can significantly lower the plasma concentrations of DTG. Thus, pharmacologists currently advise using a double dose of DTG (50 mg twice daily) to overcome the interaction with rifampicin, but specific pharmacokinetic data and clinical experience with this drug among people living with HIV and TB are very limited. Specific studies are either ongoing or planned.

- The safety of DTG in pregnancy is not well established. There are currently no published safety data available on the outcomes of treating HIV with DTG-based regimens during pregnancy. Further, calcium or iron supplements, frequently used during pregnancy, could significantly reduce DTG drug levels (*48*). Pharmacokinetic studies of DTG in pregnancy, and when coadministered with TB drugs, are either planned or in progress (*49,50*). At present, reproductive toxicity is not considered to be a risk for DTG based on the clinical and non-clinical findings to date (*51–54*). At present, there are too few data to signal a risk or lack of risk of congenital abnormalities with DTG use during pregnancy.

Considerations of using an RTV-boosted PI-containing regimen in first-line ART

As reported in the 2016 WHO consolidated ARV guidelines (*35*), PI/r-containing regimens represent the only non-NNRTI option in first-line ART for children, pregnant women and people living with HIV and TB taking rifampicin. However, recent data among pregnant women using TDF + FTC + LPV/r are concerning and deserve attention (Box 3.4).

Several studies described in the 2016 WHO consolidated ARV guidelines have demonstrated that the combination of two NRTIs plus EFV is at least as effective, if not more, in achieving viral suppression than two NRTIs plus a PI, including LPV/r. The INITIO (*55*) and ACTG 384 (*56*) trials demonstrated greater antiviral activity in the two NRTIs + EFV arm than in the two NRTIs + PI

arm and no additional benefit of using all three drug classes. The ACTG 5142 (57) trial was a multicentre open-label study of treatment-naive people who were randomly assigned to receive LPV/r plus two NRTIs, EFV plus two NRTIs or EFV plus LPV/r alone (a nucleoside-sparing arm). At 96 weeks, viral suppression (<50 copies/mL) was achieved in a significantly greater proportion of people on the EFV arm compared with either the LPV/r arm or the NRTI-sparing arm. Several metabolic abnormalities, including dyslipidaemia and insulin resistance, have been associated with PI use. Currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a pharmacokinetics-enhancing agent. Two large observational cohort studies suggested that LPV/r, IDV, FPV or FPV/r may be associated with increased rates of myocardial infarction or stroke (58,59). This association was not seen with ATV. Because of the limited number of people receiving DRV/r, this boosted-PI was not included in the analysis of the two studies. However, the D: A: D group recently reported an association between DRV/r and an increased risk of cardiovascular disease (60).

Specifically, the overall frequency of adverse events was similar in the two groups when EFV and ATV/r were compared in treatment-naive patients: rash and dizziness occurred more frequently with EFV, and jaundice and scleral icterus occurred more frequently with ATV. Serious adverse events occurred in 10% of each group (61).

Box 3.4 Challenges of using PI/r-based regimens among children and pregnant women (in accordance with the 2016 WHO consolidated ARV guidelines (35))

Until recently, PI/r use among children was limited by lack of heat-stable palatable formations that did not require a cold chain to the point of distribution and lack of fixed-dose combinations of LPV/r with an NRTI backbone. Recently, heat-stable LPV/r pellets that are easy to administer have become available (62); however, supply remains limited, and priority should be given to children younger than three years, who cannot swallow tablets. LPV/r heat-stable tablets are being procured for second-line ART use and can be used for children older than three years. RAL is approved for use among infants and children from the age of four weeks, although limited evidence informs about using RAL as a first-line drug among infants and young children (63). Use of RAL may be limited by the challenges of existing granule formulation, despite being suitable for use for infants four weeks and older, since reconstitution in water is required before administration. Although dispersion of RAL chewable tablets is considered a potential alternative, additional information regarding the appropriateness of this approach will be provided as more data become available. Other PIs, such as ATV and DRV, while safe and effective, are not co-formulated with RTV in formulations for children and present significant programmatic and administration challenges, which should be considered when selecting a non-NNRTI regimen.

A recent trial among pregnant women showed that, compared with AZT alone, ART containing TDF resulted in significantly lower rates of early HIV transmission. However, the data also suggested that the use of TDF (compared to AZT) in combination with elevated doses of LPV/r (as recommended by the United States Department of Health and Human Services) resulted in higher rates of preterm delivery before 34 weeks of gestation and early infant death, suggesting significant drug–drug interactions between TDF and LPV/r when administered at a higher dose (64). The relationship between TDF and the elevated LPV/r doses used in the third trimester of pregnancy in this study are undergoing further review in an effort to better understand the suboptimal outcomes.

3.2.3 Cost and cost–effectiveness

Cost of DTG-containing regimens

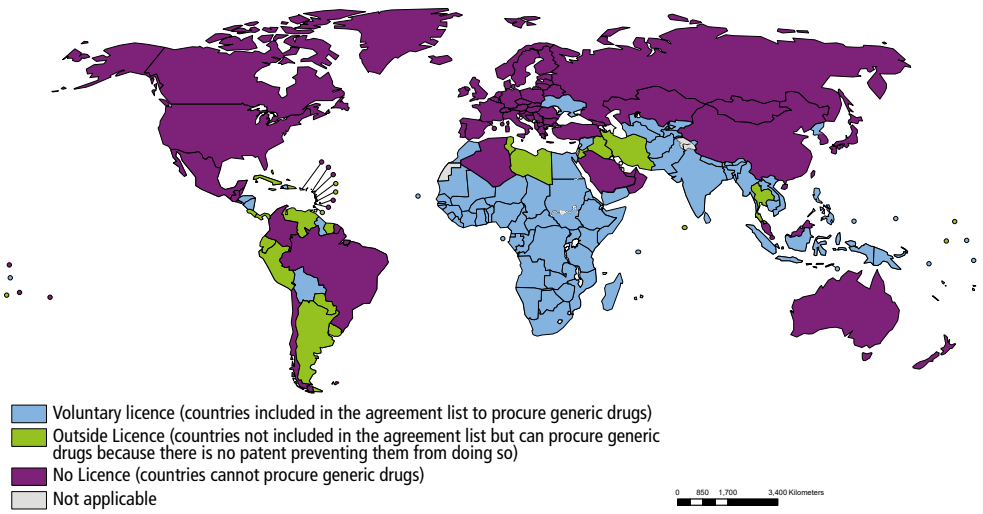
A change from EFV-based ART to DTG-based ART may initially be associated with a small increase in overall drug costs because of the cost differential between DTG 50 mg and EFV 600 mg as single formulations.

In December 2015, a pricing agreement was developed between UNITAID, UNAIDS, the Clinton Health Access Initiative and Aurobindo to launch DTG 50 mg at US$ 44 per person per year (65), so that in low- and middle-income countries that are covered by the licence from ViiV Healthcare, the cost of treatment with TDF/3TC + DTG (about US$ 93–98 per person per year) would be similar to treatment with the TDF + 3TC + EFV triple fixed-dose combination.

