HIV drug resistance

Brief report 2024

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World Health Organization

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Acronyms

3TC	lamivudine
ABC	abacavir
aOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	atazanavir/ritonavir
AZT	zidovudine
BIC	bictegravir
CAB	cabotegravir
CAB-LA	long-acting cabotegravir
CADRE	Cyclical Acquired HIV Drug Resistance
CI	confidence interval
DPV-VR	dapivirine-containing vaginal rings
DRV/c	darunavir + cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
INSTI	integrase strand-transfer inhibitor
MOSAIC	Maximizing Options to Advance Informed Choice for HIV Prevention
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse-transcriptase inhibitor
NVP	nevirapine
PEPFAR	United States President's Emergency Plan for AIDS Relief
PrEP	pre-exposure prophylaxis
RPV	rilpivirine
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TLD	TDF in combination with 3TC and DTG as a fixed-dose combination
UNAIDS	Joint United Nations Programme on HIV/AIDS

Definitions

HIV drug resistance is caused by changes (mutations) in the virus genome that affect the ability of antiretroviral (ARV) drugs to block the HIV replication. All current ARV drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus. The following are the three main categories of HIV drug resistance used in this report.

- **Acquired HIV drug resistance** develops when HIV mutations emerge because of viral replication among individuals receiving ARV drugs.
- **Transmitted HIV drug resistance** occurs when individuals are infected with HIV that has drug resistance mutations.
- **Pretreatment HIV drug resistance** refers to any drug-resistant virus detected in ARV drug–naive individuals initiating ART or individuals with previous ARV drug exposure initiating or reinitiating first-line ART. Pretreatment HIV drug resistance is either transmitted or acquired HIV drug resistance or both. Resistant virus may have been transmitted at the time of infection (transmitted HIV drug resistance) or may be selected (acquired HIV drug resistance) through previous ARV drug exposure, such as among women who received ARV drugs for preventing the mother-to-child transmission of HIV, among people who have received pre-exposure prophylaxis or among individuals reinitiating first-line ART after a period of treatment interruption.

Executive summary

HIV drug resistance can reduce the effectiveness of antiretroviral (ARV) drugs for HIV treatment and prevention, leading to an increase in HIV incidence, morbidity and mortality. Therefore, to inform public health measures, WHO recommends HIV drug resistance monitoring and surveillance as part of comprehensive antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) programmes. This brief 2024 HIV drug resistance report summarizes recent information, with a focus on HIV drug resistance in the era of integrase-strand transfer inhibitors (INSTI) for HIV prevention and treatment.

HIV drug resistance among populations receiving PrEP to prevent HIV

WHO recommends oral PrEP as a prevention option for those at risk of HIV acquisition. In 2021, more than 1.6 million people received oral tenofovir disoproxil fumarate + emtricitabine (TDF + FTC) PrEP, and in the past two years the PrEP arsenal expanded to include two new ARV drugs recommended by WHO: dapivirine-containing vaginal rings (DPV-VR) and injectable long-acting cabotegravir (CAB-LA).

Despite the success of PrEP in preventing HIV infection, the emergence of HIV drug resistance remains a concern among populations receiving it because there is a potential for overlapping resistance profiles between the ARV drugs used for PrEP and first-line ART. Monitoring resistance outside clinical trials is crucial for the effectiveness of PrEP programmes and to support national, regional and global guidance for the treatment of HIV among people acquiring HIV while taking PrEP.

Based on reports from clinical trials, open-label and demonstration studies, PrEP-associated drug resistance is low among individuals who acquire HIV while receiving oral PrEP; however, higher levels are observed if oral PrEP is initiated during undiagnosed acute HIV infection. WHO recommends surveillance of HIV drug resistance among individuals who have recently taken or are currently taking PrEP at the time of HIV diagnosis. Routine HIV drug resistance testing data can be leveraged for surveillance in countries where it is conducted for individual management.

This report summarizes the outcomes of studies published between 2020 and 2023 reporting on HIV drug resistance from users of oral TDF + FTC PrEP in clinical settings. A total of 310 unique individuals infected with HIV while taking PrEP and with drug resistance sequence information available for analysis were identified; 61 (20%) of them had PrEP-associated drug resistance.

WHO endorsed the DPV-VR in 2021 to reduce the risk of HIV infection among women. The risk of acquiring HIV while using a DPV-VR is expected to be low, although the efficacy of the DPV-VR for preventing HIV infection with drug-resistant virus remains unknown and further study is warranted.

The use of CAB-LA PrEP reduces the risk of acquiring HIV. However, there are concerns about the potential emergence of INSTI-resistant HIV. INSTI resistance has been observed in some cases with recent CAB exposure, and delayed detection and confirmation of HIV infection can increase the risk of selection of INSTI drug resistance–associated mutations. Despite the risk, the roll-out of CAB-LA PrEP should not be hindered. Since limited quantities of CAB-LA are anticipated to be available over the next 3–5 years, there is an opportunity to carefully monitor for the emergence of CAB drug resistance and to characterize the potential risk of DTG cross-resistance in well-defined populations using CAB-LA PrEP.

HIV drug resistance among infants newly diagnosed with HIV

WHO recommends monitoring HIV drug resistance among infants newly diagnosed with HIV. Only one country (Haiti) has reported data from a survey of HIV drug resistance among infants after introducing dolutegravir (DTG)-containing regimens. One infant with DTG resistance was identified whose mother had

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been receiving DTG-based ART. Effective management of high viral loads among pregnant and breastfeeding women is critical to prevent transmitting HIV to infants. The surveillance of HIV drug resistance among treatment-naive infants newly diagnosed with HIV remains highly relevant in the era of DTG-based ART, and accelerated implementation of these surveys is needed.

