

HIV DRUG RESISTANCE REPORT 2017

TRENDS



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HIV drug resistance report 2017

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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.

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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 countries¹ 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.

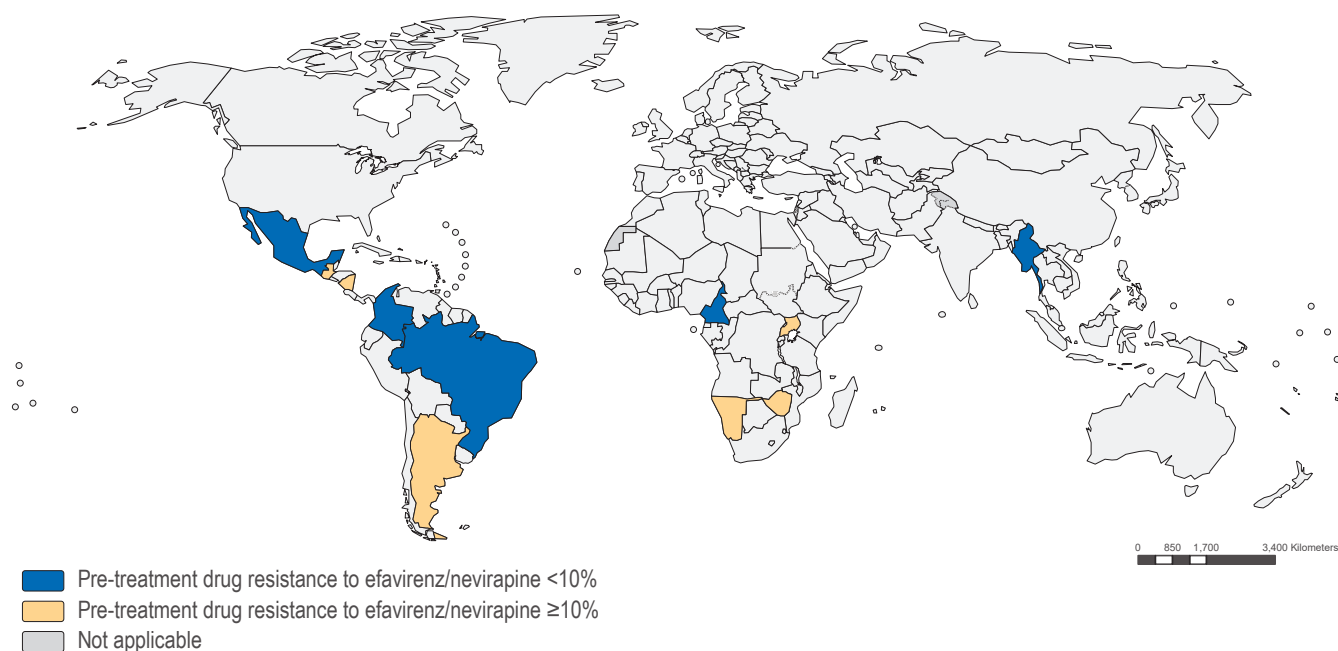
Levels of pretreatment resistance to efavirenz or nevirapine, the most affordable and widely used drugs in first-line ART, reached 10% or above in six out of 11 countries that reported PDR survey data.

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; 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-naïve 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-naïve 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-naïve 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-naïve initiators. To ensure responsible decision-making, the survey sample size has been calculated to provide a confidence interval width of $\pm 5\%$ 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-naïve and drug-exposed people yields nationally representative data on the entire population eligible to initiate first-line ART, which operationally includes both ARV drug-naïve 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.

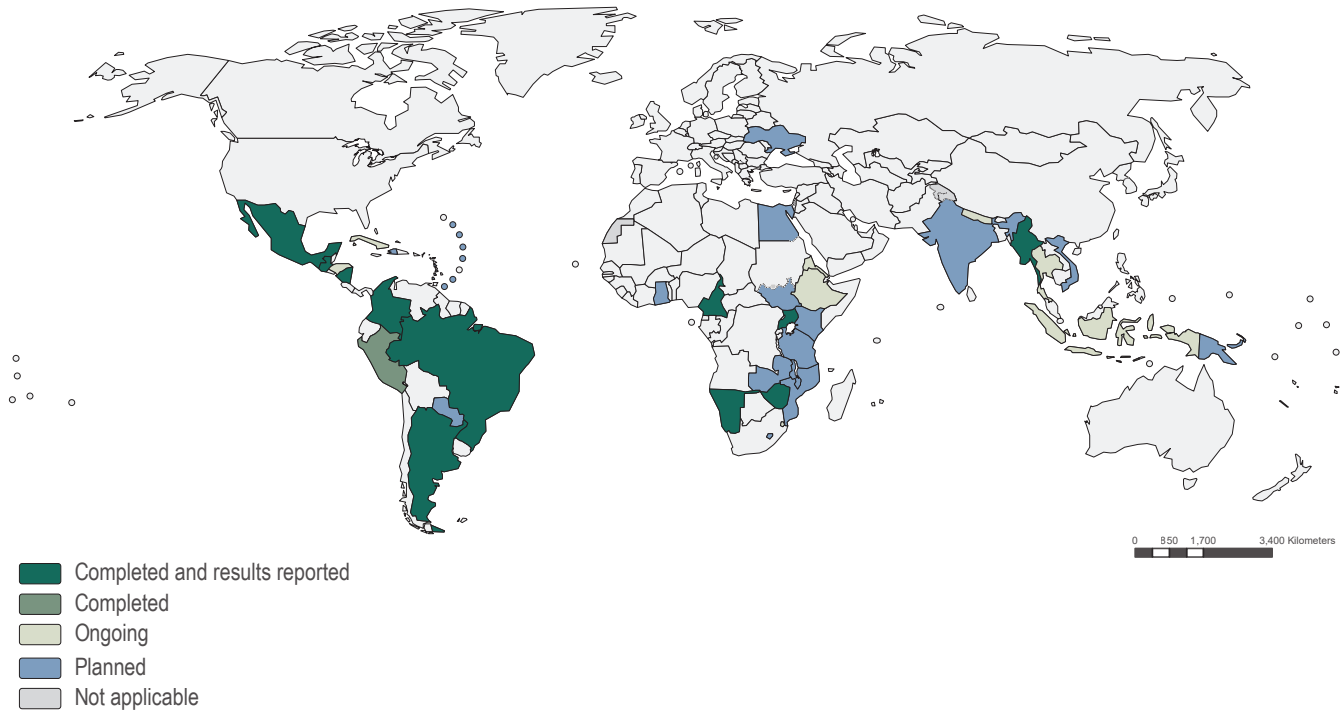
Prior ARV drug exposure may be ascertained through a variety of methods, such as use of a screening questionnaire or review of patient medical records, where available and feasible. Initiators are classified into one of three categories of prior ARV drug exposure: yes, no or unknown. Countries are advised 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 21⁵ 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, 2014–2017⁶



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)

| | Africa | Mexico, Central America | South America | South-East Asia |
|--|---|---|---|-----------------|
| N Individuals with Specimen | Cameroon: 379 Namibia: 498 Uganda: 491 Zimbabwe: 398 | Guatemala: 269 Mexico: 275 Nicaragua: 177 | Argentina: 343 Brazil: UNK Colombia: 196 | Myanmar: 375 |
| Failed Genotyping | Cameroon: 58 Namibia: 110 Uganda: 136 Zimbabwe: 37 | Guatemala: 19 Mexico: 11 Nicaragua: 1 | Argentina: 49 Brazil: UNK Colombia: 0 | Myanmar: 23 |
| Failed QA | Cameroon: 0 Namibia: 5 Uganda: 13 Zimbabwe: 8 | Guatemala: 9 Mexico: 4 Nicaragua: 5 | Argentina: 0 Brazil: 0 Colombia: 4 | Myanmar: 25 |
| N Individuals with Classifiable HIVDR Results | Cameroon: 321 Namibia: 383 Uganda: 342 Zimbabwe: 353 | Guatemala: 241 Mexico: 260 Nicaragua: 171 | Argentina: 294 Brazil: 1391 Colombia: 192 | Myanmar: 327 |

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-naïve people, while seven included both individuals initiating (or reinitiating) first-line ART who were ARV drug-naïve 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) | | Uganda¹ (Start year 2016) | | Zimbabwe² (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 |
| Mean⁴ 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, DRV or LPV; 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

| | Guatemala¹ (Start year 2016) | | Mexico² (Start year 2015) | | Nicaragua³ (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 | – |
| Mean⁵ 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) |