However, the cost would be expected to progressively decline even further, particularly as fixed-dose combinations are launched with increased volumes and competition among generic manufacturers of DTG. In addition, there would likely be savings in the long term by reducing switching rates to more costly second-line regimens. According to Clinton Health Access Initiative forecasting projections, up to 7 million people could be receiving a DTG-containing first-line regimen at the end of 2021, since DTG is expected to be provided to new ART initiators and to a proportion of people currently receiving NNRTI-based ART (for example, South Africa is planning to switch up to 4 million people to DTG within two years after its launch). By 2025, there is the potential to save drug costs up to US$ 300 million to US$ 380 million annually collectively in low- and middle-income countries accessing generic ARV drugs if DTG is widely adopted in first-line ART regimens (66).

The current price of DTG varies considerably from country to country, depending on the licence agreement and availability of generic formulation (92 countries will be able to purchase a generic version of DTG, in addition to 39 countries outside the generic licence) (Fig. 3.4).

Fig. 3.4. Current status of DTG generic licence in countries (March 2017)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization 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.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

In countries with no licence to procure generic drugs, costs vary and can be extremely high. Ninety-two countries or territories are included under the DTG voluntary licence agreement, mostly low- and middle-income countries; 39 countries or territories can procure generic drugs, because there is no patent preventing them from doing so; they are not part of the voluntary licence agreement. DTG non-generic formulations (stand-alone and fixed-dose combinations) are available at very high costs in high- and upper-middle-income countries (US$ 10 000 per person per year or more). Some low- and middle-income countries that adopted DTG early on have obtained price reductions through direct negotiations with the originator, resulting in prices of US$ 200–500 per person per year. The cost of DTG alone in Mexico is US$ 2200 per person per year. In Brazil the cost is about US$ 500 per person per year, and in Belarus it is US$ 1600 per person per year. In other countries, the cost of DTG alone is lower. For example, in Ukraine it is US$ 72 per person per year, and in Botswana it is US$ 272 per person per year. In countries where generic DTG can be purchased, the price of DTG-based ART is similar to or is lower than EFV-based ART, as described earlier (67). The first generic DTG single formulation is only just being commercialized, and triple fixed-dose combinations are likely to be available at the end of 2017 or early 2018.

Cost of a PI/r-containing regimen

The cost of generic DTG is significantly lower than the cost of PI/r: LPV/r costs US$ 223 per person per year; ATV/r costs US$ 197 per person per year; and DRV/r costs US$ 908 per person per year. However, in countries where generic DTG cannot be procured, the cost of PI/r, while high, can be lower than the cost of DTG.

Cost–effectiveness of three different policy options in the context of elevated prevalence of pretreatment HIVDR: EFV-based regimens, DTG-based regimens and pretreatment HIVDR testing

To support the development of these guidelines, modelling was performed to predict how various strategies affect adult mortality, HIV incidence and viral load suppression in sub-Saharan African countries where pretreatment HIVDR to NNRTIs exceeded 10% (median 19%). The model, described above (see section 2.5.2 and Table 3.2), compared the cost–effectiveness of three strategies.

- Policy option 1: introduce a DTG-based regimen for all new first-line ART initiators.
- Policy option 2: introduce pretreatment HIVDR testing among first-line ART initiators and switch people with detected NNRTI resistance to a DTG-based regimen.
- Policy option 3: no action (continue to use an NNRTI-containing regimen for all first-line ART starters (TDF + XTC + EFV).

Cost–effectiveness of policy option 1: using a DTG-containing regimen in first-line ART

The model showed that, in sub-Saharan Africa, if NNRTI pretreatment HIVDR exceeds 10% (median 19%), using a DTG-based ART regimen for first-line initiators (compared with using EFV-based ART) is predicted to result in better health outcomes, which are averaged over a 20-year period (Table 3.2). In particular, DTG for new first-line ART initiators is predicted to lead to:

- increased prevalence of viral load suppression (from a mean of 77% to 86%);
- reduced mortality (from 4.5 to 3.5 per 1000 population per year); and
- reduced HIV incidence (from 0.79 to 0.72 people newly infected with HIV per 100 population per year) (68).

This model predicts that, in sub-Saharan Africa and in settings in which the cost of a DTG-containing regimen is similar to the cost of an EFV-based regimen, use of DTG in first-line will be cost-effective, and could even be cost-saving, at any prevalence of pretreatment HIVDR to NNRTIs observed at the country level, because of the beneficial properties of DTG also conferred on individuals without drug-resistant HIV.

Table 3.2. Health benefits in the response to HIVDR where the prevalence of pretreatment HIVDR to NNRTIs exceeds 10% in sub-Saharan Africa

Policy option	Viral load <1000 copies/mL Annual mean %	Mortality Mean rate for people receiving ART per 100 people per year	HIV incidence Mean rate per 100 person years
DTG-based first-line ART	86%	3.5	0.72
Pretreatment HIVDR testing	83%	3.9	0.74
EFV-based first-line ART	77%	4.5	0.79

Cost–effectiveness of using a PI/r-based regimen

The option of using PI/r-based first-line ART was not compared with DTG-based first-line ART in the most recent modelling, because PI/r regimens are more expensive in sub-Saharan Africa, and randomized trials have shown the superiority of DTG as first-line treatment of HIV (*69*). However, a PI/r (ATV/r)-containing regimen was previously compared with NNRTI-based first-line ART using the same HIV synthesis model. The cost assumptions were: EFV of US$ 39 and PI/r of US$ 219. Changing first-line ART to a PI/r-regimen was cost-effective when the prevalence of pretreatment HIVDR to NNRTIs was higher than 15%, for cost–effectiveness thresholds greater than US$ 2000 per disability-adjusted life-year (DALY) averted (*70*). Of note, a cost–effectiveness threshold of US$ 2000 per DALY is unlikely to be realistic in low-income settings.

3.2.4 Acceptability

A review of the evidence relating to the acceptability of end-users was collated from online surveys and five in-person regional consultations in Africa (francophone, anglophone and lusophone), Asia, eastern Europe and Central and South America between April 2016 and March 2017 (see section 2.5.3).

Health-care workers

Between February and March 2017, WHO conducted an online survey of health-care workers. Eight key networks of health-care workers[10] were contacted, and snowball sampling was encouraged to increase the number of respondents. In total, 396 responses were received from health-care workers from 61 countries, of which 85% were from low- and middle-income countries.

The greatest perceived challenges of changing from the current first-line ART regimen to a non-NNRTI-containing first-line regimen was the need for health-care worker training and a lack of available and affordable alternative regimens in appropriate formulations.

Notably, 42% reported that their current practice is to start everyone on the same NNRTI-based first-line ART regimen, regardless of perceived pretreatment HIVDR risk. A total of 25% reported starting an alternative first-line ART regimen in cases of perceived pretreatment HIVDR risk: for example, for individuals with prior NNRTI exposure. A differentiated ART regimen approach (starting non-NNRTI-based ART only for individuals at the highest risk of pretreatment HIVDR on an alternative first-line regimen) was generally well accepted. The main challenges were ensuring the availability of regimens (the standard and the alternative first-line regimen) at the clinic or facility (66%), training health-care workers (62%) and identifying eligible people (55%).

