World Health Organization

CDC

The Global Fund

HIV DRUG RESISTANCE REPORT 2017

TRENDS







QUALITY







ACTION







World Health Organization

CDC

The Global Fund

HIV DRUG RESISTANCE REPORT 2017

HIV drug resistance report 2017

ISBN 978-92-4-151283-1

© World Health Organization 2017

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

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

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

Suggested citation. HIV drug resistance report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

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

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

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

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

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

The photographs in this material are used for illustrative purposes only; they do not imply any particular health status, attitudes, behaviors, or actions on the part of any person who appears in the photographs.

The mark "CDC" is owned by the US Dept. of Health and Human Services and is used with permission. Use of this logo is not an endorsement by HHS or CDC of any particular product, service, or enterprise.

Printed in Switzerland

CONTENTS

ABBREVIATIONS AND ACRONYMS v

DEFINITIONS vi

ACKNOWLEDGEMENTS vii

EXECUTIVE SUMMARY viii

1 INTRODUCTION 01

1.1 Scope of report 01

1.2 Context: achieving the 90-90-90 targets by 2020 – the role of HIV drug resistance 01

1.3 Global HIV drug resistance surveillance 02

2 HIV DRUG RESISTANCE IN POPULATIONS INITIATING ART: PRETREATMENT HIV DRUG RESISTANCE 03

2.1 Nationally representative surveys of pretreatment HIV drug resistance among adult ART initiators, 2014–2017 03

2.2 Nationally representative surveys of HIV drug resistance in children younger than 18 months of age, 2014–2017 17

2.3 Systematic literature review of pretreatment HIV drug resistance in adults in LMIC 18

2.4 Systematic literature review of pretreatment HIV drug resistance in children in LMIC 22

2.5 Pretreatment HIV drug resistance – summary of findings and implications 24

3 HIV DRUG RESISTANCE IN POPULATIONS ON ART: ACQUIRED HIV DRUG RESISTANCE 25

3.1 Nationally representative surveys of acquired HIV drug resistance, 2014–2017 25

3.2 Systematic literature review of acquired HIV drug resistance in adults 35

3.3 Systematic literature review of acquired HIV drug resistance in children 38

3.4 Acquired HIV drug resistance – summary of findings and implications 40

4 GLOBAL EFFORTS TO PREVENT, MONITOR AND RESPOND TO HIV DRUG RESISTANCE 41

4.1 WHO Global Action Plan on HIV drug resistance, 2017–2021 41

4.2 WHO Guidelines on the public health response to pretreatment HIV drug resistance 42

5 SUSTAINABILITY OF HIV DRUG RESISTANCE SURVEILLANCE 43

5.1 US-CDC support for HIV drug resistance surveillance 43

5.2 Global Fund support for HIV drug resistance surveillance 44

5.3 WHO support for HIV drug resistance surveillance 44

6 CONCLUSIONS 46

REFERENCES 47

ANNEX 51

Annex 1: Methodological notes 51

Section 1: WHO sequence data analysis and quality assurance for pretreatment HIV drug resistance surveys and acquired HIV drug resistance surveys 51

Section 2: Study design and methods for statistical analysis of pretreatment HIV drug resistance surveys and acquired HIV drug resistance surveys 51

Section 3: Adult pretreatment HIV drug resistance systematic literature review methods 54

Section 4: Paediatric pretreatment HIV drug resistance and acquired HIV drug resistance systematic literature review methods 65

Section 5: Adult acquired HIV drug resistance systematic literature review methods 66

ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ADR	Acquired HIV drug resistance
AMR	Antimicrobial resistance
ART	Antiretroviral therapy
ARV	Antiretroviral (drugs)
ATV/r	Atazanavir/ritonavir
CI	Confidence interval
DBS	Dried blood spot
DRM	Drug resistance mutation
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EFV	Efavirenz
EID	Early infant diagnosis
EWI	Early warning indicator of HIV drug resistance
FTC	Emtricitabine
GAP	Global Action Plan on HIV drug resistance
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HIVDR	HIV drug resistance
LMIC	Low- and middle-income countries
LPV/r	Lopinavir/ritonavir
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NRTI	Nucleoside reverse-transcriptase inhibitor
NVP	Nevirapine
PDR	Pre-treatment HIV drug resistance
PEP	Post-exposure prophylaxis
PEPFAR	United States President's Emergency Plan for AIDS Relief
PHIA	Population-based HIV Impact Assessment survey
PI	Protease inhibitor
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission (of HIV)
PPPS	Probability proportional to proxy size
PPS	Probability proportional to size
PrEP	Pre-exposure prophylaxis
PR	Protease
RT	Reverse transcriptase
SDRM	Surveillance drug resistance mutation
TDF	Tenofovir disoproxil fumarate
TDR	Transmitted HIV drug resistance
UNAIDS	Joint United Nations Programme on HIV/AIDS
US-CDC	United States Centres for Disease Control and Prevention
VL	Viral load
WHO	World Health Organization
XTC	3TC or FTC
ZDV	Zidovudine

DEFINITIONS

Operational definitions used in this report are presented below.

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 replication of the virus. All current antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus. Broadly speaking, there are three main categories of HIVDR:

1. **Acquired HIV drug resistance (ADR)** develops when HIV mutations emerge due to viral replication in individuals receiving ARV drugs.
2. **Transmitted HIV drug resistance (TDR)** is detected in ARV drug-naive people with no history of ARV drug exposure. TDR occurs when previously uninfected individuals are infected with virus that has drug resistance mutations.
3. **Pretreatment HIV drug resistance (PDR)** is detected in ARV drug-naive people initiating ART or people with prior ARV drug exposure initiating or reinitiating first-line ART. PDR is either transmitted or acquired drug resistance, or both. PDR may have been transmitted at the time of infection (i.e. TDR), or it may be acquired by virtue of prior ARV drug exposure (e.g. in women exposed to ARV drugs for the prevention of mother-to-child transmission of HIV, in people who have received pre-exposure prophylaxis, or in individuals reinitiating first-line ART after a period of treatment interruption without documented virological failure).

ARV drug-naive applies to people with no history of ARV drug exposure.

ACKNOWLEDGEMENTS

This is a joint report by the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (US-CDC) and The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund). The report was written by Hiwot Haile-Selassie (Consultant, WHO), Michael R. Jordan (Consultant, WHO, and Tufts University School of Medicine), Elliot Raizes (US-CDC), Dalila Zachary (The Global Fund), Ade Fakoya (The Global Fund) and Silvia Bertagnolio (WHO), who coordinated the overall report development with Meg Doherty (WHO), under the overall guidance of Gottfried Hirnschall (WHO) and Shannon Hader (US-CDC).

We are grateful for the contributions of Andrew Ball (WHO), Firdavs Kurbonov (Consultant Database Manager, WHO) and Jerôme Duclos (Consultant, WHO). We thank Neil Parkin (Consultant, WHO) for the HIV drug resistance analysis and development of report figures and Formato Verde for the layout and design of the report.

We would also like to thank Amandine Cournil (Consultant, IRD UMI 233, INSERM U1175, Université de Montpellier) and Sherri Pals (US-CDC) for the statistical analysis; Ravi Gupta (University College of London, United Kingdom of Great Britain and Northern Ireland) and John Gregson (London School of Hygiene and Tropical Medicine, United Kingdom) for contributing the systematic review on pretreatment HIV drug resistance; Ashley Boylan (US-CDC) for the systematic review on paediatric pretreatment HIV drug resistance and paediatric acquired HIV drug resistance; Juliana da Silva (US-CDC) for the systematic review of adult acquired HIV drug resistance; and Jessica Justman (ICAP, United States of America) for providing data from the Population-based HIV Impact Assessment surveys.

This report would not have been possible without the collaboration of national HIV programme managers and staff, who supplied the surveillance data that underpins this report. We thank the WHO HIVResNet Laboratory Network members, who have been essential for the production of high-quality drug resistance surveillance data, and we thank all members of the HIV Drug Resistance Steering Group for their guidance and support.

Financial acknowledgements

This report has been supported in part by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is a growing global public health threat, which urgently requires collective action to ensure effective prevention and treatment of infections. Minimizing the emergence and transmission of HIV drug resistance (HIVDR) is a critical aspect of the broader global response to AMR. Prevention, monitoring and response to HIVDR is key to building and sustaining gains in HIV treatment scale-up, and achieving the global 90-90-90 targets for treatment. These widely adopted targets reflect the global community's commitment to expanding access to antiretroviral therapy (ART) including: diagnosing 90% of all people with HIV infection; providing treatment to 90% of those diagnosed; and ensuring 90% of people on treatment achieve virological suppression, by 2020. By the end of 2016, 70% of people living with HIV (PLHIV) were diagnosed,77% of those who knew their HIV status received ART, and 82% of those on treatment were virally suppressed.

The human cost of HIVDR cannot be underestimated: people with non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance are less likely to achieve viral suppression; more likely to experience virological failure or death; more likely to discontinue treatment; and more likely to acquire new HIVDR mutations. Preventing, monitoring and responding to HIVDR is therefore critical to maintaining current achievements, improving treatment outcomes for PLHIV, protecting investments, and guaranteeing the long-term sustainability of care and treatment programmes. Mathematical modelling predicts that if NNRTIs continue to be included in first-line ART regimens, and the level of pretreatment HIV drug resistance (PDR) to NNRTIs reaches above 10% in sub-Saharan Africa, the global targets to end AIDS as a public health threat by 2030 will not be attained. Achieving and sustaining "the last 90" target will therefore require efforts to contain and respond to HIVDR.

Recognizing the importance of addressing HIVDR, within the context of ART scale-up, the World Health Organization (WHO), in collaboration with partners, developed a comprehensive HIVDR surveillance approach in 2004, with guidance updated in 2014 to yield nationally representative estimates of HIVDR.

This second HIVDR report has been jointly developed by WHO, the United States Centers for Disease Control and Prevention (US-CDC) and the Global Fund to Fight AIDS, Tuberculosis and Malaria ("The Global Fund"). It provides an update on recent population levels of HIVDR covering the period 2014–2016. The report includes data from 16 nationally representative surveys from 14 countries[1] estimating resistance in: adults initiating ART (PDR), children younger than 18 months newly diagnosed with HIV, and adults on ART (acquired HIV drug resistance or ADR). To contextualize results from representative HIVDR surveys, the report is supported by systematic reviews of the published literature on PDR in adults, children and adolescents, and ADR in paediatric and adult populations. Finally, the report includes the prevalence of transmitted HIV drug resistance (TDR) in recently infected people in Malawi and Zimbabwe, estimated as part of recent household Population-based HIV Impact Assessment (PHIA) surveys, supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR).

Twenty-six countries have completed or are currently implementing national HIVDR surveys, based on WHO's guidance. The swift uptake and implementation of HIVDR surveillance in recent years reflects the commitment of countries, partners and donors to AMR and the monitoring of HIVDR as part of ART scale-up efforts.

Of the 26 countries with national HIVDR surveys that are completed or ongoing, 14 have reported data to WHO, and are captured in this report. Brisk uptake of WHO's revised HIVDR surveillance methods since their publication in 2014 reflects the collective efforts and commitment of countries, and pivotal support provided by US-CDC, the Global Fund, WHO and other partners.

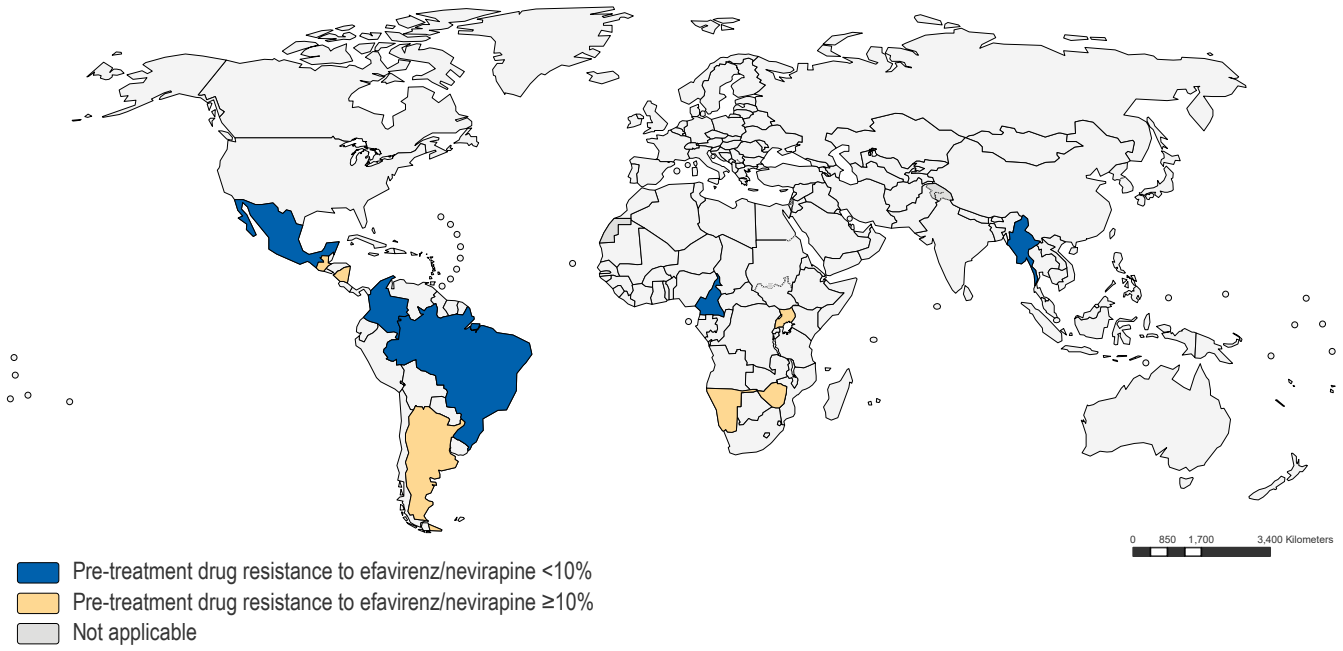
Levels of pretreatment resistance to efavirenz or nevirapine, the most affordable and widely used drugs in first-line ART, reached 10% or above in six out of 11 countries that reported PDR survey data.

Nationally representative surveys of **PDR** monitor resistance in people starting ART, including antiretroviral (ARV) drug-naive individuals and people reporting prior exposure to ARV drugs. Levels of NNRTI resistance (defined as resistance to efavirenz or nevirapine) were high (>10%) in six of the 11 countries reporting data (see figure below).

Three out of the five countries with NNRTI resistance below 10% monitored PDR only in ARV drug-naive individuals, which may explain the lower prevalence estimates observed in these countries. In the **African** Region, levels of NNRTI resistance were greater than 10% in three out of four countries, with NNRTI PDR ranging from 8.1% (95% CI 4.3–14.7) in Cameroon to 15.4% (95% CI 10.3–22.5) in Uganda. In **Mexico, Central and South America**, pretreatment NNRTI resistance exceeded 10% in three of six surveys, ranging from 6.3% (95% CI 3.8-10.2) in Colombia to 19.3% (95% CI 12.2–29.1) in Nicaragua. Finally, in Myanmar, the only country reporting PDR survey data from **South-East Asia**, NNRTI resistance was low at 3.9% (95% CI 2.1–7.4). Overall, the prevalence of NNRTI resistance reported in PDR surveys is broadly consistent with available data from the PHIA surveys among recently infected people in Malawi and Zimbabwe, where four out of 26 and two out of 30 ARV drug-naive individuals had NNRTI resistance, respectively.

[1] Argentina (PDR survey), Brazil (PDR survey), Cameroon (PDR and ADR surveys), Colombia (PDR survey), Guatemala (PDR and ADR surveys), Mexico (PDR survey), Myanmar (PDR survey), Namibia (PDR survey), Nicaragua (PDR survey), South Africa (HIVDR survey in children <18 months), Uganda (PDR survey), Viet Nam (ADR survey), Zambia (ADR survey) and Zimbabwe (PDR survey).

NNRTI pretreatment HIV drug resistance in 11 countries reporting national survey data to WHO, 2014-2016



Survey findings are also consistent with a systematic review of studies published between 2001 and 2016, which assessed levels of PDR in 56 044 adults across 63 low- and middle-income countries. NNRTI resistance was higher in more recent studies across all regions (Eastern Africa, Southern Africa, Western and Central Africa, Latin America and Asia; $P<0.05$ for all). Yearly incremental increases in NNRTI resistance were greatest for studies in Eastern Africa (29%, 95% CI 17–42) and smallest for those in Asia (11%, 95% CI 2–20).

Pretreatment drug resistance is more than two fold higher among people starting first-line ART with prior ARV drug exposure, compared to ARV drug-naive individuals. With continued ART scale-up, this group is likely to represent an increasing proportion of people initiating treatment who may not be receiving effective treatment.

Notably, individuals with prior ARV drug exposure initiating or reinitiating first-line ART had higher prevalence of NNRTI PDR in both PDR surveys and the systematic review. Across the seven PDR surveys that included both individuals with prior ARV exposure – previously on first-line ART or past exposure for prevention of mother-to-child transmission (PMTCT) – and ARV drug-naive individuals, NNRTI resistance was considerably higher among ART initiators with prior ARV drug exposure (21.6%, 95% CI 13.8–32.2), compared to ARV drug-naive treatment initiators (8.3%, 95% CI 6.0–11.4; $P<0.0001$). The high levels of NNRTI resistance in people reporting prior ARV drug exposure is particularly concerning, as this group is likely to represent an ever-increasing proportion of first-line treatment initiators in some countries.
Recognizing that levels of NNRTI resistance are increasing, and that NNRTIs are an essential component of currently recommended first-line ART, WHO has published *Guidelines on the public health response to pretreatment HIV drug resistance,* as a supplement to the 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* These guidelines include new recommendations on the selection of ARV drugs in response to high levels of PDR. They recommend countries consider changing their first-line ART regimen if levels of NNRTI PDR reach 10%. These publications are an important step forward in the global response to HIVDR.

Most available PDR data come from adult populations, while data for children and adolescents are limited. Only one nationally representative HIVDR survey among children younger than 18 months was reported between 2014 and 2016; this survey was from South Africa, and documented NNRTI prevalence as high as 63.7% (95% CI 59.0–68.4) in infants diagnosed with HIV through early infant diagnosis. The high levels of NNRTI resistance observed in this survey and in other recent publications strongly support WHO's 2013 recommendation that all children younger than 3 years of age be started on protease inhibitor (PI)-based regimens, irrespective of PMTCT exposure. Unfortunately, implementation of this policy has been slow, largely due to the unavailability, until recently, of heat stable and palatable paediatric formulations, which do not require a cold chain until the point of dispensing.

The global target of 90% virological suppression in people retained on ART was reached in two of the four countries that reported survey data. Among the four countries, it ranged from 68% to 90%, indicating variability in programme quality and service delivery that should be addressed.

Achieving optimal viral load suppression and minimizing HIVDR is critical to reaching the 90-90-90 fast track targets by 2020 and eliminating AIDS as a public health threat by 2030. Between 2014 and 2016, four countries (Cameroon, Guatemala, Viet Nam and Zambia) implemented ADR surveys among adults on ART and reported data to WHO. Only Zambia and Viet Nam reached the 90% target for viral load suppression. The heterogeneity in the viral load suppression rates reported among people on ART suggest substantial differences in programme performance across countries.

NNRTI resistance among people retained on ART ranged from 4% to 28%, while among people with unsuppressed viral load on first-line NNRTI regimens, it ranged from 47% to 90%. This speaks to the need to scale up viral load testing, promptly switch individuals with confirmed virological failure to second-line treatment, and strengthen adherence support in countries with lower levels of ADR.

Overall, the prevalence of NNRTI resistance among individuals on ART for 12–24 months ranged from 4.3% (95% CI 1.9–9.5) in Zambia to 16.7.% (95% CI 13.7–20.2) in Cameroon; among those on treatment for longer durations (36–48+ months), it ranged from 4.2% (95% CI 2.4–7.4) in Viet Nam to 28.3% in Cameroon (95% CI 17.4–42.5). Among people on first-line NNRTI-based regimens with unsuppressed viral load, the prevalence of NNRTI resistance at the 12–24 month time point ranged from 47.3% (95% CI 10.7–87.0) in Zambia to 80.0% (95% CI 51.0–93.9) in Guatemala. At the late time point, among people failing NNRTI-based first-line ART, NNRTI resistance ranged from 84.3 (95% CI 69.4–92.7) in Guatemala to 89.5% (95% CI 71.0–96.7) in Cameroon. High levels of resistance in people with unsuppressed viral load indicate the need for rapid switch to effective second-line regimens. However, ADR surveys show that the use of PI regimens was low across all countries, suggesting inadequate switch to PI-based ART in people failing first-line NNRTI-based ART.

Additional data from the PHIA surveys conducted in Malawi, Zambia and Zimbabwe suggest high levels of viral load suppression among people who self-report being on ART for a variable range of time. In this population, the prevalence of viral load suppression ranged from 86% in Zimbabwe to 91% in Malawi among adults aged 15–59 years, suggesting that ART regimens are effective for the majority of individuals who report being on treatment in these countries.

Despite the high levels of ADR observed in national surveys and supported by a review of the published literature, the mutations and mutation patterns observed among people failing treatment suggest that currently recommended PI-based second-line ART remains an effective option for most people failing first-line ART. Nonetheless, strategic use of increasingly affordable drugs with higher barriers to development of resistance (e.g. dolutegravir) has the potential to mitigate concerns regarding ongoing treatment efficacy of NNRTI-based therapy, and may possibly reverse the observed trend of increasing NNRTI resistance.

As of December 2016, 19.5 million people were receiving ART globally, and over the next decade, ever-larger numbers of people must initiate and be successfully maintained on HIV treatment for life, to achieve global targets for epidemic control. To date, several countries have reported high levels of viral load suppression among people receiving treatment, attesting to the effectiveness of available therapy and the success of ART scale-up. The fact that "the third 90" target is being achieved in several countries is reassuring. However, in other countries viral load suppression in people on ART is well below the global target, and merits attention.

This global report demonstrates that levels of PDR are increasing, mostly driven by increasing levels of NNRTI resistance. Although levels of NNRTI PDR have reached above 10% in some of the countries surveyed, viral load and TDR prevalence estimates from the PHIA surveys suggest high levels of viral load suppression among people retained in care who self-report taking ART. Taken together, these data are consistent, and indicate that the majority of PLHIV who are taking ART are likely to control their infection. However, in several countries, significant and increasing proportions of people are infected with a virus resistant to NNRTI, and are therefore significantly less likely to achieve viral suppression when they start ART. In addition, a proportion of people receiving ART may not adhere to it due to individual-, clinic- or programme-level factors, and may therefore develop NNRTI resistance. High levels of NNRTI PDR have the potential to undermine the future success of global ART scale-up; therefore, this report underscores the need to strengthen the quality of HIV programmes to prevent further increases in HIVDR, to *monitor* when levels of resistance are unknown, and to *respond* to HIVDR when levels are high.

Preventing, monitoring and responding to HIVDR form the basis of the *Global Action Plan on HIV drug resistance,* a five-year framework for action spearheaded by WHO, which engages global and local stakeholders in a coordinated and resourced response to HIVDR. The Global Action Plan focuses on five strategic objectives: 1) prevention of and response to HIVDR; 2) monitoring of HIVDR through surveillance and routine programmatic data; 3) research and innovation; 4) laboratory capacity; and 5) governance and enabling mechanisms. The Global Action Plan articulates a global consensus and commitment to minimizing AMR and preventing HIVDR from undermining attainment of global HIV targets, including an AIDS-free generation by 2030.

The treatment landscape of HIV is rapidly evolving with introduction of new classes of drugs which are becoming available and more affordable in LMIC. As new drugs become available ongoing surveillance in real world settings will be required to preserve their long term efficacy and durability.

1 INTRODUCTION

1.1 Scope of report

This report considers the levels of pretreatment HIV drug resistance (PDR) in populations initiating antiretroviral therapy (ART), and acquired HIV drug resistance (ADR) in people receiving ART in low- and middle-income countries (LMIC), in the context of treatment scale-up and global efforts to eliminate AIDS as a public health threat by 2030. The report presents recent data (2014–2016) from 16 surveys (15 in adults) conducted in 14 LMIC,[2] which are contextualized by findings from four systematic reviews of the relevant published medical literature. The systematic review of HIV drug resistance (HIVDR) in adults starting ART assesses the period 1993–2016 corresponding to studies published between 2001 and 2016. The literature reviews assessing resistance in adults and children taking ART, and the review on children initiating ART, assess the literature published between 2014 and 2017.

1.2 Context: achieving the 90-90-90 targets by 2020 – the role of HIV drug resistance

The global scale-up of ART under the public health approach of standardized and simplified regimens has registered significant gains, with increasing access to treatment for millions of people, and a reduction in new infections and HIV-associated morbidity and mortality. In 2014, the Joint United Nations Programme on HIV/ AIDS (UNAIDS) set ambitious global targets, including "90-90-90" by the year 2020 – i.e. 90% of all people living with HIV (PLHIV) will know their status; 90% of all people with diagnosed HIV infection will receive sustained ART; and 90% of all people taking ART will have suppressed viral load – as well as the elimination of AIDS as a public health threat by 2030 *(1)*. By December 2016, 19.5 million people were receiving ART worldwide *(2)*. However, to achieve the HIV targets, an additional 17.2 million people must initiate treatment and be maintained on it for life. In 2016, 42% of people on ART globally are estimated to have received treatment and accessed viral load testing to monitor their HIV infection[3]; of these 82% had viral load suppression *(2)*.The 2016 World Health Organization (WHO) *Consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection* recommend treatment for all people diagnosed with HIV, pre-exposure prophylaxis (PrEP) for people at high risk of acquiring HIV *(3)*, and the expansion of viral load testing. Implementation of these guidelines will further reduce new infections and HIV-related mortality, and propel the global community towards attaining the 90-90-90 treatment targets and the prevention target of fewer than 500 000 new infections. Despite the tremendous successes of the last decade, it is likely that as the number of people on treatment and average duration of therapy increases, there will be an increase in levels of HIVDR, even in the context of well-managed HIV treatment programmes. Quality gaps in HIV service delivery can further increase levels of HIVDR, if they are not properly managed.

Modelling predicts that as more people receive treatment, fewer HIV transmissions will occur, but a higher prevalence of HIVDR will be observed – a phenomenon that can occur due to treatment failure and the transmission of HIV drug-resistant virus to newly infected people *(4,5)*. Mathematical modelling also predicts that if non-nucleoside reverse transcriptase inhibitors (NNRTIs) continue to be included in first-line ART regimens, and PDR to NNRTI reaches above 10% in sub-Saharan Africa, the global targets to end AIDS as a public health threat by 2030 may not be attained *(6,7)*.

Preventing, monitoring and responding to HIVDR is therefore critical to maintaining current achievements, improving patient outcomes, protecting investments, and guaranteeing the long-term sustainability of care and treatment programmes. The human cost of HIVDR cannot be underestimated: HIVDR is associated with poor virological outcomes *(8)*, increased mortality *(9,10)*, and reduced durability and effectiveness of regimens. Specifically, a recent systematic literature review and meta-analysis found that compared to those without NNRTI resistance, people with NNRTI PDR who receive NNRTI-containing regimens are 30% less likely to achieve viral suppression, 23 times more likely to experience virological failure or death, and nine times more likely to discontinue treatment *(11)*.

Responding to HIVDR in a responsible manner is key to achieving the 90-90-90 targets, particularly "the third 90", which relates to viral load suppression among individuals on treatment. If resistance to ARV drugs increases unchecked, this target may not be reached due to limited therapeutic options and the higher costs of second- and third-line treatments, which are, respectively, three times and 14 times more expensive than current first-line nucleoside reverse-transcriptase inhibitor (NRTI)-based regimens *(12)*.The monitoring and surveillance of HIVDR is an essential component of the public health approach to ART delivery and the optimization of HIV treatment and care. As such, it is a key strategic objective of the *Global Action Plan on HIV drug resistance.* The Global Action Plan covers the period 2017–2021 and reflects a global consensus that HIVDR requires a coordinated and well-resourced response, with all stakeholders playing a fundamental role.

This report on HIVDR is a collaboration between WHO, the United States Centers for Disease Control and Prevention (US-CDC) and The Global Fund to Fight AIDS, Tuberculosis and Malaria (" The Global Fund"). The report is an update of the *WHO HIV drug resistance report 2012*, *(13)* which signalled increasing levels of HIVDR among people recently infected with HIV, reaching 6.8% in 2010, with resistance levels driven largely by the NNRTI drug class, particularly in sub-Saharan Africa.

[2] Argentina (PDR survey), Brazil (PDR survey), Cameroon (PDR and ADR surveys), Colombia (PDR survey), Guatemala (PDR and ADR surveys), Mexico (PDR survey), Myanmar (PDR survey), Namibia (PDR survey), Nicaragua (PDR survey), South Africa (HIVDR survey in children <18 months), Uganda (PDR survey), Viet Nam (ADR survey), Zambia (ADR survey) and Zimbabwe (PDR survey).

[3] Based on 96 out of 168 countries with available data on viral load testing coverage.

Since publication of the 2012 report, a number of studies in discrete populations or geographical areas have reported higher levels of PDR among people initiating first-line ART across a range of settings including: Angola (16.3%) *(14)*, Botswana (9.7%) *(15)*, the Democratic Republic of the Congo (10.0%) *(16)*, Honduras (11.5%) *(17)*, Papua New Guinea (16.1%) *(18)*, South Africa (18%) (personal communication, National Institute of Communicable Diseases, South Africa, May 2017) *(19)*, and Uganda (11.6%)*(20)*. In Aruba, 54% of 104 individuals who tested positive for HIV during the years 2010–2015 received pretreatment HIVDR testing; among this group, the prevalence of NNRTI PDR was 32% (95% CI 23–41) *(21)*. Even higher levels of PDR have been reported among people initiating first-line ART who report prior exposure to ARV drugs because of either treatment interruption or prevention of mother-to-child transmission (PMTCT) of HIV. In one recent South African study, among 303 individuals starting ART, 25% reported prior exposure to ARV drugs. Of those, 42.0% had NNRTI PDR, compared to 11.1% among ARV drug-naive individuals *(19)*.

In 2014, WHO, in collaboration with US-CDC and WHO HIVResNet (a global network of over 50 institutions, laboratories, clinicians, epidemiologists and other HIVDR experts), developed new survey methods that generate nationally representative estimates of HIVDR in adult populations initiating and receiving ART. This report presents data generated by countries using these survey methods. It aims to provide a contemporary account of the global HIVDR situation for the purpose of supporting countries and ART programmes to better understand their HIV epidemics and optimize treatment and care.

1.3 Global HIV drug resistance surveillance

Understanding the emergence and transmission of HIVDR at the population level, and the interaction between its various determinants, requires routine monitoring of the performance of health services in delivering ART, as well as nationally representative surveillance of HIVDR. To ensure that high-quality assessment of resistance is available to support country decision-making, WHO in collaboration with partners developed comprehensive HIVDR surveillance methods in 2004, with guidance updated in 2014 *(22)*. Implementation of HIVDR surveillance is supported by ministries of health and partners such as US-CDC and The Global Fund. Global HIVDR surveillance guidance is being rolled out simultaneously with efforts to extend universal access to ART. WHO's HIVDR surveillance guidance recommends and prioritizes annual monitoring of early warning indicators (EWI) of HIVDR, embedded within the national HIV monitoring and evaluation system. In addition, the following HIVDR surveys are recommended as priority surveillance activities:

- surveillance of PDR in populations initiating first-line ART
- surveillance of ADR in adults and children on treatment
- surveillance of HIVDR in ART-naive children younger than 18 months of age.

The recommended survey methods yield nationally representative estimates of HIVDR, and results support countries in the selection of first-, second- and third-line ART regimens. In addition, a network of laboratories designated by WHO for the purpose of HIVDR surveillance has been established to support HIVDR surveillance activities. As of July 2017, there are 31 laboratories in five of WHO's six regions (African Region, Region of the Americas, South-East Asia Region, European Region and Western Pacific Region) designated by WHO for HIVDR testing for the purpose of public health surveillance.[4] National HIVDR survey data may be stored in WHO's global HIVDR database, a repository which nationally designated HIV programme staff may access to support quality assurance and use of data (see Section 5.3 for further details).

[4] More information about designated laboratories and WHO's HIVDR laboratory strategy may be found online at http://www.who.int/hiv/topics/drugresistance/laboratory/en/

2 HIV DRUG RESISTANCE IN POPULATIONS INITIATING ART: PRETREATMENT HIV DRUG RESISTANCE

Key findings

- PDR survey data (2014–2016) from 11 countries indicate NNRTI resistance has reached levels above 10% in six countries (Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe).
- Across seven PDR surveys, which assessed both people with and without prior ARV drug exposure, NNRTI resistance was significantly higher among first-line treatment initiators reporting prior ARV drug exposure (treatment restarters or PMTCT-exposed women), compared with ARV drug-naive individuals (21.6%, 95% CI 13.8–32.2 versus 8.3%, 95% CI 6.0–11.4 respectively; P<0.0001).
- Recent Population-based HIV Impact Assessment (PHIA) surveys from Malawi and Zimbabwe among recently infected people found four out of 26, and two out of 30, individuals with NNRTI resistance, respectively.
- A systematic review of published literature on PDR in adults from 63 LMIC found NNRTI resistance was higher in more recent studies across all regions (Eastern Africa, Southern Africa, Western and Central Africa, Latin America and Asia; P<0.05 for all). Yearly incremental increases in NNRTI resistance were greatest in studies in Eastern Africa (29%, 95% CI 17–42) and Southern Africa (23%, 95% CI 16–29), and smallest in studies in Asia (11%, 95% CI 2–20).
- Only one survey of HIVDR in children younger than 18 months was reported between 2014 and 2016. This survey was from South Africa and documented a high NNRTI prevalence of 63.7% (95% CI 59.0–68.4) in infants diagnosed with HIV through early infant diagnosis (EID).
- A systematic literature review of PDR in children between 2014 and 2017 documented high rates of resistance among children starting ART (median NNRTI resistance: 49.3%, range 7.5–100%), particularly in PMTCT-exposed children (four out of seven studies found that over 50% of PMTCT-exposed children had NNRTI PDR).

2.1 Nationally representative surveys of pretreatment HIV drug resistance among adult ART initiators, 2014–2017

2.1.1 Survey methods for pretreatment HIV drug resistance surveys in adults

In 2014, WHO together with US-CDC and WHO HIVResNet published methods to assess PDR in adults *(1)*. The recommended survey methods yield nationally representative prevalence estimates of HIVDR among populations initiating ART. Use of these standardized methods allows comparison of PDR between countries, and facilitates assessment of trends over time within a country. These surveys are high-priority activities, and recommended to be implemented in countries regularly, typically once every three years. PDR surveys are cross-sectional and employ a two-stage cluster sampling design. The first stage involves the selection of ART clinics using probability proportional to size (PPS) sampling, a method by which the probability of selecting an ART clinic is proportional to the size of the population initiating ART at a given clinic. The second stage involves consecutive enrolment of eligible individuals initiating ART at the sampled clinics until the pre-determined sample size for each is achieved.