HIV drug resistance among adults initiating or reinitiating ART

Eleven countries reported pretreatment HIV drug resistance to DTG among adults initiating ART. Only one country (South Sudan) detected resistance to DTG at a rate of 0.2%. However, surveys were conducted before DTG was introduced or during the early stages of transition in these countries. As the use of DTG-based ART expands, it will be important to remain vigilant to any potential increasing levels of pretreatment HIV resistance to DTG and nucleoside reverse-transcriptase inhibitors, which could affect population-level treatment outcomes.

Acquired HIV drug resistance among individuals receiving ART

WHO recommends DTG-based ART as the preferred first- and second-line treatment, and more than 25 million people currently are receiving it. As part of the scale-up and maintenance of populations on ART, WHO recommends routinely implementing HIV drug resistance surveillance for DTG-based ART roll-out to effectively manage and prevent potential resistance. Given the evolving science on what would be considered concerning population levels of DTG-resistant HIV, WHO does not currently suggest thresholds of DTG resistance that would require specific actions at the country level. However, nationally, survey outcomes should address the programmatic and public health implications in the context of the most up-to-date science. When available, the aggregate analysis of survey results from various countries will be valuable at the global level in supporting the development of WHO recommendations for drug-switching strategies for people for whom DTG-based ART has failed.

In a systematic analysis of published clinical trials summarized in this report, the prevalence of INSTI-associated drug-resistance mutations among previously INSTI-naive individuals receiving DTG-containing ART with failure to suppress viral load was below 3%. Data from eight HIV cohorts, seven from high-income countries and one from an upper-middle-income country, showed that 4.8% of participants receiving DTG-based ART with unsuppressed viral load had resistance to DTG. Recent studies supported by the United States President's Emergency Plan for AIDS Relief in some low- and middle-income countries report prevalence estimates of DTG resistance among individuals receiving DTG-based ART with detectable viraemia ranging from 3.9% to 19.6%.

As of July 2023, only 10 countries had implemented surveys of acquired HIV drug resistance among adults receiving DTG-based ART; three surveys are ongoing, and 24 are planned. Additionally, only six countries have implemented surveys on acquired HIV drug resistance among children and adolescents receiving DTG-based ART, one survey is ongoing in one country and 14 are planned. More data from standardized surveys of acquired HIV drug resistance and from longitudinal observational cohorts are urgently needed from more countries in all regions to provide enhanced insight into risk factors and patterns of drug resistance emergence among individuals exposed to DTG-based ART regimens.

Assessment of programme quality indicators associated with the emergence of HIV drug resistance

Monitoring programme quality indicators associated with the emergence of HIV drug resistance remains critical for the success of ART programmes. Routine monitoring of quality-of-care indicators at the clinic and national levels and subsequent response to suboptimal performance forms the foundation of WHO's HIV drug resistance prevention, monitoring and response strategy. Key quality-of-care indicators include on-time ART pick-up, retention on ART, viral load testing coverage, timely second-viral load test, viral load suppression, ARV drug stock-outs and timely switch to second-line ART.

Between 2017 and 2022, 44 of 45 WHO focus countries reported programmatic data through the Joint United Nations Programme on HIV/AIDS (UNAIDS). In most countries, programmatic quality indicators for HIV treatment did not achieve established global targets, highlighting the need to proactively improve the quality of HIV treatment and care services. In 2022, only 12 of these 45 focus countries reported conducting ad hoc surveys or had integrated the monitoring of early warning indicators into routine monitoring and evaluation systems. It is important to improve data reporting systems so that all countries can effectively monitor and report quality-of-care indicators. This will ultimately help to improve the quality of HIV service delivery and prevent the development of HIV drug resistance.

The introduction of DTG-containing regimens coupled with the expansion of PrEP for preventing HIV infection, including new drugs such as CAB-LA, promises to revolutionize HIV care and prevention. However, early signals of DTG resistance among people for whom DTG-containing regimes fail to achieve viral suppression highlight the ongoing need for vigilance and intensified efforts to optimize the quality of HIV care delivery to maximize individual and population-level outcomes coupled with standardized routine surveillance of HIV drug resistance to prevent, monitor and respond to the potential threat of HIV drug resistance.

Introduction

When HIV replicates in the presence of antiretroviral (ARV) drugs, drug-resistant HIV can be selected. HIV drug resistance can compromise the efficacy of ARV drugs for HIV prevention and treatment, contributing to a rise in HIV incidence, morbidity and mortality *(1,2)*. WHO therefore recommends the systematic and periodic surveillance of HIV drug resistance to inform public health recommendations at the local, national and global levels *(3)*.

WHO recommends oral TDF-containing pre-exposure prophylaxis (PrEP), dapivirine-containing vaginal rings (DPV-VR) and injectable long-acting cabotegravir (CAB-LA) as prevention options for those at risk of acquiring HIV *(4–8)*. WHO recommends that PrEP scale-up be accompanied by surveillance of HIV drug resistance. This report includes a summary of studies published between 2020 and 2023 reporting on HIV drug resistance from users of oral tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) PrEP in clinical settings, an example of a country implementing routine surveillance of HIV drug resistance among PrEP users diagnosed with HIV and a brief on HIV integrase resistance in the setting of CAB-LA PrEP use (Section 1).

In 2019, WHO recommended dolutegravir (DTG)-based antiretroviral therapy (ART) as the preferred first-line regimen for children, adolescents and adults living with HIV and as the preferred second-line ART for individuals receiving NNRTI-based ART with unsuppressed viral load *(9)*. WHO recommends monitoring HIV resistance to DTG in surveys of pretreatment and acquired HIV drug resistance *(3)*.

This report summarizes data on HIV drug resistance to DTG among treatment-naive infants from one country that has implemented a survey among treatment-naive infants after introducing DTG-containing regimens and has shared data with WHO (Section 2).