¹15 participants had missing data for initiated first-line; ²Prior ARV drug exposed participants were not included in the survey, 52 participants had missing data for initiated first-line; ³One participant had missing data for initiated first-line; ⁴Study design-weighted proportion and 95% confidence interval; ⁵Study design-weighted mean and 95% confidence interval; ⁶NNRTI-based first-line regimens include EFV or NVP; ⁷PI-based first-line regimens include ATV, DRV or LPV; 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) | | Brazil¹ (Start year 2013) ² | | Colombia³ (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) | | | | |
| Mean⁵ 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 |

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

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

| | Myanmar ¹ (Start year 2016) | | Myanmar ¹ (Start year 2016) | |
|---|---|-------------------------|---|-------------------------|
| | N = 327 | | N = 327 | |
| | n | % (95% CI) ² | n | % (95% CI) ² |
| Gender | | | | |
| Women | 115 | 36.6 (29.8–43.9) | | |
| Men | 206 | 63.4 (56.1–70.2) | | |
| Mean³ 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 | – | | |
| 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 | | |

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

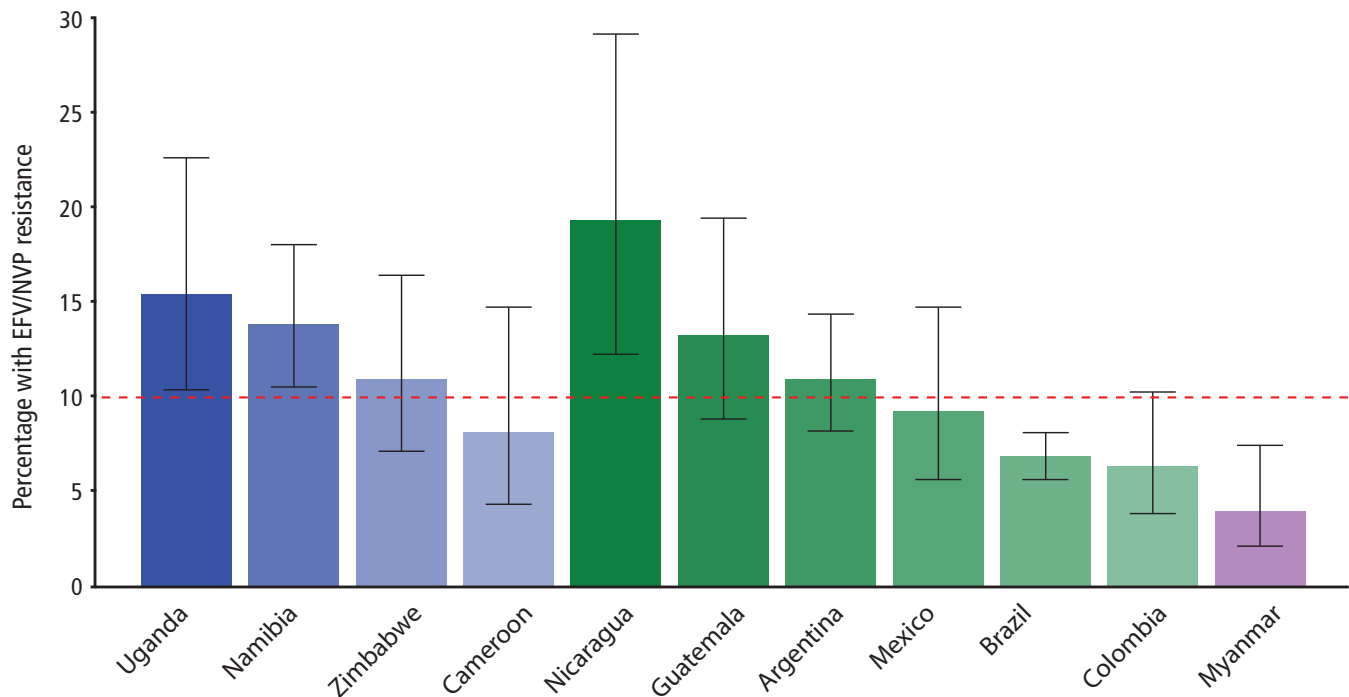
Of the 11 countries with PDR survey results, seven (Argentina, Guatemala, Mexico, Namibia, Nicaragua, Uganda and Zimbabwe) had prevalence of any PDR greater than 10%.⁹ Overall, levels of PDR were driven by NNRTI resistance,¹⁰ which exceeded 10% in six of the countries (excluding Mexico) (Fig. 3).

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-naïve 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 resistance¹¹



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-naïve 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-naïve 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 starting 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-naïve 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-naïve (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) |
| All¹ | | | | | | | | |
| 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 efaviranz (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanavir/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) |
| All¹ | | | | | | |
| 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 efavirinez (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanavir/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) |
| All¹ | | | | | | |
| 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 efavirinez (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanavir/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

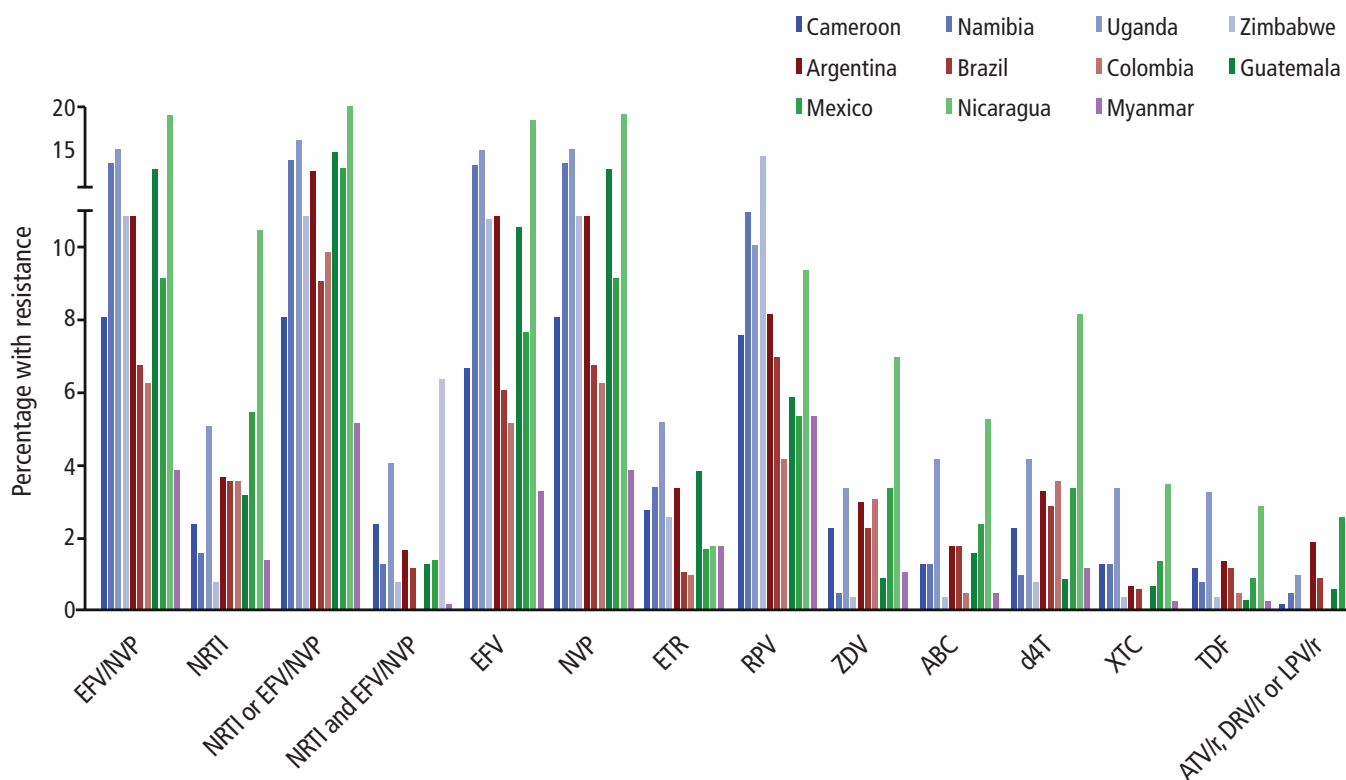
| | Myanmar | | | Myanmar | |
|------------------------|---------|-----------------------|----------------------|---------|-----------------------|
| | n/N | Prevalence % (95% CI) | | n/N | Prevalence % (95% CI) |
| All¹ | | | Prior-exposed | | |
| Any | 21/327 | 5.4 (3.1–9.2) | PI | 0/32 | – |
| NNRTI | 16/327 | 3.9 (2.1–7.4) | NNRTI+NRTI | 0/32 | – |
| NRTI | 5/327 | 1.4 (0.5–3.7) | Women | | |
| PI | 1/326 | 0.2 (0.0–1.8) | Any | 7/115 | 5.2 (2.1–12.2) |
| NNRTI+NRTI | 1/327 | 0.2 (0.0–1.3) | NNRTI | 5/115 | 3.6 (1.2–10.3) |
| Naive | | | NRTI | 2/115 | 1.6 (0.3–7.4) |
| Any | 14/287 | 4.3 (2.3–8.0) | PI | 0/115 | – |
| NNRTI | 9/287 | 2.7 (1.2–6.0) | NNRTI+NRTI | 0/115 | – |
| NRTI | 5/287 | 1.5 (0.6–4.2) | Men | | |
| PI | 1/286 | 0.3 (0.0–2.0) | Any | 13/206 | 5.3 (2.9–9.7) |
| NNRTI+NRTI | 1/287 | 0.2 (0.0–1.4) | NNRTI | 10/206 | 3.9 (1.9–7.9) |
| Prior-exposed | | | NRTI | 3/206 | 1.3 (0.4–4.5) |
| Any | 6/32 | 15.7 (5.5–37.4) | PI | 1/205 | 0.4 (0.0–2.9) |
| NNRTI | 6/32 | 15.7 (5.5–37.4) | NNRTI+NRTI | 1/206 | 0.3 (0.0–2.1) |
| NRTI | 0/32 | – | | | |