PDR surveys provide evidence to inform the selection and effectiveness of first-line treatment and post-exposure prophylaxis (PEP) regimens and PrEP when used. The overarching goals of PDR surveys are 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 ARV drug-naive initiators. To ensure responsible decision-making, the survey sample size has been calculated to provide a confidence interval width of ± 5% for these prevalence estimates. In addition, PDR surveys estimate the proportion of individuals starting or restarting first-line ART with any reported prior ARV drug exposure, and the PDR prevalence in this group. The inclusion of both ARV drug-naive and drug-exposed people yields nationally representative data on the entire population eligible to initiate first-line ART, which operationally includes both ARV drug-naive and drug-exposed individuals.

PDR surveys enrol all eligible individuals initiating ART on or after a predetermined survey start date. At enrolment, information on prior ARV drug exposure is obtained at the time of specimen collection. These data are then used to stratify the sample and calculate the outcomes of interest.

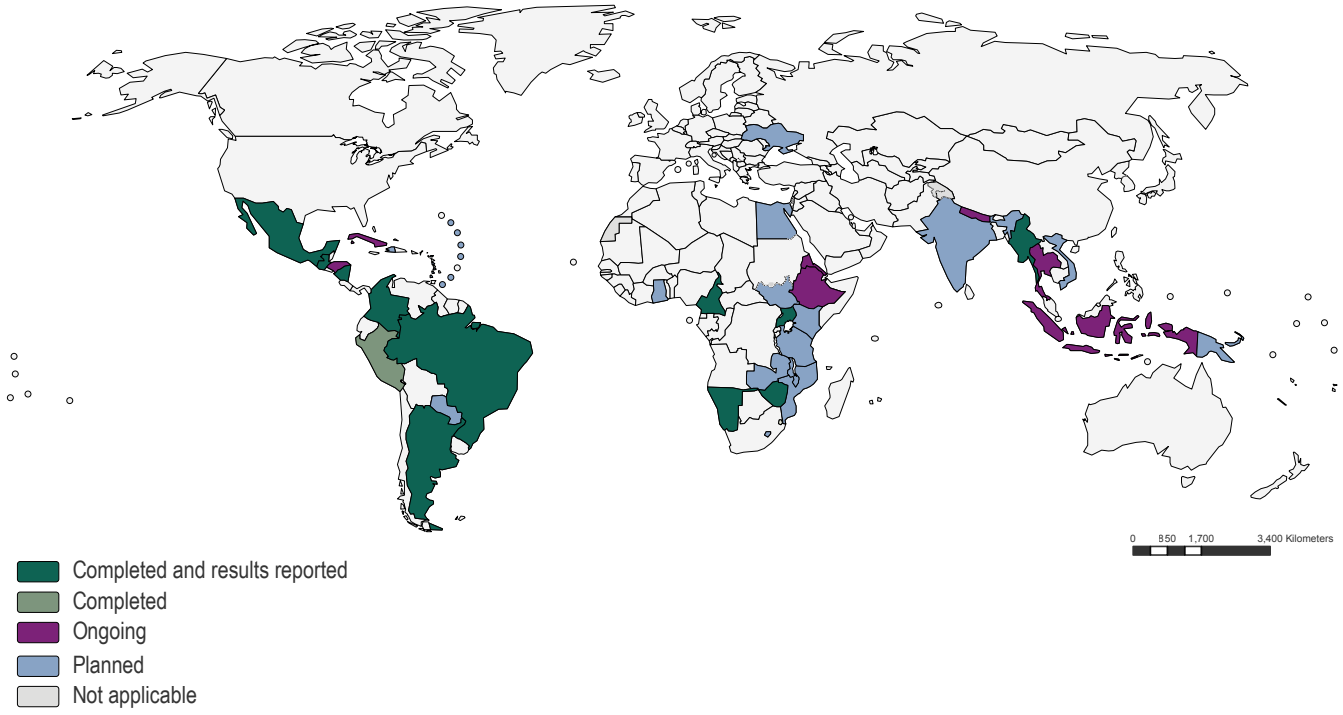
Prior ARV drug exposure may be ascertained through a variety of methods, such as use of a screening questionnaire or review of patient medical records, where available and feasible. Initiators are classified into one of three categories of prior ARV drug exposure: yes, no or unknown. Countries are advised to decide *a priori* which method(s) to employ to identify individuals' prior ARV drug-exposure histories. If prior ARV drug exposure is identified, to the extent possible, it is further classified as: (a) previous ART for treatment of HIV infection (interrupted for more than three months); (b) PrEP; (c) PEP; (d) PMTCT; or (e) a combination of exposures. The information on type of prior exposure is used in descriptive analysis at the national level, and may be aggregated across surveys to generate regional and global estimates by type of ARV drug exposure when sufficient data are available.

The number of individuals to be included in PDR surveys will vary according to a number of factors, such as the number of ART sites in a country, but typically falls within the range of 300–500. The survey is designed to have a duration of 3–6 months; in countries with high HIV prevalence, it can be shorter. For further details of study design and statistical analysis methods see "Section 2: Study design and methods for statistical analysis of PDR and ADR surveys" of the Annex.

2.1.2 Implementation status of HIV drug resistance surveys in ART initiators, 2014–2017

Between 2014 and 2017, 20 countries had completed or were in the process of implementing PDR surveys. A further 16 PDR surveys are anticipated to be implemented in 21[5] countries by late 2017, an encouraging development signalling the importance that countries are now placing on HIVDR surveillance as part of their treatment scale-up efforts (Fig. 1).

Fig. 1: Implementation of WHO pretreatment HIV drug resistance surveys, 2014–2017[6]



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

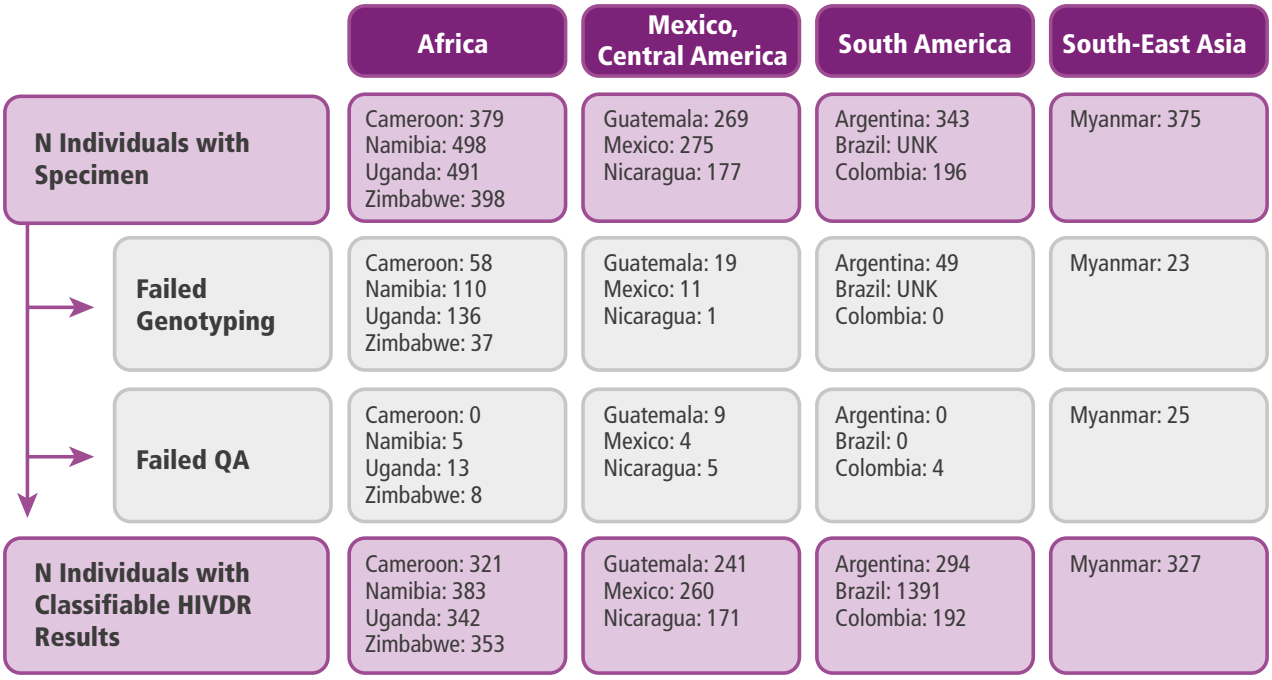
[6] Implementation status as of May 2017. Surveys that have not begun enrolment are classified as planned.

2.2.3 Results of national pretreatment HIV drug resistance surveys in adults, 2014–2016

A total of 11 countries completed PDR surveys during 2014–2016 and reported data to WHO: four in sub-Saharan Africa (Cameroon, Namibia, Uganda and Zimbabwe); three in Mexico, Central America (Guatemala, Mexico and Nicaragua); three in South America (Argentina, Brazil and Colombia); and one in South-East Asia (Myanmar).

A flow diagram of available data from these 11 countries is presented in Fig. 2. The number of individuals with quality-assured genotypes included in the analysis ranged from 171 in Nicaragua to 1391 in Brazil. Overall, amplification failure rates and exclusion of specimens due to poor-quality sequencing[7,8] ranged from 0–28% and from 0–7%, respectively. Details of statistical methods used for the analysis can be found in "Section 2: Study design and methods for statistical analysis of PDR and ADR surveys" of the Annex.

Fig. 2: Flow chart of pretreatment HIV drug resistance surveys (Africa, Mexico, Central America, South America, South-East Asia)



N=number; QA= quality assurance; UNK=unknown.

Population characteristics

Over half the population surveyed in sub-Saharan Africa was female (ranging from 56.7% to 65.4%), while the population was predominantly male in the surveys in Mexico, Central and South American (ranging from 65.9% to 88.5%) and Myanmar (63.4%). Across all 11 PDR surveys, the vast majority of participants were older than 25 years of age (between 78.4% and 90.5% in the four African surveys, and between 65.1% and 83.7% in Mexico, Central and South America). In the four African surveys and in Myanmar, virtually all first-line ART starters received NNRTI-based therapy, while in the surveys in Mexico, Central and South America, NNRTI-based regimens were provided to between 68.4% and 97.1% of treatment initiators.

Of the 11 surveys, four (Brazil, Colombia, Mexico and Zimbabwe) included only ARV drug-naive people, while seven included both individuals initiating (or reinitiating) first-line ART who were ARV drug-naive and who self-reported prior ARV drug exposure. In these surveys, the proportion of individuals with self-reported prior ARV drug exposure (including women with previous exposure for PMTCT and people reporting prior use of ART) ranged from 1.2% (95% CI 0.4–3.7) in Uganda to 18.6% (95% CI 12.2–27.3) in Argentina. In Cameroon and Nicaragua, the most commonly reported type of prior ARV drug exposure was PMTCT; while in Argentina, Myanmar, Namibia and Uganda people reporting prior discontinuation of ART and reinitiation of first-line treatment were more common. Population characteristics for PDR surveys, grouped by geographical region, are presented in Tables 1-4.

[7] With the exception of Cameroon's survey, all sequences were quality assured by WHO following its standard quality-assurance procedures, which are described in Section 1 of the Annex.

[8] With the exception of Argentina's PDR survey, all HIVDR testing was performed at WHO HIVResNet member laboratories, designated by WHO for HIVDR testing for the purpose of HIVDR surveillance.

Table 1: Characteristics of the population for national pretreatment HIV drug resistance surveys – Africa

	Cameroon (Start year 2015)		Namibia (Start year 2015)		Uganda[1] (Start year 2016)		Zimbabwe[2] (Start year 2015)	
	N = 321		N = 383		N = 342		N = 353	
	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]	n	% (95% CI)[3]
Gender								
Women	203	65.4 (60.0–70.6)	248	64.8 (59.3–69.8)	208	61.4 (51.8–70.2)	207	56.7 (50.1–63.0)
Men	118	34.6 (29.4–40.1)	135	35.2 (30.1–40.7)	133	38.4 (29.7–48.0)	145	43.3 (36.9–49.8)
Other	0	–	0	–	0	–	1	<0.5
Mean[4] age (95% CI), years	37.7 (36.5–38.9)		35.3 (33.5–37.1)		34.1 (31.2–37.0)		34.7 (32.6–36.8)	
≤ 25 years	33	9.5 (6.2–14.4)	60	15.9 (11.4–21.7)	72	21.6 (15.1–29.9)	54	18.9 (14.0–25.0)
> 25 years	288	90.5 (85.6–93.8)	317	84.1 (78.3–88.6)	270	78.4 (70.1–84.9)	299	81.1 (75.0–86.0)
Initiated first-line								
NNRTI-based[5]	320	100.0 (99.7–100.0)	379	99.7 (98.0–100.0)	321	100.0	353	100.0
PI-based[6]	1	<0.5	0	–	0	–	0	–
Other	0	–	1	<0.5	0	–	0	–
Prior ARV exposure								
Yes	29	7.8 (4.2–14.0)	69	18.0 (13.2–24.0)	9	1.2 (0.4–3.7)	NA	NA
No	223	80.6 (72.2–86.9)	313	81.7 (75.6–86.6)	296	88.9 (77.2–95.0)	NA	NA
Unknown	69	11.6 (6.2–20.9)	1	<0.5	37	9.9 (4.2–21.2)	NA	NA
Type of ARV exposure								
PMTCT	14	47.4 (17.2–79.7)	16	23.2 (13.3–37.1)	1	8.1 (0.3–74.7)	NA	NA
ART	9	24.0 (5.7–62.4)	53	76.8 (62.8–86.6)	6	59.9 (7.3–96.6)	NA	NA
Other	6	28.6 (4.6–76.9)	0	–	0	–	NA	NA
Unknown	0	–	0	–	2	32.0 (2.2–90.7)	NA	NA

[1] One participant had missing data for gender and 21 participants had missing data for initiated first-line; [2] Prior ARV drug exposed participants were not included in the survey; [3] Study design-weighted proportion and 95% confidence interval; [4] Study design-weighted mean and 95% confidence interval; [5] NNRTI-based first-line regimens include EFV or NVP; [6] PI-based first-line regimens include ATV/r, DRV/r or LPV/r; NA = not available as individuals with prior ARV exposure were excluded from the survey.

Table 2: Characteristics of the population for national pretreatment HIV drug resistance surveys – Mexico, Central America

	Guatemala[1] (Start year 2016)		Mexico[2] (Start year 2015)		Nicaragua[3] (Start year 2016)	
	N = 241		N = 260		N = 171	
	n	% (95% CI)[4]	n	% (95% CI)[4]	n	% (95% CI)[4]
Gender						
Women	66	32.7 (20.1–48.4)	39	16.1 (11.3–22.5)	48	28.1 (21.5–35.7)
Men	173	66.7 (51.0–79.4)	221	83.9 (77.5–88.8)	123	71.9 (64.3–78.5)
Other	2	0.6 (0.2–2.3)	0	–	0	–
Mean[5] age (95% CI), years	32.9 (31.8–34.1)		32.9 (31.5–34.4)			
≤ 25 years	50	19.9 (14.7–26.3)	76	27.7 (21.3–35.1)	42	24.6 (20.5–29.1)
> 25 years	191	80.1 (73.7–85.3)	183	72.3 (64.9–78.7)	129	75.4 (70.9–79.5)
Initiated first-line						
NNRTI-based[6]	220	96.7 (91.3–98.8)	176	82.6 (76.0–87.8)	165	97.1 (94.7–98.4)
PI-based[7]	5	2.9 (1.0–8.3)	31	16.8 (11.8–23.4)	5	2.9 (1.6–5.3)
Other	1	<0.5	1	0.6 (0.1–4.1)	0	–
Prior ARV exposure						
Yes	7	2.8 (0.7–11.1)	NA	NA	21	12.3 (5.8–24.3)
No	229	93.9 (81.9–98.1)	NA	NA	146	85.4 (75.4–91.7)
Unknown	5	3.3 (0.8–12.9)	NA	NA	4	2.3 (1.0–5.4)
Type of ARV exposure						
PMTCT	1	12.0 (0.1–94.0)	NA	NA	8	38.1 (18.3–62.8)
ART	0	–	NA	NA	2	9.5 (1.2–47.6)
Other	0	–	NA	NA	1	4.8 (0.3–41.9)
Unknown	6	88.0 (6.0–99.9)	NA	NA	10	47.6 (34.9–60.6)

[1]15 participants had missing data for initiated first-line; [2]Prior ARV drug exposed participants were not included in the survey, 52 participants had missing data for initiated first-line; [3]One participant had missing data for initiated first-line; [4]Study design-weighted proportion and 95% confidence interval; [5]Study design-weighted mean and 95% confidence interval; [6]NNRTI-based first-line regimens include EFV or NVP; [7]PI-based first-line regimens include ATV/r, DRV/r or LPV/r; NA=not available as individuals with prior ARV exposure were excluded from the survey.

Table 3: Characteristics of the population for pretreatment HIV drug resistance national surveys – South America

	Argentina (Start year 2014)		Brazil[1] (Start year 2013)[2]		Colombia[3] (Start year 2016)	
	N = 294		N = 1391		N = 192	
	n	% (95% CI)[4]	n	% (95% CI)[4]	n	% (95% CI)[4]
Gender						
Women	97	33.3 (27.0–40.2)	380	30.3 (26.7–34.1)	22	11.5 (8.1–15.9)
Men	195	65.9 (58.8–72.4)	874	69.7 (65.8–73.3)	170	88.5 (84.1–91.9)
Other	2	0.8 (0.2–3.2)				
Mean[5] age (95% CI), years	36.2 (34.8–37.7)		35.6 (35.0–36.2)		31.7 (30.5–32.9)	
≤ 25 years	46	16.3 (11.4–22.9)	264	21.9 (19.1–24.9)	67	34.9 (29.0–41.2)
> 25 years	248	83.7 (77.1–88.6)	942	78.1 (75.0–80.9)	125	65.1 (58.8–71.0)
Initiated first-line						
NNRTI-based[6]	202	68.4 (58.3–77.1)	NA	NA	NA	NA
PI-based[7]	89	30.1 (22.2–41.0)	NA	NA	NA	NA
Other	3	0.7 (0.2–2.3)	NA	NA	NA	NA
Prior ARV exposure						
Yes	54	18.6 (12.2–27.3)	NA	NA	NA	NA
No	239	81.0 (72.4–87.4)	NA	NA	NA	NA
Unknown	1	<0.5	NA	NA	NA	NA
Type of ARV exposure						
PMTCT	10	20.7 (10.2–37.6)	NA	NA	NA	NA
ART	43	77.0 (62.1–87.3)	NA	NA	NA	NA
Other	1	<0.5	NA	NA	NA	NA
Unknown	0	–	NA	NA	NA	NA

[1]Prior ARV drug exposed participants were not included in the survey; initiated first-line was not available; 137 participants had missing information for gender, and 185 had missing information for age; [2]Survey enrolment between 2013 and 2016 with the majority (~80%) of survey participants enrolled in 2014; [3]Prior exposed participants were not included in the survey; initiated first-line was not available; [4]Study design-weighted proportion and 95% confidence interval; [5]Study design-weighted mean and 95% confidence interval; [6]NNRTI-based first-line regimens include EFV or NVP; [7]PI-based first-line regimens include ATV/r, DRV/r or LPV/r; NA = not available.

Table 4: Characteristics of the population for national pretreatment HIV drug resistance surveys – South-East Asia

	Myanmar[1] (Start year 2016)	
	N = 327	
	n	% (95% CI)[2]
Gender		
Women	115	36.6 (29.8–43.9)
Men	206	63.4 (56.1–70.2)
Mean[3] age (95% CI), years	35.6 (34.1–37.2)	
≤ 25 years	51	16.0 (11.6–21.6)
> 25 years	270	84.0 (78.3–88.4)
Initiated first-line		
NNRTI-based[4]	263	100.0
PI-based[5]	0	–
Other	0	–

	Myanmar[1] (Start year 2016)	
	N = 327	
	n	% (95% CI)[2]
Prior ARV exposure		
Yes	32	8.4 (5.0–13.8)
No	287	90.0 (83.7–94.0)
Unknown	8	1.6 (0.5–5.6)
Type of ARV exposure		
PMTCT	4	10.1 (2.9–29.7)
ART	24	76.3 (41.2 –93.7)
Other	3	13.2 (2.7–45.5)
Unknown	1	<0.5

[1]Six participants had missing information for age and gender, and 64; [2]Study design-weighted proportion and 95% confidence interval; [3]Study design-weighted mean and 95% confidence interval; [4]NNRTI-based first-line regimens include EFV or NVP; [5]PI-based first-line regimens include ATV/r, DRV/r or LPV/r.

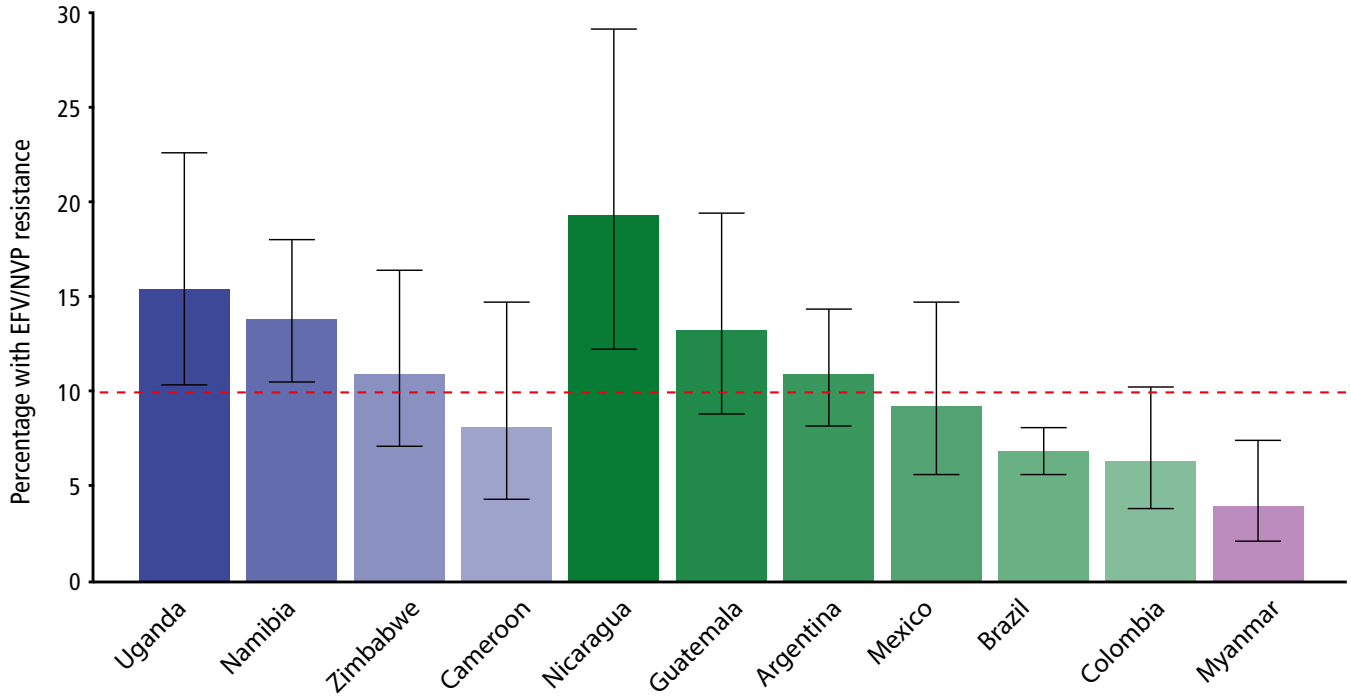
Of the 11 countries with PDR survey results, seven (Argentina, Guatemala, Mexico, Namibia, Nicaragua, Uganda and Zimbabwe) had prevalence of any PDR greater than 10%.[9] Overall, levels of PDR were driven by NNRTI resistance,[10] which exceeded 10% in six of the countries (excluding Mexico) (Fig. 3).

Countries with NNRTI resistance less than 10% were Brazil, Cameroon, Colombia, Mexico and Myanmar. However, Brazil, Colombia and Mexico monitored PDR only in ARV drug-naive individuals; this may explain the lower prevalence estimates observed in these countries.

[9] The threshold of NNRTI PDR at which new WHO guidelines recommend countries urgently consider using an alternative non-NNRTI-containing first-line regimen. World Health Organization. Guidelines on the public health response to pretreatment HIV drug resistance. Available at: http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/

[10] NNRTI resistance is defined as resistance to NVP or EFV. NRTI resistance is defined as resistance to any NRTI; and any PI resistance is defined as resistance to ATV/r, LPV/r or 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 (version 8.3): sequences classified as having predicted low-, intermediate- or high-level resistance are considered "resistant".

Fig. 3: NNRTI (EFV/NVP) pretreatment HIV drug resistance[11]



EFV= efavirenz; NVP= nevirapine.

In the African Region, levels of any PDR and NNRTI resistance were greater than 10% in three out of four countries, with NNRTI PDR ranging from 8.1% (95% CI 4.3–14.7) in Cameroon to 15.4% (95% CI 10.3–22.5) in Uganda. Prevalence of any PDR was greater than 10% in four of six surveys in Mexico, Central and South America, ranging from 9.8% (95% CI 8.1–12.0) in Brazil to 23.4% (95% CI 14.4–35.6) in Nicaragua; NNRTI PDR ranged from 6.3% (95% CI 3.8–10.2) in Colombia to 19.3% (95% CI 12.2–29.1) in Nicaragua.

Gender and prevalence of pretreatment HIV drug resistance

The prevalence of any PDR and NNRTI resistance was higher among women than men (Tables 5–8) in all surveys, except those in Brazil, Colombia and Myanmar. Among ARV drug-naive individuals across the different surveys, NNRTI PDR was two times higher in women (12.2%, 95% CI 9.1–16.3) than men (6.3%, 95% CI 5.0–8.1); $P<0.0001$.

Prevalence of pretreatment HIV drug resistance among individuals with self-reported prior ARV exposure

In all seven surveys that included both ARV drug-naive individuals and people starting first-line ART with prior ARV drug exposure, the prevalence of any PDR and NNRTI resistance was consistently higher in those with prior ARV drug exposure, compared to those with no prior ARV drug exposure. In the African surveys, resistance to NNRTI in people with prior exposure ranged from 17.5% (95% CI 2.3–65.2) in Uganda to 34.8% (95% CI 25.2–45.8) in Namibia; in Mexico, Central and South America it ranged from 17.8% (95% CI 10.0–29.5) in Argentina to 76.2% (95% CI 52.9–90.1) in Nicaragua; and in Myanmar, NNRTI resistance was 15.7% (95% CI 5.5–37.4).

The difference between levels of NNRTI PDR in people staring first-line ART with and without prior ARV drug exposure was most pronounced in Namibia, where NNRTI resistance was 9.3% (95% CI 6.1–13.8) in the ARV-naive group versus 34.8% (95% CI 25.2–45.8) in the exposed group; in Nicaragua it was 11.0% (95% CI 6.0–19.3) versus 76.2% (95% CI 52.9–90.1); and in Myanmar it was 2.7% (95% CI 1.2–6.0) versus 15.7% (95% CI 5.5–37.4). Across the seven surveys, NNRTI resistance was significantly higher among previously exposed ART initiators (21.6%, 95% CI 13.8–32.2) than in the ARV drug-naive (8.3%, 95% CI 6.0–11.4), $P<0.0001$. The high levels of resistance in people reporting prior ARV drug exposure who are initiating or reinitiating first-line ART is particularly concerning, as this group can represent a significant proportion of the population initiated on first- line ART. For example, 18.0% of treatment starters (95% CI 13.2–24.0) in Namibia, 12.3% of treatment starters (95% CI 5.8–24.3) in Nicaragua, and 18.6% of treatments starters (95% CI 12.2–27.3) in Argentina reported prior ARV drug exposure. In Cameroon, while the prevalence of NNRTI PDR among ART starters was below 10% (8.1%, 95% CI 4.3–14.7), it was much higher in people with prior exposure to ARV drugs (20.5%, 95% CI 6.8–47.8).

[11] Sequences classified as having low-, intermediate- or high-level resistance to EFV/NVP by the Stanford HIVdb algorithm (version 8.3) are considered "resistant".

Table 5: **National prevalence estimates of pretreatment HIV drug resistance – Africa**

	Cameroon		Namibia		Uganda		Zimbabwe	
	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)
All[1]								
Any	24/321	8.3 (4.4–15.0)	56/383	14.6 (11.6–18.2)	48/342	17.4 (12.1–24.3)	NA	NA
NNRTI	23/321	8.1 (4.3–14.7)	53/383	13.8 (11.1–17.1)	43/342	15.4 (10.3–22.5)	NA	NA
NRTI	5/321	2.4 (0.4–12.9)	6/383	1.6 (0.6–3.8)	11/342	5.1 (2.4–10.3)	NA	NA
PI	1/321	0.2 (0.0–1.7)	2/383	0.5 (0.1–2.2)	2/342	1.0 (0.2–4.6)	NA	NA
NNRTI+NRTI	5/321	2.4 (0.4–12.9)	5/383	1.3 (0.5–3.6)	8/342	4.1 (1.8–9.0)	NA	NA
Naive								
Any	13/223	7.9 (3.8–15.9)	31/313	9.9 (6.5–14.9)	44/296	18.1 (12.7–25.2)	34/353	10.9 (7.1–16.4)
NNRTI	12/223	7.7 (3.6–15.7)	29/313	9.3 (6.1–13.8)	39/296	15.9 (10.2–24.0)	34/353	10.9 (7.1–16.4)
NRTI	2/223	2.8 (0.4–16.3)	1/313	0.3 (0.0–2.5)	11/296	5.7 (2.7–11.5)	3/353	0.8 (0.2–3.3)
PI	1/223	0.3 (0.0–2.1)	2/313	0.6 (0.2–2.6)	2/296	1.1 (0.2–5.4)	0/353	–
NNRTI+NRTI	2/223	2.8 (0.4–16.3)	1/313	0.3 (0.0–2.5)	8/296	4.6 (2.1–9.9)	3/353	0.8 (0.2–3.3)
Prior-exposed								
Any	8/29	20.5 (6.8–47.8)	25/69	36.2 (25.6–48.5)	2/9	17.5 (2.3–65.2)	NA	NA
NNRTI	8/29	20.5 (6.8–47.8)	24/69	34.8 (25.2–45.8)	2/9	17.5 (2.3–65.2)	NA	NA
NRTI	3/29	1.6 (0.2–9.9)	5/69	7.2 (2.7–18.2)	0/9	–	NA	NA
PI	0/29	–	0/69	–	0/9	–	NA	NA
NNRTI+NRTI	3/29	1.6 (0.2–9.9)	4/69	5.8 (1.7–17.9)	0/9	–	NA	NA
Women								
Any	17/203	10.6 (5.2–20.3)	39/248	15.7 (11.3–21.5)	31/208	19.2 (11.8–29.8)	26/207	16.1 (10.9–23.0)
NNRTI	16/203	10.2 (4.9–20.0)	37/248	14.9 (10.7–20.4)	28/208	16.5 (9.5–27.2)	26/207	16.1 (10.9–23.0)
NRTI	4/203	3.6 (0.6–18.7)	4/248	1.6 (0.5–5.3)	9/208	7.3 (3.3–15.4)	3/207	1.4 (0.4–5.6)
PI	1/203	0.3 (0.0–2.6)	2/248	0.8 (0.2–3.2)	1/208	1.3 (0.2–7.5)	0/207	–
NNRTI+NRTI	4/203	3.6 (0.6–18.7)	4/248	1.6 (0.5–5.3)	7/208	5.9 (2.4–13.9)	3/207	1.4 (0.4–5.6)
Men								
Any	7/118	4.0 (1.4–10.4)	17/135	12.6 (9.1–17.2)	17/133	14.5 (9.9–20.7)	8/145	4.1 (1.1–14.3)
NNRTI	7/118	4.0 (1.4–10.4)	16/135	11.9 (8.2–16.8)	15/133	13.7 (9.1–20.3)	8/145	4.1 (1.1–14.3)
NRTI	1/118	0.1 (0.0–0.8)	2/135	1.5 (0.3–6.2)	2/133	1.5 (0.3–7.1)	0/145	–
PI	0/118	–	0/135	–	1/133	0.4 (0.0–3.6)	0/145	–
NNRTI+NRTI	1/118	0.1 (0.0–0.8)	1/135	0.7 (0.1–6.0)	1/133	1.2 (0.2–8.1)	0/145	–

[1] Estimates of HIVDR in all ART initiators include ARV naive individuals, those with prior ARV drug exposure, and those with unknown ARV exposure; NA = not available as individuals with prior ARV exposure were excluded from the survey; 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".

Table 6: National prevalence estimates of pretreatment HIV drug resistance – Mexico, Central America

	Guatemala		Mexico		Nicaragua	
	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)
All[1]						
Any	34/241	15.1 (11.5–19.6)	NA	NA	40/171	23.4 (14.4–35.6)
NNRTI	29/241	13.2 (8.8–19.4)	NA	NA	33/171	19.3 (12.2–29.1)
NRTI	9/241	3.2 (1.5–6.8)	NA	NA	18/171	10.5 (4.9–21.1)
PI	2/241	0.6 (0.1–3.7)	NA	NA	0/171	–
NNRTI+NRTI	4/241	1.3 (0.4–3.9)	NA	NA	11/171	6.4 (2.7–14.7)
Naive						
Any	31/229	14.9 (11.0–19.9)	34/260	13.5 (9.4–19.1)	23/146	15.8 (8.8–26.6)
NNRTI	27/229	13.3 (8.5–20.1)	22/260	9.2 (5.6–14.7)	16/146	11.0 (6.0–19.3)
NRTI	8/229	3.0 (1.5–6.0)	14/260	5.5 (3.0–9.9)	10/146	6.8 (2.7–16.1)
PI	2/229	0.6 (0.1–3.8)	7/260	2.6 (1.2–5.3)	0/146	–
NNRTI+NRTI	4/229	1.4 (0.4–4.2)	3/260	1.4 (0.5–4.4)	3/146	2.1 (0.6–7.0)
Prior-exposed						
Any	3/7	38.7 (12.6–73.4)	NA	NA	16/21	76.2 (52.9–90.1)
NNRTI	2/7	26.7 (3.2–80.1)	NA	NA	16/21	76.2 (52.9–90.1)
NRTI	1/7	12.0 (1.6–53.8)	NA	NA	7/21	33.3 (13.9–60.8)
PI	0/7	–	NA	NA	0/21	–
NNRTI+NRTI	0/7	–	NA	NA	7/21	33.3 (13.9–60.8)
Women						
Any	10/66	19.2 (11.1–31.2)	9/39	20.7 (8.4–42.5)	18/48	37.5 (20.8–57.8)
NNRTI	10/66	19.2 (11.1–31.2)	5/39	14.8 (4.7–38.0)	15/48	31.3 (19.6–45.8)
NRTI	1/66	1.0 (0.1–9.1)	5/39	10.3 (3.5–26.5)	7/48	14.6 (5.0–35.5)
PI	0/66	–	2/39	4.2 (0.9–17.0)	0/48	–
NNRTI+NRTI	1/66	1.0 (0.1–9.1)	2/39	5.9 (1.5–20.4)	4/48	8.3 (2.8–22.4)
Men						
Any	24/173	13.2 (9.6–17.9)	25/221	12.1 (8.3–17.4)	22/123	17.9 (9.9–30.2)
NNRTI	19/173	10.4 (6.4–16.4)	17/221	8.1 (5.1–12.6)	18/123	14.6 (8.0–25.3)
NRTI	8/173	4.3 (2.1–8.5)	9/221	4.6 (2.2–9.5)	11/123	8.9 (4.0–18.8)
PI	2/173	0.9 (0.1–5.1)	5/221	2.2 (0.9–5.4)	0/123	–
NNRTI+NRTI	3/173	1.4 (0.7–3.1)	1/221	0.6 (0.1–4.3)	7/123	5.7 (2.4–13.1)

[1] Estimates of HIVDR in all ART initiators include ARV naive individuals, those with prior ARV drug exposure, and those with unknown ARV exposure; NA = not available as individuals with prior ARV exposure were excluded from the survey; 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".