Programme managers

Between February and March 2017, WHO carried out an online survey of ART programme managers to determine the acceptability of possible public health interventions in response to the elevated prevalence of pretreatment HIVDR. In total, 57 ART programme managers from 43 countries responded to the survey, of which 82% were from low- and middle-income countries.

Of the respondents, 77% perceived a transition to a DTG-containing regimen for all new first-line ART initiators as being both acceptable and feasible. The major challenges of changing to an alternative non-NNRTI-containing regimen were cost (86%), followed by drug supply chain management (43%). Although overall well accepted, the challenges for a differentiated ART regimen approach (starting those at highest risk of pretreatment HIVDR on an alternative first-line regimen) were perceived to be health-care workers identifying eligible individuals (57%) and correctly implementing a differentiated model of care (46%).

During WHO consultations held in Africa, Asia, eastern Europe and Central and South America (see section 2.5.3), 97 HIV programme managers expressed a need for public health or programmatic action in a country if 15% of the treatment initiators had resistance to EFV and were therefore at high risk of not responding to first-line ART. When provided with a choice of optional responses, 25% favoured changing first-line ART from EFV-based to DTG-based therapy for all treatment initiators; 42% preferred introducing pretreatment HIVDR testing for all treatment initiators to guide regimen selection; 23% favoured repeating a pretreatment HIVDR survey to assess for further increases in HIVDR; 9% preferred other unspecified options; and 1% favoured none of the options.

[10] International Association of Providers of AIDS Care, Inter-Agency Task Teams on Children and HIV and AIDS, Paediatric AIDS Treatment for Africa, African Network for Care of Children Affected by HIV/AIDS, European AIDS Treatment Group, Global Network of People living with HIV, Association of Nurses in AIDS Care and International AIDS Society.

Scientists, academics and HIV experts

In a survey of 101 scientists and academics attending the WHO HIVResNet meeting in February 2016, respondents were asked whether the prevalence of pretreatment HIVDR of 15% justified a policy intervention, and if so, what intervention they considered most appropriate. Of the respondents, 81% indicated an urgent need to respond to pretreatment HIVDR. Indeed, when presented with different options, 37% favoured changing first-line ART from EFV-based to DTG-based therapy for all treatment initiators; 40% preferred introducing HIVDR testing for all treatment initiators to guide regimen selection; 19% favoured repeating a pretreatment HIVDR survey to assess for further increases in HIVDR; and 4% preferred other unspecified options.

In a survey of 39 HIV experts, including programme managers, attending a WHO think tank on drug optimization in February 2016, 59% favoured moving away from NNRTI-based first-line ART (such as in favour of a first-line INSTI-based regimen) in the setting of a nationally representative survey documenting 15% NNRTI resistance among ART initiators.

3.2.5 Values and preferences

WHO conducted an online values and preferences survey among people living with HIV. Civil society networks were contacted[11] and snowball sampling was encouraged. In total, 404 responses were received from people living with HIV from 71 different countries. Of the respondents, 45% were from low- and middle-income countries. There was representation from all WHO regions, but a minority of respondents were from the Eastern Mediterranean Region, Western Pacific Region and South-East Asia Region. Sixty per cent of the respondents were men. More than two thirds (69%) were older than 35 years.

Of the 264 participants who responded to a question regarding a strategy in which an alternative first-line ART regimen was used only for those at highest risk of pretreatment HIVDR to NNRTI, such as individuals with prior NNRTI exposure, 80% found this strategy to be acceptable. Respondents identified as 163 (62%) men, 93 (35%) women and 3 (1%) transgender, and the remainder did not answer the question on gender. There was no difference in acceptability between male and female respondents. In addition, respondents from both high-income countries and low- and middle-income countries viewed this strategy as acceptable (79% of those from high-income countries and 83% of those from low- and middle-income countries).

People living with HIV identified some challenges, however, (respondents could select more than one response, and 264 responded to this question): patient treatment literacy (70%); the need for health-care workers to understand and provide different treatments for different groups (66%); and the need to ensure drug availability (65%).

[11] Global Network of People living with HIV, International Coalition of Women Living with HIV, International Treatment Preparedness Coalition and European AIDS Treatment Group among other networks.

3.2.6 Equity

Considerations of equity included the possible effects (positive and negative) of introducing an alternative first-line regimen for everyone starting ART in countries in which individualized HIVDR testing is unavailable. Given the balance of risks and benefits, the move to an alternative first-line regimen that includes DTG is likely to benefit equity, even in countries with a relatively low prevalence of pretreatment HIVDR, and especially in countries in which drugs can be procured at low prices. However, pregnant women living with HIV, people requiring concomitant treatment with rifampicin for TB, and children, for whom safety and efficacy data is currently lacking, would not be currently eligible to receive standard DTG-based therapy; rather, they would receive an alternative first-line ART regimen (such as a PI/r regimen), which may have more undesirable side-effects compared with a DTG-based regimen. Nevertheless, changing to an alternative first-line ART regimen for most people will have even greater positive effects on equity.

Because of the benefits of DTG-containing first-line regimens for all people living with HIV who initiate or reinitiate first-line ART (except for some groups for whom safety data are unavailable), introducing an alternative non-NNRTI-based first-line regimen should be the preferred option in cases of high prevalence of pretreatment HIVDR to NNRTIs. However, if a change in first-line treatment is not feasible on a large scale, an alternative intervention is needed (i.e. introducing HIVDR testing). In settings in which HIVDR testing is not feasible, giving priority to people with previous exposure to ARV drugs, and possibly further groups at increased risk of HIVDR, seems justified.

3.2.7 Feasibility

To date, two low- and middle-income countries are gathering experience in using DTG-containing first-line regimens. As of June 2016, all newly initiating individuals in Botswana started on DTG-based ART. This change in national policy was supported by an in-country cost–effectiveness study. Despite limited data for people living with HIV and TB and pregnant women, the new drug was provided to these populations, and the safety and efficacy of DTG are monitored through surveillance of toxicity and adverse events. Concern about the prevalence of pretreatment HIVDR, which increased from just 3% in 2009 to about 10% in 2014–2015 in Gaborone (71), contributed to the decision to introduce DTG in first-line ART. The Ministry of Health reports that lack of an available fixed-dose combination of TDF + XTC + DTG has not been a barrier, given the high tolerability of the regimen.

In January 2017, Brazil's Ministry of Health adopted nationwide implementation of DTG for individuals initiating first-line ART. It is anticipated that 82 000 people will start DTG-based therapy in 2017, excluding pregnant women and people with active TB. The reasons for moving to DTG in Brazil included fewer adverse effects and improved viral response compared with EFV, and the prevalence of overall NNRTI resistance reaching about 7% in 2013–2015 and up to 11% in south-eastern Brazil (72). In addition, Brazil determined that, although cost implications are associated with this new policy (the negotiated cost for DTG was approximately US$ 500 per person per year), the impact was minimized by optimizing the use of other ARV drugs through improved rational use, optimizing drug selection (such as high-cost ARV drugs that could be replaced by less expensive equivalents) and more efficient procurement.

Moreover, it was felt that providing different treatment regimens to subpopulations (such as children, pregnant women and people with active TB) would enable more personalized care. Lastly, a once-a-day regimen was reported to be the critical element (rather than a fixed-dose combination) in maintaining optimal adherence. Overall, health professionals in the country received this change in policy positively.