WHO recommends genotyping the integrase region in addition to the reverse-transcriptase and protease regions of HIV for the surveys of pretreatment HIV drug resistance *(3)*. Section 3 summarizes the results from surveys of pretreatment HIV drug resistance to DTG in surveys conducted before DTG-based ART was introduced or during the early stages of transition countries reporting data. As the scale-up and maintenance of DTG-based ART continues, implementation of surveys of pretreatment HIV drug resistance will take on increasing priority since vigilance for signs of detectable levels of pretreatment HIV resistance to DTG will be critical in assessing programme functioning and in informing regimen selection.

WHO recommends as a high priority monitoring HIV drug resistance to DTG by implementing surveys of acquired HIV drug resistance *(3)*. WHO has published survey methods for the surveillance of acquired HIV drug resistance to DTG *(10–12)*. As of July 2023, only 10 countries had conducted surveys of acquired HIV drug resistance among adults receiving DTG-based ART, and only six countries had conducted such surveys among children and adolescents. Substantially more data from standardized surveys are urgently needed from more countries to characterize the prevalence and patterns of drug resistance-associated mutations among individuals receiving DTG-based ART. This report briefly summarizes available data from clinical trials on the prevalence of DTG resistance among people for whom DTG-containing regimens are failing. In addition, early signs of HIV resistance to DTG outside clinical trials are presented, including data from cohort studies and cross-sectional surveys (Section 4).

Finally, this report frames the results of quality-of-care indicators associated with HIV drug resistance and/or viral load suppression generated through the reporting of Global AIDS Monitoring (Section 5). Monitoring of quality-of-care indicators associated with HIV drug resistance is highly relevant to identify gaps in service delivery that can be corrected at the clinic or programme level to minimize the possible risk of HIV drug resistance and optimize overall ART programme performance.

Chapter 1

HIV drug resistance among populations receiving PrEP to prevent HIV

In 2015, WHO recommended daily oral TDF + FTC PrEP as an additional prevention option for individuals at substantial risk of acquiring HIV *(4)*. Event-driven PrEP is an alternative option recommended for cisgender men who have sex with men *(5)*. In addition, WHO recommended using DPV-VR in 2021 and CAB-LA in 2022 as additional HIV prevention options *(6–8)*. As of September 2023, the cumulative number of people initiating PrEP globally was about 5.7 million *(13)*.

> ARV drugs as a component of combination HIV prevention are a highly effective tool in reducing the incidence of HIV.

The risk of drug resistance among individuals who acquire HIV while taking PrEP remains a concern since the drugs and drug classes used for PrEP overlap with those that comprise first-line ART with TDF + FTC and DTG. PrEP-associated HIV drug resistance can occur if PrEP is taken during undetected acute infection, if PrEP is continued after infection or if PrEP fails to protect against the transmission of drug-resistant HIV *(14)*.

> HIV drug resistance may occur if PrEP is initiated during acute HIV infection, continued after infection or fails to protect against acquiring drug-resistant virus.

As PrEP is rolled out, resistance monitoring will be required to estimate the prevalence of HIV drug resistance among PrEP users who acquire HIV in real-world settings *(15)*. WHO recommends that the scale-up of PrEP be accompanied by surveillance of HIV drug resistance that may compromise the effectiveness of first-line ART among PrEP users who acquire HIV and future PrEP use *(3,8,16)*. Since HIV infection is expected to be rare among individuals using PrEP, WHO recommends a cross-sectional survey that aims to gather information about all individuals who have recently taken (≤3 months) or are currently taking PrEP at the time of HIV diagnosis *(16)*. In countries where HIV drug resistance testing is conducted for individual management, routine drug resistance test results can be aggregated annually to estimate the prevalence of HIV drug resistance among those who have recently taken PrEP or are taking PrEP at the time of HIV diagnosis.

> WHO recommends monitoring HIV drug resistance that may arise because of scaling up PrEP.

Few countries have initiated surveillance of HIV drug resistance among PrEP users. In 2022, Indonesia adopted oral PrEP as a preventive strategy, and HIV drug resistance testing was included in the clinical management for PrEP users diagnosed with HIV (Box 1).

Box 1. HIV drug resistance testing among PrEP users diagnosed with HIV in Indonesia

In 2022, Indonesia began administering PrEP as a preventive measure against HIV infection. The roll-out was implemented in 57 health-care facilities across 10 provinces. Because of concerns about drug-resistant HIV among PrEP users, the Ministry of Health of Indonesia included HIV drug resistance testing as part of the clinical care management for PrEP users diagnosed with HIV.

In accordance with Indonesia's guidelines, individuals taking a daily or event-driven oral PrEP, with either TDF alone or combined with FTC, undergo HIV testing every three months. If PrEP users test positive for HIV, they immediately initiate ART. At the time of ART initiation, a blood specimen is taken, and HIV drug resistance testing is performed at the National Reference Laboratory in accordance with WHO-recommended methods *(16)*.

Between January 2022 and June 2023, 5653 individuals initiated PrEP (unpublished data, Ministry of Health, Indonesia). On average, PrEP users were retained in the programme for 5 months. Four PrEP users were diagnosed with HIV infection, and drug resistance testing was performed on all four. One of the four PrEP users diagnosed with HIV had the M184I mutation in reverse transcriptase, conferring resistance to 3TC + FTC.

To effectively mitigate the risk of resistance and obtain deeper understanding of the long-term implications of drug-resistant HIV among PrEP users, Indonesia plans to sustain ongoing surveillance efforts and to conduct additional operational research to support the improvement of HIV prevention strategies.

1.1 Update on HIV drug resistance among people seroconverting on oral TDF+ FTC PrEP

The prevalence of PrEP-associated resistance (defined by the detection of the TDF-associated nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) mutation K65R and/or the 3TC-associated mutation M184I/V) is low (15 reports of PrEP-associated resistance among 281 incident infections; 5%) for individuals who acquire HIV while receiving PrEP; the prevalence is more than 10-fold higher (18 of 31; 58%) if PrEP is initiated during undiagnosed acute infection, based on reports from clinical trials, open-label and demonstration studies *(14)*.