Table 7: National prevalence estimates of pretreatment HIV drug resistance – South America

	Argentina		Brazil		Colombia	
	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)
All[1]						
Any	41/294	13.8 (10.3–18.3)	NA	NA	NA	NA
NNRTI	33/294	10.9 (8.2–14.3)	NA	NA	NA	NA
NRTI	10/294	3.7 (1.9–7.0)	NA	NA	NA	NA
PI	6/294	1.9 (0.7–4.8)	NA	NA	NA	NA
NNRTI+NRTI	5/294	1.7 (0.6–4.6)	NA	NA	NA	NA
Naive						
Any	31/239	12.8 (9.2–17.4)	137/1391	9.8 (8.1–12.0)	19/192	9.9 (7.5–12.9)
NNRTI	24/239	9.4 (6.4–13.4)	94/1391	6.8 (5.6–8.1)	12/192	6.3 (3.8–10.2)
NRTI	8/239	3.6 (1.7–7.6)	50/1391	3.6 (2.8–4.7)	7/192	3.6 (1.7–7.6)
PI	5/239	2.1 (0.7–5.9)	13/1391	0.9 (0.6–1.5)	0/192	–
NNRTI+NRTI	3/239	1.1 (0.3–3.6)	17/1391	1.2 (0.8–1.9)	0/192	–
Prior-exposed						
Any	10/54	18.6 (10.7–30.4)	NA	NA	NA	NA
NNRTI	9/54	17.8 (10.0–29.5)	NA	NA	NA	NA
NRTI	2/54	4.1 (0.7–20.7)	NA	NA	NA	NA
PI	1/54	0.9 (0.1–4.9)	NA	NA	NA	NA
NNRTI+NRTI	2/54	4.1 (0.7–20.7)	NA	NA	NA	NA
Women						
Any	14/97	15.5 (9.7–24.0)	26/380	6.8 (5.5–8.5)	2/22	9.1 (2.1–31.5)
NNRTI	12/97	11.9 (6.5–20.9)	19/380	5.0 (3.8–6.6)	1/22	4.5 (0.6–26.9)
NRTI	5/97	6.2 (2.3–15.4)	11/380	2.9 (1.7–4.9)	1/22	4.5 (0.5–30.5)
PI	1/97	1.2 (0.1–8.3)	1/380	0.3 (0.0–2.1)	0/22	–
NNRTI+NRTI	4/97	3.7 (1.1–12.2)	5/380	1.3 (0.7–2.5)	0/22	–
Men						
Any	27/195	13.1 (8.8–19.2)	100/874	11.4 (9.2–14.2)	17/170	10.0 (7.5–13.3)
NNRTI	21/195	10.5 (6.9–15.8)	66/874	7.6 (6.0–9.5)	11/170	6.5 (4.0–10.4)
NRTI	5/195	2.4 (0.9–6.4)	37/874	4.2 (3.2–5.6)	6/170	3.5 (1.5–7.9)
PI	5/195	2.3 (0.9–5.4)	11/874	1.3 (0.7–2.3)	0/170	–
NNRTI+NRTI	1/195	0.6 (0.1–4.4)	11/874	1.3 (0.7–2.3)	0/170	–

[1] Estimates of HIVDR in all ART initiators include ARV naive individuals, those with prior ARV drug exposure, and those with unknown ARV exposure; NA = not available as individuals with prior ARV exposure were excluded from the survey; 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".

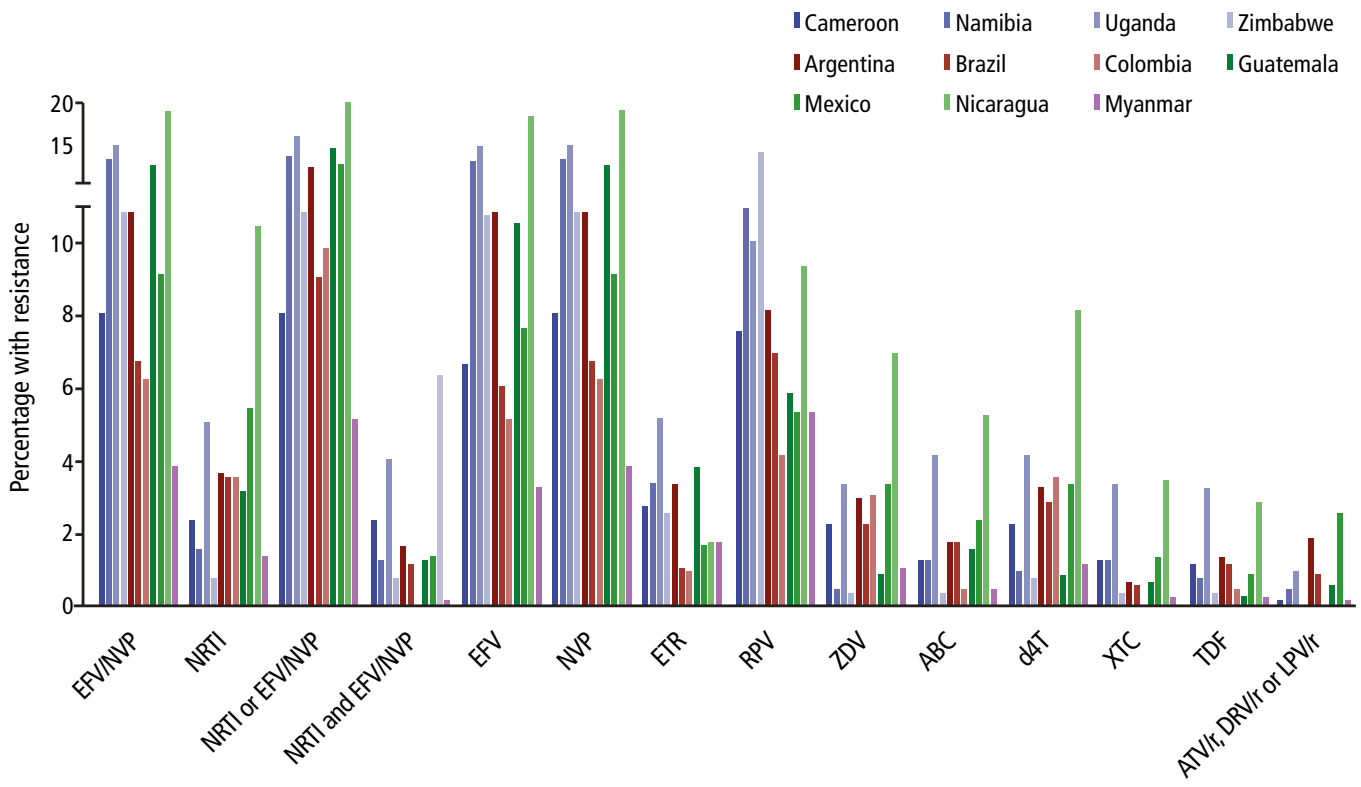
Table 8: National prevalence estimates of pretreatment HIV drug resistance – South-East Asia

	Myanmar	
	n/N	Prevalence % (95% CI)
All[1]		
Any	21/327	5.4 (3.1–9.2)
NNRTI	16/327	3.9 (2.1–7.4)
NRTI	5/327	1.4 (0.5–3.7)
PI	1/326	0.2 (0.0–1.8)
NNRTI+NRTI	1/327	0.2 (0.0–1.3)
Naive		
Any	14/287	4.3 (2.3–8.0)
NNRTI	9/287	2.7 (1.2–6.0)
NRTI	5/287	1.5 (0.6–4.2)
PI	1/286	0.3 (0.0–2.0)
NNRTI+NRTI	1/287	0.2 (0.0–1.4)
Prior–exposed		
Any	6/32	15.7 (5.5–37.4)
NNRTI	6/32	15.7 (5.5–37.4)
NRTI	0/32	–
PI	0/32	–
NNRTI+NRTI	0/32	–
Women		
Any	7/115	5.2 (2.1–12.2)
NNRTI	5/115	3.6 (1.2–10.3)
NRTI	2/115	1.6 (0.3–7.4)
PI	0/115	–
NNRTI+NRTI	0/115	–
Men		
Any	13/206	5.3 (2.9–9.7)
NNRTI	10/206	3.9 (1.9–7.9)
NRTI	3/206	1.3 (0.4–4.5)
PI	1/205	0.4 (0.0–2.9)
NNRTI+NRTI	1/206	0.3 (0.0–2.1)

[1] Estimates of HIVDR in all ART initiators include ARV naive individuals, those with prior ARV drug exposure, and those with unknown ARV exposure; 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".

Prevalence of NRTI, NNRTI and PI resistance by drug are shown in Fig. 4. Levels of resistance to efavirenz (EFV) or nevirapine (NVP) ranged from 4.9% in Myanmar to 19.3% in Nicaragua. Overall, prevalence of resistance to any NRTI was low, except for Nicaragua where NRTI resistance exceeded 10%, driven by resistance to thymidine analogues. Broadly speaking, tenofovir resistance was low, ranging from 0.4% in Guatemala to 2.9% in Nicaragua. Not unexpectedly, PDR to the protease inhibitors (PIs) atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r) and darunavir/ritonavir (DRV/r) was low, ranging from 0% in Uganda to 2.7% in Mexico.

Fig. 4: Prevalence of pretreatment HIV drug resistance by country



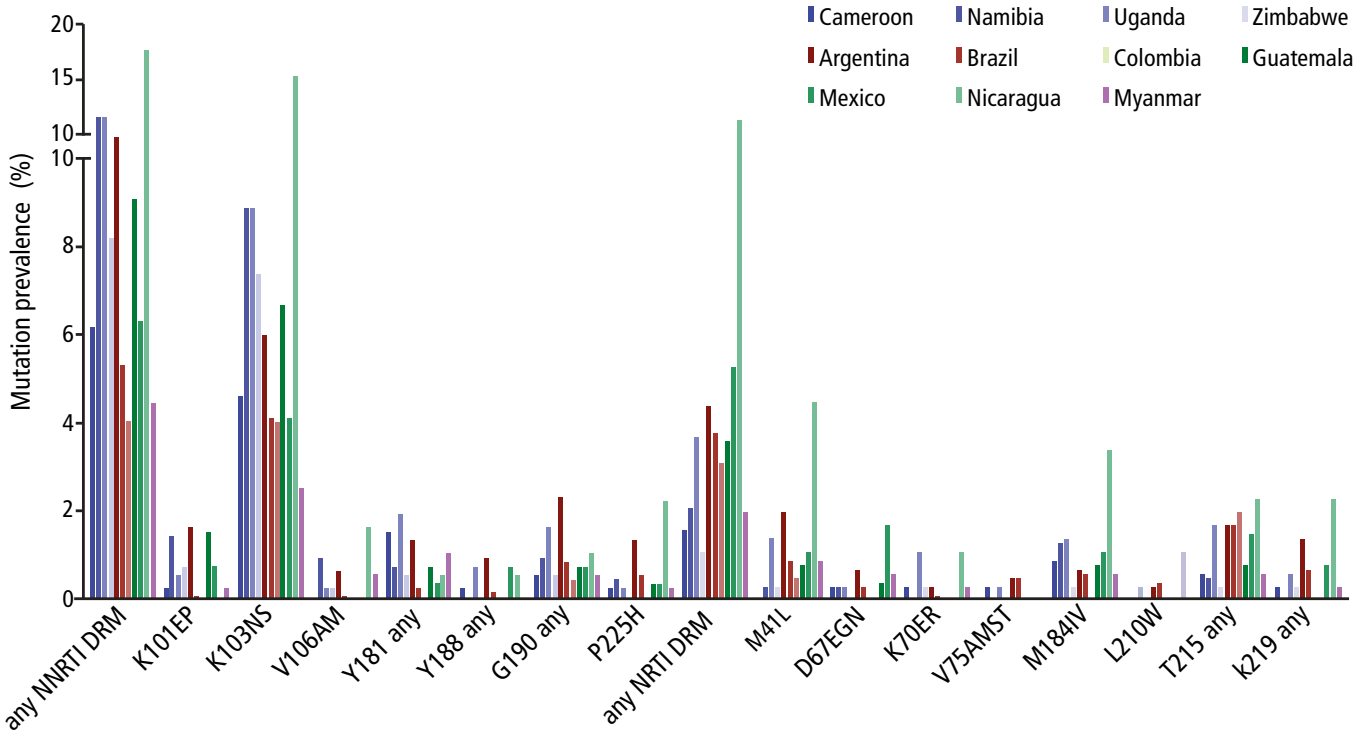
EFV= efavirenz; NVP= nevirapine; NRTI = Nucleoside reverse-transcriptase inhibitor; ETR= etravirine; RPV= rilpivirine; ZDV=zidovudine; ABC= abacavir; d4T= stavudine; XTC= lamivudine or emtricitabine; TDF= tenofovir disoproxil fumarate; ATV/r= atazanavir/ritonavir; DRV/r=darunavir/ritonavir; LPV/r= lopinavir/ritonavir.

The proportion of individuals starting a fully active first-line ART regimen (i.e. having a virus susceptible to all prescribed ARV drugs) among ARV drug-naive individuals ranged from 84.1% (95% CI 75.8–90.0) in Uganda to 96.9% (95% CI 92.6–98.7) in Myanmar. Among individuals with prior ARV drug exposure, the proportion starting fully active ART ranged from 33.3% (95% CI 15.5–57.6) in Nicaragua to 84.6% (95% CI 73.1–91.8) in Argentina.

The frequency of any surveillance drug resistance mutation (SDRM) *(2)* across all surveys is shown in Fig. 5.[12] The most commonly observed NRTI-associated resistance mutations were at amino acid positions 41, 184 and 215 of the viral reverse transcriptase (RT); the most commonly observed NNRTI-associated mutations were at RT positions 103, 181 and 190. No PI SDRM were detected at a frequency above 0.2%.

[12] Mutations present at a level of >0.2% are reported.

Fig. 5: Pretreatment HIV drug resistance mutations by country [13]



PHIA surveys, supported by the United States President's Emergency Plan for AIDS Relief (PEPFAR), are designed to generate population-level HIV incidence rates and estimates of viral load suppression. They also inform on the prevalence of transmitted HIV drug resistance (TDR) in recently infected people. An example of PHIAs implemented in Malawi and Zimbabwe are described in Box 1.

Box 1: Population-based HIV Impact Assessment surveys in Malawi and Zimbabwe: frequency of drug resistance mutations among incident HIV infections

PHIA surveys are used to estimate the national incidence of HIV among adults (15–59 years), and the national prevalence of viral load suppression (HIV RNA <1000 copies/ml) among all adults with self-reported use of ART at the time of the survey. PHIAs are carried out using a nationally representative, cross-sectional two-stage cluster sample household survey. Results from PHIA surveys conducted in three countries (Malawi, November 2015–August 2016; Zambia, March–August 2016; and Zimbabwe, October 2015–August 2016) showed that the prevalence of viral load suppression ranged from 86% in Zimbabwe to 91% in Malawi for adults aged 15–59 years who reported taking ART at the time of the survey. The high prevalence of viral load suppression suggests that the prevalence of HIV drug resistance mutations (DRM) are not common among people who self-report being on ART.

One of the secondary objectives of the PHIAs is to estimate the prevalence of HIVDR among adults classified as recently infected (≤ five months based on WHO criteria for recent infection using limiting antigen (LAg) avidity enzyme immunoassay and viral load criteria). Estimates of the prevalence of DRMs among recently infected people from Zimbabwe's and Malawi's PHIAs are presented below.

Any HIVDR is defined with respect to one or more of the following drugs or drug classes: NVP, EFV, any NRTI, DRV/r, LPV/r or ATV/r. HIVDR predicted to affect susceptibility of available ARV drugs is defined in sequences classified as having low-, intermediate- or high-level resistance according to the Stanford HIVdb algorithm *(3).*

[13] Non-polymorphic drug resistance-associated mutations present at a frequency of >0.2% are shown.

Box 1: Population-based HIV Impact Assessment surveys in Malawi and Zimbabwe: frequency of drug resistance mutations among incident HIV infections (continued)

The annual HIV incidence among 15-49 year-olds in Malawi's PHIA survey was 0.32% (95% CI 0.16–0.48). Among those specimens (n=26) classified as recently infected, and with genotype data available, DRMs were detected in four out of 26 specimens. One sequence had high-level EFV/NVP resistance with K103R/S; two had low-level resistance to EFV and intermediate to NVP with A98G; and a fourth had multiple mutations impacting both NRTIs and NNRTIs (A62V, K65N, D67I, A98G, K103NE, Y181C, G190A and H221Y).

Overall, annual HIV incidence among 15–49 year-olds in Zimbabwe's PHIA survey was 0.48% (95% CI 0.29–0.66). Among the small number (n=30) of specimens classified as recently infected with genotype data available, DRMs were detected in three specimens. One sequence had high-level EFV/NVP resistance with K103N; one had low-level resistance to LVP/ATV with L90M; and a third had multiple mutations impacting both NRTIs and NNRTIs (A62V, K65R, M184V, A98G, K101E, K103N, Y181C and G190A).

The prevalence of HIVDR observed among recently infected people in Zimbabwe and Malawi is broadly consistent with the prevalence of HIVDR observed in the PDR surveys in the African Region. As mentioned above, the overall prevalence of viral load suppression among adults reporting current ART was nearly 90%.

For each survey, one of the specimens classified as recently infected with HIVDR had multiple DRMs, suggesting prior ARV drug exposure and possible misclassification. In contrast to the estimates generated from the PDR surveys, the HIVDR estimates from the PHIA surveys do not capture PDR in individuals with chronic infection initiating first-line ART – either those with undisclosed ART or those with prior ARV drug exposures(s) – and could therefore underestimate the population-level burden of PDR among ART initiators.

2.2 Nationally representative surveys of HIV drug resistance in children younger than 18 months of age, 2014–2017

2.2.1 Survey methods for nationally representative surveys in children younger than 18 months of age

These surveys assess the prevalence of HIVDR among children younger than 18 months, who have been newly diagnosed with HIV through EID and have not received treatment for HIV infection. These surveys are relevant in settings where many infants are exposed to or acquire HIV infection. Results inform the choice of standard first-line ART and may also inform PI-sparing strategies *(4)*, which consist of changing children from PI-based regimens to NNRTI-based regimens once they have achieved viral load suppression, to avoid potential PI-associated toxicities and adverse events.

The methodology leverages a random sample or census of remnant dried blood spot (DBS) specimens collected as part of routine EID testing during a 12-month period. In all countries, all laboratories performing EID contributed DBS to the sample, with the number of specimens contributed per laboratory proportional to the number of EID specimens tested. In each laboratory, eligible DBS are sampled using simple random sampling without replacement. The recommended effective sample size, designed to yield a prevalence estimate with a 95% confidence interval of ±7%, is 245. This sample size was based on the assumption that the true HIVDR prevalence was 50% and amplification success rate from DBS was 80% *(5)*.

2.2.2 Implementation status of surveys in children younger than 18 months of age, 2014–2017

Three countries implemented HIVDR surveys in children younger than 18 months of age between 2014 and 2017. Two of these countries (Nigeria and South Africa) completed their surveys, and one country (South Africa) reported results to WHO.

An additional four countries (Ethiopia, Kenya, Malawi and Uganda) plan to implement surveillance of HIVDR in children younger than 18 months in late 2017 (Fig. 6). Prior to 2014, six countries (the Democratic Republic of the Congo, Mozambique, Swaziland, Togo, Uganda and Zimbabwe) implemented surveys in this population.

Fig. 6: Implementation of HIV drug resistance surveillance in children younger than 18 months of age, 2014–2017[14]



2.2.3 Results of national surveys of HIV drug resistance in children younger than 18 months of age, 2014–2016

In South Africa's survey, the prevalence of any HIVDR, NNRTI resistance and NRTI resistance was high, at 63.7% (95% CI 59.0–68.4), 62.7% (95% CI 58.0–67.4), and 13.9% (95% CI 10.5–17.3), respectively. Information on maternal and neonatal ARV drug exposure was unavailable; thus, associations between resistance and PMTCT exposure were not explored. The high levels of NNRTI resistance observed in children in South Africa, in other recent publications from Togo *(6)*, and in a different cohort from South Africa *(7)*, support WHO's 2013 recommendation that all children younger than 3 years of age be started on LPV/r-based regimens, irrespective of PMTCT exposure *(8)*. Unfortunately, implementation of this policy has been slow. In a 2016 WHO global survey on ARV drug use conducted in 66 LMIC, which assessed paediatric ARV regimens used in 2015, only 14% of 748 638 children aged 0–15 years were receiving PI/r-based first-line ART regimens *(9)*. Reasons for poor uptake of this policy include the lack, until recently, of heat stable and palatable paediatric formulations of LPV/r, which do not require cold chain until the point of dispensing, as well as no available fixed-dose combination of LPV/r with an NRTI backbone. Results from South Africa's survey of HIVDR in children younger than 18 months reinforce the urgent need to overcome barriers to scale up paediatric PI-based regimens in sub-Saharan Africa. They also underscore the need to accelerate the study and approval of integrase inhibitors for use in young children.

2.3 Systematic literature review of pretreatment HIV drug resistance in adults in LMIC

A systematic review of the literature published between 1 January 2001 and 31 December 2016 was conducted to estimate changes in the prevalence of PDR among adults (15+ years of age) by geographical region and calendar year in resource-limited settings. Unpublished data from national PDR and TDR surveys that followed WHO methods, including those documented in this report, were also included. This review updates a previous systematic literature review and meta-analysis published in 2012 *(10)*.

A total of 358 datasets were identified, comprising 56 044 adults across 63 countries sampled between 1993 and 2016 (for a list of studies included see Table A1, Section 3 of Annex 1). Meta-analysis was performed using meta-regression models with a random effect at study level to allow for between-study heterogeneity and to model resistance over time (detailed methods are described in Section 3 of Annex 1). The baseline characteristics of studies included in the review are presented in Table 9. The majority of datasets (92.6%) were derived from urban settings. The median number of genotypes per study was 95.

[14] Implementation status as of May 2017. Surveys for which HIVDR testing of EID specimens has not commenced are classified as planned.

Table 9: Baseline characteristics of studies and surveys included in the pretreatment HIV drug resistance systematic review in adults[1]

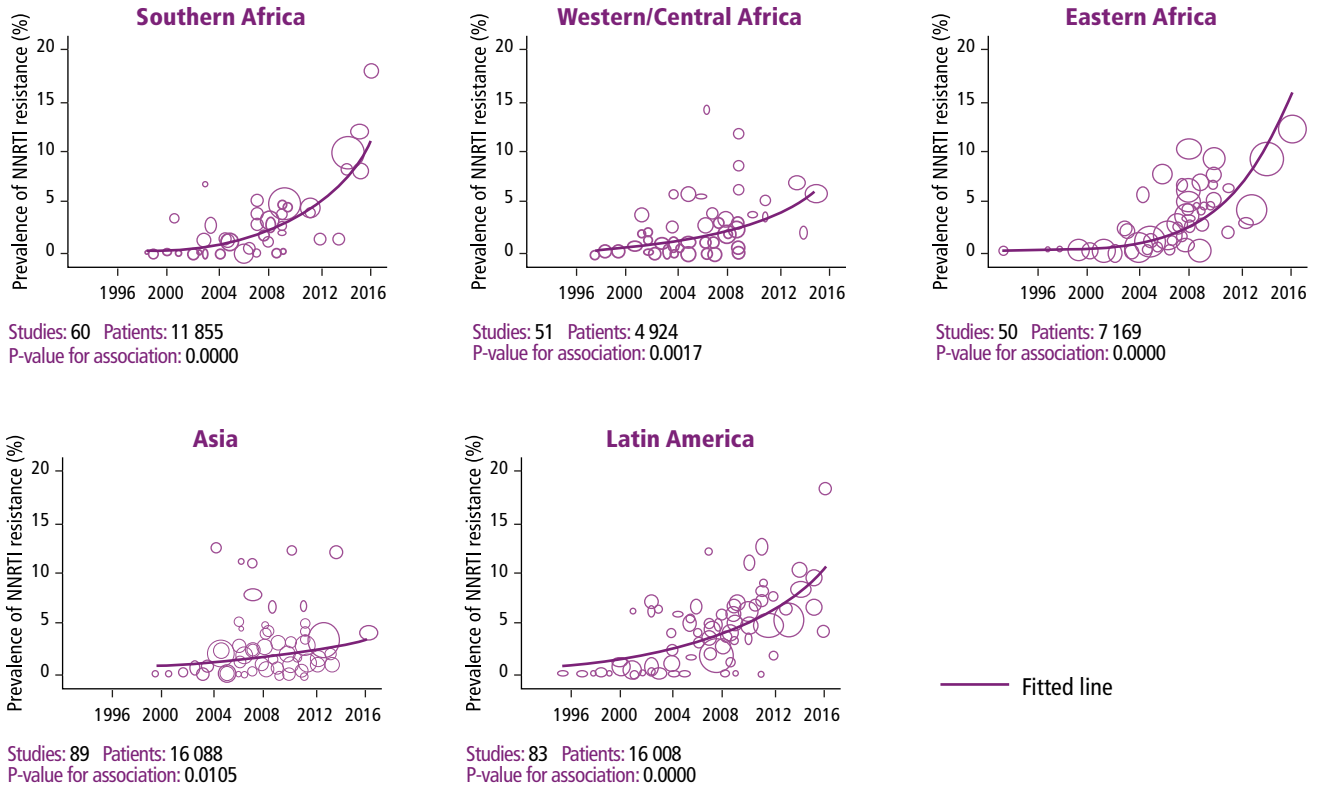
Geographical region	Number of studies	Total number of genotypes	Median number of genotypes per study (range)	Median sampling year (range)	Studies in urban populations, n/N[2] (%)
Eastern Africa	53	7 169	92 (11-517)	2007.5 (1993.5–2016)	32/44 (72.7%)
Southern Africa	61	11 855	102 (21–1 719)	2007 (1998.5–2016)	41/47 (87.2%)
Western/Central Africa	56	4 924	78.5 (18–271)	2007 (1998–2015)	48/50 (96.0%)
Latin America	90	16 008	97.5 (16–1 655)	2007.5 (1995.5–2016)	67/69 (97.1%)
Asia	98	16 088	97 (12–306)	2008.5 (1999.5–2016)	89/89 (100.0%)
Overall	358	56 044	94.5 (11–1719)	2007.5 (1993.5-2016)	277/299 (92.6%)

[1]For this systematic literature review, countries in the South-East Asia region, Western Pacific region, Eastern Mediterranean region and Turkey (Europe region) are grouped under the regional heading of 'Asia'; [2]Data for urban rural classification of populations was missing for 59 studies.

Key findings

Overall, analysis of trends over time show that NNRTI resistance was significantly higher in more recent studies in all regions ($P<0.05$ in each region). Statistically significant increases in the prevalence of NNRTI PDR were observed over time across all LMIC regions studied by year of sampling (Fig. 7). The estimated annual incremental increase of NNRTI PDR was 23% (95% CI 16–29) in Southern Africa; 29% (95% CI 17–42) in Eastern 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.

Fig. 7: Prevalence of NNRTI pretreatment resistance by calendar year across studies included in the systematic review



Sub-analyses, restricted to studies sampling individuals from 2014 to 2016 (Table 10), showed levels of NNRTI resistance close to 10% in three of the five regions analysed: 10.1% in Eastern Africa (95% CI 8.1–12.2); 10.7% in Southern Africa (95% CI 8.4–13.7); and 8.8% in Latin America (95% CI 6.2–12.4). Slightly lower levels of resistance were observed in Western and Central Africa (5%, 95% CI 2.7–7.9) and Asia (4%, 95% CI 2.1–6.7). Notably, the number of available studies for certain regions was limited.

When applying the current trend of resistance to 2016, the predicted prevalence estimates of NNRTI PDR were 11% (95% CI 7.5–15.9) in Southern Africa; 15.5% (95% CI 7.7–28.8) in Eastern Africa; 7.2% in Western and Central Africa (95% CI 2.9–16.5); and 10.6% in Latin America (95% CI 8.0–14.0). Prevalence of NNRTI PDR for Asia for the year 2016 was not estimated, due to the absence of data after 2014 for this region.

Table 10: Prevalence of resistance by drug class, region and calendar year in pretreatment HIV drug resistance systematic review in adults, 2014–2016

Class of mutation	Region	Studies	2014–2016
Any	Asia	1	5.5 (3.3–8.6)
Any	Eastern Africa	2	11.7 (9.6–14.0)[1]
Any	Latin America	6	12.4 (9.2–16.6)
Any	Southern Africa	6	12.2 (9.7–15.1)
Any	Western/Central Africa	1	4.1 (0.5–14.0)
NNRTI	Asia	1	4.0 (2.1–6.7)
NNRTI	Eastern Africa	2	10.1 (8.1–12.2)[1]
NNRTI	Latin America	6	8.8 (6.2–12.4)
NNRTI	Southern Africa	6	10.7 (8.4–13.7)
NNRTI	Western/Central Africa	2	5.0 (2.7–7.9)[1]
NRTI	Asia	1	1.5 (0.5–3.5)
NRTI	Eastern Africa	1	3.2 (1.6–5.7)
NRTI	Latin America	6	4.1 (2.5–6.5)
NRTI	Southern Africa	6	2.2 (1.2–3.8)
NRTI	Western/Central Africa	2	3.4 (1.5–5.9)[1]

[1]Estimates marked with a star use the Freeman-Tukey arcsine transformation, because mixed models did not converge, and so could not provide an estimated prevalence.

The prevalence of NNRTI PDR was higher among individuals starting first-line ART with prior ARV drug exposure, compared to ARV drug naive individuals in all regions. This was statistically significant in Asia (26.1% versus 3.2%, $P<0.0001$), Latin America (36.5% versus 9.3% ($P<0.0001$), and Southern Africa (31.5% versus 3.8% ($P<0.0001$). NRTI resistance was also significantly higher among individuals with prior ARV exposure, compared to ARV drug-naive individuals in all regions (Table 11).

Table 11: Prevalence of resistance by drug class,[15] region and ARV drug exposure category in the pretreatment HIV drug resistance systematic review in adults

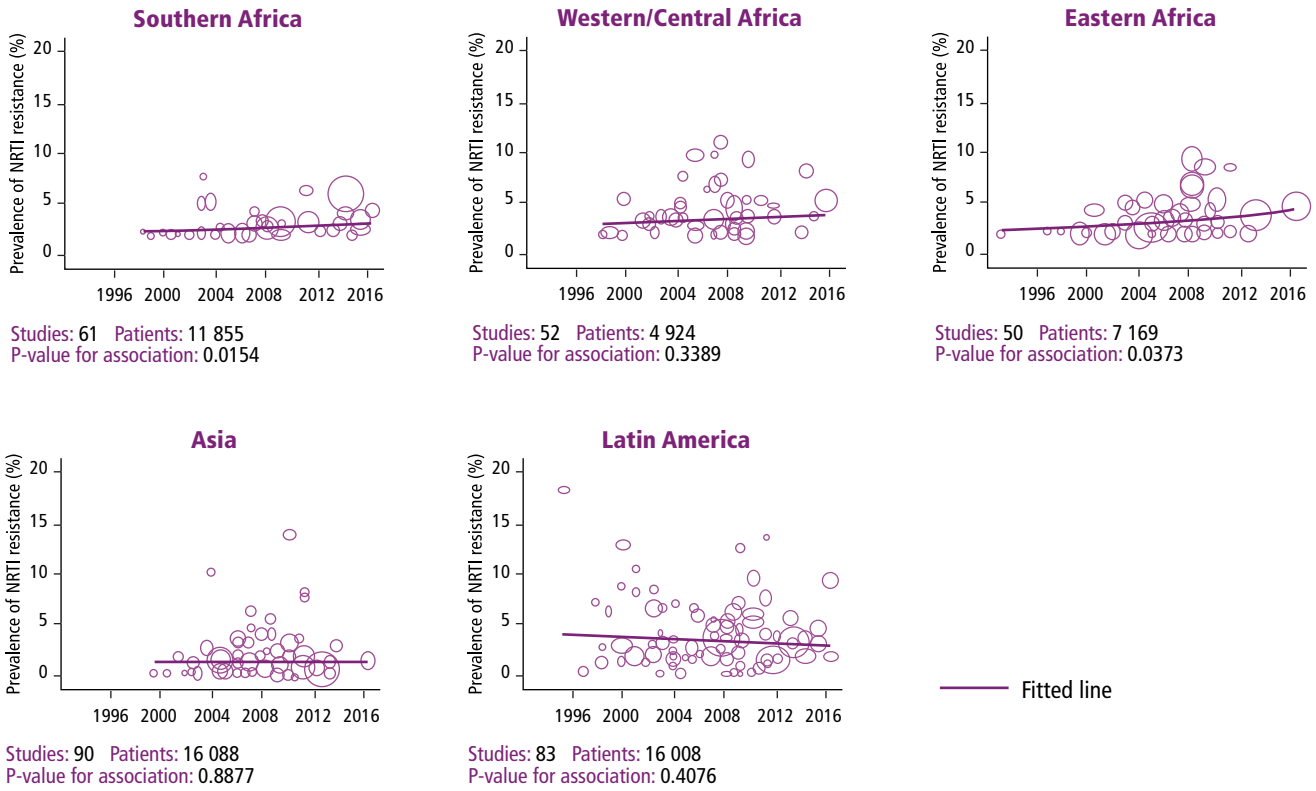
Class of mutation	Region	Studies	ARV drug naive	Studies	Prior ARV drug exposure	P-value[2]
Any	Asia	4	4.2 (2.9–6.2)	4	34.1 (14.0–2.3)	<0.0001
Any	Eastern Africa	7	8.3 (5.7–11.9)	7	22.4 (13.5–34.9)	0.0031
Any	Latin America	4	12.2 (9.8–15.0)	4	48.3 (18.8–79.0)	<0.0001
Any	Southern Africa	9	4.9 (3.2–7.3)	9	34.3 (27.5–41.9)	<0.0001
Any	Western/Central Africa	2	2.4 (0.9– 4.4)[1]	2	25.0 (3.4–76.2)	0.0845
NNRTI	Asia	4	3.2 (2.0–5.0)	4	26.1 (15.5–40.5)	<0.0001
NNRTI	Eastern Africa	7	5.5 (3.3–8.9)	7	12.1 (5.9–23.2)	0.0737
NNRTI	Latin America	4	9.3 (7.3–11.8)	4	36.5 (12.9–69.0)	<0.0001
NNRTI	Southern Africa	9	3.8 (2.3–6.0)	9	31.5 (23.3–40.9)	<0.0001
NNRTI	Western/Central Africa	4	2.6 (0.8–5.2)[1]	3	25.0 (3.4–76.2)	0.0622
NRTI	Asia	4	1.9 (1.1–3.5)	4	14.3 (0.3–90.8)	0.0004
NRTI	Eastern Africa	7	3.5 (1.8– 6.7)	6	6.9 (2.6–17.0)	0.3650
NRTI	Latin America	4	4.3 (2.8–6.6)	4	15.0 (4.5–39.9)	0.0009
NRTI	Southern Africa	9	0.7 (0.4–1.4)	9	7.9 (4.9–12.5)	<0.0001
NRTI	Western/Central Africa	4	0.3 (0.0–1.2)[1]	4	25.0 (3.4–6.2)	0.0210

[1]Estimates use the Freeman-Tukey arcsine transformation, because mixed models did not converge; [2]P value for significant testing comparing pooled prevalence of drug mutations in ARV drug naive versus ARV drug prior exposed populations. Analysis restricted to studies reporting PDR in both ARV drug naive and ARV drug previously exposed populations initiating ART.