Using a non-NNRTI-based regimen only for individuals at the highest risk of pretreatment HIVDR because of previous NNRTI drug exposure is considered standard practice in high-income countries and some middle-income countries (73).

The Guideline Development Group considered that a differentiated approach to first-line ART treatment delivery (that is, initiation of a non-NNRTI regimen in people with prior ARV drug exposure in countries with prevalence of pretreatment HIVDR to NNRTIs among all first-line starters <10%) could be considered when feasible and equitable.

3.3 Pretreatment HIVDR testing

The Guideline Development Group reviewed the evidence and supporting information related to using pretreatment HIVDR testing to select the first-line ARV regimen.

Given the lack of direct evidence from the systematic review undertaken to inform individual HIVDR genotypic testing – coupled with concerns around the feasibility of, and the resources required for, implementing this intervention – the Guideline Development Group decided not to make a formal recommendation to either endorse or discourage the use of pretreatment HIVDR testing for all people starting first-line ART.

Although a WHO recommendation was not made, the Guideline Development Group included HIVDR testing as a consideration of the consensus statement, indicating that "where the national prevalence of pretreatment HIVDR to NNRTIs is ≥10% and the use of a non-NNRTI-containing regimen in first-line ART cannot be implemented at the population level, countries may consider using pretreatment HIVDR testing to guide first-line ART regimen selection" (see section 3.2, Fig. 3.3).

This consideration was made recognizing the indirect evidence discussed in section 3.2, which indicates worse treatment outcomes for people with pretreatment HIVDR to NNRTIs who are treated with NNRTI-based ART.

An additional consideration was made for the people at high risk of pretreatment HIVDR because of previous NNRTI exposure: in this group, pretreatment HIVDR testing can be considered where the test is feasible and where an alternative non-NNRTI-containing regimen cannot be used at a large scale because of cost and other considerations.

3.3.1 Rationale for the considerations on pretreatment HIVDR testing

The rationale for this decision is described below in more detail.

- Direct evidence supporting the use of pretreatment HIVDR testing is lacking. The systematic review did not identify any controlled studies designed to assess the effect of using HIVDR testing to guide the selection of first-line ART regimens for people initiating or reinitiating ART compared with initiating a standard NNRTI-based regimen without information from HIVDR testing.
- Indirect evidence from the systematic review described in section 3.2 shows that pretreatment HIVDR to NNRTI is associated with worse treatment outcomes for people starting an NNRTI-containing regimen, suggesting the possible individual benefits for pretreatment HIVDR testing.
- Current standard practice in high-income countries includes using pretreatment HIVDR testing to guide regimen selection (74–77). In these countries, the decision was based on clinical and cohort data showing that starting an NNRTI regimen among people with pretreatment HIVDR was associated with suboptimal outcomes.
- The Guideline Development Group highlighted the public health challenges in implementing and scaling up HIVDR testing, particularly in low-income countries, because of the high cost of HIVDR testing and laboratory infrastructure as well as concerns around the feasibility of scaling up this intervention.
- The consideration for using HIVDR testing to guide the selection of first-line ART was made with particular reference to middle-income countries that have pre-existing laboratory infrastructure, which can already support routine pretreatment HIVDR testing, but are currently unable to procure generic ARV drugs. The differential cost between drugs (NNRTI versus non-NNRTI) therefore becomes a major consideration in their HIV programming. In such countries, implementing pretreatment HIVDR testing may be an option and less costly compared with introducing a non-NNRTI based regimen.

Overall, there was some variability in the acceptability related to the use of HIVDR testing. The intervention was acceptable to programme managers and health-care providers in middle-income countries but less acceptable in low-income countries. Equity was likely to increase with access to non-NNRTI regimens for those in the greatest need (people for whom NNRTI treatment was more likely to fail because of pretreatment HIVDR).

3.3.2 Cost and cost–effectiveness

Cost of pretreatment HIVDR testing

Performing HIVDR testing in a new setting involves initial costs to establish the laboratory infrastructure, followed by the costs per test performed and the costs of equipment maintenance, personnel training and salary and quality control. The estimated cost of establishing a HIVDR genotype laboratory in low- and middle-income countries is about US$ 600 000. This estimate includes the costs of purchasing software, laboratory equipment and initial stock of reagents. After the laboratory is established, the costs of each HIVDR test must be considered. In a 2016 survey conducted among WHO's 31 laboratories (9 in Africa, 10 in Asia and 12 in Europe and North America), which were designated for HIVDR testing for surveillance purposes, the most frequently used assay was an in-house assay; its price ranged from US$ 40 to US$ 317 (average

US$ 130). The laboratories using ViroSeq™ reported prices ranging from US$ 125 to US$ 460 (average US$ 276). Laboratory start-up and maintenance, and the costs of kits and reagents, do not include the costs of labour, equipment maintenance, specimen transport, genotype interpretation and returning test results to the care provider.

The cost of resistance testing kits has declined in recent years; a new kit was recently commercialized for as little as US$ 50 per test, or even less for resource-limited settings, with potential for further reductions as demand increases. In future, new user-friendly, point-of-care HIVDR testing technologies may become available and may be cost-effective across a wider range of settings.

Cost–effectiveness of pretreatment HIVDR testing

A review of studies reporting cost–effectiveness analysis of pretreatment HIVDR testing showed that, in high-income countries, this strategy improves clinical outcomes if NNRTI-based regimens are first-line ART. At a cost of US$ 400 per test, HIVDR testing could be cost-effective (incremental cost–effectiveness ratio <US$ 50 000 per quality-adjusted life-year (QALY), even at very low prevalence of pretreatment HIVDR (1.5%) (*78*).

Two further models, one from Brazil (*79*) and one from Kenya (*80*), show that HIVDR testing could improve clinical outcomes. The Brazilian model suggests that HIVDR testing at the time of treatment initiation is cost-saving, since it minimizes the use of more costly regimens. Nevertheless, this model assumes five times more expensive ART; assumes a 100% switch rate when HIVDR is detected; and does not include the costs associated with specimen collection and transport, personnel training and other considerations. Neither model considers the challenges associated with scaling up HIVDR testing implementation. The Kenya model suggests it is cost-effective at US$ 230 per QALY, assuming that very low-cost testing for HIVDR is available.

The more recent analysis from the HIV synthesis model (see section 2.5.2 and Table 3.2) shows that, in sub-Saharan Africa, introducing pretreatment HIVDR testing (using DTG for people with NNRTI resistance) is predicted to lead to better outcomes compared with continuing with EFV-based first-line ART. Specifically, the model predicts increased levels of virological suppression from 77% to 83%, a reduction in mortality from 4.5 to 3.9 per 1000 people per year, and a reduction in HIV incidence from 0.79 to 0.74 people newly infected with HIV per 100 people per year. At the current projected DTG cost of US$ 44 per person per year, however, pretreatment HIVDR testing is not cost-effective compared with using a DTG-based regimen for all new ART initiators. Nevertheless, if the cost of DTG exceeded US$ 100 per person per year, pretreatment HIVDR testing could become the most cost-effective option, depending on the prevalence of pretreatment HIVDR.