A literature review was conducted assessing the literature published between 2020 and 2023 using PubMed with the search terms "HIV", "PrEP" and "resistance" that reported on HIV drug resistance from users of oral TDF + FTC PrEP in population or community-based cohorts or implementation projects or extracted from public health data. Nine cohort studies and six case reports were included in the analysis. In addition to cases identified in the literature review, available data from the ongoing national PrEP monitoring protocols through the Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) consortium are reported.

In total, 470 seroconversions on oral PrEP have been reported in studies performed in clinical settings (the nine studies included and MOSAIC data; see Table 1), of which HIV drug resistance sequence data are available for 310 cases (66%). Of the 310 unique cases identified, 61 (20%) had PrEP-associated resistance mutations (K65R mutation conferring resistance to TDF and/or M184IV mutation conferring 3TC + FTC resistance). Because these seroconversions occurred in a clinical or implementation setting, retrospective data were unavailable to determine whether any of these individuals had initiated PrEP during undetected acute infection. Further, the infection rate among the total number of individuals prescribed PrEP is unknown since many cohorts extracted PrEP use from the clinical records of all newly diagnosed individuals in a specific setting.

> "Of the 310 reported seroconversions on oral PrEP between 2020 and 2023 in clinical settings, 20% had PrEP-associated resistance.

Table 1. HIV drug resistance among reported cases of HIV-1 seroconversion among people receiving TDF + FTC PrEP in clinical settings

Cohort	Study period	Data source	Number of PrEP users[a] who acquired HIV	Number sequenced	Number (%) with PrEP-associated resistance (K65R and/or M184I or V)
King County, Washington, United States of America *(17)*	10/2013–08/2021	Clinical or public health records	19	18	8 (44%)
EPIC-NSW, New South Wales, Australia *(18)*	03/2016–04/2018	Implementation study	32	30	1 (3%)
56 Dean St, London, United Kingdom *(19)*	01/2015–12/2020	Clinical or public health records	52	52	13 (25%)
San Francisco, California, United States of America *(20)*	01/2011–12/2018	Clinical or public health records	7	7	1 (14%)
SEARCH; western Kenya and Uganda *(21)*	06/2016–04/2019	Implementation study	25	10	1 (10%)
CohMSM-PrEP; Burkina Faso, Côte d'Ivoire, Mali and Togo *(22)*	11/2017–06/2021	Community-based clinical cohort	25	20	1 (5%)
Shenzhen, China *(23)*[b]	01/2021–03/2022	Retrospective clinical cohort	17	17	2 (12%)
NEPOS, Germany *(24)*	09/2019–12/2020	National cohort	4	4	1 (25%)
Mombasa, Kenya *(25)*	06/2017–06/2019	Vaccine-preparedness cohort	5	5	0 (0%)
GEMS/MOSAIC, Eswatini, Kenya, South Africa and Zimbabwe *(14,26)*	12/2017–07/2023	National protocols	284	147	33 (22%)
Total			**470**	**310**	**61 (20%)**

[a] PrEP use includes individuals reporting using PrEP, having documented recent or previous PrEP use, having been dispensed PrEP or receiving PrEP at the time of HIV diagnosis.

[b] Seroconversions include individuals receiving PrEP or post-exposure prophylaxis; the data are not disaggregated in the report.

In addition to the cohort's studies, between 2020 and 2023, six case reports of PrEP-associated resistance after breakthrough infection have been reported; four of these six also reported ART outcomes (Table 2). An individual in Amsterdam, Netherlands (Kingdom of the) on event-driven PrEP was diagnosed with HIV-1 harbouring the K65R and M184V mutations *(27)*, and an individual in San Francisco, United States of America receiving daily oral PrEP with high adherence was identified as being infected with HIV-1 and having multiple mutations in the reverse-transcriptase region: K70N, M184V, V179R and P225H *(28)*. In a third case, a woman receiving oral PrEP in KwaZulu-Natal, South Africa diagnosed with HIV infection with virus having the K65R and M184V mutations after prolonged undetected HIV infection achieved suppression of viral load with zidovudine (AZT) + 3TC + efavirenz (EFV) *(29)*. In a fourth case, an adolescent male with HIV having the M184V mutation continued to have suppressed viral load at two years while receiving FTC + TDF + bictegravir *(30)*. One case in Barcelona, Spain with irregular PrEP adherence for six months was diagnosed with HIV with M184V and K103N; a second case in Barcelona seroconverted one month after starting PrEP and had HIV with M184V. Both individuals achieved viral suppression on FTC + tenofovir alafenamide (TAF) + bictegravir (BIC) + darunavir + cobicistat (DRV/c) 45 days after ART initiation *(31)*. Although data are scarce, these case reports suggest that people with PrEP-associated NRTI-resistant virus may achieve suppressed viral loads with currently available ART, although continued monitoring to assess long-term outcomes is needed and more data are needed from low- and middle-income countries.

Table 2. Cases of seroconversion on TDF + FTC PrEP and subsequent treatment outcomes

Case	PrEP regimen	Self-reported adherence	Mutations in reverse transcriptase at seroconversion	Timepoint at which viral suppression[a] was achieved and treatment regimen
Amsterdam *(27)*	Event-driven PrEP	Excellent	K65R, M184V	Unknown
San Francisco *(28)*	Oral daily PrEP	High	K70N, M184V, V179R, P225H	Unknown
KwaZulu-Natal *(29)*	Oral daily PrEP	High	K65R, M184V	5 months; AZT + 3TC + EFV
Los Angeles *(30)*	Oral daily PrEP	Excellent	M184V	5 months; FTC + TDF + BIC
Barcelona *(1,31)*	Oral daily PrEP	Irregular	M184V, K103N	45 days; initiated on FTC + TAF + BIC + DRV/c then simplified to FTC + TAF + BIC
Barcelona *(2,31)*	Oral daily PrEP	Unknown	M184V	45 days; initiated on FTC + TAF + BIC + DRV/c then simplified to FTC + TAF + BIC

[a] Viral suppression defined as undetectable HIV-1 RNA at the time of measurement, listed in days or months after initiation of ART.