A significant increase in NRTI resistance over time was observed in Southern and Eastern Africa (Fig. 8), but not in other regions. Sub-analysis of studies sampling individuals between 2014 and 2016 found lower levels of PDR NRTI: 2.2% (95% CI 1.2–3.8) in Southern Africa; 3.2% (95% CI 1.6–5.7) in Eastern Africa; 3.4% (95% CI 1.5–5.9) in Western and Central Africa; 4.1% (95% CI 2.5–6.5) in Latin America; and 1.5% (95% CI 0.5–3.5) in Asia (Table 10).

[15] Where feasible, DRMs were defined as those appearing on the 2009 WHO SDRM list. Otherwise, the study authors' interpretation was used.

Fig. 8: Prevalence of NRTI pretreatment resistance by calendar year across included in the systematic review



Overall, the findings of this systematic literature review suggest a significant increase in the prevalence of NNRTI PDR over time. Predicted prevalence estimates of NNRTI PDR in 2016 were around 10% or higher in all regions except Asia, with estimated annual incremental increases in NNRTI PDR of around 20% or higher per year across sub-Saharan Africa.

2.4 Systematic literature review of pretreatment HIV drug resistance in children in LMIC

Use of ARV drugs for PMTCT of HIV has led to significant reductions in paediatric HIV infections over the last decade. However, a substantial number of infections continue to occur, with about 160 000 new paediatric infections estimated in 2016 *(11)*. Due to exposure to maternal ARV drugs during pregnancy and breastfeeding, and use of infant ARV drug prophylaxis, children with perinatal infection despite PMTCT interventions are at an increased risk of PDR. PDR is associated with a poor response to first-line ART, and results in further accumulation of DRMs. As with adults, the prevalence of PDR among infants is expected to increase with increasing coverage and uptake of PMTCT with a triple-drug NNRTI-containing regimen. Due to higher prevalence of NNRTI resistance in perinatally infected children, WHO has recommended PI-based ART for children younger than 3 years of age *(12)* since 2010. However, limited options for paediatric formulations have resulted in slow uptake and implementation in resource-limited settings.

Studies published during the period 1 January 2014 to 30 April 2017 were systematically reviewed to assess the prevalence of HIVDR in children starting ART in LMIC. Systematic review methods are presented in Section 4 of Annex 1.

Key findings

A total of seven studies were identified, describing resistance in 1128 HIV-infected children aged 4–114 months; no studies included data on younger adolescents (13–15 years old). Overall, 31.3% (354/1128) of children had detectable DRMs to any drug. Four studies found more than 50% of PMTCT-exposed children with NNRTI PDR. High levels of HIVDR were also detected in infants not exposed to ART through PMTCT. A 2016 study from Nigeria found PDR in 15.9% of PMTCT-naive children; all harboured NNRTI mutations *(13)*. A 2016 Ugandan study found PDR prevalence of 10% in children younger than 12 years of age, with most (83.5%) having no reported prior PMTCT exposure; PDR prevalence was higher (15.2%) in children aged under 3 years *(14)*. General characteristics of study participants are found in Table 12.

Table 13 shows key results from the studies reviewed.

Table 12: Characteristics of studies included in the paediatric pretreatment HIV drug resistance literature review

	PDR	
	Median	Range
Age (months)	20.2	4.75–114
Males (%)	52.3	45.6–64
Number of participants	161	24–319
Number of participants with DRM	50	8–122
(%) with NNRTI resistance	49.3	7.5–100
Year data collection ended	–	2009–2013
Year published	–	2014–2017

Table 13: Findings from studies included in the paediatric pretreatment HIV drug resistance literature review

Study (author, year of data collection, country)	Age groups included	N sequenced genotypes	N with DRM	(%) DRM overall	(%) DRM among PMTC exposed	(%) DRM among PMTCT naive	(%) DRM unknown PMTCT exposure
Inzaule S et al. 2009–2010 (Kenya)	<6 months old	24	16	66.7	66.7	NA	NA
Kebe K et al. 2010–2011 (Senegal)	<13 months old	25	8	32	53.8	8.3	NA
Salou M et al. 2012–2013 (Togo)	<18 months	201	121	60.2	75.6	26.8	37.9
Kuhn L et al. 2011 (South Africa)	<2 years old	230	122	53.0	56.8[1]	24.0[1]	NA
Kanthula R et al. 2011–2013 (South Africa)	<5 years old	88	46	52.3[1]	52.3[1]	NA	NA
Kityo C et al. 2010–2011 (Uganda)	<12 years old	279	28	10.0	35.7	7.7	15.6
Boerma R et al. 2012–2013 (Nigeria)	<12 years old	82	13	15.9	NA	15.9	NA

NA= data not included; [1] NNRTI mutation only reported.

A relatively small number of studies were available, reflecting the paucity of data on this topic. In addition, there was marked heterogeneity across studies in terms of participant age and PMTCT exposure status. Moreover, reporting and analysis of DRMs varied significantly. Some studies reported only mutations associated with NNRTIs, while others reported mutations associated with multiple drug classes. Because of study variation, pooled analysis was not feasible.

The findings of this systematic review are largely consistent with a recent systematic literature review of PDR in children in sub-Saharan Africa, with information from 2617 children from 13 countries published between 2010 and 2016. This published review reported a higher pooled PDR prevalence among PMTCT-exposed children, compared to PMTCT-unexposed children: 42.7% (95% CI 26.2–59.1) versus 12.7% (95% CI 6.7–18.7), *P*=0.004 respectively. In addition, this recent publication estimated NNRTI mutations in 32.4% (95% CI 18.7–46.1) of PMTCT-exposed children, and in 9.7% (95% CI 4.6–14.8) of PMTCT-unexposed children in sub-Saharan Africa *(15)*.

Available information is sparse, but demonstrates very high levels of PDR in children. Moreover, information on PDR in adolescents was equally scarce, a finding with significant implications, given that adolescent girls and young women aged 15–24 years accounted for 20% of new HIV infections globally, and 30% of new HIV infections in sub-Saharan Africa, in 2016 *(11)*.

2.5 Pretreatment HIV drug resistance – summary of findings and implications

WHO recommends that the prevalence of PDR among people starting ART be routinely monitored to help inform selection of recommended first-line ART regimens, and to support treatment optimization. As part of national efforts to limit antimicrobial resistance (AMR), a growing number of countries are implementing PDR surveys among people initiating first-line ART. By the end of 2017, 41 countries are anticipated to have implemented national surveillance of PDR. This brisk uptake of PDR surveys, which were first recommended in 2014, reflects the collective efforts and commitment of countries and the global community to limit AMR, as well as the emphasis placed by US-CDC, The Global Fund and WHO on routine HIVDR surveillance as part of treatment scale-up and ART programme optimization.

NNRTIs form the backbone of recommended first-line ART regimens, and their effectiveness should be preserved for as long as possible. During the period 2014–2016, 11 countries implemented and reported PDR survey data, with six countries reporting levels of NNRTI resistance above 10%. This indicates that NNRTI resistance in people starting ART may be at levels that should trigger public health action. Specifically, systematic review and meta-analysis demonstrates that people with NNRTI PDR are less likely to achieve viral suppression; more likely to experience virological failure; more likely to experience virological failure or death (composite outcome); more likely to discontinue treatment; and more likely to acquire new HIVDR mutations *(16)*. PDR to NNRTI has steadily increased over the last decade, a finding stemming from meta-analysis demonstrating an annual incremental increase ranging from 11% to 29%, with predicted 2016 NNRTI prevalence estimates ranging from 7.2% to 15.5%. Results from the meta-analysis are consistent with nationally representative PDR results, and with data from surveys of people recently infected with HIV, identified through household-based PHIA surveys.

As ART is scaled up and millions of people must be maintained on ART for life, even in programmes delivering the highest quality of care and treatment, retention on ART is imperfect. Some people will inevitably start and stop ART, a factor that predisposes them to selection of drug-resistant virus. It is therefore not surprising that findings from national PDR surveys and the systematic review show that PDR to NNRTI is significantly higher in people starting first-line ART with prior ARV exposure, compared to ARV drug-naive individuals. This difference is also significant for resistance to NRTIs.

The high levels of NNRTI and NRTI resistance in people reporting prior ARV drug exposure are particularly concerning, as this group may represent a significant and ever-increasing proportion of first-line treatment initiators in some countries. These results have important clinical and programmatic implications: in most LMIC, individuals reporting prior ARV drug exposures are routinely initiated on an NNRTI-based ART, which is predicted not to be fully effective in a significant proportion of individuals.

In 2017, recognizing that NNRTI PDR in people starting ART may be reaching levels that have the potential to undermine or reverse hard-won gains in HIV-associated morbidity and mortality, WHO released a supplement to its 2016 *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (17).* The 2017 *Guidelines on the public health response to pretreatment HIV drug resistance* recommend that use of non-NNRTI-based first-line ART regimens be considered in countries with national levels of NNRTI resistance above 10%. Although not a recommendation, in certain settings when non-NNRTI regimens are unaffordable and HIVDR testing capacity exists, consideration may be given to HIVDR testing of people starting ART *(18).*

There is a disconcerting lack of data informing the prevalence of PDR in children and adolescents. Only one nationally representative HIVDR survey among children younger than 18 months was reported between 2014 and 2016; this survey was from South Africa and documented NNRTI prevalence of 63.7% (95% CI 59.0–68.4) in infants diagnosed with HIV through the country's EID programme. The systematic literature review presented in this report also documents high rates of resistance among children starting ART, particularly in PMTCT-exposed children. Overall, these data support WHO's 2013 recommendation that all children younger than 3 years of age be started on PI-based regimens, irrespective of PMTCT exposure. Unfortunately, implementation of this policy has been slow, largely due to the unavailability, until recently, of heat stable and palatable paediatric formulations. While data are limited in young children, there is a glaring lack of data in older children and adolescents: to date, no national PDR survey has been done in these two important subpopulations.

While some PDR is expected as a consequence of ART scale-up, its prevalence in select countries has reached levels that necessitate a public health response. Routine periodic surveillance of PDR in all people initiating or reinitiating first-line ART; minimizing the emergence of HIVDR by closing gaps in service delivery; and modifying the first-line therapy to a non-NNRTI regimen once the threshold of 10% NNRTI PDR is reached, are essential components of the GAP. This response will greatly enhance treatment optimization and maximize population-level treatment outcomes over the next decade. In the future, emphasis must be placed on surveillance of PDR in children and adolescents; this will help ensure success in eliminating AIDS as a public health treat by 2030.

3 HIV DRUG RESISTANCE IN POPULATIONS ON ART: ACQUIRED HIV DRUG RESISTANCE

Key findings

- Between 2014 and 2016 four countries (Cameroon, Guatemala, Viet Nam and Zambia) implemented and reported national surveys of ADR among adults on ART. Of these, Viet Nam and Zambia reached the 90% target for viral load suppression, demonstrating that achievement of "the last 90" target on viral load suppression is feasible. However, two countries did not reach the target; in one, the prevalence of virological suppression was as low as 68%.
- Across the four countries, prevalence of NNRTI ADR ranged from 4.3% to 16.7% among individuals on ART for 12–24 months, and from 4.2% to 28.3% among those on treatment for longer durations (36–48+ months). Levels of NNRTI resistance among individuals on NNRTI first-line ART for 12–24 months with unsuppressed viral load ranged from 47.3% in Zambia to 76.0% in Guatemala. Among individuals on NNRTI first-line ART with unsuppressed viral load for longer durations (36–48+ months), levels of NNRTI resistance ranged from 84.3% in Guatemala to 89.5% in Cameroon.
- A systematic review of studies from LMIC on ADR in adults published between 2014 and 2017 found an overall pooled prevalence of viral load suppression among individuals on treatment of 82.1% (range 11–90%, 95% CI 81.4–82.9). In this pooled analysis, 9.7% (95% CI 9.2–10.3) of the individuals on ART were found to have any DRM (n=1069). Among those failing NNRTI-based regimens with genotypic data available, 68% had one or more DRM detected.
- There is a lack of nationally representative survey data on resistance in HIV-infected children receiving ART. Between 2014 and 2016, no national surveys of ADR in children were reported.
- A systematic review of ADR in children assessing literature published between 2014 and 2017 documented a limited number of studies in this population. Nevertheless, the limited data available indicate high levels of ADR in children (the median NNRTI resistance across studies was 69.4%, range 12–95%). No studies were identified on ADR in adolescents.

3.1 Nationally representative surveys of acquired HIV drug resistance, 2014–2017

3.1.1 Survey methods for acquired HIV drug resistance

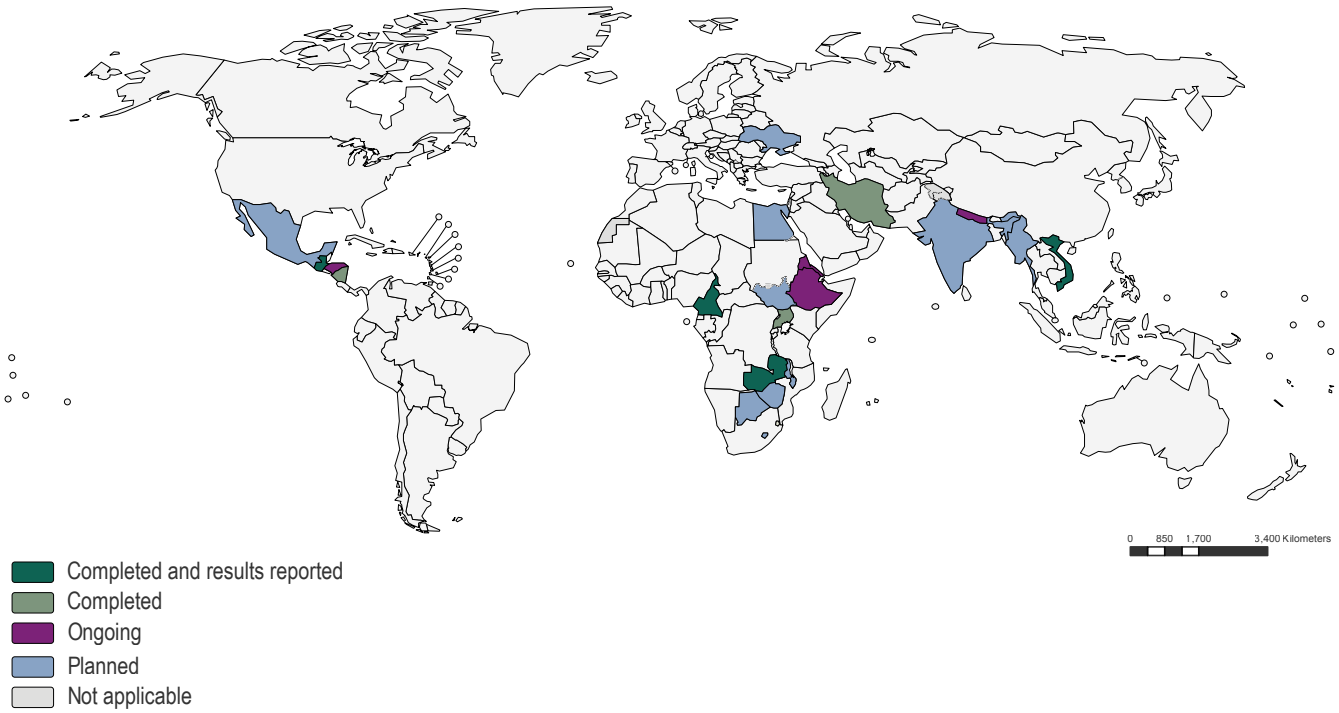
The ADR survey method is designed to yield nationally representative prevalence estimates of HIVDR in populations receiving ART for 12 (±3) months (referred to as *early time point* surveys) and in populations receiving ART for 48+ months (referred to as *late time point* surveys), in addition to estimates of viral load suppression in these respective populations *(1)*. ADR surveys provide an indication of the proportion of individuals on ART at 12 months and 48+ months who are failing treatment and should be switched to second-line ART.

ADR survey results provide critical information to assess programme performance in achieving viral load suppression, and to inform the optimal selection of second- and potentially third-line regimens, based on prevalence of resistance in individuals failing treatment. It is recommended that countries implement ADR surveys once every three years, and the approximate sample size of 400. The ADR survey is designed to have a duration of 3–6 months; in countries with high HIV prevalence it can be shorter. As with the PDR survey, it is recommended that the duration of patient enrolment be limited to a maximum of six months, to ensure results are available in a timely fashion to inform programmatic action. ADR and PDR surveys have a similar two-stage cluster design. ART clinics are first sampled using probability proportional to proxy size (PPPS) sampling based on the eligible population of people on ART, followed by consecutive enrolment of survey participants at the selected sites, until the required sample size is achieved. For further details see "Section 2: Study design and methods for statistical analysis of pretreatment HIV drug resistance and acquired HIV drug resistance surveys" of the Annex.

3.1.2 Implementation status of acquired HIV drug resistance surveys in populations on ART, 2014–2017

A total of seven ADR surveys were completed between 2014 and 2017, all among adults. Results from four of these surveys have been reported to WHO and findings are presented below. As of May 2017, ADR surveys are ongoing in another five countries, with a further 11 countries planning to implement ADR surveys (Fig. 9).

Fig. 9: Implementation of surveys of acquired HIV drug resistance, 2014–2017[16]



3.1.3 Results of acquired HIV drug resistance surveys, 2014–2016

Four countries (Cameroon, Guatemala, Viet Nam and Zambia) have implemented ADR surveys and reported results to WHO. Three surveys (Cameroon, Guatemala and Zambia) assessed HIVDR and viral load suppression among people on ART for 12–24 months (early time point). Three surveys (Cameroon, Guatemala and Viet Nam) reported data from individuals on ART for longer periods of time: from 36+ months in Viet Nam, from 48+ months in Guatemala, and from 48 to 60 months in Cameroon (later time points). Cameroon and Guatemala monitored viral load suppression and HIVDR at both time points. A flow diagram of available viral load and HIVDR data is shown in Fig. 10. For the early time point surveys, the total number of individuals contributing viral load specimens ranged from 222 (Guatemala) to 1064 (Cameroon), while for the late time point surveys this ranged from 365 (Viet Nam) to 388 (Cameroon).

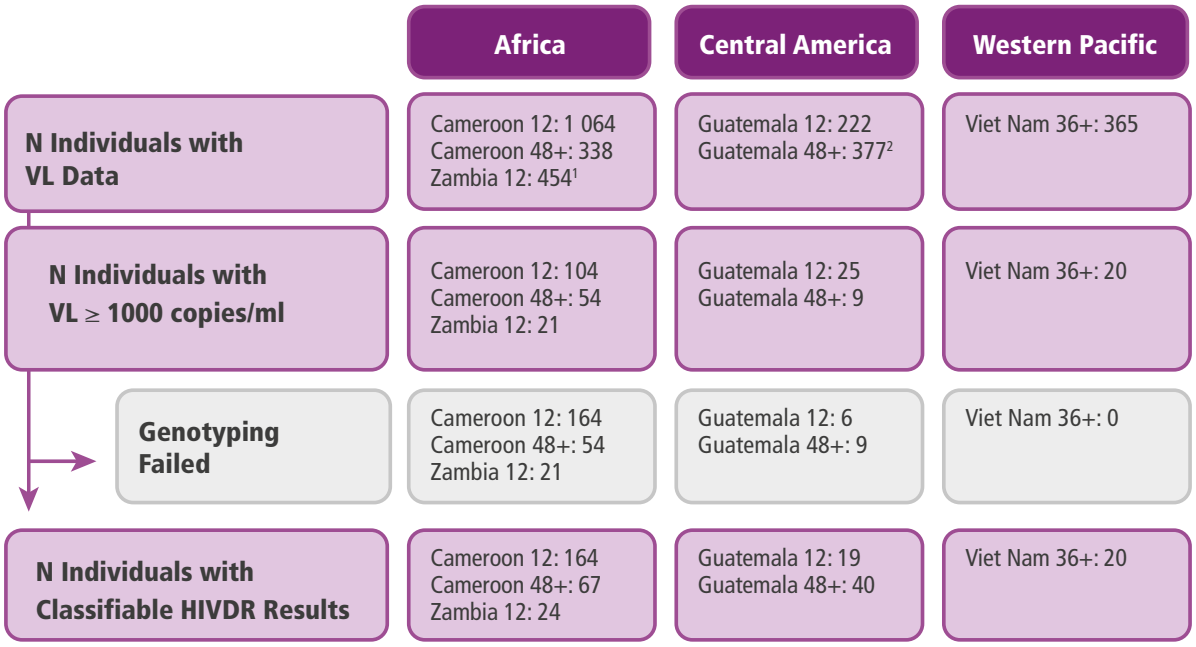
The number of HIV genotypes included in the analysis is a function of the proportion of people with viral load over 1000 copies/ml. For the early time point surveys the total number of genotypes ranged from 19 (Guatemala) to 164 (Cameroon); for the late time point surveys the total number of genotypes ranged from 20 (Viet Nam) to 67 (Cameroon). Overall, amplification failure rates and exclusion of specimens due to poor quality sequencing[17] ranged from 18% to 55% and from 0.3% (1/378) to 0.4% (2/456), respectively.[18] Details of statistical methods used for the analysis can be found in "Section 2*:* Study design and methods for statistical analysis of PDR and ADR surveys" of the Annex.

[16] Implementation status as of May 2017. Surveys which have not started enrolment are classified as planned. Viet Nam implemented an ADR survey in 2014 and is planning to implement another ADR survey in 2017.

[17] With the exception of Cameroon's surveys, all sequences were quality assured by WHO following its standard quality-assurance procedures, which are described in Section 1 of the Annex.

[18] With the exception of Zambia's ADR survey, all HIVDR testing was performed at WHO HIVResNet member laboratories, designated by WHO for HIVDR testing for the purpose of HIVDR surveillance.

Fig. 10: **Flow chart of acquired HIV drug resistance surveys**



VL=viral load; HIVDR=HIV drug resistance; [1]Two individuals out of 456 were excluded because sequences failed WHO Quality assurance; [2]One individual out of 378 was excluded because the sequence failed WHO Quality assurance.

Population characteristics: surveys of acquired HIV drug resistance

In Guatemala and Viet Nam, the majority of individuals enrolled in the surveys were male (70.3% and 56.8% respectively in the Guatemala early and late time point surveys, and 68.4% in Viet Nam). In Cameroon and Zambia, the majority were female (77.9% and 75.3% respectively in the Cameroon early and late time point surveys, and 60% in Zambia). In all surveys across both time points, most participants were 25 years or older: above 90% in the African surveys, in Viet Nam, and in the late time point survey in Guatemala; and above 80% in the early time point survey in Guatemala.

The mean time on ART for early time point surveys ranged from 12.2 months in Guatemala and Zambia to 17.9 months in Cameroon. For late time point surveys, the mean time on ART ranged from 53.3 months in Cameroon to 91.8 months in Guatemala.

At the early time point, nearly all survey participants were receiving NNRTI-based first-line ART: 97.3% in Guatemala, 98.9% in Cameroon, and 100% in Zambia. Regimens were predominately EFV-based. In late time point surveys, use of NNRTI-based first-line ART was 85.7% in Guatemala, 94.4% in Cameroon, and 93.7% in Viet Nam. Use of PI regimens was low across all ADR surveys: at the early time point, this ranged from <0.5% (Zambia) to 2.7% (Guatemala) versus 5.4% (Cameroon) to 13.8% (Guatemala) at the late time point (Tables 14 and 15).

Table 14: Population characteristics of early time point (12–24 months) for national acquired HIV drug resistance surveys

	Cameroon (12–24 mo.)		Guatemala (12 ± 3 mo.)		Zambia[1] (12 ± 3 mo.)	
	N = 1064 (Start year 2015)		N = 222 (Start year 2016)		N = 454 (Start year 2016)	
	n	% (95% CI)[2]	n	% (95% CI)[2]	n	% (95% CI)[2]
Gender						
Women	808	77.9 (75.4–80.2)	66	29.7 (21.1–40.1)	257	60.0 (56.3–63.4)
Men	256	22.1 (19.8–24.6)	156	70.3 (59.9–78.9)	197	40.1 (36.6–43.7)
Mean[3] age (95% CI), years	40.0 (39.4–40.7)		35.7 (33.8–37.6)			
≤ 25 years	61	5.7 (4.7–7.1)	41	18.5 (14.3–23.5)	35	9.3 (5.2–15.9)
> 25 years	1003	94.2 (92.9–95.3)	181	81.5 (76.5–85.7)	416	90.7 (84.1–94.8)
Individuals on first-line ART	1050	99.0 (98.1–99.5)	220	99.1 (96.4–99.8)	453	100.0 (99.6–100)
Individuals on NNRTI-based first-line ART	1048	98.9 (97.8–99.4)	216	97.3 (93.8–98.9)	453	100.0 (99.6–100)
Current ART						
TDF + XTC + EFV	758	71.4 (63.3–78.4)	199	89.6 (74.5–96–96.2)	450	99.8 (99.3–100.0)
TDF + XTC + NVP	109	9.0 (6.1–13.0)	0	–	3	<0.5
ZDV + XTC + EFV	32	3.6 (2.1–6.3)	3	1.4 (0.4–4.8)	0	–
ZDV + XTC + NVP	148	14.8 (10.5–20.4)	3	1.4 (0.3–5.2)	0	–
PI-based regimen	16	1.1 (0.6–2.2)	6	2.7 (1.1–6.2)	1	<0.5
Other	1	<0.5	11	5.0 (1.2–17.7)	0	–
Mean[3] time on ART (95% CI), months	17.9 (17.4–18.4)		12.2 (12.0–12.4)		12.2 (11.8–12.6)	

[1]Three participants had missing data for age; [2]Study design-weighted proportion and 95% confidence interval; [3]Study design-weighted mean and 95% confidence interval.

Table 15: Population characteristics of late time point (36–40+months) for national acquired HIV drug resistance surveys

	Cameroon (48-60 mo.)		Guatemala (≥ 48 mo.)		Viet Nam (≥ 36 mo.)	
	N = 388 (Start year 2015)		N = 377 (Start year 2016)		N = 365 (Start year 2014)	
	n	% (95% CI)[1]	N	% (95% CI)[1]	n	% (95% CI)[1]
Gender						
Women	287	75.3 (66.6–82.3)	161	42.7 (35.0–50.7)	118	31.6 (25.9–37.9)
Men	101	24.7 (17.7–33.4)	214	56.8 (48.5–64.7)	247	68.4 (62.1–74.1)
Other	0	0	2	0.5 (0.1–2.1)	0	0
Mean[2] age (95% CI), years	43.1 (42.0–44.3)		42.7 (41.4–43.9)		38.2 (37.0–39.4)	
≤ 25 years	8	2.0 (0.7–5.7)	8	2.1 (1.1–4.1)	1	<0.5
> 25 years	380	98.0 (94.3–99.3)	369	97.9 (95.8–98.9)	364	99.6 (97.1–100)
Individuals on first-line ART	364	94.4 (83.9–98.2)	350	92.9 (81.8–97.4)	345	93.8 (88.3–96.8)
Individuals on NNRTI-based first-line ART	364	94.4 (83.9–98.2)	323	85.7 (78.3–90.9)	344	93.7 (88.3–96.8)
Current ART						
TDF + XTC + EFV	229	58.8 (46.2–70.3)	185	49.0 (43.5–54.6)	93	25.6 (18.5–34.3)
TDF + XTC + NVP	58	16.0 (7.9–29.8)	27	7.2 (4.1–12.3)	47	12.3 (7.7–19.1)
ZDV + XTC + EFV	4	1.0 (0.1–6.5)	70	18.5 (14.7–23.1)	54	13.7 (9.6–19.2)
ZDV + XTC + NVP	73	18.6 (9.1–34.3)	14	3.7 (1.8–7.7)	148	41.4 (32.9–50.5)
PI-based regimen	23	5.4 (1.8–15.4)	52	13.8 (8.5–21.6)	20	6.2 (3.2–11.6)
Other	1	<0.5	29	7.7 (3.6–15.9)	3	0.8 (0.2–2.9)
Mean[2] time on ART (95% CI), months	53.3 (52.1–54.6)		91.8 (84.5–99.1)		75.5 (69.0–81.9)	

[1]Study design-weighted proportion and 95% confidence interval; [2]Study design-weighted mean and 95% confidence interval.

Prevalence of viral load suppression

The prevalence of viral load suppression (defined as viral load <1000 copies/ml) among individuals on ART at the early time point (12–24 months) was 72.1% (95% CI 66.2–77.2) in Cameroon, 88.7% (95% CI 77.4–94.8) in Guatemala, and 90% (95% CI 80.1–94.2) in Zambia (Fig. 11).

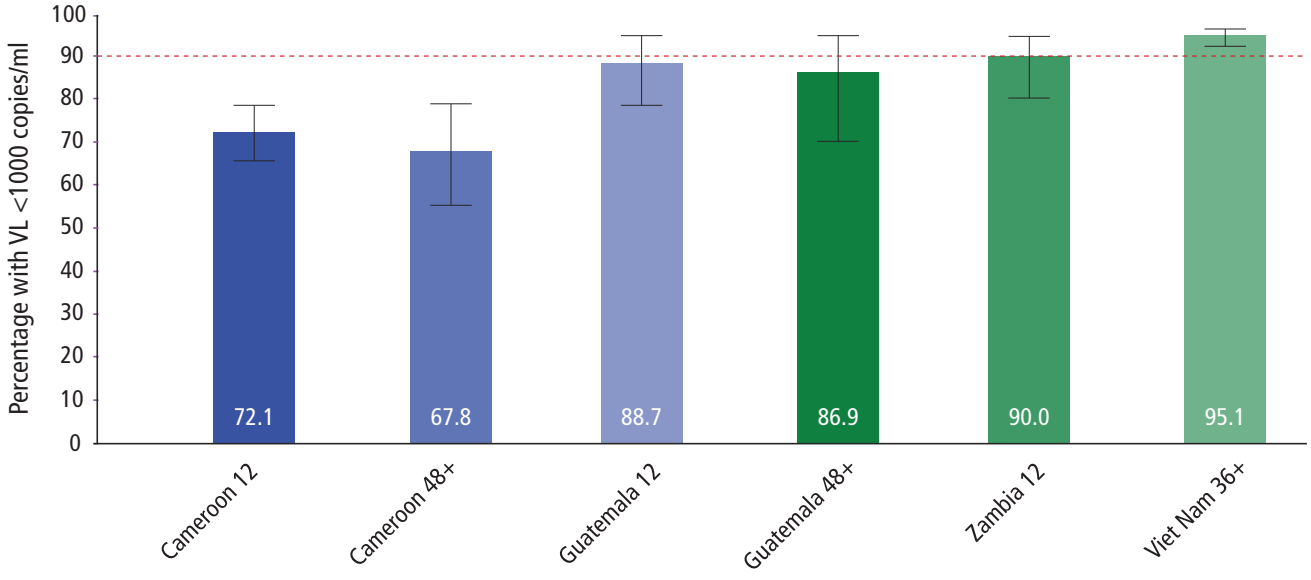
Similar viral load suppression prevalence estimates were observed among individuals on any ART regimen, any first-line ART regimen, and NNRTI-containing first-line ART for 12–24 months (Table 16).

Table 16: Prevalence of viral load suppression (VL < 1000 copies/mL) for individuals on ART, early time point (12–24 months), national acquired HIV drug resistance surveys

	Cameroon (12–24 mo.)		Guatemala (12 ± 3 mo.)		Zambia[1] (12 ± 3 mo.)	
	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)
VL suppression among individuals on ART	796	72.1 (66.2–77.2)	197	88.7 (77.4–94.8)	409	90.0 (80.1–94.2)
VL suppression among individuals on first-line ART	786	72.1 (66.5–77.2)	195	88.6 (77.1–94.7)	408	88.9 (80.2–94.1)
VL suppression among individuals on NNRTI-based first-line ART	785	72.1 (66.4–77.2)	193	89.3 (79.2–94.9)	408	88.9 (80.2–94.1)
VL suppression among women on ART	624	75.0 (69.4–79.9)	56	84.8 (73.0–92.0)	228	86.3 (74.1–93.3)
VL suppression among men on ART	172	61.6 (51.7–70.6)	141	90.4 (76.0–96.5)	181	92.9 (83.5–97.1)
VL suppression among individuals on ART aged ≤ 25 years	45	75.2 (54.4–88.5)	34	82.9 (64.6–92.8)	30	80.8 (46.5–95.3)
VL suppression among individuals on ART aged > 25 years	751	71.9 (66.0–77.1)	163	90.0 (75.3–96.4)	376	89.8 (83.2–93.9)

[1]Three participants had missing data for age.