Using the same model outputs but considering the costs for middle-income countries (and using a cost–effectiveness threshold of US$ 5000 per DALY averted), transition to DTG in all new ART initiators was predicted to be cost-effective at a DTG cost of about US$ 500 or lower. At a higher DTG cost, pretreatment HIVDR testing (at a cost of US$ 150 per test) is the more cost-effective option, depending on the combination of the DTG cost and the prevalence of pretreatment HIVDR to NNRTI. For example, if the cost of DTG is US$ 1000–1250 and the prevalence of pretreatment HIVDR to NNRTI is 5%, pretreatment HIVDR testing is a cost-effective intervention and is more cost-effective than using DTG.

All models have limitations. The HIV synthesis model is based on epidemics in sub-Saharan Africa, and the Brazil and Kenya models are country-specific. It is therefore difficult to generalize about cost–effectiveness across low- and middle-income countries because of variation in drug and other costs and varying cost–effectiveness thresholds.

3.3.3 Acceptability

Health-care workers

The majority of health-care workers (57%) reported no access to routine HIVDR testing in the clinics in which they work. Only 14% of respondents from low- and middle-income countries reported carrying out HIVDR testing before treatment initiation. The most commonly perceived challenges to introducing pretreatment HIVDR testing were difficulty in interpreting results followed by the delay in receiving results and ensuring that people are retained in care during this waiting period.

Programme managers

Responses to the online survey of 57 programme managers described above varied with respect to access to HIVDR testing and the perceived acceptability and feasibility of implementing routine pretreatment HIVDR testing. The main challenges of introducing HIVDR testing, as perceived by programme managers, were cost, inadequate laboratory capacity and lack of suitably trained personnel.

Scientists, academics and HIV experts

The survey of scientists, academics and HIV experts is described in section 3.2.4. Notably, when respondents were presented with options to address pretreatment HIVDR, their preferences were equal for the options of introducing an alternative first-line ART regimen and introducing HIVDR testing for all treatment initiators to guide regimen selection.

Values and preferences

Explicit questions on acceptability, values and preferences related to pretreatment HIVDR testing were not asked of people living with HIV. However, the civil society representation at the Guideline Development Group meeting presented the key considerations of people living with HIV, through consultations within their network, for the Group to consider in the discussion. This included highlighting that there should be equity in the standard of care provided to people living with HIV, based on the optimal interventions to minimize disparity between geographical settings.

3.3.4 Feasibility

Pretreatment HIVDR testing is not widely available in low- and middle-income countries. In a WHO-led survey of programme managers (February 2017), 31% of respondents from ten low-and middle-income countries considered doing pretreatment HIVDR testing to be feasible or somewhat feasible.[12] The main challenges perceived programme managers were cost, interpreting results, delays in receiving results, ensuring that people are retained in care while waiting for their HIVDR results and adequate and continuous stock of alternative first-line ART regimens.

[12] Antigua and Barbuda, Botswana, Dominica, Grenada, Kenya, the Lao People's Democratic Republic, Lebanon, Mexico, Togo and the United Republic of Tanzania.

Consideration of individual pretreatment HIVDR testing at the country level will depend on pre-existing laboratory infrastructure, negotiated costs of DTG or other non-NNRTI-containing regimens and the number of people receiving first-line ART. When assessing this trade-off, full consideration should be given to the logistical, training and reporting needs of introducing pretreatment HIVDR testing.

3.4 Threshold for triggering a public health response for pretreatment HIVDR to NNRTIs

Consensus statement

Countries in which the prevalence of pretreatment HIVDR to NNRTIs among people initiating first-line ART, regardless of previous ARV drug exposure, is ≥10% should urgently consider an alternative first-line ART regimen that does not contain NNRTIs (as defined in the 2016 WHO consolidated ARV guidelines).

Considerations on the consensus statement

- Where the national prevalence of pretreatment HIVDR to NNRTIs is ≥10% and use of a non-NNRTI-containing regimen in first-line ART cannot be implemented at the population level, countries can consider using pretreatment HIVDR testing to guide the selection of first-line ART regimens and continued viral load monitoring (Fig. 3.3).
- Individuals at high risk of pretreatment HIVDR to NNRTIs as a result of previous exposure to NNRTI drugs can be considered for pretreatment HIVDR testing where the test is considered feasible and alternative non-NNRTI-containing regimens cannot be used at a large scale because of cost and other considerations.

3.4.1 Rationale for establishing a threshold for pretreatment HIVDR to NNRTIs

Historically, the prevalence of transmitted HIVDR has been defined as low (<5%), moderate (5–15%) and high (>15%) (*81*). This classification was based solely on expert opinion, and each prevalence level was linked to public health actions to limit further increases in HIVDR.

The agreed threshold of ≥10% (high) for HIVDR was achieved through the consensus of Guideline Development Group experts, based on the following considerations.

- Data from the systematic review showed the strong effect of pretreatment HIVDR to NNRTIs on treatment outcome compared with no pretreatment HIVDR to NNRTIs when people initiate an NNRTI-based regimen.
- Available data show that several countries had already reached prevalence of 10% for pretreatment HIVDR to NNRTI.
- The HIV synthesis model did not yield a breakpoint for virological failure, mortality or HIV incidence at which the benefits of transition to DTG first appear. Rather, it showed a monotonic increasing beneficial effect on these outcomes of transition to DTG as the prevalence of pretreatment HIVDR to NNRTI increased. The model predicts that, in a

sub-Saharan African country with a population of 10 million adults, 600 000 people receiving ART and a prevalence of pretreatment HIVDR to NNRTI of 7.5–10%, over the next 20 years 4200 additional people per year will experience viral failure one year from the start of ART; 5200 additional people receiving ART will die per year; and 4000 additional people will acquire HIV infection per year, if NNRTIs continue to be used in first-line ART, compared with a transition to DTG. Given these predicted benefits of transitioning to DTG at this prevalence of pretreatment HIVDR to NNRTI and the accompanying reduction in costs, it was considered unjustifiable to delay action at or above 10% pretreatment HIVDR to NNRTIs.

- A lag between the availability of pretreatment HIVDR survey results and the implementation of the intervention is expected. Therefore, if a prevalence of 10% of pretreatment HIVDR to NNRTIs is detected, no further delay is warranted and should trigger a public health response, starting with an in-country dialogue and specific country actions to improve the quality of services and introducing non-NNRTI first-line ART regimens.
- Benefits are expected at the population level because of DTG's potency, safety and apparently high genetic barrier to selection of drug-resistant virus.

In summary, to reach a consensus on the threshold for action for pretreatment HIVDR to NNRTIs, the Guideline Development Group considered the following evidence:

- the negative treatment outcomes associated with pretreatment HIVDR to NNRTIs among people starting an NNRTI-based regimen;
- the indication from programme managers that an agreed threshold was highly valuable to guide decision-making at the country level;
- the indication of the feasibility and acceptability of the public health response when a threshold was reached;
- the indication from programme managers of the feasibility of measuring the prevalence of pretreatment HIVDR to NNRTIs using available survey methods (92); and
- the cost–effectiveness of averting future treatment failures caused by pretreatment HIVDR to NNRTIs through an appropriate response.