1.2 Ongoing studies with other PrEP alternatives: DPV-VR and CAB-LA

Some level of resistance to DPV and CAB may be anticipated among PrEP users who acquire HIV while using the DPV-VR or CAB-LA. The risk of acquiring drug-resistant virus among those infected with HIV despite using a DPV-VR is anticipated to be low based on two Phase 3 studies that showed that non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance selection was independent of study arm *(32–34)*. In contrast, the efficacy of DPV-VR against transmitted resistant strains in regions with high prevalence of NNRTI pretreatment drug resistance remains unknown.

Although the risk of acquiring HIV is substantially reduced among CAB-LA PrEP users, there have been concerns about the potential emergence of integrase strand-transfer inhibitor (INSTI)-resistant HIV because of the prolonged pharmacokinetic "tail" of CAB-LA after cessation of injections and the delayed detection and confirmation of HIV infection among people using CAB-LA PrEP (Box 2). These factors can increase the risk for selection of HIV with INSTI resistance-associated mutations before ART initiation. To date, 10 cases of INSTI resistance have been reported among people who received CAB-LA PrEP in HPTN 083; all 10 cases had mutations that confer cross-resistance to DTG.

A modelling study from sub-Saharan Africa predicted a rise in the total number of individuals living with INSTI-resistant HIV *(36)*. The study estimated that, 20 years after CAB-LA PrEP introduction, about 13% of ART initiators would have INSTI resistance versus 1.7% in the absence of CAB-LA PrEP. Nevertheless, implementing CAB-LA PrEP would lead to 29% decrease in the incidence of HIV and a reduction in the number of people dying from HIV-related causes *(35)*.

The roll-out of CAB-LA PrEP should not be deterred by concerns about HIV INSTI resistance. Instead, maintaining a vigilant approach to monitoring and managing potential resistance is imperative. WHO is currently examining the optimal approach to surveillance of pretreatment HIV drug resistance among CAB-LA PrEP users diagnosed with HIV and anticipates updating its PrEP survey guidance to specifically address drug resistance concerns in the era of CAB-LA as PrEP. In addition, operational research and monitoring data from PrEP programmes are essential to identify factors associated with HIV acquisition and emergence of HIV drug resistance and to examine how PrEP-associated HIV drug resistance can potentially affect the effectiveness of WHO-recommended first-line ART.

> "Although the risk of HIV INSTI resistance poses a potential challenge, it should not hinder the roll-out of CAB-LA PrEP.

Moreover, the most effective HIV testing strategies and their frequency during CAB-LA implementation have yet to be defined *(6)*. Several key aspects must be addressed, such as the risk of late diagnosis and treatment, the best methods for detecting HIV infection following CAB-LA initiation and the feasibility and acceptance of HIV testing approaches and frequency in real-world settings.

1.3 Considerations for future ART among individuals with PrEP-related resistance

DTG-based ART may prove to be successful for individuals who seroconvert on oral PrEP with TDF or FTC resistance, although the long-term outcomes remain unknown and additional study is required. The efficacy of the DPV-VR against transmitted resistant strains in regions with high prevalence of NNRTI pretreatment drug resistance remains unknown; however, NNRTI resistance among DPV-VR seroconversions would not affect currently recommended ART regimens. Surveillance of drug resistance among those who acquire HIV-1 in the setting of CAB-LA will be essential as will evaluation of their long-term viral outcomes on DTG-based ART.

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Box 2. INSTI resistance in the setting of CAB-LA PrEP

CAB is an HIV INSTI. Other INSTIs, such as DTG, are anchoring agents recommended for HIV treatment worldwide *(8,36)*. The HIV Prevention Trials Network (HPTN) 083 and 084 trials demonstrated the superiority of CAB-LA PrEP versus daily oral TDF + FTC PrEP for preventing the sexual transmission of HIV *(37,38)*. HPTN 083 enrolled men who have sex with men and transgender women in North America, South America, Asia and Africa, and HPTN 084 enrolled cisgender women in sub-Saharan Africa. In both trials, infections were rare among people randomized to CAB-LA PrEP, and most of the people acquiring HIV in the CAB-LA study arm were people with no recent CAB exposure *(39–41)*.

Despite the low frequency of HIV infections with CAB-LA PrEP, concerns have been raised that using an INSTI for HIV PrEP may increase the emergence and possible transmission of INSTI-resistant HIV, compromising HIV treatment and prevention efforts over time. Two factors could contribute to the emergence of INSTI resistance in the setting of CAB-LA PrEP. First, CAB has a long terminal half-life (or pharmacokinetic "tail") after cessation of injections; CAB concentrations were still quantifiable in 23% of cisgender men and 63% of cisgender women 52–60 weeks after a final injection in the Phase 2a HPTN 077 trial *(42)*. Second, detection and confirmation of HIV infection are often delayed among people who acquire HIV infection in the setting of CAB-LA PrEP because of prolonged viral suppression, diminished or delayed antibody production and an absence of symptoms associated with acute HIV infection *(40,41,43)*. These factors can provide an extended period of drug exposure, increasing the risk for selection of HIV with INSTI resistance-associated mutations before ART initiation *(39–41,44)*.