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 efavirine (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanavir/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



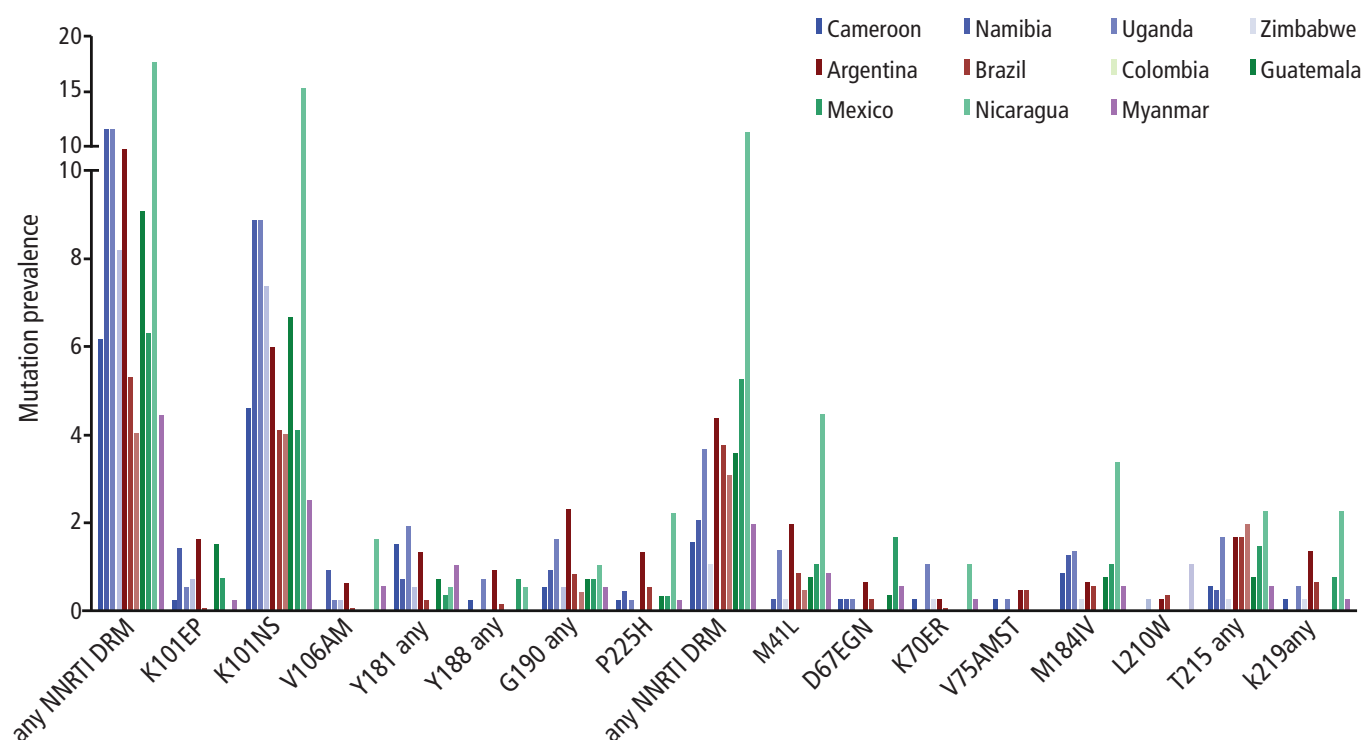
EFV= efavirenz; NVP= nevirapine; NRTI = Nucleoside reverse-transcriptase inhibitor; ETR= etravirine; RPV= rilpivirine; ZDV= zidovudine; ABC= abacavir; d4t= stavudine; XTC= lamivudine or emtricitabine; TDF= tenofovir disoproxil fumarate; ATV/r= atazanavir/ritonavir; DRV/r= darunavir/ritonavir; LPV/r= 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-naïve 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 PHIA 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. PHIA surveys 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 PHIA surveys is to estimate the prevalence of HIVDR among adults classified as recently infected (\leq 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 PHIA surveys 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.

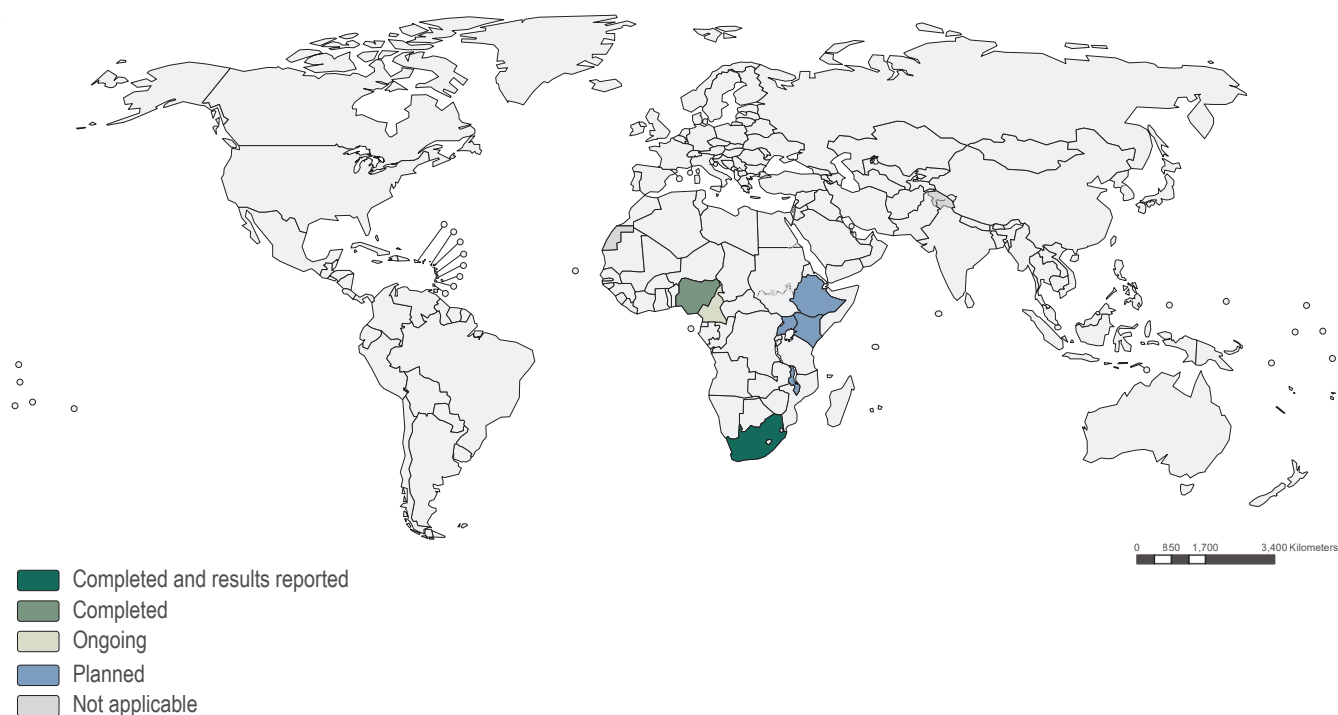
The methodology leverages a random sample or census of remnant dried blood spot (DBS) specimens collected as part of routine EID testing during a 12-month period. In all countries, all laboratories performing EID contributed DBS to the sample, with the number of specimens contributed per laboratory proportional 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 $\pm 7\%$, 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, 2014–2017¹⁴