Fig. 11: Viral load suppression among individuals on ART



Estimates of viral load suppression apply to individuals taking ART, and therefore reflect survivor bias, as individuals who are no longer receiving ART are not sampled. By definition, people who are not retained in care have had a treatment interruption, and are therefore are at high risk of virological failure. This survivor bias can impact the interpretation of viral load suppression estimates, which would likely be lower if estimated among individuals who started ART, as opposed to individuals retained in care.

Although the stated global goal is to achieve 90% viral suppression among individuals retained on ART, it is still important to contextualize estimates of viral suppression with programmatic performance in retaining people on ART. When considering what impact retention may potentially have on population-level viral load suppression, it is important to have reliable, nationally representative data, derived from a cohort contemporary to that of the population surveys. Cameroon and Guatemala have retention estimates corresponding to the time of their respective ADR surveys. In 2015, in Cameroon, retention was estimated from a random sample of ART clinics, following WHO guidance on EWI of HIVDR *(2)*. Retention on ART 12 months after ART initiation was 54% *(3)*. Thus, the viral load suppression estimate adjusted for retention would be 39% (95% CI 36.0–42.0),[19] considerably lower than the "on treatment at 12–24 months" estimate of 72%. Likewise, Guatemala

[19] For further details of methods used for the retention adjusted estimates of viral load suppression, see Annex 1, "Section 2: Study design and methods for statistical analysis of pretreatment HIV drug resistance and acquired HIV drug resistance surveys".

reported a contemporary 12-month retention estimate of 74% *(4)*; thus, its retention adjusted viral load suppression estimate is 66% (95% CI 58.0–74.0),[20] lower than the "on treatment at 12 months" estimate of 89%. These examples highlight the importance of considering retention, which is a major component of achieving "the second 90" target, when interpreting programme performance with respect to levels of viral load suppression.

In the late time point surveys (individuals on ART 36+ months or 48+ months), the prevalence estimates of viral load suppression among those on ART were lower than the estimates observed in the early time point surveys; these differences, however, were not statistically significant (Table 17 and Fig. 11).

Table 17: Prevalence of viral load suppression (VL < 1000 copies/mL) for individuals on ART, late time point (36–48+ months), national acquired HIV drug resistance surveys

	Cameroon (48–60 mo.)		Guatemala (≥ 48 mo.)		Viet Nam (≥ 36 mo.)	
	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)
VL suppression among individuals on ART	267	67.8 (55.8–77.7)	328	86.9 (70.4–94.8)	345	95.1 (92.3–96.9)
VL suppression among individuals on first-line ART	255	68.7 (56.0–79.1)	308	87.9 (71.5–95.4)	325	94.8 (92.1–96.6)
VL suppression among individuals on NNRTI-based first-line ART	255	68.7 (56.0–79.1)	286	88.4 (71.8–95.8)	325	94.9 (92.1–96.7)
VL suppression among women on ART	202	69.4 (57.2–79.3)	137	85.0 (67.2–94.0)	112	95.7 (89.8–98.2)
VL suppression among men on ART	65	62.7 (41.8–79.7)	189	88.2 (71.8–95.7)	233	94.9 (90.1–97.4)
VL suppression among individuals on ART aged ≤ 25 years	3	39.1 (11.6–75.8)	5	62.5 (45.9–76.6)	–	–
VL suppression among individuals on ART aged > 25 years	264	68.3 (56.1–78.4)	323	87.4 (70.3–95.2)	344	95.1 (92.3–96.9)

Prevalence of acquired HIV drug resistance

The prevalence of ADR among individuals on ART for 12–24 months is reported in Table 18. Among individuals on ART with viral load ≥1000 copies/ml, the prevalence of NNRTI resistance[21] was high: 59.7% (95% CI 49.3–69.4) in Cameroon, 47.3% (95% CI 10.7–87.0) in Zambia, and 76.0% (95% CI 51.2–90.5) in Guatemala.

Levels of **NRTI resistance** at the early time point ranged from 46.9% (95% CI 10.6–86.7) in Zambia to 60.0% (95% CI 33.5–81.7) in Guatemala. No PI resistance was detected among participants in Guatemala and Zambia, and only one participant had PI resistance in Cameroon.

Among all individuals on ART for 12–24 months (not just those with viral load ≥1000 copies/ml), the prevalence of **NNRTI resistance** was higher in Cameroon at 16.7% (95% CI 3.7–20.2), compared to Zambia (4.3%, 95% CI 1.9–9.5) and Guatemala (8.6%, 95% CI 4.1–17.1).

[20] For further details of methods used for the retention adjusted estimates of viral load suppression, see Annex 1, "Section 2: Study design and methods for statistical analysis of pretreatment HIV drug resistance and acquired HIV drug resistance surveys".

[21] NNRTI resistance is defined as resistance to NVP or EFV. NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to ATV/r, LPV/r or 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".

Table 18: Prevalence of acquired HIV drug resistance among individuals on ART, early time point (12–24 months), national acquired HIV drug resistance surveys

	Cameroon (12–24 mo.)		Guatemala (12 ± 3 mo.)		Zambia (12 ± 3 mo.)	
	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)
HIVDR among individuals on ART						
Any	111/960	17.1 (14.0–20.7)	16/216	9.5 (4.1–20.2)	18/433	4.3 (1.9–9.5)
NNRTI	109/960	16.7 (13.7–20.2)	15/216	8.6 (4.1–17.1)	18/433	4.3 (1.9–9.5)
NRTI	97/960	14.7 (11.3–18.9)	11/216	6.8 (2.6–16.7)	17/433	4.3 (1.9–9.5)
PI	1/960	0.3 (0.0–2.2)	0/216	–	0/433	–
NNRTI+NRTI	96/960	14.6 (11.3–18.7)	10/216	5.9 (2.6–12.8)	17/433	4.3 (1.9–9.5)
HIVDR among individuals on ART with VL≥1000 copies/mL						
Any	111/164	61.1 (50.3–70.9)	16/19	84.0 (57.4–95.3)	18/24	47.3 (10.7–87.0)
NNRTI	109/164	59.7 (49.3–69.4)	15/19	76.0 (51.2–90.5)	18/24	47.3 (10.7–87.0)
NRTI	97/164	52.6 (41.2–63.7)	11/19	60.0 (33.5–81.7)	17/24	46.9 (10.6–86.7)
PI	1/164	1.1 (0.1–7.5)	0/19	–	0/24	–
NNRTI+NRTI	96/164	52.3 (41.1–63.2)	10/19	52.0 (32.9–70.5)	17/24	46.9 (10.6–86.7)
HIVDR among individuals on first-line ART with VL≥1000 copies/mL						
Any	110/162	61.2 (50.3–71.0)	16/19	84.0 (57.4–95.3)	18/24	47.3 (10.7–87.0)
NNRTI	108/162	59.8 (49.3–69.5)	15/19	76.0 (51.2–90.5)	18/24	47.3 (10.7–87.0)
NRTI	96/162	52.6 (41.2–63.7)	11/19	60.0 (33.5–81.7)	17/24	46.9 (10.6–86.7)
PI	1/162	1.1 (0.1–7.5)	0/19	–	0/24	–
NNRTI+NRTI	95/162	52.3 (41.0–63.3)	10/19	52.0 (32.9–70.5)	17/24	46.9 (10.6–86.7)
HIVDR among individuals on NNRTI first-line ART with VL≥1000 copies/mL						
Any	109/161	61.1 (50.2–70.9)	15/17	88.9 (58.4–97.9)	18/24	47.3 (10.7–87.0)
NNRTI	107/161	59.7 (49.2–69.4)	14/17	80.0 (51.0–93.9)	18/24	47.3 (10.7–87.0)
NRTI	95/161	52.5 (41.1–63.6)	10/17	62.2 (37.5–81.9)	17/24	46.9 (10.6–86.7)
PI	1/161	1.1 (0.1–7.6)	0/17	–	0/24	–
NNRTI+NRTI	94/161	52.2 (40.9–63.2)	9/17	53.3 (37.5–68.5)	17/24	46.9 (10.6–86.7)

NNRTI resistance is defined as resistance to NVP or EFV. NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to ATV/r, LPV/r or 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".

The **prevalence of NNRTI resistance** among individuals on ART with viral load ≥1000 copies/ml was higher at the late time point than at the early time point, though the difference was not statistically significant: 74.2% (95% CI 51.8–88.5) in Guatemala, 87.0% (95% CI 53.6–97.5) in Viet Nam, and 87.7% (95% CI 67.4–96.1) in Cameroon. This was similar to the prevalence of NNRTI resistance among those on first-line ART and those on NNRTI-containing first-line ART with viral load ≥1000 copies/ml, with the exception of Guatemala, where prevalence of NNRTI resistance among those on first-line ART and NNRTI first-line ART was higher than those on ART overall (81.1% and 84.3% respectively, versus 74.2%).

Levels of **NRTI resistance** among those on ART with viral load >1000 copies/ml at the late time point ranged from 63.0% (95% CI 43.7–78.9) in Guatemala to 87.7% (95% CI 55.4–97.6) in Viet Nam. PI resistance in this group was low: no PI resistance was detected among survey participants in Viet Nam, while levels in Cameroon and Guatemala were 0.8% (95% CI 0.1–9.4) and 2.6% (95% CI 0.3–21.6), respectively. Predicted levels of NRTI, NNRTI and PI resistance by drug class and drug are shown in Fig. 12 and Fig. 13.

As with the earlier time point, the prevalence of NNRTI resistance among all individuals on ART[22] ranged from 4.2% (95% CI 2.4–7.4) in Viet Nam to 28.3% (95% CI 17.4–42.5) in Cameroon (Table 19).

Table 19: Prevalence of acquired HIV drug resistance among individuals on ART, late time point (36–48+), national acquired HIV drug resistance surveys

	Cameroon (48–60 mo.)		Guatemala (≥ 48 mo.)		Viet Nam (≥ 36 mo.)	
	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)	n/N	Prevalence % (95% CI)
HIVDR among individuals on ART						
Any	59/334	28.3 (17.4–42.5)	30/368	9.5 (3.0–26.2)	19/365	4.6 (2.8–7.5)
NNRTI	59/334	28.3 (17.4–42.5)	29/368	9.2 (2.9–25.6)	18/365	4.2 (2.4–7.4)
NRTI	53/334	25.2 (14.0–40.9)	25/368	7.8 (2.5–22.2)	18/365	4.3 (2.4–7.4)
PI	1/334	0.3 (0.0–3.7)	1/368	0.3 (0.0–4.1)	0/365	–
NNRTI+NRTI	53/334	25.2 (14.0–40.9)	24/368	7.5 (2.4–21.4)	17/365	3.9 (2.0–7.3)
HIVDR among individuals on ART with VL≥1000 copies/mL						
Any	59/67	87.7 (67.4–96.1)	30/40	76.5 (55.6–89.4)	19/20	94.8 (64.4–99.5)
NNRTI	59/67	87.7 (67.4–96.1)	29/40	74.2 (51.8–88.5)	18/20	87.0 (53.6–97.5)
NRTI	53/67	77.9 (50.2–92.5)	25/40	63.0 (43.7–78.9)	18/20	87.7 (55.4–97.6)
PI	1/67	0.8 (0.1–9.4)	1/40	2.6 (0.3–21.6)	0/20	–
NNRTI+NRTI	53/67	77.9 (50.2–92.5)	24/40	60.7 (42.6–76.2)	17/20	79.9 (46.6–94.8)
HIVDR among individuals on first-line ART with VL≥1000 copies/mL						
Any	57/63	89.5 (71.0–96.7)	29/35	83.8 (57.8–95.1)	19/20	94.8 (64.4–99.5)
NNRTI	57/63	89.5 (71.0–96.7)	28/35	81.1 (59.3–92.6)	18/20	87.0 (53.6–97.5)
NRTI	51/63	79.3 (50.4–93.5)	25/35	71.6 (42.4–89.6)	18/20	87.7 (55.4–97.6)
PI	1/63	0.8 (0.1–10.1)	1/35	2.9 (0.3–23.4)	0/20	–
NNRTI+NRTI	51/63	79.3 (50.4–93.5)	24/35	68.9 (44.3–86.1)	17/20	79.9 (46.6–94.8)
HIVDR among individuals on NNRTI first-line ART with VL≥1000 copies/mL						
Any	57/63	89.5 (71.0–96.7)	27/31	87.3 (67.8–95.7)	18/19	94.7 (64.1–99.4)
NNRTI	57/63	89.5 (71.0–96.7)	26/31	84.3 (69.4–92.7)	17/19	86.8 (53.3–97.5)
NRTI	51/63	79.3 (50.4–93.5)	24/31	76.9 (47.1–92.5)	17/19	87.5 (55.1–97.6)
PI	1/63	0.8 (0.1–10.1)	1/31	3.3 (0.3–26.5)	0/19	–
NNRTI+NRTI	51/63	79.3 (50.4–93.5)	23/31	73.9 (49.6–89.0)	16/19	79.7 (46.1–94.7)

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".

[22] This outcome estimates the proportion of individuals sampled with viral load ≥1000 copies/ml and detected HIVDR among all individuals sampled with viral load testing successful and results classifiable.

In contrast to other surveys, no zidovudine (ZDV) resistance was detected in Guatemala; this may reflect use of non-thymidine analogues (i.e. tenofovir disoproxil fumarate (TDF)) in the country. TDF resistance ranged from 26.3% in Guatemala to 66.7% in Viet Nam.

Levels of resistance to XTC – lamivudine (3TC) or emtricitabine (FTC) – were also high, ranging from 52.6% in Guatemala to 77.6% in Cameroon. Etravirine and rilpivirine resistance were generally high, ranging from 19.0% in Zambia to 77.0% in Viet Nam.

Fig. 12: Prevalence of acquired HIV drug resistance by drug class and country[23]

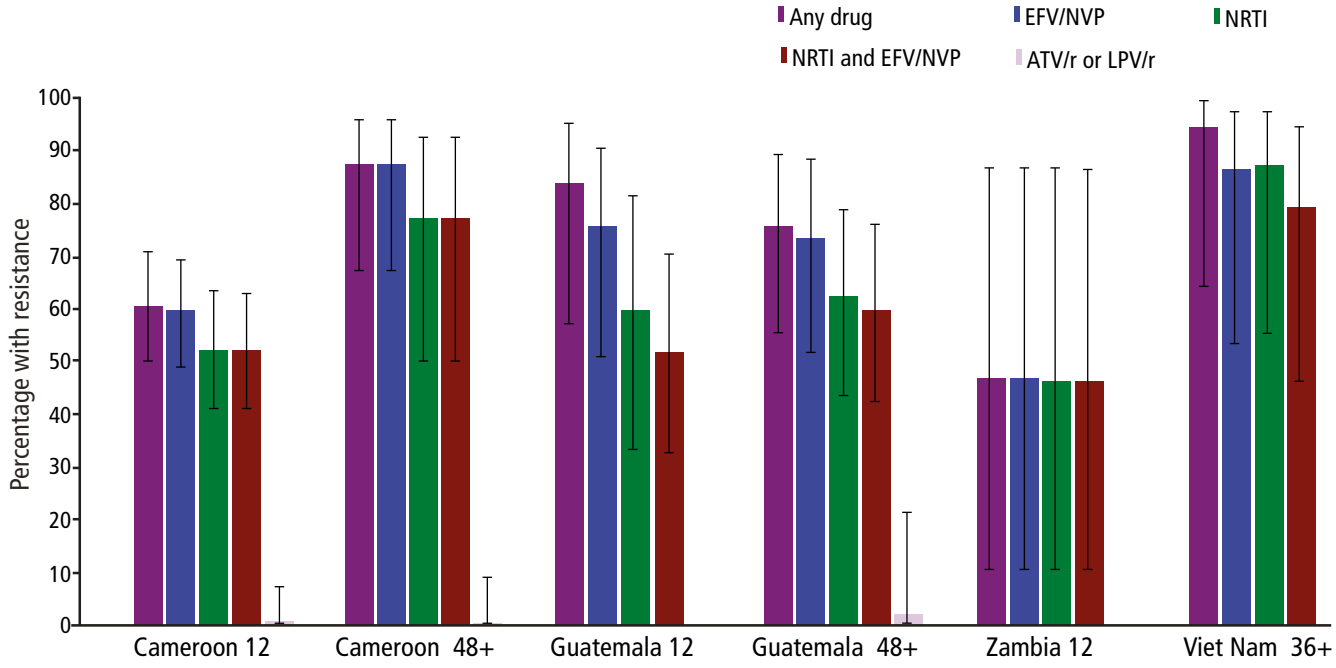
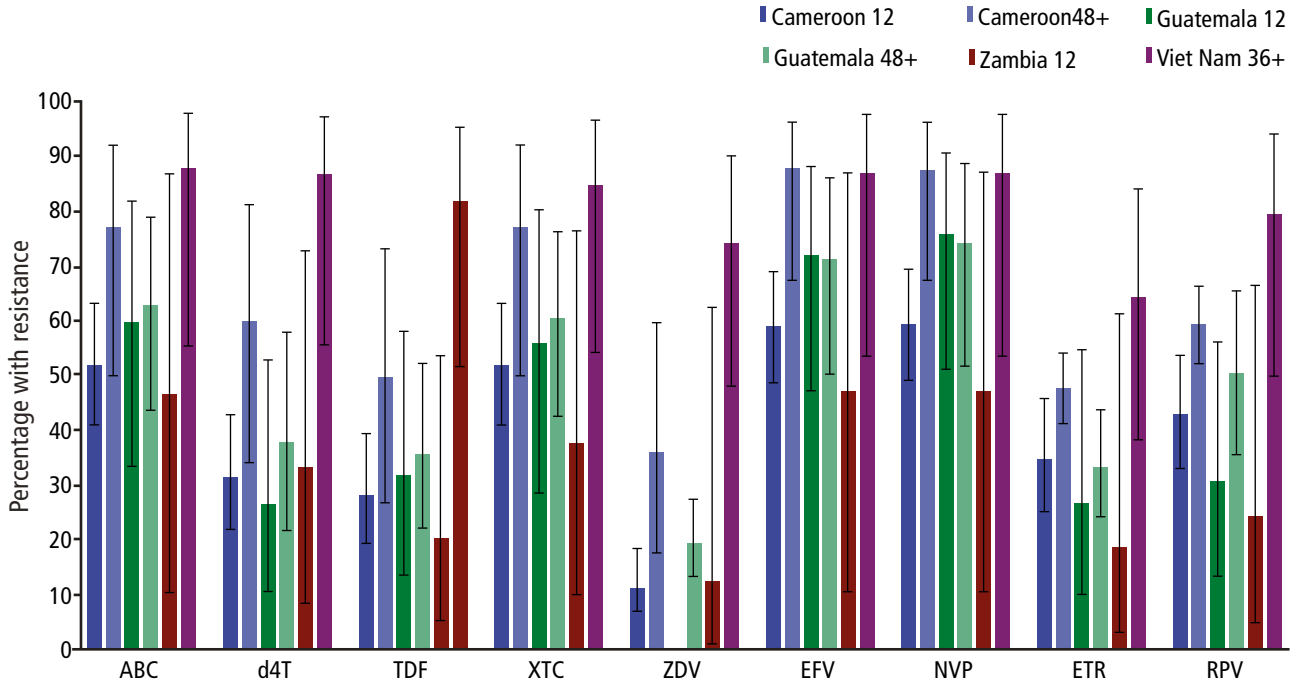


Fig. 13: Prevalence of acquired HIV drug resistance by drug and country[24]



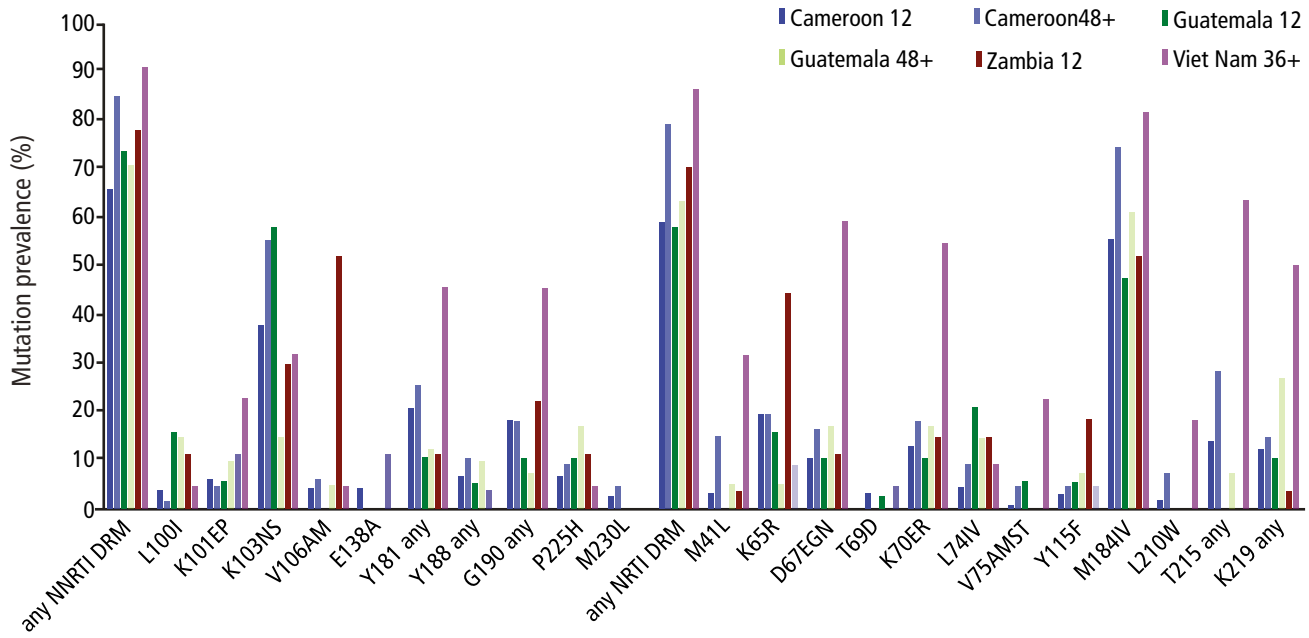
ABC= abacavir; d4T= stavudine; TDF= tenofovir disoproxil fumarate; XTC= lamivudine or emtricitabine; ZDV=zidovudine; EFV= efavirenz; NVP= nevirapine; ETR= etravirine; RPV= rilpivirine.

[23] NNRTI resistance is defined as resistance to NVP or EFV. NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to ATV/r, LPV/r or 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 (version 8.3): sequences classified as having predicted low-, intermediate- or high-level resistance are considered "resistant".

[24] Sequences classified as having predicted low-, intermediate- or high-level resistance by the Stanford HIVdb algorithm (version 8.3) to the drugs reported are considered "resistant".

The frequency of HIVDR mutations, as defined by the WHO SDRM list and detected at a frequency greater than 1% of all sequences analysed, is shown in Fig. 14. Considerable variability was observed between surveys, likely driven by different regimens and small sample sizes. The most commonly observed NRTI-associated resistance mutations were at codons 184 and 65; the most commonly observed NNRTI-associated mutations were at positions 103, 181 and 190. PI mutations were extremely rare, with a frequency of 1.8%.

Fig. 14: Acquired HIV drug resistance mutations by country[25]



NNRTI: non-nucleoside reverse-transcriptase inhibitor; NRTI: nucleoside reverse-transcriptase inhibitor; DRM: drug resistance mutations.

3.2 Systematic literature review of acquired HIV drug resistance in adults

A systematic review of studies published between 1 January 2014 and 30 April 2017 on ADR in adults was performed. The aim of this review was to estimate the burden of drug resistance among individuals initiated on NNRTI-based regimens; to estimate the overall prevalence of any DRM among those for whom genotyping was performed; to estimate the geographic distribution and the patterns of HIVDR mutations for the latter; and to describe the HIVDR cascade based on available data.

Methods are provided in Section 5 of the Annex. Briefly, studies were eligible if they included at least 30 people and participants were older than 15 years of age.

A total of 30 research cohorts from 26 studies in 30 countries were included in the analysis. Cohorts within a study were considered separately if the authors chose to report most variables disaggregated by the cohort's subpopulation (e.g. by country in a multicountry study or by treatment duration). Cohorts were further separated into those designed to establish levels of viral load suppression and to characterize HIVDR among those not achieving viral suppression ("viral load and genotype cohorts"), and those designed to describe the pattern of resistance among individuals with known virological failure on first-line NNRTI-based regimens ("genotyping only cohorts").

Table 20 describes the general profile of the studies included. Eighteen of the 26 studies were cross-sectional in design; seven were prospective; and one was retrospective.

Table 20: Characteristics of studies included in the literature review of acquired HIV drug resistance in adults (n=26)

	Median	Range
Age[1]	38	33–43
Males (%)[1]	52%	21–91%
Number of participants	444	44–2223
% patients on NNRTI-based regimen[1]	79%	67–100%
Measured treatment duration before failing ART (months)[1]	18	12–89
Minimum duration on ART for inclusion in study (months)[1]	15	6–48
Year data collection ended	–	2007–2015
Year published	–	2014–2016

[1]weighted mean to reflect study heterogeneity.

[25] Mutations are defined as per the WHO 2009 SDRM list; only mutations present at ≥ 1% of all sequences analysed are shown.

Table 21 describes the geographic distribution of included cohorts.

Table 21: Number of cohorts included in the literature review of acquired HIV drug resistance in adults, by region

	Number of cohorts
Africa	16
Central Africa	1
Eastern Africa	4
Southern Africa	3
Western Africa	8
Asia	8
East Asia	6
Middle East	2
Central America	2
Multi country	4
Total	30

Key findings

Data were available from a total of 13 338 individuals. Among those, 10 967 were from "viral load and genotype cohorts". An additional 2371 individuals were from "genotyping only cohorts".

Overall, the pooled prevalence of viral load suppression from the 18 "viral load and genotype cohorts" was 82.1% (range 11–90%, 95% CI 81.4–82.9), while 9.7% (95% CI 9.2–10.3) of the individuals on ART were found to have any DRM (n=1069). Among those failing NNRTI-based regimens, 79% had a genotype performed; among those with genotypes, 68% had one or more DRM detected.

Conversely, among those failing a first-line NNRTI-based regimen, nearly one third (32%) experienced treatment failure without detectable resistance, indicating that in these cases, failure to achieve viral suppression could not be attributable to ADR. This suggests that these individuals may be able to achieve viral suppression with improved adherence alone, without the need for more expensive and more difficult-to-tolerate second-line regimens.

Table 22 reports findings by country and by study/cohort (cohort data is shown for studies where data was disaggregated by country). Note that most studies used convenience samples; thus, prevalence estimates are not meant to be representative of the levels of DRM for the individual country. "Number of people genotyped" was used as the common denominator to standardize estimates across studies.

Table 22: Estimates of HIV drug resistance among people failing ART, by study/cohort and region in the acquired HIV drug resistance literature review in adults

Country	Study author	% with resistance	CI (%)
Africa			
Cameroon	Zoufaly et al.	71%	54.1–84.6
Guinea	Diouara et al.	68%	47.6–84.1
Kenya	Hassan et al.	53%	38.8–66.3
Kenya	Kantor et al.	91%	78.7–97.5
Kenya	Koigi et al.	41%	26.3–56.7
Liberia	Loubet et al.	71%	55.9–83
Mali	Diouara et al.	93%	68–99.8
Mali	Fofana et al.	92%	83.5–96.5
Mauritania	Fall-Malick et al.	73%	59.7–83.6
Mozambique	Bila et al.	47%	30.4–64.5
Mozambique	Ruperez et al.	89%	77.7–95.2
Senegal	Diouara et al.	70%	49.8–86.2
Senegal	Diouara1 et al.	79%	65.3–88.9
Togo	Konou et al.	99%	96.6–99.9

Table 22: Estimates of HIV drug resistance among people failing ART, by study/cohort and region in the acquired HIV drug resistance literature review in adults (continued)

Country	Study author	% with resistance	CI (%)
Asia			
Uganda	Kaleebu et al.	71%	56.7–83.4
Zambia	Seu et al.	99%	92–99.9
China	Leng et al.	39%	31.5–46.5
China	Wang et al.	67%	55.9–76.2
China	Wang et al.	28%	14.6–43.8
China	Yang et al.	47%	40.9–53.5
China	Zhan et al.	69%	60.4–77.1
China	Zhou et al.	52%	44.3–58.7
Iran (Islamic Republic of)	Baesi et al.	58%	44.8–70.5
Iran (Islamic Republic of)	Naziri et al.	42%	29.5–65.1
Central America			
Honduras	Avila-Rios et al.	83%	78.7–86.5
Multicountry			
See annex	Aghokeng et al.	79%	74.6–82.5
See annex	Wallis et al.	96%	91.3–98.5
See annex	Tenores et al.	66%	63.5–69.2

For regions with sufficient data, pooled regional estimates were calculated using a random effects model (Table 23). Notably, ADR was high among individuals in studies primarily utilizing first-line NNRTI-based regimens, irrespective of the NRTI backbone used. Western Africa had the highest level of ADR at 87.8%.

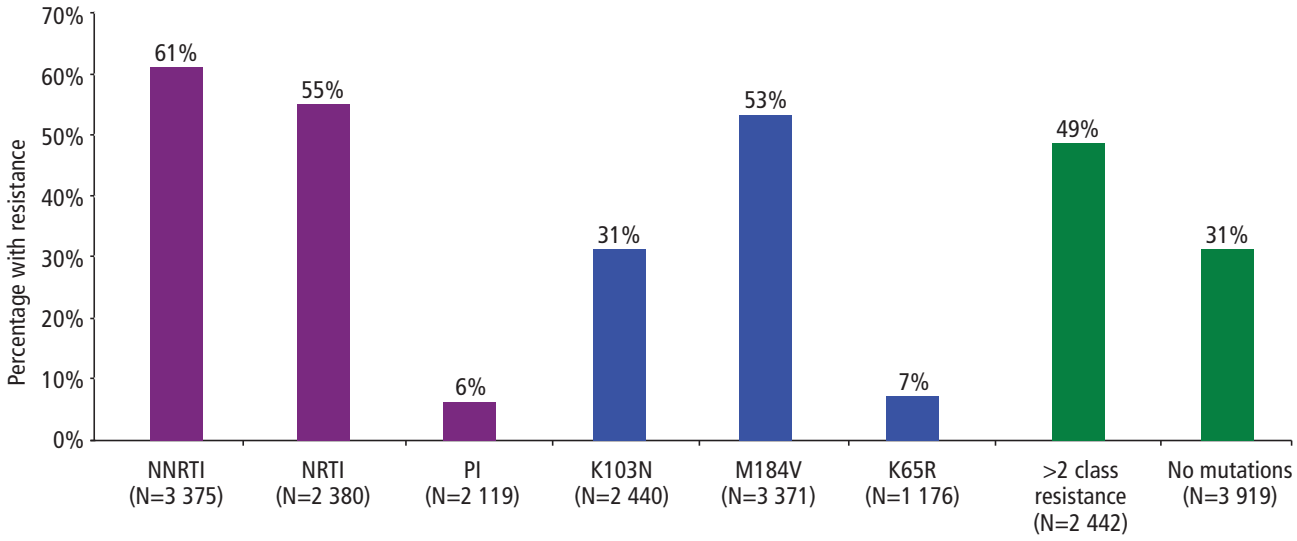
Table 23: Pooled estimates of HIV drug resistance among people failing NNRTI-based ART by region in the acquired HIV drug resistance literature review in adults

Region	Mean (%)	95% CI (%)
Africa	80.7	56.1–93.2
Eastern Africa	64.7	29.9–99.0
Southern Africa	87.3	37.2–99.9
Western Africa	87.8	50.8-98.0
Asia		
China	50.3	18.2–98.2
Multicountry cohorts[1]	79.2	18.2–99.8
Total[2]	70.7	45.2–87.6

[1]Multicountry cohorts had patients recruited in all continents that could not be disaggregated for analysis.
[2]"Total" includes studies from Central America, the Middle East and Central Africa, not shown in the table.

Genotype data were available for a total of 3919 individuals from both "viral load and genotype cohorts" and "genotyping only cohorts". In this subgroup, the pooled estimates using a random effects model show that 70.7% were found to have any DRM. Resistance to NNRTI had the highest observed rate (61%), followed by NRTI (55%). The profile of HIVDR is summarized in Fig. 15.

Fig. 15: Acquired HIV drug resistance among individuals on ART (systematic literature review, 2014–2017)



NNRTI=non-nucleoside reverse-transcriptase inhibitor
NRTI=nucleoside reverse-transcriptase inhibitor
PI=protease inhibitor

Results from this systematic review suggest that currently recommended second-line PI-based regimens remain an effective option for the majority of individuals failing first-line regimens. The relatively high prevalence of resistance to NNRTI should be interpreted in the context of each study, including the sampling approach and methodology used. Nonetheless, the availability of affordable drugs with higher barriers to resistance (e.g. dolutegravir, or "DTG") has the potential to address concerns about emerging resistance to NNRTI-based regimens in settings where individual drug resistance testing is not feasible.

3.3 Systematic literature review of acquired HIV drug resistance in children

Literature published between 1 January 2014 and 30 April 2017 was systematically reviewed to characterize the prevalence of HIVDR in children failing ART; detailed methods are presented in Section 4 of Annex 1. A total of 10 studies, inclusive of 2579 children on ART, were identified. Of these children, 988 had DRMs. General characteristics of study participants contributing data to ADR surveys are described in Table 24.

Table 24: Characteristics of studies included in literature review of acquired HIV drug resistance studies among children

ADR		
	Median	**Range**
Age (years)	8.84	1–12.2
Males (%)	50.8	40–59
Number of participants	257	65–599
Number of participants with DRM	98	35–354
(%) with NNRTI resistance	69.4	12–95
Year data collection ended	–	2009–2013
Year published	–	2014–2017

Key findings

Across all studies, K103N and M184V were the most commonly detected mutations found in RT (39.8% and 76.6%, respectively) (Table 25). A 2016 study from South Africa found that among 101 children with evidence of virological failure on first-line ART, 91% demonstrated at least one DRM *(5);* for those on NNRTI-based regimens (n=73), the majority of genotypes had both NRTI- and NNRTI-associated mutations. A 2017 United Republic of Tanzania study found that among 213 children on ART for a median duration of 4.3 years, 25.4% had virological failure. Ninety per cent of those failing had drug-resistant virus and 79% had virus with mutations associated with multiclass drug resistance *(6)*. Pretreatment genotypes suggested that more than 85% of these children had acquired DRMs while on ART.