INSTI resistance has been observed in HPTN 083 but has not been observed to date in HPTN 084. In HPTN 083, INSTI resistance was observed in 10 of 16 of the cases with recent CAB-LA exposure but has not been observed to date among participants with no recent CAB-LA exposure (no injections within six months of the first HIV-positive visit) *(40)*. This time window may be longer among cisgender women because of the longer apparent terminal half-life of CAB among people assigned female at birth *(42)*. Among people who acquired HIV infection in the setting of CAB-LA PrEP, major INSTI resistance-associated mutations often emerged early and continued to accumulate when the viral load was below the level usually required for HIV genotyping (<500 copies/mL) *(44)*. Delayed detection and confirmation of HIV infection and delayed ART initiation enabled the accumulation of INSTI resistance-associated mutations in many cases *(44)*. In all cases reported to date, cross-resistance to DTG was predicted based on the pattern of INSTI resistance-associated mutations detected; in some cases, predicted DTG resistance increased over time before the infection was detected using rapid tests and a combined laboratory-based antigen and antibody test. Additional studies are needed to assess the clinical response to INSTI-containing ART among people who acquire HIV infection in the setting of CAB-LA PrEP.

In HPTN 083, using a sensitive HIV RNA assay for HIV screening would have detected infection before major INSTI resistance-associated mutations emerged in most cases and before INSTI resistance-associated mutations accumulated in other cases *(40,44)*. Although HIV RNA screening does enable earlier detection of HIV infection in this setting, it is not feasible or affordable in many settings. False-negative HIV RNA screening test results are also problematic in the setting of CAB-LA PrEP since RNA levels may drop below the level of detection, and other tests routinely used for HIV diagnosis may be negative or non-reactive for prolonged periods, complicating clinical management *(43)*. Given the proven high efficacy of CAB-LA PrEP and the low frequency of infections among people with on-time injections, cases with INSTI resistance among people using this regimen are likely to be infrequent compared with cases in which INSTI resistance emerges during treatment failure with INSTI-based regimens *(36,45)*. Additionally, because HIV RNA levels are often low among people using CAB-LA PrEP, the risk of transmission of INSTI-resistant HIV to others through sexual contact may be low in early infection. In short, close monitoring for HIV infection during and following CAB-LA PrEP use with prompt ART initiation would likely reduce INSTI resistance risk and possible onward transmission of INSTI resistant-HIV.

Chapter 2

HIV drug resistance among infants newly diagnosed with HIV

WHO recommends monitoring HIV drug resistance among treatment-naive infants newly diagnosed with HIV *(3)* to estimate the prevalence of drug resistance among treatment-naive infants younger than 18 months in a given year *(46)*. As countries shift to DTG-based ART for adults and children, this surveillance approach remains relevant, and WHO advises genotyping the integrase region along with the reverse-transcriptase and protease regions.

> As the use of DTG-based ART is scale up, remaining vigilant in preventing and monitoring HIV drug resistance among infants newly diagnosed with HIV is imperative.

Two countries have shared with WHO data on their surveillance of HIV drug resistance to DTG among treatment-naive infants newly diagnosed with HIV following WHO-recommended methods. In Namibia, no INSTI drug resistance was observed among infants in a survey conducted in 2016. However, this survey was conducted before DTG was introduced in the country. In contrast, Haiti determined that a treatment-naive infant newly diagnosed with HIV whose mother was receiving DTG-based ART had INSTI drug resistance (Box 3).

Effectively managing high viral loads among pregnant and breastfeeding women is critical to prevent transmitting HIV to infants. The infant with reported DTG resistance in Haiti serves as a reminder of the need for HIV drug resistance surveillance among infants in the DTG-treatment era. Additionally, it underscores the need for promptly managing high viral loads among pregnant and breastfeeding women and supports HIV drug resistance surveillance efforts targeting ART-naive infants born to mothers in low- and middle-income countries scaling up and maintaining populations on DTG-containing regimens. WHO encourages countries to conduct HIV drug resistance surveys among infants as DTG-based ART is scaled up.

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Box 3. A perinatally HIV-infected infant in Haiti with DTG resistance

Drug-resistant HIV can infect infants who contract HIV from their mothers during childbirth, or they may develop HIV drug resistance from exposure to low levels of ARV drugs present in breast-milk or from subtherapeutic postnatal infant prophylaxis. Haiti documented a case of an infant who was infected with HIV postnatally during breastfeeding, had not received any previous treatment and was found to be resistant to DTG *(47)*.

The mother was generally non-adherent to clinical appointments and had a detectable HIV viral load three weeks before delivery (7761 copies/mL) while receiving TDF + 3TC + DTG. Information on the mother's previous ART and previous HIV diagnosis is unavailable.

This case was documented during a nationwide HIV drug resistance survey in Haiti implemented following WHO-recommended methods. The survey involved 83 infants born to mothers taking DTG-based regimens and diagnosed with HIV through the national early infant diagnosis programme between April 2020 and March 2021.

The infant had a virus with the R263K mutation in the integrase region, which confers intermediate-level resistance to DTG, and the M184V mutation in the reverse-transcriptase region, conferring low- and high-level resistance to abacavir (ABC) and 3TC, respectively, and the K103N mutation conferring resistance to EFV + nevirapine (NVP). Drug resistance was interpreted using the Stanford HIV drug resistance algorithm (Version 9.09). The recommended regimen for children of DTG + ABC + 3TC had a genotypic susceptibility score of 0.75, with a score of less than 2 considered to have suboptimal activity.

One week after diagnosis, the infant was initiated on lopinavir + ritonavir + ABC + 3TC and remained on it for 10 months when he was transitioned to DTG + ABC + 3TC because of a lopinavir-ritonavir drug shortage and the national recommendation on the transition to DTG. Drug resistance information was not available to guide treatment initiation or transition. Seven months after transitioning to DTG + ABC + 3TC, the infant had a viral load of 839 copies/mL.

Unfortunately, no drug resistance testing of the mother's virus is available. In addition, there was an inability to ascertain whether the infant was infected with a DTG-resistant virus or whether the resistance was selected because of ingesting subtherapeutic levels of DTG in breast-milk. However, since the infant did not receive NNRTI-containing postnatal prophylaxis, the observed resistance is likely to at least be attributed to infection with a resistant virus.

This first case reported underscores the need for promptly managing high viral loads among pregnant and breastfeeding women to prevent neonatal transmission of HIV and promote HIV drug resistance surveillance efforts targeting ART-naive infants born to mothers in low- and middle-income countries.