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 adults¹

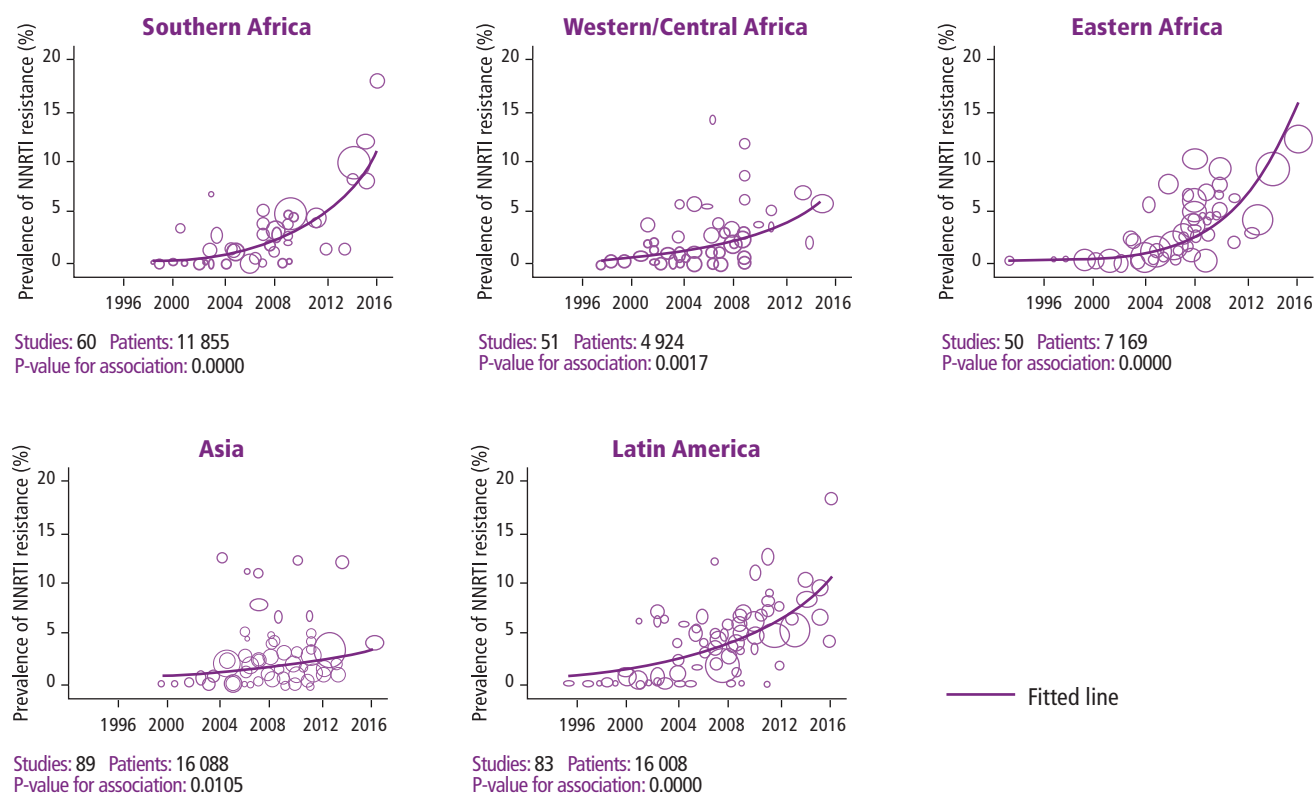
| Geographical region | Number of studies | Total number of genotypes | Median number of genotypes per study (range) | Median sampling year (range) | Studies in urban populations, n/N ² (%) |
|------------------------|-------------------|---------------------------|--|------------------------------|--|
| 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%) |

¹For 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'; ²Data 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 |

¹Estimates 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

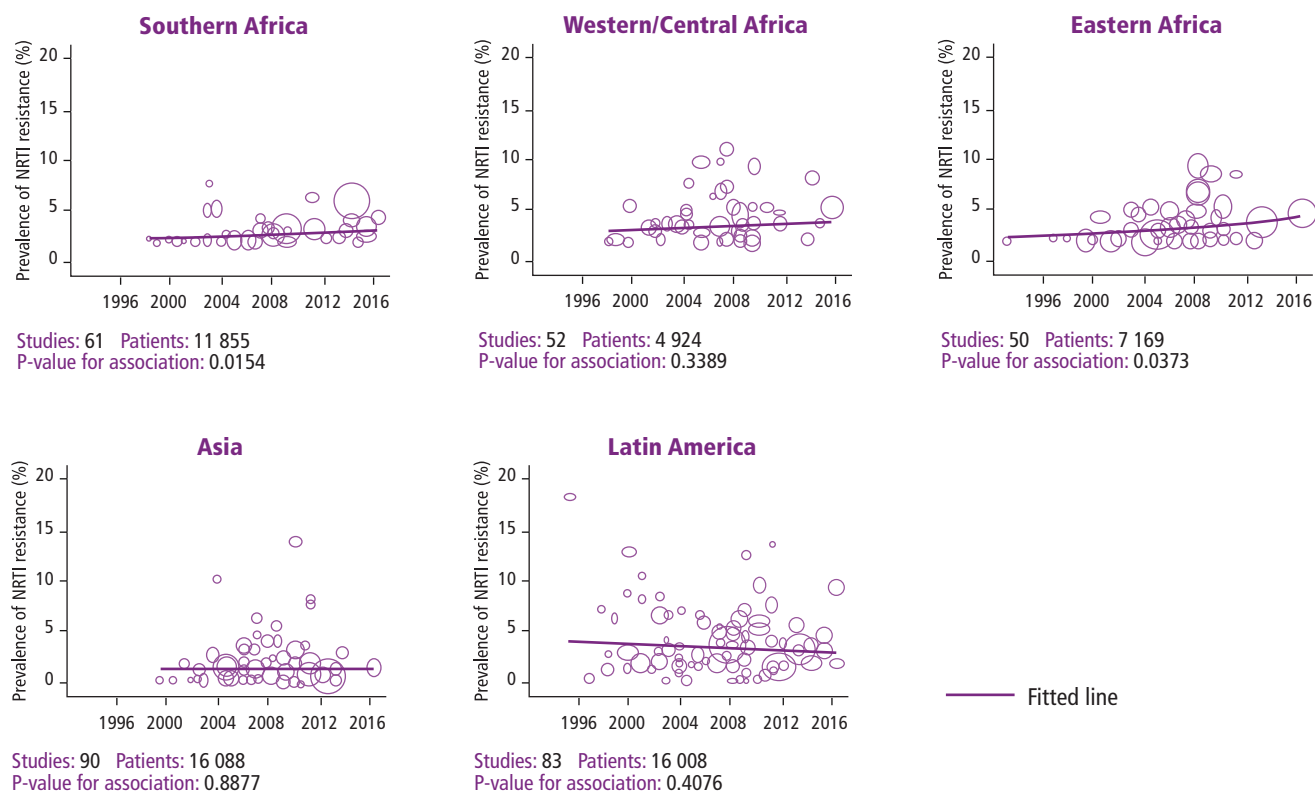
| Class of mutation | Region | Studies | ARV drug naive | Studies | Prior ARV drug exposure | P-value ² |
|-------------------|------------------------|---------|-----------------------------|---------|-------------------------|----------------------|
| Any | Asia | 4 | 4.2 (2.9–6.2) | 4 | 34.1 (14.0–79.0) | <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 |

¹Estimates use the Freeman-Tukey arcsine transformation, because mixed models did not converge; ²P 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 PMTC naive | (%) DRM unknown PMTC 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-naïve 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.