Table 25: Findings from studies included in literature review of acquired HIV drug resistance among children

Study (author, year of data collection, country)	N Sequenced genotypes	N with DRM	Line/ART regimen	% with any DRM	%with NNRTI DRM	%with NRTI DRM	%K103N	%M184V	%K65R
Muri L et al. 2013 (United Republic of Tanzania)	52	47	First-line; NNRTI	90.4	90.2	80.8	49	77	6
Makadzange A et al. 2012–2013 (Zimbabwe)	102	69	First-line; NNRTI	67.6	69.5	21.7	31.9	59.4	3
Dow D et al. 2008–2009 (United Republic of Tanzania)	54	35	First-line; NNRTI	64.8	89	49	40	89	0
Mutwa P et al. 2009–2010 (Rwanda)	57	55	First-line; NNRTI	96.5	95	91	95	96	13
Prasitsuebsai W et al. 2011–2012 (Indonesia, Thailand and Viet Nam)	277	156	Second-line; PI	56.3	92	64	27	82	10
Pillay S et al. 2011–2012 (South Africa)	89	81	First-line; NNRTI (≥3 yrs) PI (<3 yrs)	91.0	72	82	54	79	5
Mossoro-Kpinde C et al. 2013 (Central African Republic)	58	54	First-line; NNRTI and second-line; PI	93.1	60	45	31	43	N/A
Meyers T et al. 2000–2011 (South Africa)	75	75	First-line line; PI	100	12	57	N/A	58	N/A
Rossouw T et al. 2008–2012 (South Africa)	65	65	First-line; PI	100	45	97	23	89	3
Steegen K et al. 2010–2013 (South Africa)	370	354	First-line NNRTI and PI (<3 yrs)	95.7	N/A	57	N/A	89	4

Overall, the high levels of ADR observed in children failing ART argue for close virological monitoring and a prompt switch to a different line of treatment. Since the majority of these DRMs developed over the course of treatment, extra attention is needed to ensure high adherence and retention among children on ART.

This systematic review highlights the paucity of global data on HIVDR in HIV-infected children, while demonstrating high levels of ADR in this population. In addition, information on adolescent ADR was sparse, a finding with significant implications, given that virological suppression in adolescents on ART is substantially lower than in adults *(7)*.

LMIC may consider prioritizing surveillance of HIVDR among children and adolescents, disaggregated for age groups 2–9 and 10–19 year-olds, particularly for children who have been on ART for an extended period of time, to better inform programmatic and policy decision-making.

3.4 Acquired HIV drug resistance – summary of findings and implications

ADR occurs when resistance mutations are acquired due to drug-selective pressure in people receiving ART. ADR may emerge because of suboptimal adherence, treatment interruption, inadequate plasma drug concentrations, or the use of suboptimal drugs or drug combinations.

Only four countries have implemented and reported national surveys of ADR in adults between 2014 and 2016. Although uptake has been slower than for PDR surveys, an additional 11 countries are anticipated to implement ADR surveys by the end of 2017.

Achieving high levels of viral load suppression and minimizing ADR is critical to reaching the 90-90-90 treatment targets. Only two of the four countries (Viet Nam and Zambia) achieved a prevalence of ≥90% viral load suppression; heterogeneity in the level of viral load suppression reported among people on ART in the four countries suggests that there may be substantial differences in programme performance across countries.

Results from PHIA surveys conducted in Malawi, Zambia and Zimbabwe demonstrate high levels of viral load suppression among people who self-report being on ART. In the PHIA surveys, the prevalence of viral load suppression among adults was 88.6% across all three countries, suggesting that "the third 90" can be achieved, and that the prevalence of clinically relevant DRMs in the populations surveyed is relatively low. However, some countries continue to report virological suppression rates as low as 68%, indicating that gaps in the quality of service delivery need to be addressed to meet the 90% target for virological suppression.

High levels of NNRTI resistance among individuals on first-line ART with unsuppressed viral load were observed in ADR surveys, ranging from 47.3% in Zambia to 76.0% in Guatemala. Even higher levels of ADR were observed among individuals on first-line ART for longer durations (36–48+ months), ranging from 84.3% in Guatemala to 89.5% in Cameroon. Survey findings are consistent with a systematic review of recent published literature, which found similarly high levels of resistance (68% overall) among individuals failing NNRTI-based regimens.

Despite the high levels of ADR observed in national surveys, the mutations and mutation patterns detected among people failing therapy suggest that currently recommended PI-based second-line ART remains an effective option for the vast majority of individuals failing first-line ART. Nonetheless, strategic use of increasingly affordable drugs with higher barriers to development of resistance (e.g. DTG) has the potential to mitigate concerns regarding ongoing treatment efficacy of NNRTI-based therapy, and may possibly reverse the observed trend of increasing NNRTI resistance. Future use of drugs such as DTG may be particularly promising in settings where individual drug resistance testing is not feasible.

Prompt identification and switch of individuals failing first-line ART will be important to preserve the NRTI component of second-line ART.

Of concern is the scarcity of global data on resistance in HIV-infected children receiving ART, as evidenced by the lack of national paediatric ADR surveys implemented between 2014 and 2016. The systematic review of the recent published literature also documented a limited number of studies in this population, while the studies that were available indicated high levels of ADR in the paediatric population. Moreover, the paucity of data on ADR in adolescents is of significant concern, given lower rates of virological suppression in this population compared to adults. Going forward, more data on ADR in both children and adolescents will be needed in order to inform programmatic and policy decision-making.

To date, several countries have reported high levels of viral load suppression among people receiving treatment, attesting to the effectiveness of available therapy and the success of ART scale-up. The fact that "the third 90" target is being achieved in several countries is reassuring. However, in other countries, viral load suppression in people on ART is well below the global target, and merits attention. Levels of resistance in people failing ART are high, indicating the need to scale up viral load testing, and promptly switch individuals with confirmed virological failure to second-line treatment. These interventions, coupled with strengthening programme quality, can limit the accumulation of drug resistance and help ensure even higher levels of population-level viral load suppression. These actions will help propel the global community towards the elimination of AIDS as a public health threat.

4 GLOBAL EFFORTS TO PREVENT, MONITOR AND RESPOND TO HIV DRUG RESISTANCE

To address concerns around the recently observed elevated levels of PDR to the NNRTI drug class among people with or without prior ARV drug exposure who are initiating or reinitiating first-line ART, and the potential negative impact of NNRTI PDR on treatment outcomes, WHO is strengthening its response to HIVDR through the broader efforts described in the *Global Action Plan on HIV drug resistance (1)* and *Guidelines on the public health response to pretreatment HIV drug resistance (2)* .

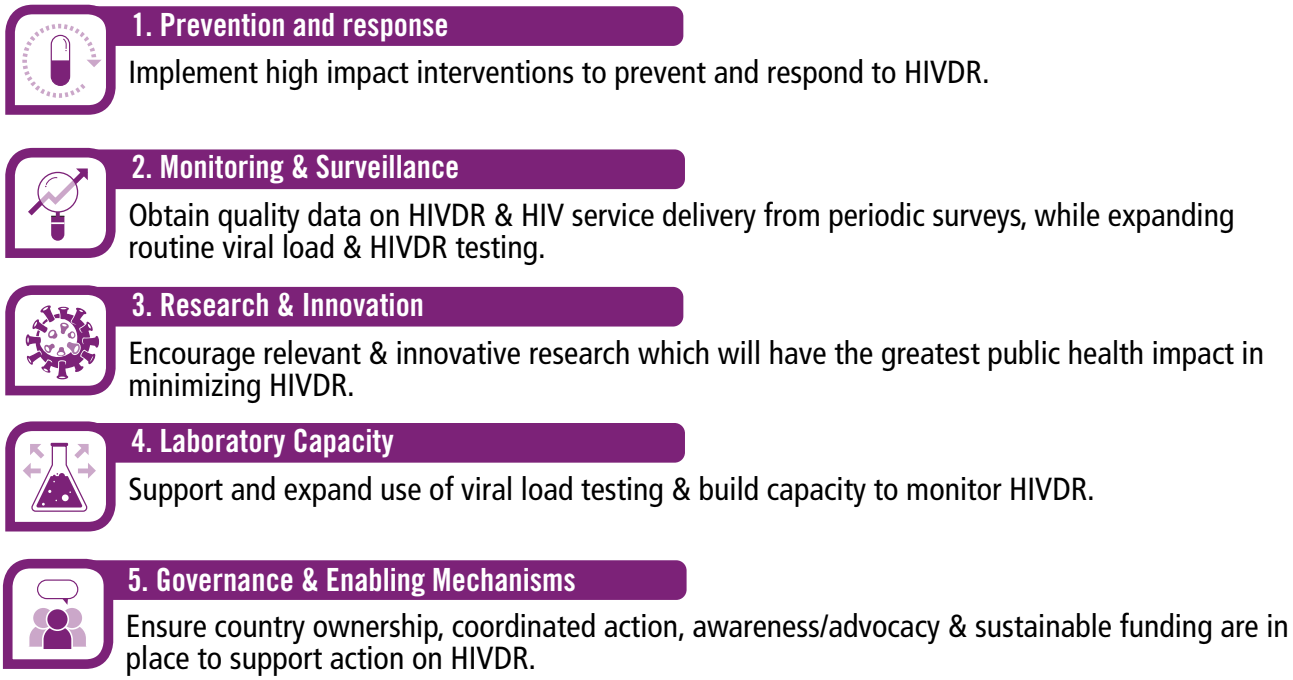
4.1 WHO Global Action Plan on HIV drug resistance, 2017–2021

The 2016 Political Declaration on HIV and AIDS *(3)*, and endorsement of the *Global Health Sector Strategy on HIV 2016–2021* by the World Health Assembly *(4)*, demonstrate the United Nations Member States' commitment to ending the AIDS epidemic by 2030. To realize this goal, the GAP on HIVDR was developed through an extensive consultative process, involving more than 800 individuals, 100 countries and 350 organizations.

WHO's development of a five-year GAP *(1)* on HIVDR reflects a global consensus that increasing levels of HIVDR in LMIC require a coordinated and resourced response to increase awareness, commitment and action at all levels.

The GAP on HIVDR is a call for collective action, grounded in normative guidance, which provides a standardized and robust approach to monitoring, preventing and responding to HIVDR over the next five years (2017–2021). The GAP identifies areas for concerted and collective action in order to better understand the current and future levels of HIVDR; to prevent HIVDR from undermining achievement of the global targets on health and HIV; and to provide the most effective treatment to all PLHIV, including adults, key populations[26] pregnant and breastfeeding women, children and adolescents. Ensuring effective treatment for all PLHIV, and ending the AIDS epidemic, are public health imperatives. The GAP provides countries and international and national partners with a framework for action which, when implemented collectively, will contribute to the Fast-Track global targets of 95-95-95 by 2030: 95% of all PLHIV will know their HIV status; 95% of all people diagnosed with HIV infection will receive ART; and 95% of all people accessing ART will achieve viral suppression *(5)*. The GAP outlines the roles of countries, global and national partners, and WHO over the next five years. It is structured around five strategic objectives (Fig. 16).

Fig. 16: The five strategic objectives of the Global Action Plan on HIV drug resistance



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

[26] Men who have sex with men; people who inject drugs; people in prisons and other closed settings; sex workers; and transgender people.

Countries have not only committed to ending AIDS – the global community has recognized that combatting AMR requires coordinated action across all government sectors and levels of society. Minimizing the emergence and transmission of HIVDR is a vital part of the global commitment to meeting the challenges of AMR, which threaten the effective prevention and treatment of infections caused by bacteria, parasites, viruses and fungi. Building on the GAP, regions and countries must develop operational plans that will translate these broader global commitments into context-specific strategies for implementation. To this end, important work is underway in the WHO African Region, the first region to develop a road map for implementing the GAP on HIVDR. Similar initiatives in other regions must follow.

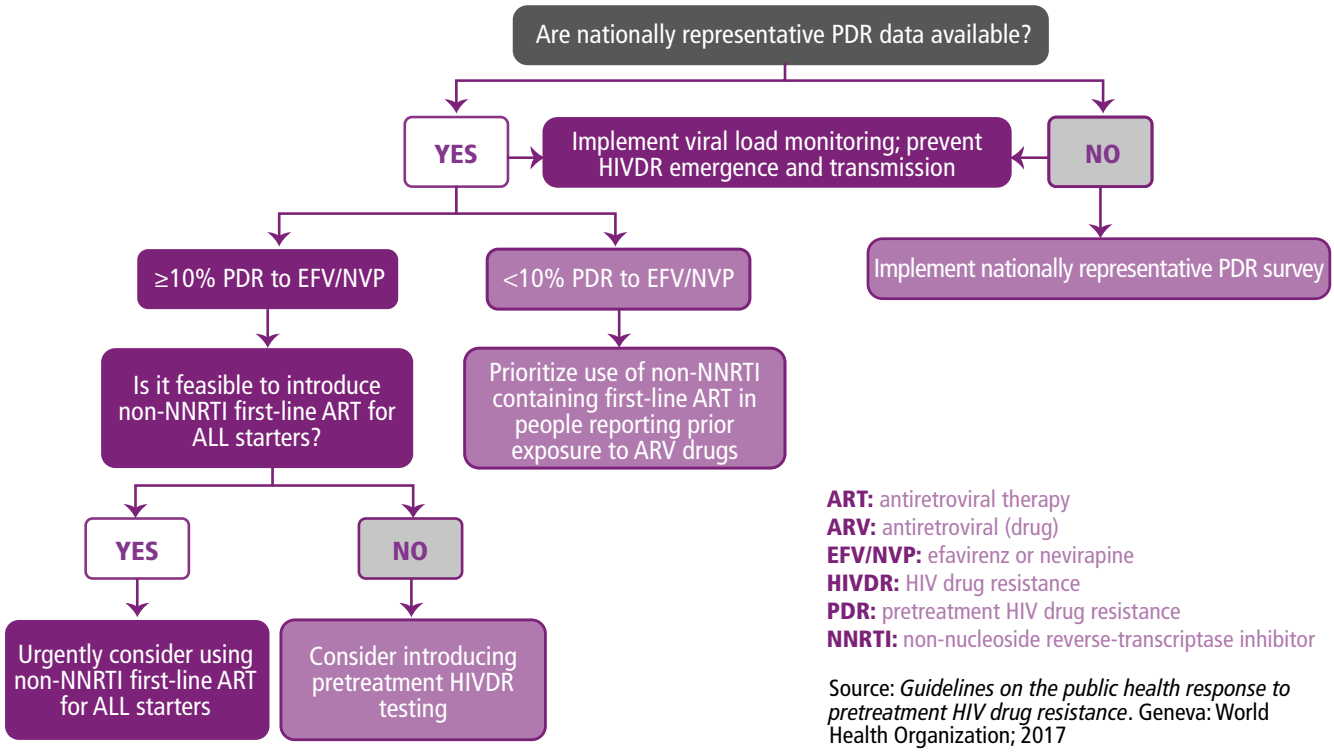
4.2 WHO Guidelines on the public health response to pretreatment HIV drug resistance

WHO's 2017 *Guidelines on the public health response to pretreatment HIV drug resistance (2)* support countries in responding appropriately to levels of NNRTI PDR in people initiating or reinitiating first-line ART. The overall aim of the guidance is to: 1) attain and maintain the treatment target of 90% virological suppression in all people receiving ART, gradually increasing to the longer-term goal of 95%; and 2) address the first strategic objective of WHO's GAP on HIVDR for 2017–2021: **prevention and response to HIVDR**.

WHO's 2016 *Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (6)* recommend an NNRTI-based first-line regimen for populations initiating (or reinitiating) first-line ART (adopted by 82/137 LMIC as of July 2017) *(7)*, except in the case of children younger than 3 years of age. In this group, a regimen containing PI/r is recommended as the preferred first-line, due to high rates of resistance associated with exposure to NNRTIs for PMTCT and other considerations. The 2016 WHO guidelines recommend NNRTI-based ART both in people starting first-line without prior ARV drug exposure and in ARV drug-exposed individuals. Indeed, the vast majority of LMIC do not differentiate between the two groups, providing an NNRTI-based first-line ART regimen regardless of whether a person is starting ART for the first time or restarting first-line treatment.

The 2017 WHO HIVDR guidelines recommend that countries with levels of pretreatment resistance to NNRTI of 10% or more urgently consider using an alternative non-NNRTI-containing first-line regimen. The use of HIVDR testing to guide first-line regimen selection in individuals was reviewed for the guidelines, but no formal recommendation was made. A schematic flow of operationalizing the guidance is provided in Fig. 17.

Fig. 17: Response to estimated levels of pretreatment HIV drug resistance to NNRTI



ART: antiretroviral therapy
ARV: antiretroviral (drug)
EFV/NVP: efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: pretreatment HIV drug resistance
NNRTI: non-nucleoside reverse-transcriptase inhibitor

Source: *Guidelines on the public health response to pretreatment HIV drug resistance*. Geneva: World Health Organization; 2017

Nationally representative data on the levels of PDR to NNRTI can inform countries whether an urgent transition to a non NNRTI containing first-line ART regimen should be considered *(60)*. The 2017 guidelines further note that in people at high risk of PDR to NNRTI as a result of prior exposure to NNRTIs (or from other risks), a non-NNRTI-containing regimen may be preferable, regardless of the country level of NNRTI PDR, and without the need to document the presence of NNRTI resistance using an HIVDR test (Fig. 17).

The WHO guidelines and GAP provide countries facing increased HIVDR with evidenced-based recommendations and consensus advice on how to best respond to and prevent HIVDR, particularly PDR, before it becomes a true public health threat.

5 SUSTAINABILITY OF HIV DRUG RESISTANCE SURVEILLANCE

The sustainability of HIVDR surveillance requires commitment from both donors and national governments to secure and allocate sufficient resources, and to develop HIVDR strategies that are integrated into national HIV strategic plans. While it is expected that national governments take technical and financial ownership of surveillance, funders and international stakeholders are recommended to support countries in this effort. Investments in HIVDR should be seen as part of the cost of ART delivery and essential to ensuring quality treatment programmes; they represent a modest cost to the overall programme *(1)*. The US-CDC, The Global Fund and WHO have each committed to ensuring the sustainability of HIVDR surveillance. Their respective plans and activities are described in the following sections.

5.1 US-CDC support for HIV drug resistance surveillance

US-CDC support for HIVDR surveillance includes:

- support for surveillance of HIVDR in adults, infants, children and adolescents, as well as special populations, such as pregnant and breastfeeding women;
- support for strengthening laboratory capacity for HIVDR testing for surveillance, research and patient management;
- housing of US-CDC-generated HIVDR related data in a data warehouse for the purpose of multicountry analyses and, where appropriate, public access; and
- the use of routine programmatic data to inform the risk of HIVDR.

HIVDR surveillance in adults – US-CDC is currently supporting implementation and analysis of cross-sectional surveys (PDR and/or ADR) of adults in 17 PEPFAR-supported countries, including nine countries with the highest burdens of PLHIV in sub-Saharan Africa, using local adaptations of WHO-recommended methodologies. US-CDC is also working to leverage expansion of routine viral load testing and exploring the use of case-based surveillance as a potential mechanism for routinized and widespread use of genotyping to gather information on HIVDR.

HIVDR surveillance in infants, children and adolescents – Data from numerous studies and programmes have revealed alarmingly high rates of virological failure in children and adolescents, so prompt identification and response is critical to prevent accumulation of DRMs. Adoption of WHO guidelines for the use of PI-based ART for children younger than 3 years is also a key issue for HIVDR in children; US-CDC is working closely with countries to accelerate implementation of this policy.

Given the high rates of PDR in children, in addition to the high prevalence of virological failure in children and adolescents, monitoring and surveillance of HIVDR (both PDR and ADR) in children and adolescents is a US-CDC priority. Thus far, most countries have focused on the adult population. Hence, US-CDC actively advocates increasing inclusion of children and adolescents in planned HIVDR surveillance and research activities, using innovative approaches to enrol sufficient numbers of children living with HIV, so that rigorous and actionable data can be collected and stratified by various age bands. This approach has included use of case surveillance for children with virological failure in South Africa.

HIVDR surveillance in pregnant and breastfeeding women – US-CDC is working to support inclusion of pregnant and breastfeeding women in HIVDR surveillance and research activities, given the widespread use of ART; the risk of fragmented and interrupted care with transfer between maternal and child health and ART facilities; and the potential for transmission of HIV infection and HIV DRMs to infants. This will ensure that HIVDR development does not threaten progress towards elimination of mother-to-child transmission or the ability to treat children who acquire peri-natal infection despite maternal ART. Work is ongoing to determine ideal protocols, frequency and monitoring approaches to collect timely and rigorous data for these populations.

Laboratory capacity-building – US-CDC prioritizes support for quality-assured HIVDR activities in PEPFAR-supported programmes, through strengthening human resources in laboratories, providing technical assistance to increase capacity for local HIVDR testing, and engaging in research collaborations. US-CDC also supports HIVDR surveillance, and provides limited genotyping services to individuals enrolled in care and treatment programmes in PEPFAR-supported countries. It is engaged in operational research into new technologies to improve programme efficiencies and effectiveness of HIVDR testing laboratories.

Database development – US-CDC has developed an HIVDR data warehouse to store all HIVDR data shared by countries. This data warehouse is a relational database supported by SQL Server Integration Services processes, for the import and management of HIVDR data, including de-identified survey participants, laboratory results, treatment regimens, sequences on the HIV virus, and mutations specific to the HIV virus associated with drug resistance. US-CDC is also willing to provide the empty template and architecture for this database to countries that would like to house their country-specific HIVDR data. Use of this data warehouse would empower countries to import, manage and analyse their own drug resistance data.

Use of routine programmatic data – US-CDC is working to ensure EWI of HIVDR are included as routine programmatic data, to ensure more consistent and widespread collection of programme factors that contribute to HIVDR development. As part of this process, major emphasis is placed on collection and use of data that are disaggregated by age and population (e.g. pregnant and breastfeeding women, key populations).

5.2 Global Fund support for HIV drug resistance surveillance

The Global Fund Strategy 2017–2022, "Investing to End Epidemics", aims to rapidly reduce HIV incidence and mortality through the scale-up of universal access to HIV prevention and treatment *(2)*. Its strategic goals and targets are explicitly linked to the UNAIDS Strategy 2016–2021, "On the Fast-Track to end AIDS" *(3)*, which aims to reach the 2020 Fast-Track goals and targets, including the prevention target of fewer than 500 000 new infections and the 90-90-90 treatment targets, grounded in a human-rights based approach. In full alignment with Sustainable Development Goal, the Global Fund strategy envisions ending the AIDS epidemic as a public threat by 2030.

The Global Fund is aligned with WHO recommendations regarding HIVDR surveillance, and is embedding programme quality and efficiency within all Global Fund processes in order to maximize programme impact. In line with the funding principles of country ownership and country-led programmes, The Global Fund is committed to funding country requests that include HIVDR surveillance, response and preventive activities, such as improved treatment adherence and retention. In the past, there was limited monitoring of HIVDR surveillance within Global Fund grants. In this new funding cycle, The Global Fund is able to capture data-driven prioritization of investments for planned activities or initiatives in this area. The Global Fund will be able to identify investments in HIVDR surveillance, as these are listed as separate activities within the modular framework.

A review of data from the modular frameworks, cost inputs, and budgets from 2015 to 2017 found investments in HIVDR in 24 countries, totalling approximately US$ 4.7 million. Much of this investment will fund surveys of PDR and ADR, surveys of HIVDR in children younger than 18 months of age, and routine monitoring of EWI of HIVDR at ART clinics.

For the next funding cycle from 2018 to 2020, The Global Fund's updated HIV information note *(4)* has a dedicated section on HIVDR. It recommends countries consider WHO recommendations for routine implementation of EWI and HIVDR surveys, as critical components of every national ART scale-up plan. HIVDR surveillance is an essential part of national HIV programmes and plays an important role in improving the quality and efficiency of programmes.

5.3 WHO support for HIV drug resistance surveillance

In its role as **global convener on HIVDR**, WHO has led the development of a GAP on HIVDR to prevent HIVDR from undermining attainment of the global targets on health and HIV, and to enable provision of the most effective treatment to all PLHIV. WHO is committed to supporting countries and global, regional and national partners in implementing and monitoring progress of the GAP.

Standardized methods for HIVDR surveillance *(1)*, developed by WHO, guide countries and the global community in understanding levels of resistance to currently available ARVs and the emergence of resistance to new drugs, both in populations starting and failing ART. Analysis and interpretation of data generated from surveillance enable countries to identify appropriate responses, including adopting treatment regimens that will be most effective for the population of PLHIV. WHO has developed PDR and ADR survey data abstraction and reporting tools to facilitate survey implementation, data cleaning, analysis and reporting. Training is offered to country-designated users to support use of the WHO survey tools and database.

Prevention of HIVDR remains a central element of the global response. Annual monitoring of clinic-level and programme quality-of-care indicators, which are associated with and predictive of HIVDR (including monitoring of EWI of HIVDR) *(5)*, is critical to characterize ART clinic and programme performance with regard to: patient adherence to ART, levels of retention on ART, coverage of viral load testing and viral load testing outcomes, and appropriate switch to second-line ART. EWI monitoring also enables clinic- and programme-level management to identify gaps in service delivery, which can be addressed through public health and/or programmatic interventions. WHO recommends these indicators be fully integrated into a country's national routine HIV programme monitoring system, and supports ministries in actively using the data for corrective actions. To facilitate EWI data abstraction and reporting, WHO has developed guidance and field-friendly tools.

The 2017 **WHO Guidelines on the public health response to pretreatment HIV drug resistance** (see Section 4.2) provide recommendations to guide countries in the response to HIVDR. These new guidelines form a core component of WHO's global HIVDR strategy.

WHO's commitment to release regular **global reports on HIVDR**, providing timely estimates of epidemiological data, is essential for understanding the changing epidemic in all regions. Following the *WHO HIV drug resistance report 2012 (6)*, the 2017 report encouragingly demonstrates that many ministries of health have been supported by WHO and implementing partners to conduct surveys using WHO-recommended standardized methods for sampling, implementation and analysis. Global dissemination of results allows greater clarity on population levels of PDR, ADR and resistance in infants, and facilitates analysis of trends in HIVDR over time. Going forward, future WHO HIVDR reports will include reporting on the five strategic objectives of the GAP on HIVDR (see Section 4.1 for details).

To adequately capture information on country-level HIVDR data, WHO has developed a **global repository of HIVDR survey data**, which includes de-identified patient-level genotypic and epidemiological information. The database is a relational database supported by Microsoft SQL Server for the import and management of HIVDR data. It includes de-identified survey participants, laboratory results, treatment regimens and HIV sequences. As WHO's database and US-CDC's data warehouse are both SQL-based, data upload and reporting are streamlined at country level.

The global database has a country user interface and is designed to assist countries in managing and interpreting their data for effective public health action. This database empowers national teams to access and understand their data, and to contribute to the public health good of global HIVDR surveillance. In the future, WHO plans to expand the database to also capture routine HIVDR programme data in order to further depict the evolving epidemiology of resistance. Further details on the global HIVDR database, including how to access the database, can be found at http://www.who.int/hiv/topics/drugresistance/hiv-drug-resistance-database/en/.

In addition to providing **technical assistance** to ministries of health and national ART programmes to support **surveillance activities** (survey protocol development, implementation, data interpretation and response), WHO provides technical guidance to countries seeking designation of a national reference laboratory for HIVDR testing. It also coordinates the **global WHO HIVResNet Laboratory Network**, which currently includes 31 WHO-designated laboratories for HIVDR testing on plasma or DBS. Countries that are willing to monitor HIVDR levels, but do not have in-country HIVDR testing capacity, can receive support from this network.

WHO is committed to supporting all countries in every region to achieve the end of AIDS. It will continue to guide and facilitate the response, while being prepared to adapt to the changing face of the epidemic and critical issues as they arise. Notably, WHO will continue its convening role to ensure successful implementation and monitoring of the GAP on HIVDR. Critically, WHO will leverage funding, and continue advocacy and communication efforts to ensure that proactively preventing, monitoring and responding to HIVDR remain global priorities.

6 CONCLUSIONS

Enormous strides have been made in the scale-up of ART over the last decade. To achieve the ambitious global targets of 90-90-90 by 2020, and the elimination of AIDS as a public health threat by 2030, millions of people need to be started and maintained on ART. High levels of viral load suppression must be sustained, and HIVDR prevention prioritized.

This report reviews data on HIVDR in LMIC between 2014 and 2016. Several main conclusions stand out.

First, with the expansion of treatment achieved over the last decade, levels of NNRTI PDR have continued to increase in all regions, and have reached or exceeded 10% in several countries. Therefore, as recommended in WHO's 2017 *Guidelines on the public health response to pretreatment HIV drug resistance*, transition to a non-NNRTI-based regimen should be urgently considered when these levels of resistance are reached.

Second, levels of pretreatment NRTI resistance were lower than NNRTI PDR, and were found to be increasing over time only in Eastern and Southern Africa. Rising levels of NNRTI PDR are nevertheless concerning, and underscore the fact that renewed efforts at all levels are required to promote ARV stewardship, adherence and retention, and to minimize emergence of preventable HIVDR – thus maximizing the long-term effectiveness of currently available and future ART regimens. PDR to PIs was universally very low.

Third, levels of viral load suppression among people on ART in countries reporting survey and PHIA data are generally high. Although not all countries with available data achieved the desired target, results reinforce the fact that achieving "the third 90" is a feasible goal, and that minimizing ADR through programme optimization will help ensure that the viral load suppression target is achieved.

Fourth, with respect to ADR, levels in people failing therapy varied between countries. In some countries, the majority of failures occurred with a drug-resistant virus, necessitating a prompt switch to second-line treatment. In countries with lower levels of ADR, adherence support is likely to result in substantial levels of viral re-suppression. Nevertheless, ADR-associated DRMs and mutation patterns observed suggest that if people are switched to second-line regimens soon after virological failure, currently recommended second-line treatment combinations are likely to be effective for most people failing first-line treatment. ADR surveys show that the use of PI regimens was low across all countries, suggesting inadequate identification and switch of people failing first-line ART. Rapid expansion in the coverage of, and access to, routine viral load testing is required to enable early detection of virological failure.

Fifth, this report highlights the need for greatly increased surveillance of PDR and ADR among all age groups and populations affected by HIV. Policy and programme decision-making must be based on reliable data that is analysed regularly to improve programme performance. As countries move toward maintaining ever-more people on ART for life, fully integrating HIVDR surveillance into emerging national AMR strategies becomes essential. In many countries, there are limited data from relatively small studies designed with other objectives, or data generated from readily available specimens or a convenience sample, which are unlikely to be representative of the ART programme in a specific country. In addition, data are lacking on HIVDR in key populations (men who have sex with men, people who inject drugs, people in prison, sex workers and transgender people), children, adolescents and women who have taken ARV drugs for PMTCT on more than one occasion. Limited data also exist on the proportion of individuals with prior ARV drug exposure who are reinitiating ART after treatment interruption; this group is at particularly high risk of carrying resistant virus and poor response to ART. Furthermore, where relevant data do exist, timely dissemination to national and global stakeholders is not prioritized, and appropriate action is not always taken. To address these issues, and to support the process of integrating HIVDR surveillance into the AMR context, WHO has coordinated development of, and recently launched, a GAP on HIVDR.

The new five-year GAP on HIVDR reflects a global consensus that increasing levels of HIVDR in LMIC require a coordinated and well-resourced response to increase awareness, commitment and action at all levels. The GAP lays out a framework for action for all stakeholders. WHO, US-CDC and The Global Fund funding priorities and country support for HIVDR surveillance are aligned to the GAP. In light of the findings presented in this report, public health and programmatic response is clearly indicated to maximize the long-term effectiveness of available and future first-line regimens. Efforts focused on optimizing the functioning of national HIV treatment programmes include: establishment of robust supply chains to prevent drug stock-outs and treatment interruptions; scale-up of routine viral load monitoring to detect early failures; systems to promptly switch those with confirmed failure; elimination of structural barriers to adherence; and routine defaulter tracing to maximize retention on ART.

Finally, this report reaffirms that national AMR and HIV plans need to include routine nationally representative surveillance of PDR and ADR, coupled with vigorous programmatic measurement, and HIVDR prevention and response. Through a well-coordinated, sustained global effort to prevent and respond to HIVDR, we can help ensure a future generation free from AIDS.

REFERENCES

Chapter 1

1. 90–90–90: An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS; 2014 (available at http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf).

2. UNAIDS, WHO. Global AIDS monitoring. Geneva: UNAIDS; 2017.

3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. Geneva: World Health Organization; 2016 (available at http://www.who.int/hiv/pub/arv/arv-2016/en/).

4. Nichols BE, Sigaloff KC, Kityo C, Mandaliya K, Hamers RL, Bertagnolio S et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study for antiretroviral therapy initiation. AIDS. 2014;28(1):73-83.doi:10.1097/01.

5. Cambiano V, Bertagnolio S, Jordan MR, Pillay D, Perriëns JH, Venter F et al. Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral initiation. AIDS. 2014;28(Suppl 1):S15–S23.

6. Phillips A, Cambiano V, Nakagawa F, Revill P, Jordan MR, Hallett T et al. Cost-effectiveness of public health policy options in the presence of pre-treatment NNRTI drug resistance in sub-Saharan Africa. Submitted.

7. Guidelines on the public health response to pre-treatment HIV drug resistance. Geneva: World health Organization; 2017 (available at http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/).

8. Hamers RL, Schuurman R, Sigaloff KC, Wallis CL, Kityo C, Siwale M et al. PharmAccess African Studies to Evaluate Resistance (PASER) Investigators. Effect of pre-treatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. Lancet Infect Dis. 2012; Apr;12(4):307-17.

9. Pinoges L, Schramm B, Poulet E, Balkan S, Szumillin E, Ferreyra C et al. Risk factors and mortality associated with resistance to first-line antiretroviral therapy: a multicentric cross-sectional and longitudinal analyses. J Acquir Immune Defic Syndr. 2015; 15;68(5) 527–35.

10. Cambiano V, Bertagnolio S, Jordan MR, Lundgren JD, Phillips A. Transmission of drug resistant HIV and its potential impact on mortality and treatment outcomes in resource-limited settings. J Infect Dis. 2013; 15;207 Suppl 2 S57–62.

11. Mbuagbaw L, Aves T, Borhan S, Leenus A, Jordan MJ, Parkin N et al. Systematic reviews and meta-analyses used to inform the guidelines on the public health response to pre-treatment HIV drug resistance. 2017. [Publication pending]. Web Annex 2. Guidelines on the public health response to pre-treatment HIV drug resistance. Geneva: World health Organization; 2017 (available at http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/).

12. Global Price Reporting Mechanism [online database]. Geneva: World Health Organization; 2016 (available at http://www.who.int/hiv/amds/gprm/en/).

13. WHO HIV drug resistance report. 2012. Geneva: World Health Organization; 2012 (available at http://www.who.int/hiv/pub/drugresistance/report2012/en/).

14. Afonso JM, Bello G, Guimarães ML, Sojka M, Morgado MG. HIV-1 genetic diversity and transmitted drug resistance mutations among patients from the North, Central and South regions of Angola. PLoS ONE. 2012;7(8):e42996.