The Guideline Development Group also considered the most recent and available pretreatment HIVDR data, and WHO's approaches to establish thresholds in other diseases or health interventions (such as malaria, TB and caesarean sections). The Guideline Development Group discussed whether a graded response or single threshold was optimal and determined that a single threshold would best fit with current programmatic approaches. Without direct evidence to support a specific threshold, the Guideline Development Group reached a decision on the threshold for the prevalence of pretreatment HIVDR to NNRTI by consensus.

By establishing the threshold for the prevalence of pretreatment HIVDR to NNRTI at which public health action is warranted as 10%, the Guideline Development Group expresses a level of urgency of action and signals that countries with documented prevalence below the threshold should attempt to minimize HIVDR. HIVDR prevention activities should be implemented to minimize HIVDR in all settings, even when the prevalence of pretreatment HIVDR to NNRTI is below the 10% threshold.

3.4.2 Cost of assessing the national prevalence estimate of pretreatment HIVDR

Since pretreatment HIV drug resistance testing is currently not routinely implemented in most of the low- and middle-income countries, surveys can offer a valid alternative approach to measure the national prevalence of pretreatment HIVDR. The cost of implementing a pretreatment HIVDR survey using WHO-standardized methods, assuming a sample size of 460 specimens collected from 20 randomly selected ART sites and genotyping costs of US$ 150 per specimen, is about US$ 240 000 (82). All figures should be adapted to reflect the local context and costs. The survey cost can be significantly reduced if countries are willing to ship survey specimens to one of the laboratories within the WHO HIVResNet network that offer genotyping at no cost or considerably reduced cost. Given the expected frequency of the survey and benefits associated with its implementation, the cost of this investment is limited, particularly in countries with large ART programmes.

3.4.3 Acceptability of using a global threshold to trigger a national response

In an online survey of programme managers, respondents were asked the following question: "Would it be helpful for your country if WHO developed guidance on the level of HIVDR in people initiating ART (e.g. 10%, 15%, 20%) above which a public health response should be triggered?" The programme managers represented on the Guideline Development Group and 35 ART programme managers responding to the online survey (85%) reported that establishing a global threshold of HIVDR above which public health action is necessary would be a valuable step to advance country policies.

3.4.4 Feasibility of obtaining a national prevalence estimate of pretreatment HIVDR

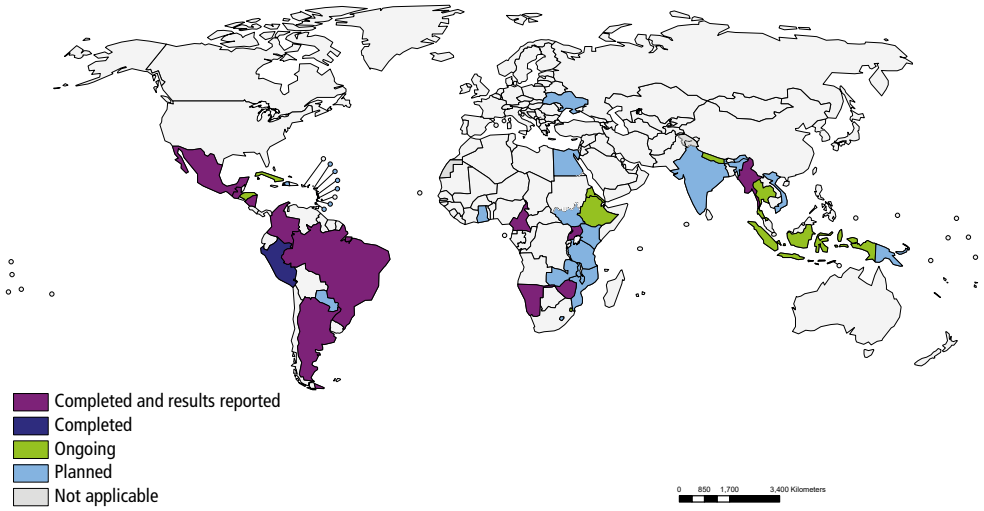
In 2014, WHO together with HIVResNet and the United States Centers for Disease Control and Prevention developed survey methods to enable nationally representative estimates of pretreatment drug resistance to be obtained, including NNRTI resistance among adults initiating first-line ART. WHO recommends that countries periodically conduct surveys of pretreatment HIV drug resistance every three years as part of efforts to scale up ART (Box 3.6) (82).

Implementation of WHO's recommended nationally representative survey of pretreatment HIVDR was evaluated as feasible or somewhat feasible by all the programme managers responding to the WHO online survey (section 2.5.3) who had implemented or were planning to implement the pretreatment HIVDR survey in their country.

Between 2014 and 2017, 19 countries implemented pretreatment HIVDR surveys, with an additional 17 pretreatment HIVDR surveys in 22 countries[13] planned in 2017 (Fig. 3.5).

[13] One multi-country survey in the six countries of the Organisation of Eastern Caribbean States (Antigua and Barbuda, Grenada, Saint Kitts and Nevis, Dominica, Saint Lucia and Saint Vincent and the Grenadines).

Fig. 3.5. Countries implementing nationally representative pretreatment HIVDR surveys using WHO's methods (as of May 2017)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization 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.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

3.5. Implementation considerations for the guidelines

A country's response to pretreatment HIVDR should be triggered by robust national pretreatment HIVDR data. To inform the urgency of a public heath response to pretreatment HIVDR to NNRTI as recommended in these guidelines, the Guideline Development Group therefore agreed that countries should assess all available data, should strive to obtain nationally representative data on pretreatment HIVDR and should use them as their standard for national programme decisions about first-line ART. Based on the national pretreatment HIVDR estimate, Fig. 3.3 outlines the recommended public health response to pretreatment HIVDR. Countries with no information on the national prevalence of pretreatment HIVDR should urgently obtain it. WHO has developed standardized nationally representative methods to estimate the prevalence of HIVDR among people starting ART in low- and middle-income countries (7) (Box 3.6). The Guideline Development Group emphasized that, in accordance with current WHO policies (35), the guidelines should be implemented while ensuring people-centred care within HIV programming and be guided by the promotion and protection of human rights and the promotion of gender equality.

The Guideline Development Group made the following implementation considerations, in accordance with current WHO guidance, to be carried out regardless of the nationally observed prevalence of pretreatment HIVDR to NNRTIs (box 3.5), always ensuring people-centred care within HIV programmes:

Box 3.5 Implementation considerations that apply regardless of the national prevalence of pretreatment HIVDR to NNRTIs

Identify and give priority to people living with HIV at greater risk of pretreatment HIVDR to NNRTIs (people starting ART with previous exposure to NNRTIs and other groups, if identified[17]) for initiating a non-NNRTI-containing regimen in first-line ART without the need to perform pretreatment HIVDR testing (Fig. 3.3).

Monitor factors associated with the emergence of HIVDR at treatment sites using quality-of-care indicators that predict HIVDR (such as early-warning indicators of HIVDR) (*84*). Annual monitoring of these indicators characterizes ART clinic and programme performance with regard to adherence to ART, levels of retention on ART, frequency of ARV drug stock-outs, coverage of viral load testing, levels of viral load suppression and frequency of prompt and appropriate switches to second-line ART when indicated.

Use fixed-dose combinations[18] where possible and age-appropriate optimal formulations to maximize adherence and minimize selection of HIVDR.