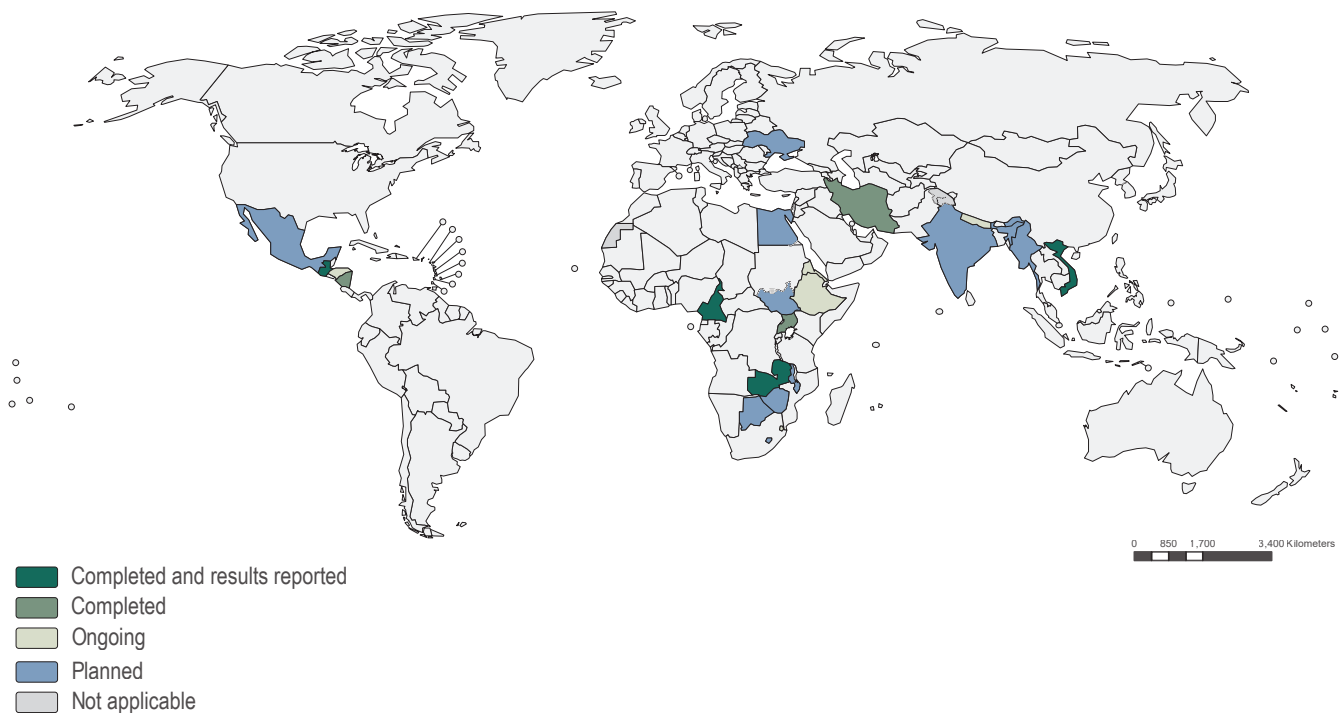
ADR survey results provide critical information to assess programme performance in achieving viral load suppression, and to inform the optimal selection of second- and potentially third-line regimens, based on prevalence of resistance in individuals failing treatment. It is recommended that countries 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, 2014–2017¹⁶



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 sequencing¹⁷ 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

| | Africa | Central America | Western Pacific |
|--|--|--|-------------------|
| N Individuals with VL Data | Cameroon 12: 1 064 Cameroon 48+: 338 Zambia 12: 454 ¹ | Guatemala 12: 222 Guatemala 48+: 377 ² | Viet Nam 36+: 365 |
| N Individuals with VL ≥ 1000 copies/ml | Cameroon 12: 104 Cameroon 48+: 54 Zambia 12: 21 | Guatemala 12: 25 Guatemala 48+: 9 | Viet Nam 36+: 20 |
| Genotyping Failed | Cameroon 12: 164 Cameroon 48+: 54 Zambia 12: 21 | Guatemala 12: 6 Guatemala 48+: 9 | Viet Nam 36+: 0 |
| N Individuals with Classifiable HIVDR Results | Cameroon 12: 164 Cameroon 48+: 67 Zambia 12: 24 | Guatemala 12: 19 Guatemala 48+: 40 | Viet Nam 36+: 20 |

VL=viral load; HIVDR=HIV drug resistance; ¹Two individuals out of 456 were excluded because sequences failed WHO Quality assurance; ²One 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.) | | Zambia¹ (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) |
| Mean³ 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 | – |
| Mean³ time on ART (95% CI), months | 17.9 (17.4–18.4) | | 12.2 (12.0–12.4) | | 12.2 (11.8–12.6) | |

¹Three participants had missing data for age; ²Study design-weighted proportion and 95% confidence interval; ³Study 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 |
| Mean² 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) |
| Mean² time on ART (95% CI), months | 53.3 (52.1–54.6) | | 91.8 (84.5–99.1) | | 75.5 (69.0–81.9) | |

¹Study design-weighted proportion and 95% confidence interval; ²Study 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).

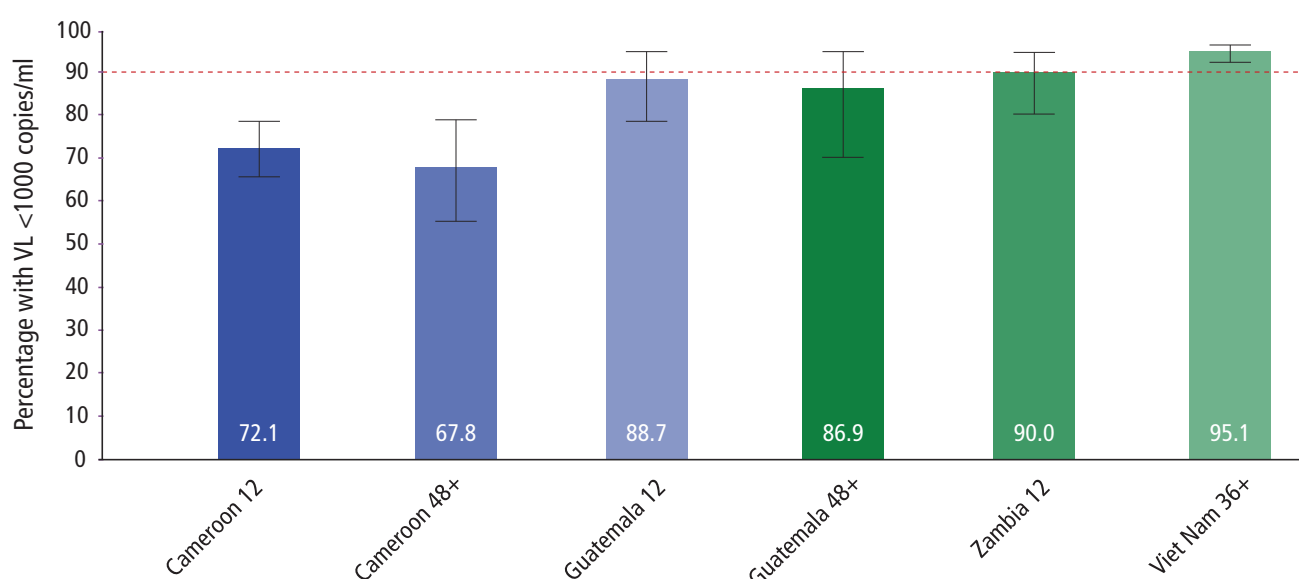
Similar viral load suppression prevalence estimates were observed among individuals on any ART regimen, any first-line ART regimen, and NNRTI-containing first-line ART for 12–24 months (Table 16).

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) |

¹Three 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 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 resistance²¹ 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 ART²² 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 efavirinez (EFV). NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to atazanavir/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 country²³