Moreover, well-designed studies are needed to determine the mechanism of DTG resistance among perinatally infected infants. This case suggests the need for frequent viral load testing of perinatally HIV-infected infants and close clinical follow-up to ensure viral load suppression. Wherever feasible and affordable, countries could consider giving priority to HIV drug resistance testing among ART-naive, DTG-exposed infants initiating DTG-containing regimens to prevent further selection and accumulation of resistance and to guide optimal regimen selection.

Chapter 3

HIV drug resistance among adults initiating or reinitiating ART

WHO recommends the surveillance of HIV drug resistance among adults initiating or reinitiating first-line ART to inform the choice of nationally recommended first-line ART regimens and regimens used for PrEP and post-exposure prophylaxis *(3,48)*. With more countries shifting to DTG-based first-line ART, WHO recommends genotyping not only the reverse-transcriptase and protease regions of HIV-1 but also the integrase region *(3)*.

Eleven countries reported data to WHO on the prevalence of pretreatment HIV drug resistance to DTG among adults initiating ART. Of the reported surveys, eight were from the Americas (Argentina, Belize, El Salvador, Guatemala, Mexico, Nicaragua, Paraguay and Uruguay) and three were from Africa (Ethiopia, South Sudan and Zambia) (Table 3). Only one country, South Sudan, detected resistance to DTG at a very low prevalence of 0.2% (95% confidence interval (CI) 0.0–1.2%), which was attributed to the rare non-polymorphic integrase mutation, S153F/Y. Critically, however, these surveys were conducted before DTG was introduced or during the early stages of transition in these countries and thus cannot provide evidence of an absence of DTG resistance in populations initiating or reinitiating ART as scale-up and maintenance on DTG-based ART continues.

Therefore, as the use of DTG-based ART expands, it will be important to remain vigilant to any potential signal of increased levels of pretreatment HIV resistance to DTG as well as the patterns of observed resistance mutations, which have the potential to negatively affect population-level treatment outcomes.

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> Before DTG-based ART was rolled out and scaled up, there was little if any population-level DTG resistance. Over time, maintaining alertness to possible increasing levels of pretreatment DTG drug resistance is relevant.

Table 3. Pretreatment HIV drug resistance to DTG among adults initiating or reinitiating ART, 2016–2021

Country	Survey population	HIV drug resistance	
	n	%	95% CI
Argentina (2019)	375	0.0	0.0–1.0
Belize (2021)	66	0.0	0.0–5.5
El Salvador (2018)	197	0.0	0.0–1.9
Ethiopia (2017)	341	0.0	0.0–1.1
Guatemala (2016)	206	0.0	0.0–1.8
Mexico (2017)	1855	0.0	0.0–0.2
Nicaragua (2016)	166	0.0	0.0–2.3
Paraguay (2019)	208	0.0	0.0–1.8
South Sudan (2018)	256	0.2	0.0–1.2
Uruguay (2018)	205	0.0	0.0–1.8
Zambia (2019)	135	0.0	0.0–2.8

HIV drug resistance was defined as predicted resistance penalty score ≥15 using the Stanford HIVdb algorithm.

Chapter 4

Acquired HIV drug resistance among individuals receiving ART

Since 2018, WHO has recommended DTG-based ART as the preferred first-line regimen for treatment for adults and adolescents living with HIV and as the preferred second-line ART for individuals receiving an NNRTI-based ART with unsuppressed viral load *(9)*. As of July 2023, 91% of 127 reporting countries have adopted DTG-based ART as the preferred first-line ART for adults and adolescents. Of 116 reporting countries, 77% have incorporated DTG as part of second-line ART for adults and adolescents. Additionally, DTG-containing regimens are preferred for initiating treatment among infants and children in 69% of 114 reporting countries *(49)*.

4.1 Viral load suppression among the population receiving DTG-based ART

High viral load suppression rates (>90%) have been reported among adults receiving DTG-based ART in four of the five countries reporting eight nationally representative surveys of acquired HIV drug resistance implemented during the early stages of DTG-based ART roll-out (Fig. 1). The prevalence of viral load suppression (<1000 copies/mL) among adults receiving DTG-based ART ranged from 83.3% in Belize among adults receiving ART regardless of the time on ART to 100% in Viet Nam among adults receiving ART for 12 (±3) months.

Only one in two children and adolescents receiving any ART regimen had viral load suppression in Belize. In Zambia, low viral load suppression rates were also observed among children and adolescents receiving ART; two in three had viral load suppression. However, a higher prevalence of viral load suppression was observed among those receiving a DTG-based ART versus NNRTI-based ART (Fig. 2). The prevalence of viral load suppression among the children and adolescents receiving DTG-based ART was 71.4% in Belize regardless of the time on ART, and 79.4% and 92.5% in Zambia among children and adolescents receiving DTG-based ART for 12 (±3) and 36 months, respectively. The determinants of comparably lower levels of viral load suppression in Belize are unknown and require investigation. Accelerating the transition to DTG-based ART recommended by WHO would likely increase and maintain viral load suppression among children and adolescents receiving ART. In addition, ART accessibility, acceptability and quality of care should be improved for these populations *(50)*.

4.2 Acquired HIV drug resistance among the population receiving DTG-based ART

In clinical trials, the prevalence of emergent INSTI-associated drug-resistance mutations among previously INSTI-naive individuals receiving DTG-containing ART regimens with failure to suppress viral load was below 3% (Box 4).