Continue to expand viral load monitoring capacity and ensure that testing is done for everyone and that facilities and providers consistently and quickly switch to second-line ART when viral failure (viral load >1000 copies/mL) is confirmed[19] (*85*).

Strengthen treatment literacy and adherence support[20] interventions, maximize retention in care, minimize loss to follow-up (*85*) and ensure regular use of programme data.

Introducing new medicines or diagnostic products is one of the most complex and unpredictable activities in any HIV programme and, as such, presents a heightened challenge for policy-makers, procurement and supply managers and manufacturers. When planning the introduction of new products, the guidance described in the 2016 WHO consolidated ARV guidelines should be followed (see Chapter 6–8, specifically section 6.13.5) (*35*). Further WHO guidance is available on the implementation considerations of transitioning to DTG (*83*).

The *WHO global strategy on people-centred and integrated health services (86)* outlines the strategy and provides an overview of evidence and good practices. Strategies to improve the quality of HIV care services are needed both at the programme management level and at the health facility and community levels where HIV care services are provided (*86*). Other tools that can help promote and protect human rights and the promotion of gender equality in HIV programming include but are not limited to the following:

- *Towards a gender-transformative HIV response (87);*
- *Guiding principles on ethical issues in HIV surveillance (88);*
- *The human rights costing tool (HRCT): a tool to cost programmes to reduce stigma and discrimination and increase access to justice (89);*

[14] Although the systematic review did not identify any other group except the one with ARV drug exposure(s) that was independently characterized by a high risk of NNRTI pretreatment HIVDR, the Guideline Development Group agreed that, if other subpopulations are identified to be at high risk of pretreatment HIVDR regardless of ART exposure, they should be given priority for receiving appropriate public health intervention while minimizing any possible risk of stigma and discrimination.

[15] Fixed-dose combinations and once-daily regimens are preferred for ART (*strong recommendation, moderate certainty of the evidence*).

[16] The 2016 WHO consolidated ARV guidelines (*35*) recommend viral load testing as the preferred monitoring approach to diagnose and confirm treatment failure (*strong recommendation, low certainty of the evidence*).

[17] Adherence support interventions should be provided to people on ART (*strong recommendation, moderate certainty of the evidence*).

- Innov8 approach for reviewing national health programmes [website] (90); and
- Health Equity Assessment Toolkit (HEAT) [online database] (91).

3.5.1 Methods to obtain national estimates of the prevalence of pretreatment HIVDR

Although all available data on HIVDR can be considered when preparing to make changes to public health and ART programme policies, countries should strive to have nationally representative pretreatment HIVDR data as a gold standard and should use these data to trigger national policy changes.

Countries without nationally representative pretreatment HIVDR data should urgently obtain it. Since pretreatment HIVDR genotypic testing is not routinely used for patient management in low-and middle-income countries, programmatic data on pretreatment HIVDR are largely absent and are thus an unreliable source of information. To fill this gap, WHO developed a survey method using standardized nationally representative sampling methods to support low- and middle-income countries in estimating the prevalence of HIVDR among people starting ART (Box 3.6). WHO standard pretreatment HIVDR survey protocols include:

- pretreatment HIVDR survey guidance in adults (92);
- pretreatment HIVDR survey sample size calculator (93); and
- pretreatment HIVDR survey guidance among children younger than 18 months (94).

Alternative methods to yield robust nationally representative estimates, which capture people with and without previous ARV drug exposure, may also be used.

Box 3.6 WHO's recommended methods to estimate the prevalence of pretreatment HIVDR using a nationally representative survey

In 2014, WHO, together with HIVResNet and in collaboration with the United States Centers for Disease Control and Prevention, developed nationally representative survey methods to estimate the prevalence of pretreatment HIVDR among adults (94). Using these standardized methods allows the prevalence of pretreatment HIVDR to be compared between countries and facilitates the assessment of trends over time within a country.

The overarching goal of the pretreatment HIVDR survey is to estimate: (1) a nationally representative prevalence of HIVDR among all ART initiators, regardless of their prior exposure to ARV drugs; and (2) a nationally representative prevalence of HIVDR among ART initiators without any previous exposure to ARV drugs. To ensure responsible decision-making, the survey sample size has been calculated to provide sufficient statistical precision for these prevalence estimates. In addition, pretreatment HIVDR surveys estimate the proportion of individuals starting or restarting first-line ART with any prior reported ARV drug exposure and the pretreatment HIVDR prevalence in this group.

Operationally, a pretreatment HIVDR survey enrols all eligible individuals initiating ART during a predetermined period. Simultaneously, information on prior ARV drug exposure is obtained when specimens are collected. These data are then used to stratify the sample and calculate the outcomes of interest.

Box 3.6 WHO's recommended methods to estimate the prevalence of pretreatment HIVDR using a nationally representative survey (continued)

Prior ARV drug exposure may be ascertained through a variety of methods, such as applying a screening questionnaire or reviewing medical records, where available and feasible. Initiators are classified into one of three categories of prior ARV drug exposure: "yes", "no" or "unknown". Countries should decide a priori which methods to use to identify people's prior ARV drug exposure histories.

If prior ARV drug exposure is identified, to the extent possible, it should be further classified as: (1) previous ART for treating HIV infection (interrupted for less than three months); (2) PrEP; (3) PEP; (4) PMTCT; or (5) a combination of types of exposure. This information may be used in a descriptive analysis at the national level and may be aggregated across surveys to generate regional and global estimates by type of ARV drug exposure.

The number of individuals to be included in a pretreatment HIVDR survey varies according to several factors such as the number of ART clinics in a country but typically ranges between 300 and 500. It is recommended that the duration of enrolment be limited to six months to ensure that the results are available in a timely fashion to inform programmatic action. These surveys are a high-priority activity for countries scaling up ART, recommended to be repeated once every three years.

Per WHO-recommended survey methods, NNRTI resistance is defined as resistance to nevirapine (NVP) or efavirnez (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanivir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r) or darunavir/ritonavir (DRV/r). Any HIVDR is defined as resistance to NVP/EFV, any NRTI, ATV/r, LPV/r or DRV/r. HIVDR is determined using the Stanford HIVdb algorithm: sequences classified as having low-, intermediate- or high-level resistance are considered "resistant".

WHO guidance on nationally representative pretreatment HIVDR surveys among children (94)

These surveys assess the prevalence of pretreatment HIVDR among infants younger than 18 months, who have been newly diagnosed with HIV using early infant diagnosis and who have not received treatment for HIV infection. These surveys are relevant in settings where many infants are exposed to or acquire HIV infection. They provide results that inform the choice for standard first- and second-line ART regimens for children. The survey methods use remnant dried blood spots routinely collected for early infant diagnosis within a predefined survey period. A representative sample of early infant diagnosis specimens is tested for HIVDR. If possible, all laboratories where early infant diagnosis is performed in a country should participate in the survey, and specimens should be linked to data on PMTCT (mother and infant) ARV drug exposure.

3.6. Key research gaps

The Guideline Development Group identified several key research gaps pertaining to HIVDR and its public health impact and individual-level HIVDR testing. These research gaps are listed below.