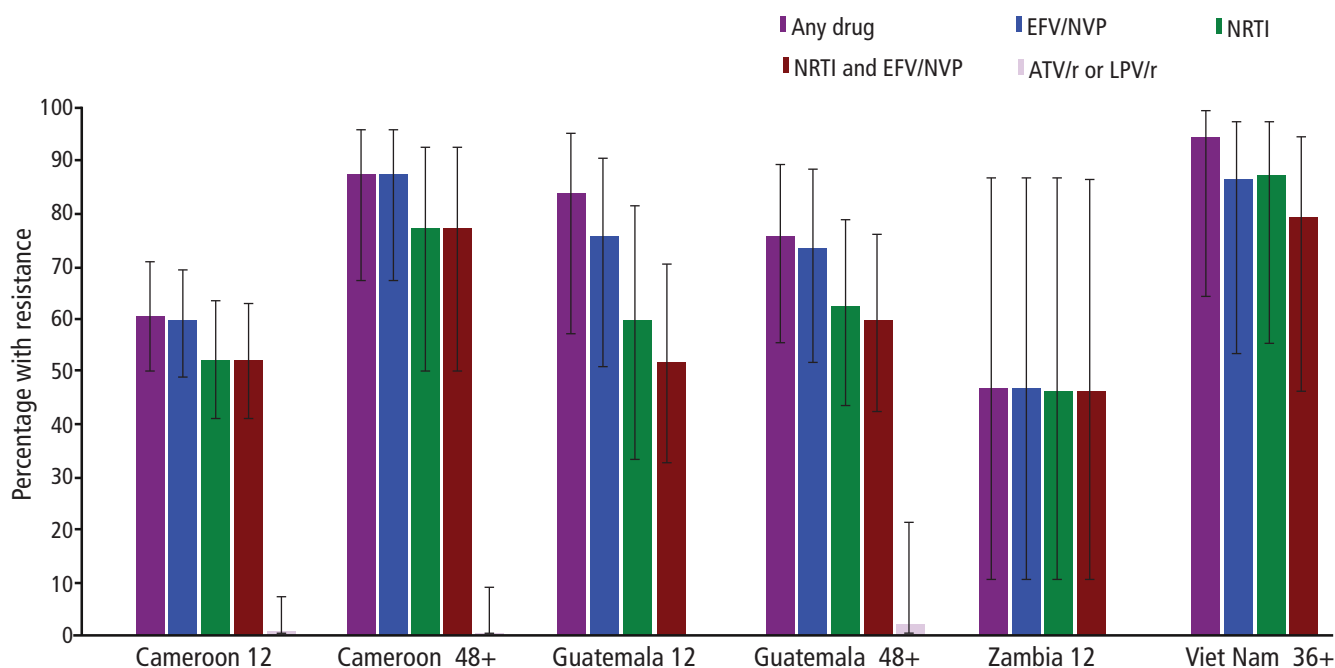
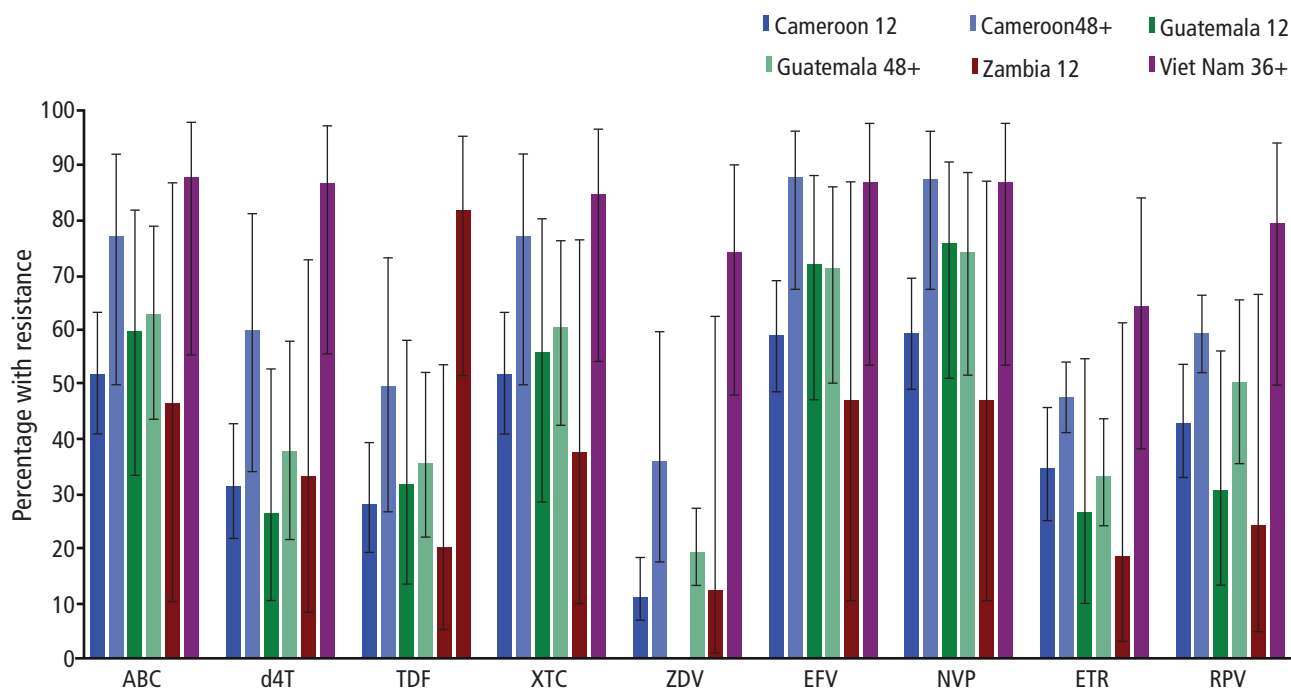


Fig. 13: Prevalence of acquired HIV drug resistance by drug and country²⁴



ABC= abacavir; d4t= stavudine; TDF= tenofovir disoproxil fumarate; XTC= lamivudine or emtricitabine; ZDV= zidovudine; EFV= efavirenz; NVP= nevirapine; ETR= etravirine; RPV= rilpivirine.

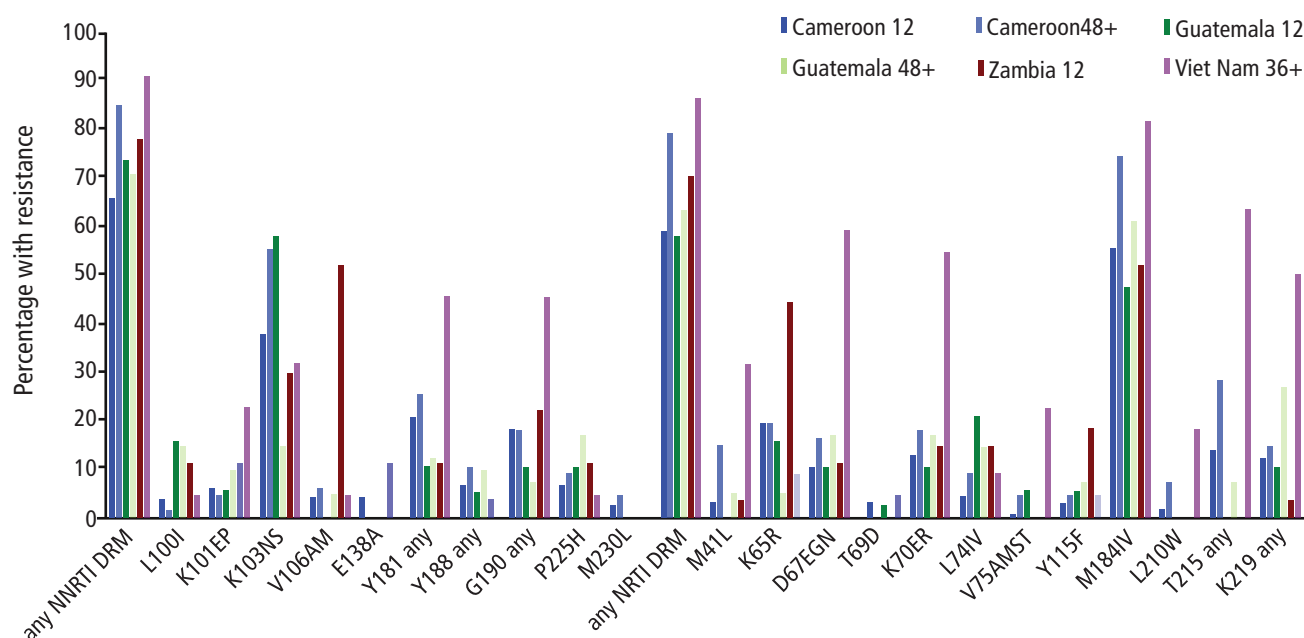
²³ NNRTI resistance is defined as resistance to NVP or EFV. NRTI resistance is defined as resistance to any NRTI, and any PI resistance is defined as resistance to ATV/r, LPV/r or DRV/r. Any HIVDR is defined as resistance to NVP/EFV, any NRTI, ATV/r, LPV/r or DRV/r. HIVDR is determined using the Stanford 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 country²⁵



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 |

¹weighted mean to reflect study heterogeneity.

²⁵ Mutations are defined as per the WHO 2009 SDRM list; only mutations present at $\geq 1\%$ 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

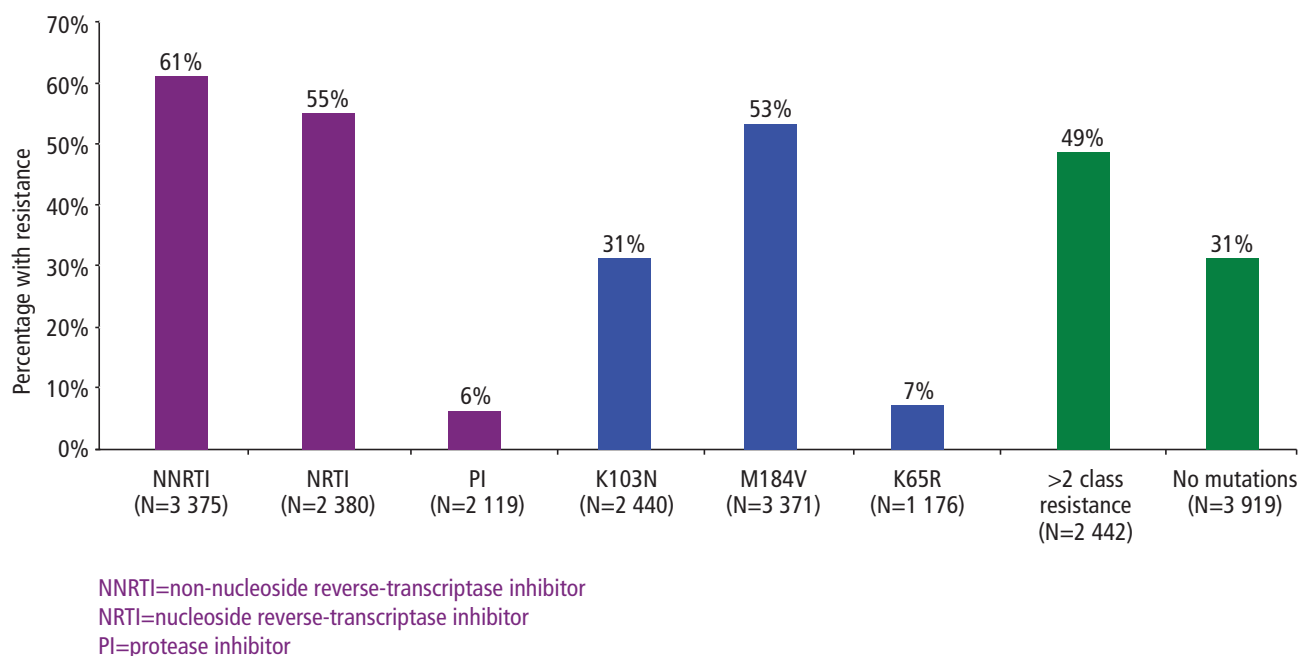
| Region | Mean (%) | 95% CI (%) |
|---|----------|------------|
| Africa | 80.7 | 56.1–93.2 |
| Eastern Africa | 64.7 | 29.9–99.0 |
| Southern Africa | 87.3 | 37.2–99.9 |
| Western Africa | 87.8 | 50.8–98.0 |
| Asia | | |
| China | 50.3 | 18.2–98.2 |
| Multicountry cohorts¹ | 79.2 | 18.2–99.8 |
| Total² | 70.7 | 45.2–87.6 |