15. Rowley CF, MacLeod IJ, Maruapula D, Lekoko B, Gaseitsiwe S, Mine M et al. Sharp increase in rates of HIV transmitted drug resistance at antenatal clinics in Botswana demonstrates the need for routine surveillance. J Antimicrob Chemother. 2016;71(5):1361–6.

16. Kamangu NE, Chatté A, Susin F, Boreux R, Kalala LR, Mvumbi LG et al. Genetic diversity and antiretroviral drug resistance among Drug-Naïve HIV Type 1 Infected Patients attending clinics in Kinshasa, Democratic Republic of Congo. Journal of HIV and AIDS. 2015; 1(1): tpp://dx.doi.org/10.16966/jha.101].

17. Avila-Ríos S, Garcia-Morales C, Tapia-Trejo D, Meza R, Nuñez S, Parham L et al. HIV Drug Resistance Surveillance in Honduras after a decade of widespread antiretroviral therapy. PLoS One. 2015 Nov 11;10(11):e0142604. doi: 10.1371/journal.pone.0142604. eCollection 2015.

18. Lavu E, Kave E, Mosoro E, Aliksic E, Gare J et al. High levels of transmitted HIV drug resistance in a study in Papua New Guinea. PLoS ONE 12(2): e0170265.

19. Prospective sentinel surveillance of human immunodeficiency virus–related drug resistance. Communicable Dis Communiqué. 2016; 15:10–1(available at http://nicd.ac.za/assets/files/NICD%20Communicable%20Diseases%20Communique_Mar2016_final.pdf).

20. Hamers RL, Wallis CL, Kityo C, Siwale M, Mandaliya K, Conradie F et al. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis 2011;11:750–759.

21. Hofstra LM, Sánchez Rivas E, Nijhuis M, Bank LEA, Wilkinson E, Kelly K et al. High rates of transmission of drug-resistant HIV in Aruba resulting in reduced susceptibility to the WHO recommended first-line regimen in nearly half of newly diagnosed HIV-infected patients. Clin Infect Dis. 2017;64:1092–1097.

22. HIV drug resistance surveillance guidance: 2015 Update. Geneva: World Health Organization; 2015 (available at http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-2015-update/en/).

Chapter 2

1. Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (Pre-treatment HIV drug resistance). Concept note. Geneva: World Health Organization; 2014 (available at http://www.who.int/hiv/pub/drugresistance/pretreatment_drugresistance/en/).

2. Bennett DE, Camacho RJ, Otelea D, Kuritzkes D, Fleury H, Kiuchi M et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance; 2009 update. PLoSOne, 2009; 4:e4724.

3. Liu TF, Shafer RW. Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. Clin Infect Dis. 2006; 42(11):1608–18.

4. Penazzato M, Prendergast AJ, Muhe LM, Tindyebwa D, Abrams E. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age. Cochrane Database Syst Rev. 22; 2014 22;(5) CD004772.

5. Surveillance of HIV drug resistance in children newly diagnosed with HIV by early infant diagnosis. Geneva: World Health Organization; 2017 (available at http://www.who.int/hiv/topics/drugresistance/en).

6. Salou M, Butel C, Konou AA, Ekouevi DK Vidal N, Dossim S et al. High rates of drug resistance among newly diagnosed HIV-infected children in the national prevention of mother-to-child Transmission program in Togo. Pediatr Infect Dis J. 2016; Aug;35(8):879–85.

7. Steegen K, Carmona S, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D et al. Moderate levels of pre-treatment HIV-1 antiretroviral drug resistance detected in the first South African national survey. PLoS One. 2016; 11(12):e0166305.

8. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (available at http://www.who.int/hiv/pub/guidelines/arv2013/en/).

9. Global ARV drug use survey 2016. Geneva: World Health Organization; unpublished data.

10. Gupta R, Jordan MR, Sultan BJ, Hill A, Davis DHJ, Gregson J et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet. 2012; 380:1250–58.

11. UNAIDS, WHO. Global AIDS monitoring. Geneva: UNAIDS; 2017.

12. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach: 2010 revision. Geneva: World Health Organization; 2010 (available at http://www.who.int/hiv/pub/paediatric/infants2010/en/).

13. Boerma RS, Boender TS, Sigaloff KC, Rinke de Wit TF, van Hensbroek MB, Ndembi N et al. High levels of pre-treatment HIV drug resistance and treatment failure in Nigerian children. J Int AIDS Soc. 2016;19(1):21140.doi: 10.7448/IAS.19.1.21140.

14. Kityo C, Sigaloff KC, Boender TS, Kaudha E, Kayiwa J, Musiime V et al. HIV Drug Resistance among children initiating first-line antiretroviral treatment in Uganda. AIDS Res Hum Retroviruses. 2016;32(7):628–35. doi: 10.1089/AID.2015.0215.

15. Boerma R, Sigaloff K, Akanmu A, Inzaule S, Boele van Hensbroek M, Rinke de Wit TF et al. Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. J Antimicrob Chemother. 2017; 72 (2): 365–371.

16. Mbuagbaw L, Aves T, Borhan S, Leenus A, Jordan MJ, Parkin N et al. Systematic reviews and meta-analyses used to inform the World health Organization Guidelines on the public health response to pre-treatment HIV drug resistance. 2017. [Publication pending]. Web Annex 2. Guidelines on the public health response to pre-treatment HIV drug resistance. Geneva: World health Organization; 2017 (available at http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/).

17. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. Geneva: World Health Organization; 2016 (available at http://www.who.int/hiv/pub/arv/arv-2016/en/).

18. Guidelines on the public health response to pre-treatment HIV drug resistance. Geneva: World Health Organization; 2017 (available at http://http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/).

Chapter 3

1. Surveillance of HIV drug resistance in adults receiving ART (acquired drug resistance). Concept note. Geneva: World Health Organization; 2014 (available at http://apps.who.int/iris/bitstream/10665/112801/1/9789241507073_eng.pdf).

2. Consolidated guidelines on person-centred HIV patient monitoring and case surveillance. Geneva: World Health Organization; 2017 (available at http://www.who.int/hiv/pub/guidelines/person-centred-hiv-monitoring-guidelines/en/).

3. Evaluation report for early warning indicators for HIV drug resistance in Cameroon in 2015. Cameroon HIV Drug Resistance Working Group; June 2016.

4. UNAIDS, WHO. Global AIDS monitoring. Geneva: UNAIDS; 2017.

5. Pillay S, Bland R, Lessells R, de Oliveira T, Danaviah S. Drug resistance in children at virological failure in a rural KwaZulu-Natal, South Africa, cohort. AIDS Research and Therapy; 2014.11:3.

6. Muri L, Gamell A, Ntamatungiro AJ, Glass TR, Luwanda LB, Battegay M et al. Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: an emerging public health concern. AIDS 2017;31(1):61–70.

7. UNAIDS fact sheet. Adolescents, young people and HIV. Geneva: UNAIDS; 2015 (available at http://files.unaids.org/en/media/unaids/contentassets/documents/factsheet/2012/20120417_FS_adolescentsyoungpeoplehiv_en.pdf).

Chapter 4

1. Global Action Plan on HIV drug resistance, 2017–2021. Geneva: World Health Organization; 2017 (available at http://who.int/hiv/pub/drugresistance/hivdr-action-plan-2017-2021/en/).

2. Guidelines for the public health response to pre-treatment HIV drug resistance. Geneva: World Health Organization; July 2017 (available at http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/).

3. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to end the AIDS Epidemic by 2030; Geneva: UNAIDS; 2016 (available at http://www.unaids.org/en/resources/documents/2016/2016-political-declaration-HIV-AIDS).

4. Global Health Sector Strategies for HIV, Viral hepatitis, STIs, 2016–2021. Geneva: World Health Organization;2016 (available at http://www.who.int/hiv/strategy2016-2021/en/).

5. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS; 2014. (available at http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf).

6. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Second edition. Geneva: World Health Organization; 2016 (available at http://www.who.int/hiv/pub/arv/arv-2016/en/).

7. UNAIDS, WHO. Global AIDS monitoring. Geneva: UNAIDS; 2017.

Chapter 5

1. HIV drug resistance surveillance guidance: 2015 Update. Geneva: World Health Organization; 2015 (available at http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-2015-update/en/).

2. Global Fund Strategy 2017–2022. Investing to End Epidemics. Geneva: The Global Fund; 2016 (available at https://www.theglobalfund.org/media/1176/bm35_02-theglobalfundstrategy2017-2022investingtoendepidemics_report_en.pdf).

3. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030. Geneva: UNAIDS; 2016 (available at http://www.unaids.org/en/resources/documents/2016/2016-political-declaration-HIV-AIDS).

4. The Global Fund HIV information note. Geneva: The Global Fund; 2016 (available at https://www.theglobalfund.org/media/4765/core_hiv_infonote_en.pdf).

5. Global report on early warning indicators of HIV drug resistance: technical report. Geneva: World Health Organisation; 2016 (available at http://apps.who.int/iris/bitstream/10665/246219/1/9789241511179-eng.pdf).

6. WHO HIV drug resistance report. 2012. Geneva: World Health Organization; 2012 (available at http://www.who.int/hiv/pub/drugresistance/report2012/en/).

Annex

1. WHO/HIVResNet HIV drug resistance laboratory operational framework. Geneva: World Health Organization; 2017 (available at http://www.who.int/hiv/topics/drugresistance/en/).

2. Surveillance of HIV drug resistance in adults initiating antiretroviral therapy (pre-treatment HIV drug resistance). Concept note. Geneva: World Health Organization; 2014 (available at http://www.who.int/hiv/pub/drugresistance/pretreatment_drugresistance/en/).

3. Surveillance of HIV drug resistance in adults receiving antiretroviral therapy (acquired HIV drug resistance). Concept note. Geneva: World Health Organization; 2014 (available at http://apps.who.int/iris/bitstream/10665/112801/1/9789241507073_eng.pdf, accessed 22 May 2017).

4. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. Clin Infect Dis. 2006; 42(11):1608–18.

5. Evaluation report for early warning indicators for HIV drug resistance in Cameroon in 2015. Cameroon HIV Drug Resistance Working Group. June 2016.

6. Gifford RJ, Rhee SY, Eriksson N, Liu T, Kiuchi M, Das A et al. Sequence editing by Apolipoprotein B RNA-editing catalytic component [corrected] and epidemiological surveillance of transmitted HIV-1 drug resistance. AIDS. 2008; 30;22(6):717–25.

7. Parkin NT. Measurement of HIV-1 viral load for drug resistance surveillance using dried blood spots: literature review and modelling of contribution of DNA and RNA. AIDS Rev. 2014; (3):160–71.

8. Wensing AM, Calvez V, Gunthard HF, Johnson V, Paredes R, Pillay D et al. 2015 Update of the Drug Resistance Mutations in HIV-1. Topics in antiviral medicine. 2015; 23(4): 132–41.

9. HIV-1 Genotypic Drug Resistance Interpretation Algorithm. Paris: ANRS; 2017 (available at http://www.hivfrenchresistance.org/).

10. Stijnen T, Hamza T, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stats Med. 2010; 29:3046–3067.

ANNEX

ANNEX 1 Methodological notes

Section 1: WHO sequence data analysis and quality assurance for pretreatment HIV drug resistance surveys and acquired HIV drug resistance surveys

Genotyping of protease and RT was performed in laboratories within the WHO Laboratory Network, mostly using in-house methods based on RT–polymerase chain reaction (PCR) of RNA extracted from plasma or DBS, followed by standard bulk sequencing techniques. In some cases, commercial kits (TruGene or ViroSeq) were used. Network member laboratories undergo an intensive inspection and review process and participate in annual external proficiency testing.

Sequence quality assurance was performed following the WHO quality assurance standard operating procedures *(1)*. Nucleotide sequences were analysed using the Stanford HIVdb algorithm version 8.3, available on the Stanford HIV database website (https://hivdb.stanford.edu/hivdb/by-mutations/), and the WHO HIVDR quality control tool developed by the British Columbia Centre for Excellence in HIV/AIDS (BCCfE), available on the BCCfE website (http://pssm.cfenet.ubc.ca/who_qc/). For PDR and ADR surveys where it was not expected to observe two highly related sequences, one member of any pair with genetic distance <0.5% was excluded.

Section 2: Study design and methods for statistical analysis of pretreatment HIV drug resistance surveys and acquired HIV drug resistance surveys

1. Study design

The recommended survey method generates nationally representative prevalence estimates of: HIVDR among populations initiating ART (PDR survey), and viral load suppression and HIVDR among populations on ART (ADR survey). The surveys are cross-sectional and employ a two-stage cluster sampling design. The first stage involves selection of a subset of ART clinics using PPS sampling, a method by which the probability of selecting an ART site is proportional to the size of its eligible population (i.e. the number of people who initiated ART or number of people who have been on ART for 12 months in a defined time period).

If information on the number of eligible people at each site during a previous time period is not available, the country can perform PPPS sampling. In PPPS sampling, the proxy measure is some measure of site size – generally the number of individuals enrolled at that site during a recent time period (the calendar year prior to survey initiation is recommended). This will not be exactly proportional to the number of eligible individuals, but it is a reasonable alternative that will distinguish between large, medium and small sites. The second stage involves consecutive enrolment of eligible individuals at the selected clinics until the pre-determined sample size for each is achieved.

In countries where there are 15 or fewer sites, all sites should be included in the survey. The survey is then a one-stage survey of individuals within sites, which is more efficient than a two-stage clustered survey. Very small sites and difficult-to-access sites can be excluded, but they should not represent more than 10% of the patient population.

PDR survey inclusion and exclusion criteria:

Inclusion criteria

- Adults 18 years or above with HIV-1 infection who can legally provide, and do provide, informed consent
- All individuals initiating ART (including as first-line treatment for their own health or through PMTCT) for the first time, or reinitiating if they have stopped for more than three months[27]

Exclusion criteria

- Individuals transferred in, who are already receiving ART
- In countries where routinely used antibody tests differentiate between HIV-1 and HIV-2, adults infected with HIV-2 or individuals with HIV-1/HIV-2 coinfection.

ADR survey inclusion and exclusion criteria:

Inclusion criteria

- Adults 18 years or above with HIV-1 infection who can legally provide, and do provide, informed consent
- Adults who have been on ART for 12 months (±3 months) for ADR 12-month surveys, or at least 48 months for ADR 48+ month surveys, at the time of clinic visit, regardless of the site of therapy initiation

Exclusion criteria

- In countries where routinely used antibody tests differentiate between HIV-1 and HIV-2, adults infected with HIV-2 or individuals with HIV-1/HIV-2 coinfection.

2. Sample size calculation

PDR and ADR survey sample size calculations are fully described in the PDR survey and ADR survey concept notes *(1)*. Briefly, for PDR the sample size is calculated to estimate the prevalence of PDR outcomes among all ART initiators and among initiators without prior exposure to ARV drugs with a desired confidence interval of ± 5%. Standard assumptions for the calculation are:

- 10% of drug resistance among all initiators
- 20% of genotyping failure
- 75% of ART initiators without prior exposure to ARVs
- 100% initiating an NNRTI-based regimen.

For ADR, sample size is calculated to estimate the prevalence of viral load suppression with a desired confidence interval of ± 5%.

[27] Individuals who have stopped ART for less than three months are still deemed to be on ART and should not be enrolled in the survey.

Standard assumptions for the calculation are:

- 85% prevalence of viral load suppression
- 15% of laboratory failure (viral load and genotyping)
- 95% of individuals sampled still receiving first-line ART
- 100% of individuals sampled receiving first-line NNRTI-based regimen.

3. Data analysis

The data analysis methods followed, and the statistical source code for analysis, are described in detail in the annex of the PDR survey *(2)* and ADR survey concept notes *(3)*.

a. Analysis population

For PDR outcomes, the analyses are performed among individuals with HIVDR results classifiable after exclusion of individuals with unsuccessful genotyping or failed sequence quality assessment. In ADR surveys, the analyses of viral suppression outcomes are performed among individuals with viral suppression data available after exclusion of a few individuals with sequences that failed quality assessment (see Fig. 10 for details). The analyses of drug resistance are performed among individuals with HIVDR results classifiable after exclusion of individuals with unsuccessful genotyping. The HIVDR outcome (among all individuals on ART) is calculated among all individuals with viral load data after exclusion of individuals with unsuccessful genotyping or with sequences that failed quality assessment.

b. Outcomes

Population characteristics

Each country's eligible survey population is described according to gender (women, men, others) and age (≤ 25 and > 25 years old), and according to type of initiated first-line (EFV- or NVP- as NNRTI-based; ATV-, DRV- or LPV as PI-based and others), prior ARV drug exposure (yes, no, unknown) and type of ARV exposure (PMTCT, ART, other, unknown) in PDR surveys and according to proportion of individuals on first-line ART, on NNRTI-based first-line ART, and type of current ART (TDF + XTC + EFV, TDF + XTC + NVP, ZDV + XTC + EFV, ZDV + XTC + NVP, PI-based regimen, other) in ADR surveys.

The proportion in each category is calculated as a ratio, where the denominator is an estimate of the number of eligible individuals in the country during the survey period, and the numerator is an estimate of the number of such individuals with the outcome or characteristic of interest.

PDR outcomes

Prevalence of any HIVDR, NNRTI, NRTI, PI and NNRTI+NRTI HIVDR is estimated among the total eligible population and among gender subpopulations. In a country where prior-exposed individuals are included in the eligible population, HIVDR is estimated among naive and prior-exposed subpopulations.
The prevalence is estimated using a ratio. The denominator is an estimate of the total number of initiators in the population or subpopulation of interest in the country during the survey period. The numerator is an estimate of the number of individuals (in the population or subpopulation of interest) with HIVDR mutations during the survey period.

Prevalence of individuals starting a fully active ART regimen among the total eligible population is also estimated, with "starting fully active ART" defined as no resistance with respect to all drugs of the initiated first-line.

ADR outcomes

Prevalence of viral load suppression (viral load <1000 copies/ml) is estimated among all individuals on ART and among individuals on first-line ART and on NNRTI-based first-line ART. It is also estimated for gender and age category (≤ 25 and > 25 years old) subpopulations.

Prevalence of any HIVDR, NNRTI, NRTI, PI and NNRTI+NRTI HIV drug resistance is estimated in individuals on ART, on first-line ART and on NNRTI first-line ART among those with viral load ≥ 1000 copies/ml and successful genotyping. It is also estimated among all individuals (see Section 3 a. Analysis population for details).

The prevalence is estimated using a ratio. The denominator is an estimate of the total number of individuals in the eligible population or subpopulation of interest in the country during the survey period. The numerator is an estimate of the number of individuals (in the population or subpopulation of interest) with the outcome of interest (viral load suppression or HIVDR) during the survey period.

HIVDR definition

Any HIVDR is defined in sequences classified as low-, intermediate- or high-level resistance (according to the Stanford HIVdb algorithm) *(4)* with respect to one or more of the following drugs: NVP, EFV, any NRTI, ATV, DRV or LPV; NNRTI resistance is defined as resistance to NVP or EFV; NRTI resistance is defined as resistance to any NRTI; and PI resistance is defined as resistance to ATV/r, DRV/r or LPV/r.

c. Weighting

In PPS or PPPS systematic sampling, the probability that a site is selected is equal to the size of the site (Mi) multiplied by the number of sites to be sampled (n) divided by the total size of all sites included in the sampling frame (M); thus the clinic sampling weight is M / (n*Mi) where M/n refers to the sampling interval. If all clinics participate in the survey, the clinic sampling weight is equal to one for all clinics. In case of missing/unavailable systematic sampling information, the sampling weight is set equal to one for all clinics.

Individual sampling weight is defined as the size of the eligible population during the survey period in each clinic divided by the number of individuals enrolled with available information for the characteristic or outcome of interest in the clinic.

The size of the eligible population in the site is the number of eligible individuals attending the clinic observed during the six-month survey period. In the case of those clinics that reach their enrolment quotas before six months, they should continue to count eligible individuals for a minimum of three months. Size of the eligible population in a specific site can be estimated as twice

the number of eligible individuals attending the site observed during the three-month period. In case of missing information regarding the six-month eligible population, it is extrapolated from the date when enrolment starts and ends in each site, or estimated from the size of the site available in the sampling frame when extrapolation from survey leads to unrealistic estimations.

Each observation is weighted by the product of site sampling weight by individual sampling weight.

d. Analysis

Data analysis for all outcomes was conducted in Stata software 14.0 (StataCorp LP, College Station, Texas, USA)[28] using SVY utilities. Variances were estimated using Taylor series linearization with finite population correction for both sampling stages (sites and individuals) when applicable. The total number of sites included in the sampling frame and the size of the six-month eligible population were used when available for finite population correction of sites and individuals sampling, respectively. A logit transformation was used to calculate 95% confidence interval. Aggregate analyses (combining the different surveys) were conducted using Stata survey (SVY) utilities, in which each country is considered as a strata. SVY logistic regressions were used to compare outcomes between groups, such as gender or prior exposure.

e. Retention-adjusted viral load suppression

For Cameroon and Guatemala, retention-adjusted viral load suppression was estimated using a national retention estimate provided in the last EWI survey report in Cameroon *(5)* and in Guatemala's Global AIDS Monitoring 2017 reporting. The retention-adjusted viral load suppression was estimated by the product of both retention and viral load suppression estimates.

$$\widehat{var}(\hat{p}_{VLS}\,\hat{p}_{RET}) = \hat{p}_{RET}^2\,\widehat{var}(\hat{p}_{VLS}) + \hat{p}_{VLS}^2\,\widehat{var}(\hat{p}_{RET}) + \hat{p}_{VLS}^2\,\widehat{var}(\hat{p}_{RET}) + 2\hat{p}_{VLS}\,\hat{p}_{RET}\,\widehat{cov}(\hat{p}_{VLS}, \hat{p}_{RET})$$

where $\hat{p}_{VLS}$ and $\hat{p}_{RET}$ are the estimates of viral load suppression and retention, respectively.

In the absence of sufficient information to form a reliable estimate of the covariance, we assumed that site-level viral load suppression and retention are independent, i.e. $\widehat{cov}(\hat{p}_{VLS}, \hat{p}_{RET}) = 0$.

4. Pretreatment HIV drug resistance and acquired HIV drug resistance survey data limitations

The number of LMIC with available data from national HIVDR surveys remains limited, which impedes the aggregation of data to generate regional or global level estimates, or make statements or inferences, beyond the countries the survey data represent. Additionally, it implies that the results and conclusions presented in this report may be biased towards programmes with above-average performance, as the implementation of surveys on drug resistance can itself indicate above-average concern with programmatic quality and treatment success.

Variations in the recommended survey time points for ADR surveys, and inclusion criteria for PDR surveys (regarding prior ARV exposed individuals), were also observed across countries, which may further limit comparability of results. Prior ARV drug exposure information was obtained from participant self-report, and thus may underestimate or overestimate the true proportion of individuals with prior ARV drug exposure, and the level of HIVDR in those with true prior ARV drug exposure.

Some surveys used DBS as the specimen type for HIVDR genotyping. Due to limitations on the volume of blood per spot, the amplification failure rate at low viral loads (e.g. below about 5000 copies/ml) is likely to be higher than for plasma, from which larger sample volumes are normally available. In addition, due to the presence of proviral DNA and cellular RNA in DBS, which is not present in plasma, it is possible that the sequence generated from DBS does not exactly match the one that would have been derived from plasma. Sequences from DNA in DBS are also more likely to represent templates that have been edited (A to G hyper-mutated) by the cellular APOBEC mechanism, reinforcing the importance of appropriate quality-assurance filters that evaluate the presence of APOBEC signature mutations – especially when accompanied by changes at positions associated with drug resistance (e.g. positions 67, 184, 190 and 230 of HIV-1 RT) *(6)*. Also, viral load results from DBS, if generated using an assay that is not selective for RNA, may be overestimated *(7)*.

HIVDR genotyping failure rates varied, but were high (Fig. 2 and Fig. 10). It is therefore possible that HIVDR may be overestimated or underestimated if genotyping failures are correlated with the presence or absence of HIVDR. If amplification failure is due to low viral load, and HIVDR is more prevalent at low viral loads (e.g. in an ADR survey), the prevalence of HIVDR may be underestimated.

In addition, limited availability of information for weighting of survey estimates for certain countries(Argentina, Colombia, Namibia, Uganda and Zimbabwe) was observed; as a result, weighted prevalence estimates for these countries could not be calculated. Due to security risks in Cameroon, five out of 29 sampled sites in the PDR survey, and six out of 29 sampled sites in the ADR survey, were excluded after selection, which may have potentially introduced bias.

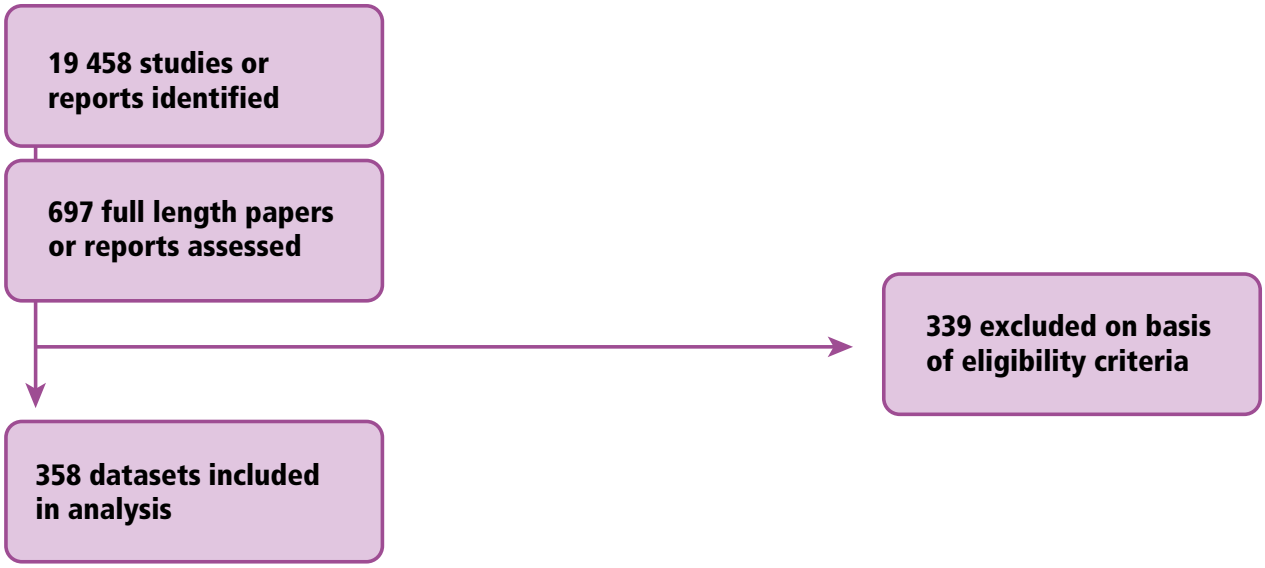
[28] StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Section 3: Adult pretreatment HIV drug resistance systematic literature review methods

PubMed, EMBASE and major conference abstracts were searched for the period 1 January 2001 to 31 December 2016, which included datasets with specimens collected between 1993 and 2016. Publications were not restricted by language. Studies were considered if they included untreated recently or chronically infected individuals older than 15 years, and had more than 10 specimens successfully genotyped. The geographical focus was limited to LMIC from Asia, sub-Saharan Africa (Eastern, Southern, Western/Central) and Latin America and the Caribbean. Studies were excluded if they only reported resistance in the context of PMTCT, included less than 10 genotypes, or used sequencing methods other than standard bulk sequencing or next generation genome sequencing (e.g. studies using allele-specific PCR were excluded).

The following data were abstracted: country, year of sample collection, sex, risk groups, setting, timing of infection, pretreatment CD4 cell count, number of pretreatment genotypes reported in the study, and prior exposure to ARV drugs prior to treatment initiation. Data were also abstracted on the number of people with more than one DRM, with one or more NRTI mutation, with one or more thymidine analogue mutation, with one or more NNRTI mutation, and with one or more PI mutation. Where feasible, DRMs were defined as those appearing in the 2009 WHO SDRM list. Otherwise, the study authors' interpretation was used. Authors used various HIVDR algorithms, including the Stanford HIVdb *(4)*, International AIDS Society *(8)* and ANRS algorithms *(9)*. Studies and WHO survey reports included in the systematic review are shown in Fig. A1.

Fig. A1: Flow chart of studies and surveys included in the pretreatment HIV drug resistance adult literature review



Statistical analysis methods

All statistical analyses were performed in Stata version 14.1 (StataCorp, USA). Studies were pooled within region and, for the purposes of tables, within levels of specific exposure variables. Exposure variables were study-level characteristics: for example, midpoint-year of survey, or whether the survey was in recently or chronically infected patients. To calculate pooled prevalences within region and at specific exposure levels, an empty logistic regression model was used with a random effect at the study level. This method has previously been shown to perform well for meta-analyses of moderately sparse binary data *(10)*. In studies with no mutations, the proportion of people with a mutation was estimated as 1/4n, where n is the total number of successful genotypes. Occasionally, for analyses where data were available from only one or a few studies, these logistic regression models did not converge. These analyses are highlighted in the tables; in these instances, studies were pooled using random-effects meta-analysis with DerSimonian-Laird weighting, after performing the Freeman-Tukey type arcsine square root transformation:

$$y = \arcsin\left[\sqrt{r / (n + 1)}\right] + \arcsin\left[\sqrt{(r + 1) / (n + 1)}\right], \text{ with a variance of } 1 / (n + 1).$$

The transformed pooled proportions and 95% confidence interval were then back-transformed. These analyses were performed using the Stata package metaprop.

To assess associations between each exposure variable and drug resistance, we performed univariate meta-regression analyses within each region. The meta-regression models were logistic regression models with a random effect at the study level, and were done separately within each region (i.e. the same methodology used to pool prevalence within region). The exposure was included as the explanatory variable, and drug resistance as the outcome variable. The output from these meta-regression models were used in three ways. Firstly, by using likelihood ratio tests comparing model fit with and without the inclusion of the exposure variable, we assessed if there was a significant association between exposure and drug resistance. Secondly, by calculating odds ratios, we quantified the estimated extent of any association. Since levels of resistance were generally modest, these odds ratios can be translated into percentage changes on the relative scale. Thirdly, by using the coefficients from these logistic regression models, we calculated trend lines showing predicted resistance at any given level of exposure. We plotted these trend lines against study-specific levels of exposure and drug resistance to present graphically the relationship between exposure and drug resistance among the studies sampled. For these meta-regression analyses, we generally included all studies with information on the exposure variable, with the exception of prior drug exposure, where we restricted our analyses to include only studies where there were patients with and without prior drug exposure. This was because in the vast majority of studies where we were able to obtain information on prior drug exposure, we were able to obtain information separately among patients with and without prior drug exposure.

Finally, we explored prevalence of specific drug mutations among all individuals with any WHO SDRM. We calculated the proportion with specific mutations after crudely pooling the number of individuals with any mutation and the number with specific mutations.

Limitations to the pretreatment HIV drug resistance literature review in adults in LMIC

Many of the studies included in this meta-analysis were performed using distinct methods, and may differ with respect to the population studied (such as recent or chronic infections), the sampling frame (such as consecutive, convenient, or random selection from general population), and the laboratory methods used (such as DBS or plasma samples, or genotyping methods used). Individual studies may also have been influenced by regional factors, such as ART coverage and availability, variation in HIV subtypes, quality of care at the individual sites and ART programmes, country income levels, and the structure or organization of health services. As such, studies may not provide a representative sample of the relevant patient population; therefore prevalence estimates may not be nationally or regionally representative.

Moreover, studies reported resistance data according to any of the internationally recognized lists – variations in how mutations are defined may have influenced individual study results and, hence, aggregate analyses. This may particularly be the case for estimates of PI resistance.
Our statistical models include a random effect to allow for unexplained heterogeneity in resistance between studies; however, the large degree of unexplained heterogeneity present reduces the statistical power to detect region-specific trends over time. Conversely, we may falsely identify region-specific trends if there are systematic differences between studies over time – for example, if more recent studies systematically occur in geographical locations with higher levels of drug resistance. This could occur, for example, if researchers interested in drug resistance target studies in populations they expect to have higher rates of resistance, and this trend becomes pronounced over time, as the research agenda on drug resistance expands. Few studies were available from rural settings; thus the analysis shows PDR trends primarily in only urban and peri-urban areas. However, as access to ART has substantially increased in sub-Saharan Africa, similar trends might well be expected in rural areas under similar ART programmatic conditions. Finally, classification of study participants as ARV drug-naive or ARV drug-exposed was based on self-reported ARV drug exposure, which may be subject to self-reporting bias.

The list of studies included in the PDR literature review is found in Table A1.