Epidemiology

- HIVDR surveillance should be implemented for:
  - integrase inhibitors, as programmes shift to DTG-based regimens; and
  - HIVDR in populations accessing PrEP.
- More HIVDR data are needed in key populations including children, pregnant women, men who have sex with men, female sex workers and people who inject drugs.
- New methods should be developed to identify hot-spots of HIVDR transmission within well-defined geographical areas or populations. These methods should be combined with innovative and targeted prevention strategies, particularly for key populations in which PrEP is being used.
- There is a need to develop case-based surveillance approaches that use routine programme data to inform public health and programme decision-making related to HIVDR.
- WHO's list of surveillance drug resistance mutations should be revised and updated to ensure current relevance and to include transmitted integrase inhibitor mutations.

Clinical and viral outcomes

- As DTG becomes more widely used, studies are needed to assess the long-term efficacy and safety of DTG, particularly levels of viral suppression and HIVDR among:
  - people treated with DTG, including children, pregnant women and people treated for TB (studies for people coinfected with TB should assess for optimal dosing);
  - people receiving NNRTI regimens who switch to DTG-containing regimens;
  - people with prior exposure to ARV drugs, including RAL, who start DTG; and
  - people using DTG in combination with one versus two additional drugs.
- As fixed-dose combinations of DTG in combination with other drugs become available, their efficacy, safety and use must be studied in relevant populations.
- Given the increasing use of DTG and the availability of other integrase inhibitors, studies evaluating their use as first-, second- and third-line regimens should be performed to fully characterize the impact of HIVDR on regimen sequencing. Specifically, studies are needed to characterize the mutations in individuals for whom second-line ART is failing and their impact on current and future third-line ART options.
- Research should investigate how pretreatment HIVDR to NRTIs may affect the outcomes of DTG-based regimens.
- Studies are needed to characterize the clinical impact of isolated NRTI mutations (such as K65R and M184V) on the efficacy of TDF-based PrEP.
- As long-acting injectable ARV drugs become available, research is needed to understand their impact on HIVDR and their optimal use: as PrEP, induction or maintenance therapy for people living with HIV.

- EFV-based regimens may continue to be used in many countries or subpopulations; thus, studies are needed to evaluate the virological and clinical impact of type and number of NNRTI mutations (including mutations present at low abundance).
- Given concerns around the emergence and transmission of TDF resistance, because it is used in PrEP, studies assessing the safety and efficacy of CCR5 antagonists as PrEP should be undertaken.

Implementation science

- Best practices for ART programmes should be characterized to optimize the phasing-in of DTG in low- and middle-income countries, in order to maximize population outcomes and minimize the emergence of drug resistance.
- Prevention of HIVDR remains a cornerstone of future global ART programme success. Studies are needed to characterize best practices to improve patient literacy, empower patients and communities and redefine patient-centred care as a way to minimize the emergence and transmission of drug-resistant virus.
- Reports defining the optimal HIVDR testing methods (most sensitive, least expensive and most actionable) and how to implement them in low- and middle-income countries are limited.

Technology

- A standardized, simplified approach to data management of next-generation sequencing outputs should be developed to support its use in low- and middle-income countries.
- A simplified evidence-informed tool should be developed and validated to interpret clinically relevant drug resistance mutations for use at the point of care.
- Explore the applicability of cheap, simple, public health–oriented tests that combine viral load with HIVDR testing for use with a variety of specimen types (such as dried blood spot, dried plasma spot and whole blood). These tests could be used at or near the point of care to ensure decentralization.
- Explore the applicability of cheap, simple tests for drug levels that can be used at or near the point of care, to support decision-making on whether HIVDR genotypic testing is indicated (to quickly identify individuals who are non-adherent to ART).

Cost–effectiveness assessment and modelling

- Robust and adaptable HIV transmission models to assess HIVDR outside sub-Saharan Africa must be developed to assess cost–effectiveness and effectiveness of public health interventions, particularly in concentrated epidemics.

4. PREVENTION OF HIVDR

The prevalence of pretreatment HIVDR cannot be viewed in isolation. A comprehensive and nationally representative assessment of HIVDR, and of ART programme functioning with regard to minimization, is needed in all countries. To support this undertaking, WHO has developed a comprehensive framework (1) including guidance on surveillance of acquired HIVDR in people for whom ART is failing (2), which includes population-level viral load suppression assessment and guidance on measuring ART clinic and programme factors associated with and predictive of HIVDR (early-warning indicators of HIVDR) (3).

Preventing HIVDR remains a pivotal element of the global and national response and the second strategic objective of WHO's Global Action Plan on HIV drug resistance 2017–2021 (4). The use of WHO-validated early-warning indicator tools to monitor drivers of resistance at the clinic level and measure programme quality enables the identification of factors related to patient care, patient behaviour and clinic- and programme-level management as well as the closure of gaps in service delivery. Annual monitoring of early-warning indicators of HIVDR characterizes ART clinic and programme performance with regard to adherence to ART, levels of retention on ART, coverage of viral load testing, levels of viral load suppression, frequency of ARV drug stock-outs and frequency of prompt and appropriate switches to second-line ART when indicated. Detailed definitions of each early-warning indicator are available in the 2017 WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance (3). Public health actions to prevent HIVDR and respond to suboptimal performance of quality-of-care indicators are found in Web Annex 3 (5).

The Guideline Development Group described additional public health actions that should be undertaken, regardless of the national prevalence of pretreatment HIVDR (see section 3.2).

5. DISSEMINATION AND UPDATING OF THE GUIDELINES

The guidelines will be disseminated as a printed publication and electronically on the WHO website in English and French. The web version of the document will include all annexes. A library of all supporting documentation and evidence will also be made available on the website in the form of annexes. WHO headquarters will work closely with WHO regional and country offices and implementing partners to ensure wide dissemination of the guidelines through regional and subregional meetings. Assistance will be provided to Member States to adapt the guidelines to their national contexts.

An evaluation of how users have implemented the guidelines has been developed to assess the uptake of the recommendations and the barriers to effective implementation. This policy analysis will be used to evaluate the use and appropriateness of the new guidelines within the context of the 2016 WHO consolidated ARV guidelines *(1)*. The Department of HIV and Global Hepatitis Programme plans to review the uptake of WHO's HIV-related recommendations at regular intervals. Continued monitoring of viral load suppression and HIVDR prevalence at the population level will inform the impact on health outcomes.

The WHO Department of HIV and Global Hepatitis Programme has strived to consolidate key products to provide a one-stop shop for programme managers and policy developers. However, as the field is ever changing, when important new evidence becomes available that requires guidance, supplements are developed and incorporated when the 2016 WHO consolidated ARV guidelines are updated. It is anticipated that developing and introducing new ARV drugs in first-line ART will likely affect the need and type of response required to address HIVDR. The choice of antiretroviral therapy in the context of pretreatment drug resistance will be considered in the next update of the 2016 WHO consolidated ARV guidelines *(1)* planned for 2019.

WHO is committed to measuring, preventing and mitigating the effect of HIVDR on treatment outcomes through country support, protocols for surveillance, and guidance on HIVDR prevention and programme strengthening to be developed and adapted as new evidence becomes available in the form of epidemiological, intervention effectiveness and implementation studies.

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For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv

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