¹Multicountry 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)



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 |
| Steegeen 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 $\geq 90\%$ 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

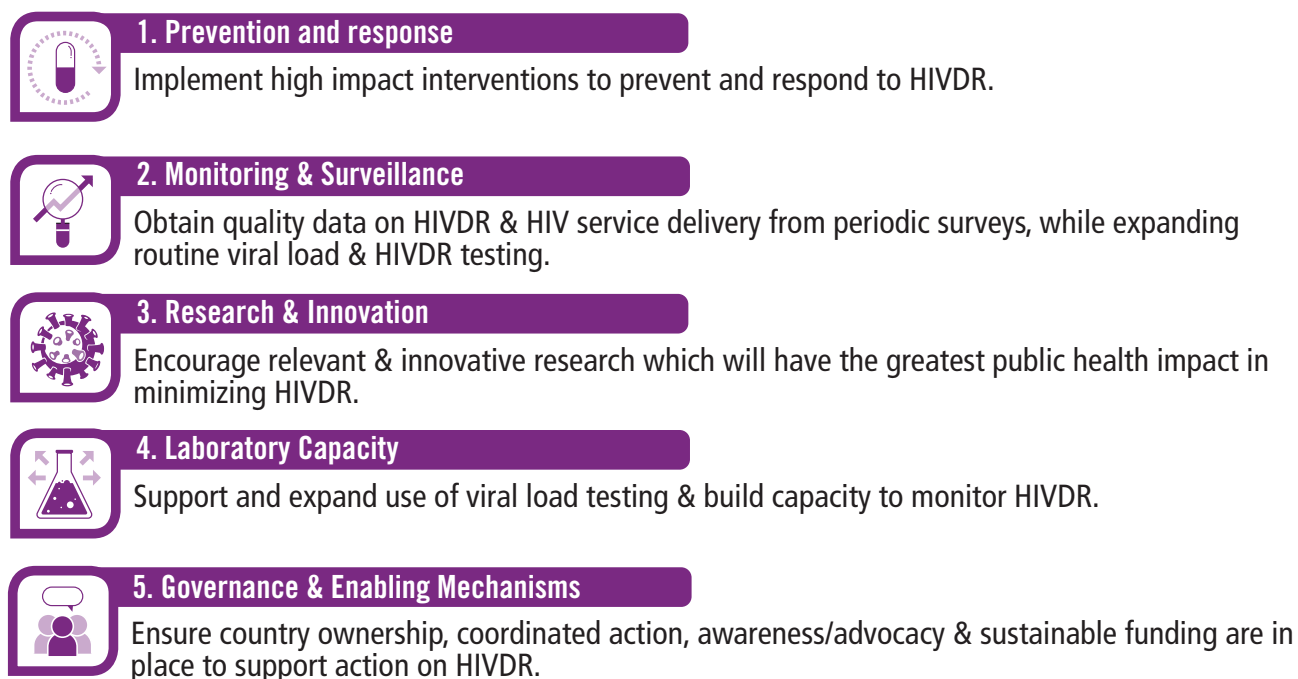
The 2016 Political Declaration on HIV and AIDS (3), and endorsement of the *Global Health Sector Strategy on HIV 2016–2021* by the World Health Assembly (4), demonstrate the United Nations Member States' commitment to ending the AIDS epidemic by 2030. To realize this goal, the GAP on HIVDR was developed 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 populations²⁶ 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

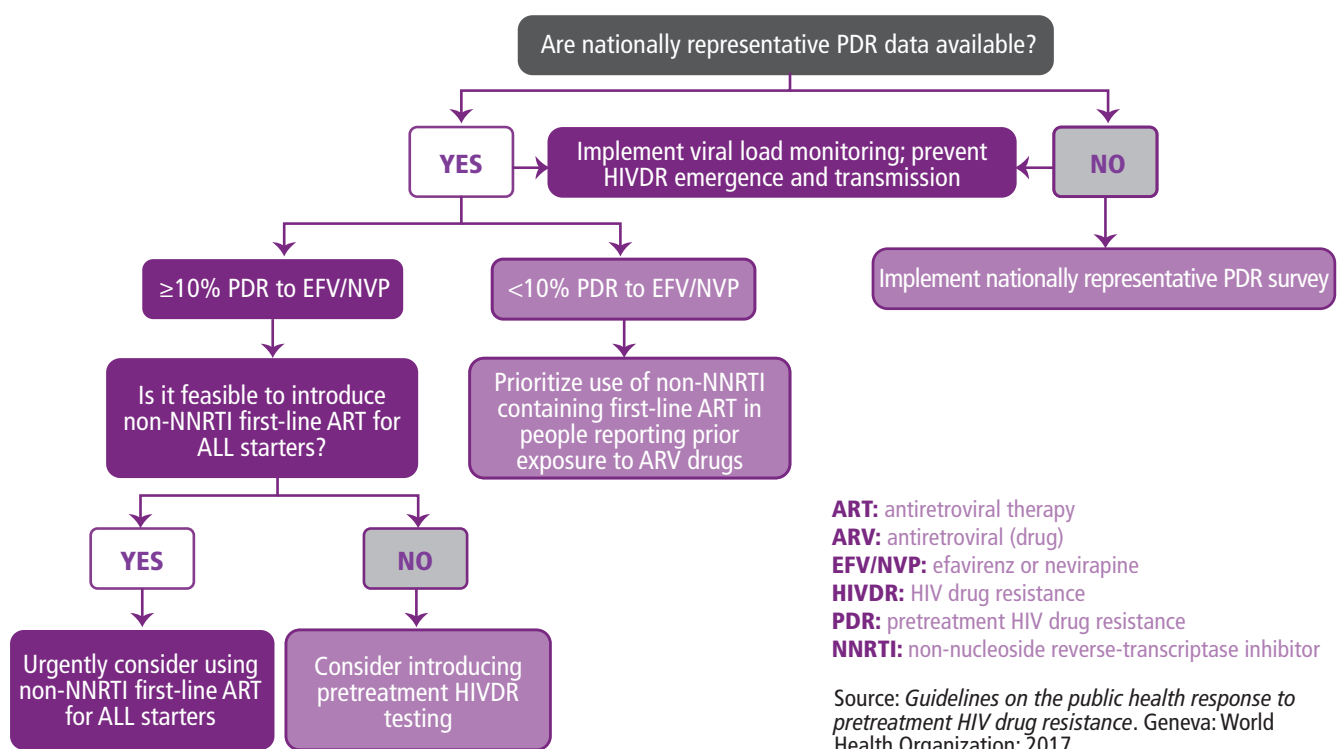
WHO's 2017 *Guidelines on the public health response to pretreatment HIV drug resistance* (2) support countries in responding appropriately to levels of NNRTI PDR in people initiating or reinitiating first-line ART. The overall aim of the guidance is to: 1) attain and maintain the treatment target of 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



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.

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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 PPS sampling. In PPS 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 months²⁷

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 $\pm 5\%$. 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 $\pm 5\%$.

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 PPSs systematic sampling, the probability that a site is selected is equal to the size of the site (M_i) 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 $M / (n * M_i)$ 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.

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

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.