Table A1: Studies included in the pretreatment HIV drug resistance literature review in adults*

Study	Region	Country	Mid-point year of recruitment
Becker-Pergola et al.	Eastern Africa	Uganda	1993.5
Teixeira et al.	Latin America	Brazil	1995.5
Kijak et al.	Latin America	Argentina	1997
Weidle et al.	Eastern Africa	Uganda	1997
Dumans et al.	Latin America	Brazil	1998
Aghokeng et al.	Western/Central Africa	Cameroon	1998
Eshleman et al.	Eastern Africa	Uganda	1998
Kijak et al.	Latin America	Argentina	1998.5
Toni Arhr et al.	Western/Central Africa	Côte d'Ivoire	1998.5
Petch et al.	Southern Africa	Malawi	1998.5
Delgado et al.	Latin America	Venezuela	1998.5
Ruibal-Brunet et al.	Latin America	Cuba	1999
Lahuerta et al.	Southern Africa	Mozambique	1999
Eshleman et al.	Asia	India	1999.5
Vergne et al.	Western/Central Africa	Senegal	1999.5
Diop-Ndiaye et al.	Western/Central Africa	Senegal	1999.5
Gale et al.	Eastern Africa	Uganda	1999.5
Teixeira et al.	Latin America	Brazil	2000
Servais et al.	Eastern Africa	Rwanda	2000
Pillay et al.	Southern Africa	South Africa	2000
Handema et al.	Southern Africa	Zambia	2000
Varella et al.	Latin America	Brazil	2000
Sucupira et al.	Latin America	Brazil	2000
Barreto et al.	Latin America	Brazil	2000
Gordonet al.	Southern Africa	South Africa	2000.5
Auswinporn et al.	Asia	Thailand	2000.5
Tovanabutra et al.	Asia	Thailand	2000.5
Eshleman Aids et al.	Eastern Africa	Uganda	2000.5
Bartolo et al.	Western/Central Africa	Angola	2001
Pando et al.	Latin America	Argentina	2001
Pires et al.	Latin America	Brazil	2001
Brindeiro et al.	Latin America	Brazil	2001
Church et al.	Southern Africa	Malawi	2001
Vergne et al.	Western/Central Africa	Cameroon	2001.5
Han Zhang et al.	Asia	China	2001.5
Toni Arhr et al.	Western/Central Africa	Côte d'Ivoire	2001.5
Church et al.	Eastern Africa	Uganda	2001.5
Sa-Ferreira et al.	Latin America	Brazil	2002
Vidal et al.	Eastern Africa	Burundi	2002
Aghokeng	Western/Central Africa	Cameroon	2002

Study	Region	Country	Mid-point year of recruitment
Adje-Toure et al.	Western/Central Africa	Côte d'Ivoire	2002
Vidal et al.	Western/Central Africa	Democratic Republic of the Congo	2002
Valle-Bahena et al.	Latin America	Mexico	2002
Ferreira et al.	Southern Africa	Mozambique	2002
Abreu et al.	Southern Africa	Mozambique	2002
Pillay et al.	Southern Africa	South Africa	2002
Chalermchockcharoenkit et al.	Asia	Thailand	2002
De Madeiros et al.	Latin America	Brazil	2002.5
Vessiere et al.	Western/Central Africa	Cameroon	2002.5
Lloyd et al.	Latin America	Honduras	2002.5
Balakrishnan et al.	Asia	India	2002.5
Escoto-Delgadillo et al.	Latin America	Mexico	2002.5
Bessong et al.	Southern Africa	South Africa	2002.5
Chonwattana et al.	Asia	Thailand	2002.5
Lama et al.	Latin America	Peru	2002.5
Eyer-Silva et al.	Latin America	Brazil	2003
Tupinambas et al.	Latin America	Brazil	2003
Vergne et al.	Western/Central Africa	Burkina Faso	2003
Perez et al.	Latin America	Cuba	2003
Kassau et al.	Eastern Africa	Ethiopia	2003
Deshpande Arhr et al.	Asia	India	2003
Perreira et al.	Southern Africa	Mozambique	2003
Bellocchi et al.	Southern Africa	Mozambique	2003
Bartolo et al.	Southern Africa	Mozambique	2003
Jacobs et al.	Southern Africa	South Africa	2003
Galluzzo et al.	Eastern Africa	Uganda	2003
Bouchard et al.	Latin America	Venezuela	2003
Ly et al.	Asia	Cambodia	2003.5
Soares et al.	Western/Central Africa	Cameroon	2003.5
Lyagoba et al.	Eastern Africa	Uganda	2003.5
Lyagoba Dunn et al.	Southern Africa	Zimbabwe	2003.5
Ferreira et al.	Western/Central Africa	Angola	2004
Sanabani et al.	Latin America	Brazil	2004
Rodrigues et al.	Latin America	Brazil	2004
Gonsalez et al.	Latin America	Brazil	2004
Koizumi et al.	Western/Central Africa	Cameroon	2004
Ndembi et al.	Western/Central Africa	Cameroon	2004
Zhang et al.	Asia	China	2004
Toni Arhr et al.	Western/Central Africa	Côte d'Ivoire	2004

Study	Region	Country	Mid-point year of recruitment
Nafisa et al.	Eastern Africa	Kenya	2004
Viani et al.	Latin America	Mexico	2004
WHO survey Mexico	Latin America	Mexico	2004
Lahuerta et al.	Southern Africa	Mozambique	2004
Pillay et al.	Southern Africa	South Africa	2004
Dilernia et al.	Latin America	Argentina	2004
Petroni et al.	Latin America	Argentina	2004.5
Liu et al.	Asia	China	2004.5
Liao et al.	Asia	China	2004.5
Ahumada-Ruiz et al.	Latin America	Panama	2004.5
Orrell et al.	Southern Africa	South Africa	2004.5
Apisarnthanarak et al.	Asia	Thailand	2004.5
Mosha et al.	Eastern Africa	United Republic of Tanzania	2004.5
WHO survey Botswana	Southern Africa	Botswana	2005
Eyer-Silva et al.	Latin America	Brazil	2005
Tebit et al.	Western/Central Africa	Burkina Faso	2005
Marechal et al.	Western/Central Africa	Central African Republic	2005
Zhong et al.	Asia	China	2005
Abegaz et al.	Eastern Africa	Ethiopia	2005
Lihana et al.	Eastern Africa	Kenya	2005
WHO survey Kenya	Eastern Africa	Kenya	2005
Derache et al.	Western/Central Africa	Mali	2005
Diop-Ndiaye et al.	Western/Central Africa	Senegal	2005
Barth Aids et al.	Southern Africa	South Africa	2005
Mcintyre et al.	Southern Africa	South Africa	2005
WHO survey Thailand	Asia	Thailand	2005
Lallemant et al.	Asia	Thailand	2005
Nyombi et al.	Eastern Africa	United Republic of Tanzania	2005
Ferreira et al.	Latin America	Brazil	2005.5
Tu et al.	Asia	China	2005.5
Murillo et al.	Latin America	Honduras	2005.5
Rangel et al.	Latin America	Venezuela	2005.5
Sirivichayakul et al.	Asia	Thailand	2005.5
Brigido et al.	Latin America	Brazil	2006
Ferreira et al.	Latin America	Brazil	2006
De Medeiros et al.	Latin America	Brazil	2006
Oliveira et al.	Western/Central Africa	Cabo Verde	2006
Zhang Kang et al.	Asia	China	2006
Han Wang et al.	Asia	China	2006
Liu Lu et al.	Asia	China	2006
Kandathil et al.	Asia	India	2006
Iqbal 2011 et al.	Asia	India	2006
WHO survey Indonesia	Asia	Indonesia	2006

Study	Region	Country	Mid-point year of recruitment
Kantor et al.	Eastern Africa	Kenya	2006
Kiptoo et al.	Eastern Africa	Kenya	2006
Kamoto et al.	Southern Africa	Malawi	2006
Van Zyl et al.	Southern Africa	South Africa	2006
Huang et al.	Southern Africa	South Africa	2006
Maphalala et al.	Southern Africa	Swaziland	2006
Apisarnthanarak et al.	Asia	Thailand	2006
Auwanit et al.	Asia	Thailand	2006
Masimba et al.	Eastern Africa	United Republic of Tanzania	2006
WHO survey, United Republic of Tanzania	Eastern Africa	United Republic of Tanzania	2006
Nguyen et al.	Asia	Viet Nam	2006
Thao Vu et al.	Asia	Viet Nam	2006
Chunfu Yang et al.	Southern Africa	Botswana	2006.5
Nouhin et al.	Asia	Cambodia	2006.5
Burda Jmv et al.	Western/Central Africa	Cameroon	2006.5
Aghokeng	Western/Central Africa	Chad	2006.5
Chin et al.	Asia	China	2006.5
Chunfu Yang et al.	Asia	China	2006.5
Chunfu Yang et al.	Southern Africa	Malawi	2006.5
Agwale et al.	Western/Central Africa	Nigeria	2006.5
Yaotse et al.	Western/Central Africa	Togo	2006.5
Lee Croi et al.	Eastern Africa	Uganda	2006.5
Ndembi et al.	Eastern Africa	Uganda	2006.5
Chunfu Yang et al.	Eastern Africa	United Republic of Tanzania	2006.5
Tshabalala et al.	Southern Africa	Zimbabwe	2006.5
Aghokeng et al.	Western/Central Africa	Cameroon	2006.5
Pando et al.	Latin America	Argentina	2007
Cardoso et al.	Latin America	Brazil	2007
De Sa Filho et al.	Latin America	Brazil	2007
Sprinz et al.	Latin America	Brazil	2007
Santos et al.	Latin America	Brazil	2007
Pilotto et al.	Latin America	Brazil	2007
Aghokeng et al.	Western/Central Africa	Cameroon	2007
WHO survey China	Asia	China	2007
Bruzzone et al.	Western/Central Africa	Congo	2007
Ayouba et al.	Western/Central Africa	Côte d'Ivoire	2007
Djoko et al.	Western/Central Africa	Democratic Republic of the Congo	2007
Caronet al.	Western/Central Africa	Gabon	2007
Chaturburj et al.	Asia	India	2007
Sinha 2012 et al.	Asia	India	2007
Lall Arhr et al.	Asia	India	2007

Study	Region	Country	Mid-point year of recruitment
Hingankar et al.	Asia	India	2007
Hamers et al.	Eastern Africa	Kenya	2007
Mokhbatet al.	Eastern Mediterranean	Lebanon	2007
WHO survey Mozambique	Southern Africa	Mozambique	2007
Ajoge et al.	Western/Central Africa	Nigeria	2007
Hamers et al.	Southern Africa	South Africa	2007
Hamers et al.	Southern Africa	South Africa	2007
Hamers Zaf et al.	Southern Africa	South Africa	2007
Ssemwanga et al.	Eastern Africa	Uganda	2007
Ishizaki et al.	Asia	Viet Nam	2007
Hamers et al.	Southern Africa	Zambia	2007
Hamers et al.	Southern Africa	Zambia	2007
Hamers et al.	Southern Africa	Zambia	2007
Nzeyimana et al.	Eastern Africa	Burundi	2007.5
Diazgranados et al.	Latin America	Colombia	2007.5
Rajesh et al.	Asia	India	2007.5
Price et al.	Eastern Africa	Kenya	2007.5
Haidara et al.	Western/Central Africa	Mali	2007.5
Avila-Rios et al.	Latin America	Mexico	2007.5
Price et al.	Eastern Africa	Rwanda	2007.5
Price et al.	Eastern Africa	Uganda	2007.5
Price et al.	Southern Africa	Zambia	2007.5
Da Silveira et al.	Latin America	Brazil	2008
Couto-Fernandez Ias et al.	Latin America	Brazil	2008
Inocencio et al.	Latin America	Brazil	2008
Cavalcanti et al.	Latin America	Brazil	2008
WHO survey Cambodia	Asia	Cambodia	2008
WHO survey China	Asia	China	2008
Zeng et al.	Asia	China	2008
Muwonga et al.	Western/Central Africa	Democratic Republic of the Congo	2008
Murillo et al.	Latin America	El Salvador	2008
Bonney et al.	Western/Central Africa	Ghana	2008
Hingankar et al.	Asia	India	2008
Hamers et al.	Eastern Africa	Kenya	2008
Wadonda-Kabondo et al.	Southern Africa	Malawi	2008
Hamers et al.	Western/Central Africa	Nigeria	2008
Ugbena et al.	Western/Central Africa	Nigeria	2008
Shah S et al.	Eastern Mediterranean	Pakistan	2008
Soria et al.	Latin America	Peru	2008
Rusine et al.	Eastern Africa	Rwanda	2008
Nwobegahay et al.	Southern Africa	South Africa	2008
Bessong et al.	Southern Africa	South Africa	2008

Study	Region	Country	Mid-point year of recruitment
Taser-S Jiamsakul et al.	Asia	Thailand	2008
Hamers et al.	Eastern Africa	Uganda	2008
Kityo et al.	Eastern Africa	Uganda	2008
Hamers et al.	Eastern Africa	Uganda	2008
Hamers et al.	Eastern Africa	Uganda	2008
Castillo et al.	Latin America	Venezuela	2008
WHO survey Viet Nam	Asia	Viet Nam	2008
Tanuma et al.	Asia	Viet Nam	2008
Phan et al.	Asia	Viet Nam	2008
Hamers et al.	Southern Africa	Zimbabwe	2008
Castelbranco et al.	Western/Central Africa	Angola	2008.5
Graf et al.	Latin America	Brazil	2008.5
Bacelar Acioli Lins et al.	Latin America	Brazil	2008.5
Arruda et al.	Latin America	Brazil	2008.5
Soares Croi et al.	Latin America	Brazil	2008.5
Ferreira et al.	Latin America	Brazil	2008.5
Carvalho et al.	Latin America	Brazil	2008.5
Taser-S Jiamsakul et al.	Asia	China	2008.5
Mavhandu et al.	Southern Africa	South Africa	2008.5
Sungkanuparph et al.	Asia	Thailand	2008.5
Bontell et al.	Asia	Viet Nam	2008.5
Dean et al.	Asia	Viet Nam	2008.5
Alonso et al.	Western/Central Africa	Angola	2009
WHO survey Angola	Western/Central Africa	Angola	2009
Bartolo et al.	Western/Central Africa	Angola	2009
Chamberland et al.	Western/Central Africa	Benin	2009
Gaspareto et al.	Latin America	Brazil	2009
Alencar et al.	Latin America	Brazil	2009
Bermudez-Aza	Latin America	Brazil	2009
Prellwitz et al. et al.	Latin America	Brazil	2009
Ferreira et al.	Latin America	Brazil	2009
WHO survey Burkina Faso	Western/Central Africa	Burkina Faso	2009
Ayouba et al.	Western/Central Africa	Burkina Faso	2009
Billong et al.	Western/Central Africa	Cameroon	2009
Li Yijia et al.	Asia	China	2009
WHO survey China	Asia	China	2009
Perez et al.	Latin America	Cuba	2009
Myers et al.	Latin America	Dominican Republic	2009
Nii-Trebiet al.	Western/Central Africa	Ghana	2009
Charpentier et al.	Western/Central Africa	Guinea	2009
Hamilton et al.	Latin America	Jamaica	2009
Hassan et al.	Eastern Africa	Kenya	2009
Lihana R et al.	Eastern Africa	Kenya	2009

Study	Region	Country	Mid-point year of recruitment
WHO survey Lesotho	Southern Africa	Lesotho	2009
WHO survey Malawi	Southern Africa	Malawi	2009
Ong et al.	Asia	Malaysia	2009
WHO survey Mozambique	Southern Africa	Mozambique	2009
Taser-S Jiamsakul et al.	Asia	Philippines	2009
Ayouba et al.	Western/Central Africa	Senegal	2009
Jacobset al.	Southern Africa	South Africa	2009
Wela Msimanga et al.	Southern Africa	South Africa	2009
Parboosing et al.	Southern Africa	South Africa	2009
WHO survey Swaziland	Southern Africa	Swaziland	2009
Colbn et al.	Asia	Thailand	2009
Ayouba et al.	Asia	Thailand	2009
Sirivichayakul et al.	Asia	Thailand	2009
Ssemwanga D et al.	Eastern Africa	Uganda	2009
Masimba et al.	Eastern Africa	United Republic of Tanzania	2009
Tanuma et al.	Asia	Viet Nam	2009
Ayouba et al.	Asia	Viet Nam	2009
Ishizaki et al.	Asia	Viet Nam	2009
Mungati et al.	Southern Africa	Zimbabwe	2009
Kasang et al.	Eastern Africa	United Republic of Tanzania	2009
Li Lu et al.	Asia	China	2009.5
Neogi Arhr et al.	Asia	India	2009.5
Bila et al.	Southern Africa	Mozambique	2009.5
Ndembi et al.	Eastern Africa	Uganda	2009.5
Pham et al.	Asia	Viet Nam	2009.5
De Moraes et al.	Latin America	Brazil	2010
Yang et al.	Asia	China	2010
Zou Ias et al.	Asia	China	2010
Chen et al.	Asia	China	2010
Guo et al.	Asia	China	2010
Li et al.	Asia	China	2010
Yang et al.	Asia	China	2010
Perez Iaset al.	Latin America	Cuba	2010
Machado et al.	Latin America	Cuba	2010
Holguin et al.	Latin America	El Salvador	2010
Huruy et al.	Eastern Africa	Ethiopia	2010
Thorat et al.	Asia	India	2010
Neogi Ias et al.	Asia	India	2010
Sigaloff et al.	Eastern Africa	Kenya	2010
Issiaka Maiga et al.	Western/Central Africa	Mali	2010
Gare et al.	Asia	Papua New Guinea	2010
Chen et al.	Asia	China	2010

Study	Region	Country	Mid-point year of recruitment
Nazziwa J et al.	Eastern Africa	Uganda	2010
Vairo et al.	Eastern Africa	United Republic of Tanzania	2010
Tanuma et al.	Asia	Viet Nam	2010
Uwash et al.	Eastern Africa	Kenya	2010
Avila Rios et al.	Latin America	Guatemala	2010.5
Kannangai et al.	Asia	India	2010.5
Jahanbakhsh et al.	Eastern Mediterranean	Iran (Islamic Republic of)	2010.5
Rodriguez-Rodriguez et al.	Latin America	Argentina	2011
Da Costa et al.	Latin America	Brazil	2011
Teixeira et al.	Latin America	Brazil	2011
Wang X Arhr et al.	Asia	China	2011
Li et al.	Asia	China	2011
Chen et al.	Asia	China	2011
Neogi et al.	Asia	India	2011
Shet et al.	Asia	India	2011
Baesi et al.	Eastern Mediterranean	Iran (Islamic Republic of)	2011
Memarnejadian et al.	Eastern Mediterranean	Iran (Islamic Republic of)	2011
Barrow et al.	Latin America	Jamaica	2011
Hassan et al.	Eastern Africa	Kenya	2011
Ruperez et al.	Southern Africa	Mozambique	2011
Bhusal et al.	Asia	Nepal	2011
Mamadou et al.	Western/Central Africa	Niger	2011
Mutagoma et al.	Eastern Africa	Rwanda	2011
Manasaet al.	Southern Africa	South Africa	2011
Sungkanuparph et al.	Asia	Thailand	2011
Manosuthi et al.	Asia	Thailand	2011
Ananworanich et al.	Asia	Thailand	2011
Tanuma et al.	Asia	Viet Nam	2011
Azam et al.	Asia	India	2011
Velasco De Castro et al.	Latin America	Brazil	2011
Imade et al.	Western/Central Africa	Nigeria	2011
De Lourdes Teixeira et al.	Latin America	Brazil	2011
Avila-Rios et al.	Latin America	Guatemala	2011.5
Cecchini et al.	Latin America	Argentina	2012
Rowley et al.	Southern Africa	Botswana	2012
Soares Moura et al.	Latin America	Brazil	2012
Jiao et al.	Asia	China	2012
Tanuma et al.	Asia	Viet Nam	2012
Sayan et al.	Europe	Turkey	2012.5
Reynolds et al.	Eastern Africa	Uganda	2012.5
WHO PDR survey Brazil[1]	Latin America	Brazil	2013
De Souza-Guimaraes et al.	Latin America	Brazil	2013

Study	Region	Country	Mid-point year of recruitment
Lu et al.	Asia	China	2013
Avila-Rios et al.	Latin America	Nicaragua	2013
Derachel et al.	Southern Africa	South Africa	2013
Kaleebu et al.	Eastern Africa	Uganda	2013
Nanfack et al.	Western/Central Africa	Cameroon	2013
Zhanget al.	Asia	China	2013
Rowley et al.	Southern Africa	Botswana	2013.5
Kamangu et al.	Western/Central Africa	Democratic Republic of the Congo	2013.5
Lavu et al.	Asia	Papua New Guinea	2013.5
Bissio et al.[1]	Latin America	Argentina	2014
Fokam et al.	Western/Central Africa	Cameroon	2014
Avila-Rios et al.	Latin America	Honduras	2014
Chimukangara et al.	Southern Africa	South Africa	2014
Steegenet al.	Southern Africa	South Africa	2014
Frenkel et al.	Eastern Africa	Kenya	2014
Rowley et al.	Southern Africa	Botswana	2014.5
WHO PDR survey Guatemala [1]	Latin America	Guatemala	2015
Avila-Rios et al.[1]	Latin America	Mexico	2015
WHO PDR survey Namibia[1]	Southern Africa	Namibia	2015
WHO PDR survey Zimbabwe[1]	Southern Africa	Zimbabwe	2015
WHO PDR survey Cameroon[1]	Western/Central Africa	Cameroon	2015
WHO PDR survey Colombia[1]	Latin America	Colombia	2016
WHO PDR survey Myanmar[1]	Asia	Myanmar	2016
WHO PDR survey Nicaragua[1]	Latin America	Nicaragua	2016
Gillian Hunt et al.	Southern Africa	South Africa	2016
WHO PDR survey Uganda[1]	Eastern Africa	Uganda	2016

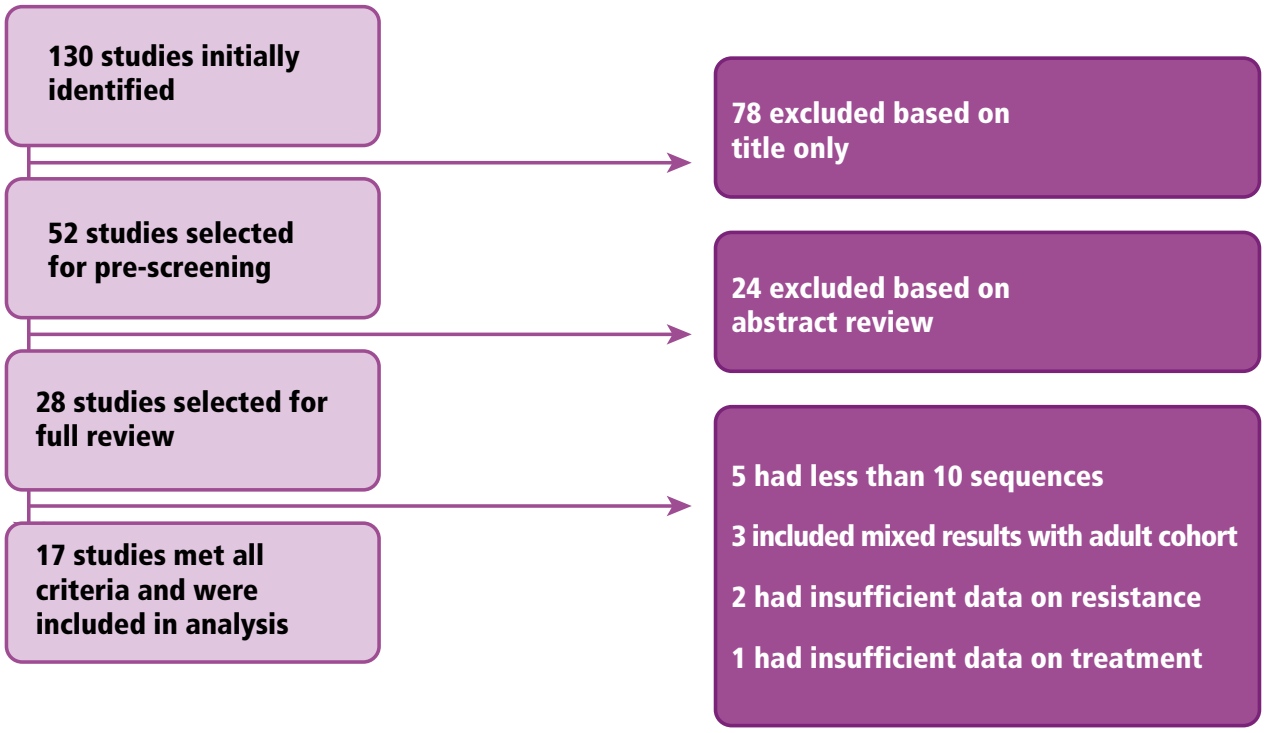
* For this systematic literature review, countries in the South-East Asia region, Western Pacific region, Eastern Mediterranean and Turkey (Europe region) are grouped under the regional heading of 'Asia'.

[1] Nationally representative WHO surveys.

Section 4: Paediatric pretreatment HIV drug resistance and acquired HIV drug resistance systematic literature review methods

To assess the current status of paediatric PDR and ADR in LMIC, PubMed was searched for relevant English-language articles published from 1 January 2014 to 30 April 2017. An overview of paediatric studies is found in Fig. A2.

Fig. A2: Flow chart of study selection for paediatric PDR and ADR systematic reviews



Search terms included "transmitted", "pretreatment", "acquired" and "primary", in combination with "drug resistance", "resistance", "HIV", and "child" or "infant". Review of 130 abstracts yielded 17 articles (10 ADR and seven PDR). Articles were included if they described original studies of HIVDR in PLHIV younger than 15 years living in LMIC. Articles were excluded if adult and paediatric results were combined or sample size was less than 10. The 17 studies included in this review were performed with varying methods of patient sampling (e.g. consecutive, convenient or random selection), sample type (e.g. DBS or plasma), and genotyping assay, so prevalence estimates may not be nationally or regionally representative.

The following variables were abstracted for PDR studies: country of study; median year of sample collection; median age of children included; PMTCT regimens used by mother and/or infant; PMTCT exposure type; number of children with genotypic resistance testing results; number of children with virus harbouring any HIVDR mutations to NNRTIs, NRTIs and PIs, or with dual- or triple-class resistance.

The following variables were abstracted for ADR studies: demographic characteristics; study design and characteristics; first- or second-line ART regimen; median ART duration before failure; minimal ART duration for study eligibility; prevalence of virological suppression (if available); number of participants on NNRTI-based regimens and PI-based regimens; number of individuals successfully genotyped; prevalence of DRMs by class, by selected mutation, and by number of classes.

Limitations to the paediatric pretreatment HIV drug resistance literature review

A relatively small number of studies were published during the given time period, reflecting the scarcity of data on this topic. In addition, there was marked heterogeneity across studies in terms of participant age and PMTCT exposure status. In addition, reporting and analysis of DRMs varied significantly; some studies included only mutations associated with NNRTIs, while others reported overall DRMs across multiple drug classes. Because of this study variation, pooled analysis was not feasible.

Limitations to the paediatric acquired HIV drug resistance literature review

Limitations to this analysis included substantial variation in study population and inclusion criteria among the included ADR studies. For example, some ADR studies focused on first-line ART failures, while others included children failing second-line ART. Additionally, first-line ART regimens differed substantially, reflecting varying implementation of WHO-recommended LPV/r-based ART for children younger than 3 years of age. Viral suppression information was only provided in five out of 10 ADR studies, and the definition of virological failure was inconsistent, with virological suppression thresholds ranging from <400 copies/ml to <1000 copies/ml. Studies varied in their requirements for repeat (confirmatory) viral load testing (i.e. one elevated viral load measurement or two elevated viral loads), and not all studies utilized viral load monitoring.

Studies included in the PDR and ADR paediatric literature reviews are found in Table A2 and Table A3, respectively.

Table A2: Studies included in the literature review of pretreatment HIV drug resistance in children

Study	Region	Country	Mid-point year of recruitment
Boerma et al.	Western Africa	Nigeria	2012
Inzaule et al.	Eastern Africa	Kenya	2009
Kanthula et al.	Southern Africa	South Africa	2012
Kebe et al.	Western Africa	Senegal	2010
Kityo et al.	Eastern Africa	Uganda	2010
Kuhn et al.	Southern Africa	South Africa	2011
Salou et al.	Western Africa	Togo	2013

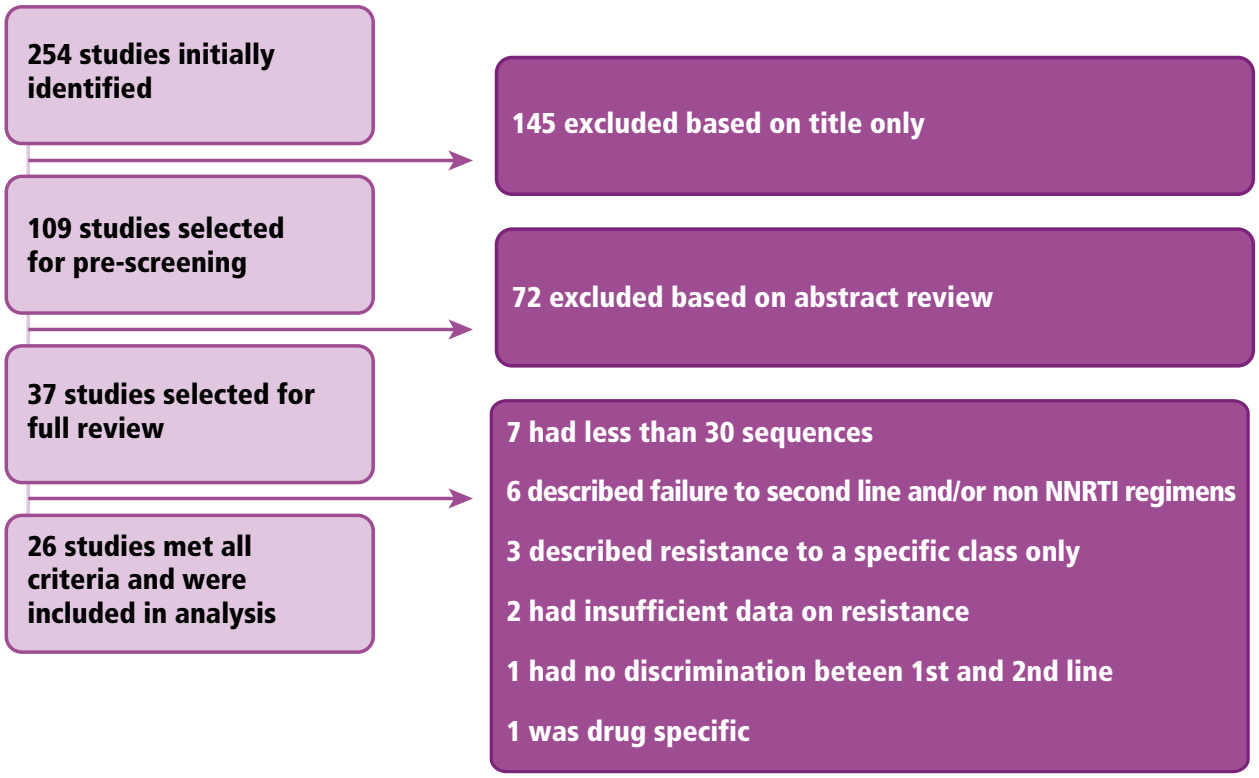
Table A3: Studies included in the literature review of acquired HIV drug resistance in children

Study	Region	Country	Mid-point year of recruitment
Dow et al.	Eastern Africa	United Republic of Tanzania	2009
Makadzange et al.	Southern Africa	Zimbabwe	2012
Meyers et al.	Southern Africa	South Africa	2006
Mossoro-Kpinde et al.	Central Africa	Central African Republic	2013
Muri et al.	Eastern Africa	United Republic of Tanzania	2013
Mutwa et al.	Eastern Africa	Rwanda	2010
Pillay et al.	Southern Africa	South Africa	2012
Prasitsuebsai et al.	Asia	Indonesia, Thailand, Viet Nam	2011
Rossouw et al.	Southern Africa	South Africa	2010
Steegen et al.	Southern Africa	South Africa	2011

Section 5: Adult acquired HIV drug resistance systematic literature review methods

The peer-reviewed literature was searched to describe resistance among people failing first-line NNRTI-based ART in LMIC (as defined by the World Bank) that use a public health approach (i.e. government procured drugs, national guidelines for first- and second-line regimens). The PubMed database was queried for prospective, cross-sectional or retrospective studies published in the peer-reviewed literature between 1 January 2014 and 30 April 2017. Combinations of the following search terms were used: "acquired drug resistance", "HIV", "survey", "treatment failure", "first line". The initial search yielded 254 articles; a detailed overview of article selection is provided in Fig. A3.

Fig. A3: Flow chart of study selection for systematic review of ADR in adults



Studies were considered if, in addition to the previously mentioned factors, they described data for individuals over 15 years of age; reported genotype results for at least 30 individuals; used either plasma or DBS; had a majority (two thirds) of the included individuals on an NNRTI-based regimen; and individuals had been on ART for at least six months.

Data were abstracted on the demographic characteristics of subjects; study design and characteristics; median treatment duration before failure; minimal treatment duration for study eligibility; rates of virological response; proportion of individuals reported to be on an NNRTI-based regimen; number of individuals successfully genotyped; and prevalence of DRM by class, by selected mutation, and by number of classes.

The variables common to each of these studies were the number of individuals included in the cohort, the number of individuals who had genotype performed, and the number of individuals with any DRM.

Meta-analysis using a random effects model was performed to determine "the number of individuals with any DRM / number of individuals who had genotype performed, by region".

Other considerations were as follows.

a. Denominators for reporting proportion of mutations were standardized as "number with genotype performed".

b. For articles that reported mixed cohorts (pretreatment and acquired, multiple countries, high- and low-income), studies were included if data were described with enough detail for LMIC separately.

c. When not directly reported, raw numbers and percentages per class and mutation were calculated.

d. Viral suppression definition varied from <400 copies/ml to <5000 copies/ml.

Limitations to the adult acquired HIV drug resistance systematic review

Limitations of this pooled analysis include, but are not limited to, the following considerations: studies may differ with respect to the population assessed (such as recent or chronic infections); sampling frame (such as consecutive, convenient or random selection); laboratory methods used; variation in ART coverage; variation in HIV subtypes; variation in the quality of care received; variation in country income levels; structure or organization of health services; and international standards used to define mutations.

It is worth noting that information on duration of therapy was derived at the study level as a median duration, so the actual duration of therapy for individuals is distributed around the median. In addition, resistance at treatment failure may have been related to the resistance already present at baseline; participants recruited into these studies may not be representative of the general population with HIV on ART; and prevalence estimates may not be nationally or regionally representative.

Moreover, although all studies included were published between 2014 and 2017, collected data went as far back as 1998. Lastly, it is possible that the results presented in this report may be biased towards sites with above-average performance, as the implementation of studies on drug resistance can itself indicate above-average programme quality.

The studies included in the review are found in Table A4.

Table A4: Studies included in the literature review of acquired HIV drug resistance in adults.

Study	Region	Country	Mid-point year of recruitment
Aghokeng	Multicountry	Burkina Faso, Cameroon, Côte d'Ivoire, Senegal, Thailand, Togo, Viet Nam	2011
Avila-Rios	Central America	Honduras	2015
Baesi	Eastern Mediterranean	Iran (Islamic Republic of)	2011
Bila	Southern Africa	Mozambique	2010
Diouara	Western Africa	Guinea, Mali, Senegal	2011
Diouara	Western Africa	Senegal	2009
Fall-Malick	Western Africa	Mauritania	2010
Fofana	Western Africa	Mali	2012
Hassan	Eastern Africa	Kenya	2011
Kaleebu	Eastern Africa	Uganda	2013
Kantor	Eastern Africa	Kenya	2007
Koigi	Eastern Africa	Kenya	2013
Konou	Western Africa	Togo	2012
Leng	Western Pacific	China	2012
Loubet	Western Africa	Liberia	2013
Naziri	Eastern Mediterranean	Iran (Islamic Republic of)	2014
Ruperez	Southern Africa	Mozambique	2013
Seu	Southern Africa	Zambia	2012
TenoRes	Multicountry	36 countries[1]	2015
Wallis	Multicountry	India, Malawi, South Africa, United Republic of Tanzania, Thailand	N/A
Wang	Western Pacific	China	2012
Wang2	Western Pacific	China	2012
Yang	Western Pacific	China	2012
Zhan	Western Pacific	China	2010
Zhou	Western Pacific	China	2012
Zoufaly	Central Africa	Cameroon	2010

[1] Across Asia, sub-Saharan Africa, Western Europe, North America and Central and South America.

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

ISBN 978 92 4 151283 1