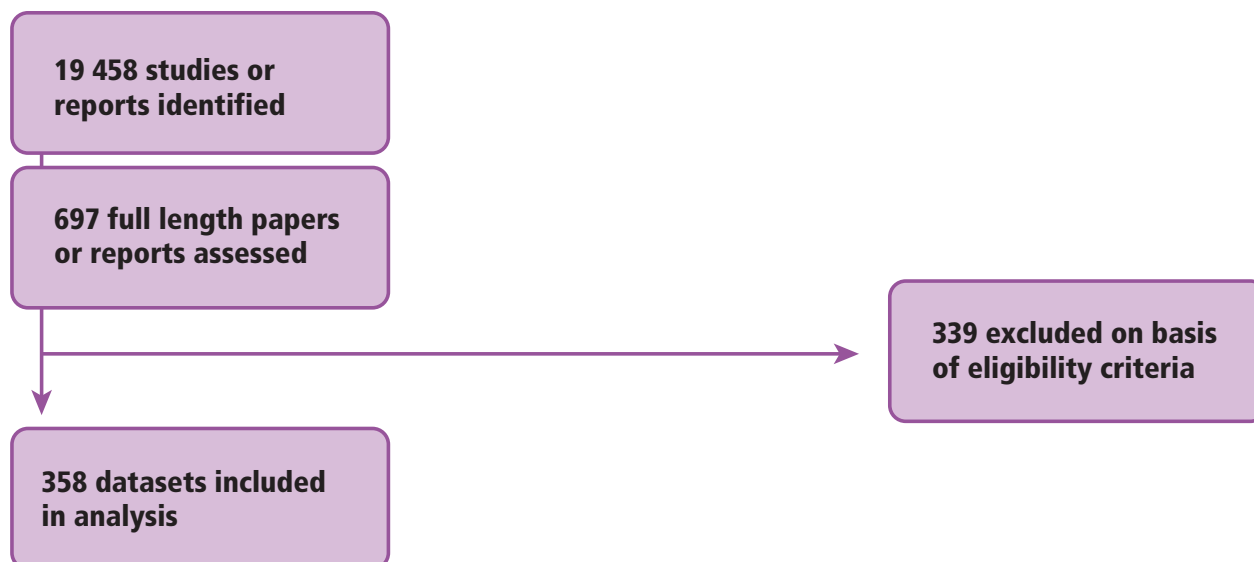
²⁸ StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

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:

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

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 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 |
| Chalermchokcharoenkit 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 |
| Gonzalez 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 |
| Dileria 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 |
| Yatse 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 |
| Ayoubu 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 las 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-Trebiat 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 las 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 laset 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 las 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 |
| Steeget 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 |

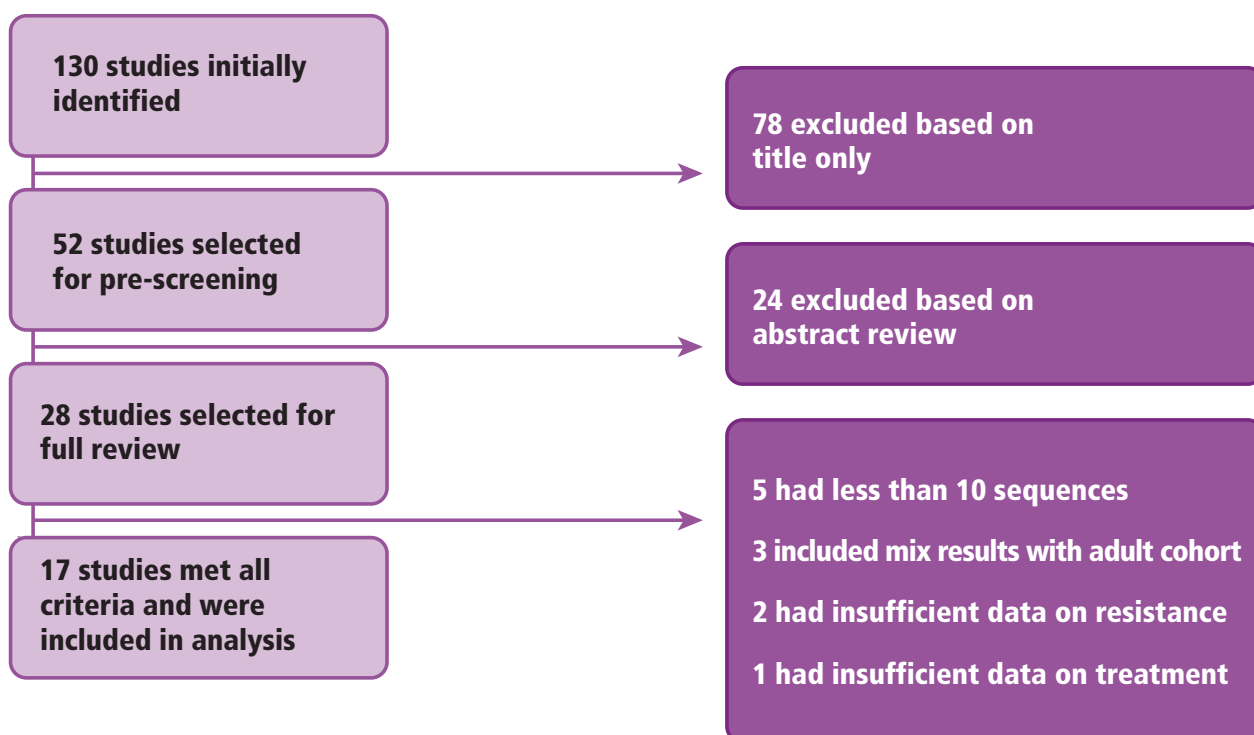
* For this systematic literature review, countries in the South-East Asia region, Western Pacific region, Eastern Mediterranean and Turkey (Europe region) are grouped under the regional heading of 'Asia'.

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 |

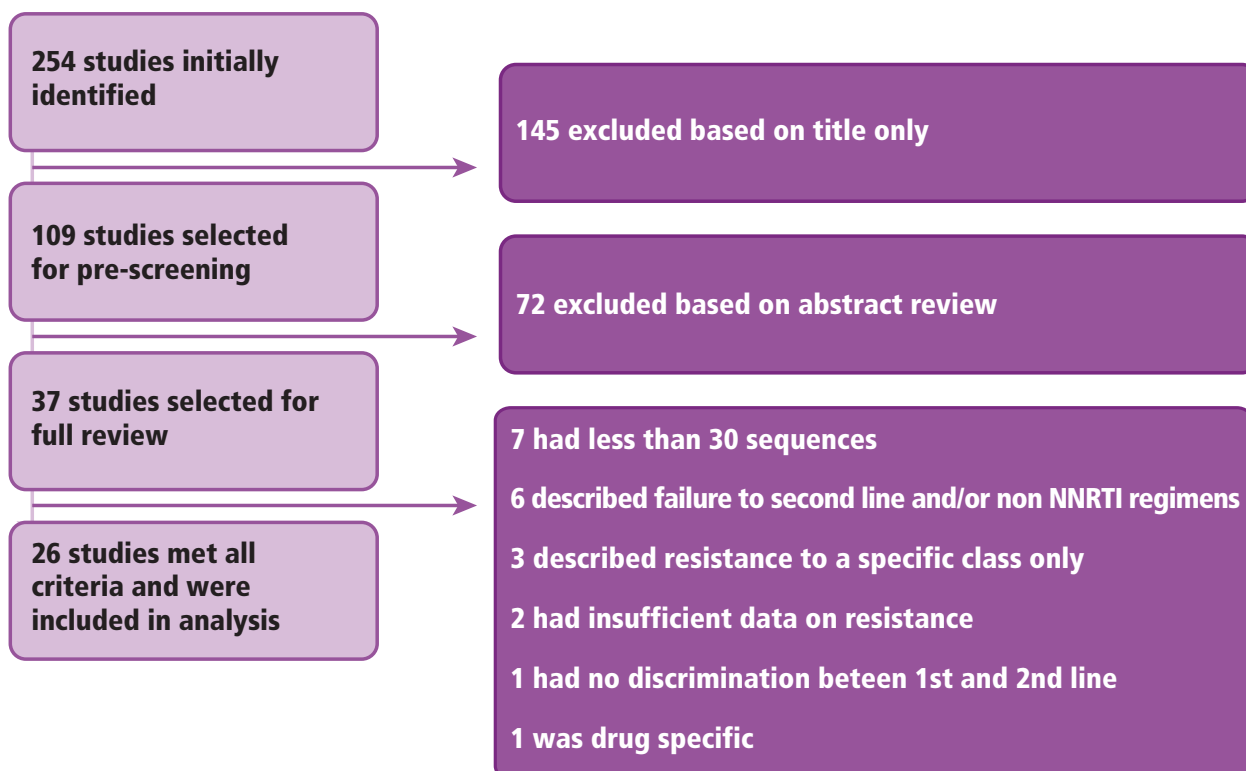
Table A3: Studies included in the literature review of acquired HIV drug resistance in children

| 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 |
| Steegeen 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.

- Denominators for reporting proportion of mutations were standardized as “number with genotype performed”.
- 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

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