Fig. 1. Prevalence of viral load suppression among adults receiving ART, 2019–2022

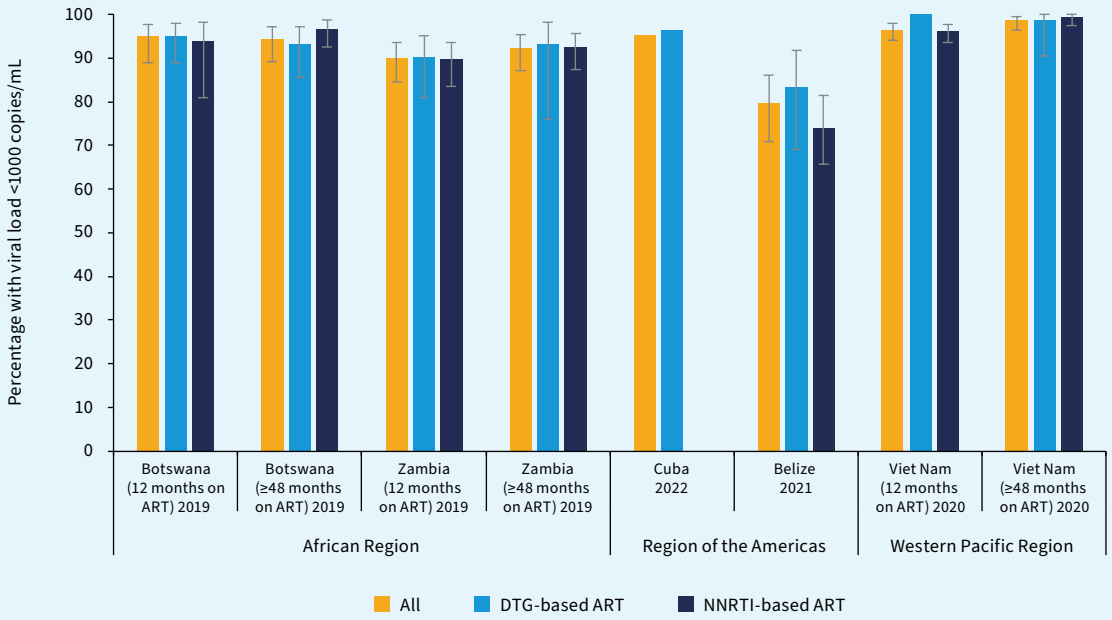

Fig. 1 shows the study design-weighted prevalence and 95% confidence interval (error bars) of HIV viral load suppression among adults receiving ART by regimen. HIV viral load suppression was defined as <1000 copies/mL. The data from Cuba correspond to all eligible cases during the survey period; thus, confidence intervals are not included. Data source: nationally representative surveys.

Fig. 2 Prevalence of viral load suppression among children and adolescents receiving ART, 2019–2021

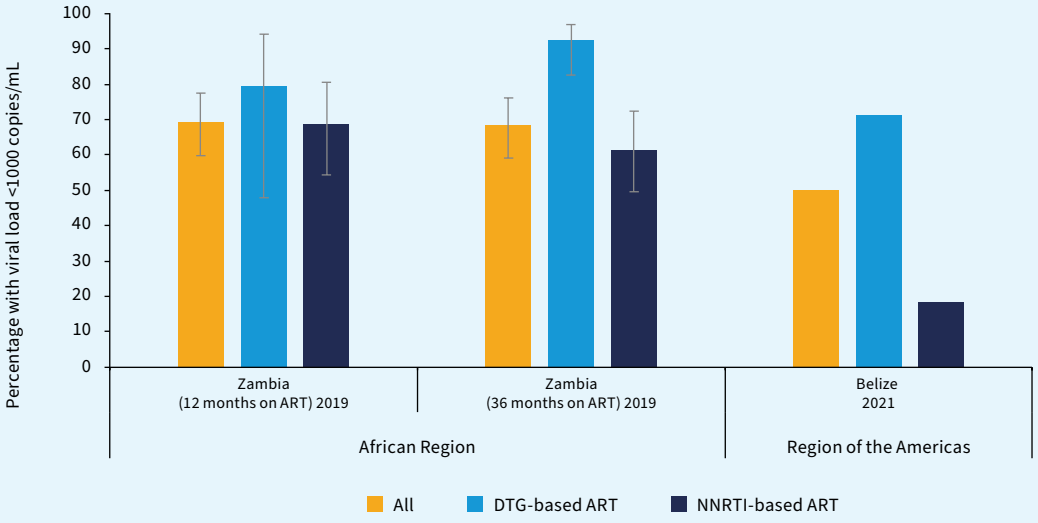

Fig. 2 shows the study design-weighted prevalence and 95% confidence interval (error bars) of HIV viral load suppression among children and adolescents receiving ART by regimen. HIV viral load suppression was defined as <1000 copies/mL. A census was conducted in Belize; thus, confidence intervals are not included. Data source: nationally representative surveys.

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Box 4. Prevalence of DTG resistance among people living with HIV with failure to suppress viral load while receiving DTG-based ART in clinical trials

A rapid review was performed to estimate the risk of failure to suppress viral load and emergent INSTI-associated drug resistance mutations in clinical trials of INSTI-naive people living with HIV receiving a DTG-containing regimen. Each trial was characterized by the ART history of the trial participants, whether participants had suppressed viral load when DTG was initiated and the type of the DTG-containing regimen. As of 24 August 2023, 78 publications describing 42 trials assessed the risk of failure to suppress viral load and emergent INSTI-associated drug resistance mutations in six clinical scenarios based on previous ART history, viral status and the DTG-containing regimen:

- **scenario 1:** ART-naive people living with HIV who started DTG plus two NRTIs (15 trials, 4588 people living with HIV);
- **scenario 2:** ART-naive people living with HIV who started DTG + 3TC (three trials, 967 people living with HIV);
- **scenario 3:** ART-experienced people living with HIV with failure to suppress viral load on an NNRTI-containing regimen who were switched to DTG plus two NRTIs (six trials, 1428 people living with HIV);
- **scenario 4:** ART-experienced people living with HIV with suppressed viral load who were switched to DTG plus two NRTIs (four trials, 930 people living with HIV);
- **scenario 5:** ART-experienced people living with HIV with suppressed viral load who were switched to DTG-based dual therapy (10 trials, 1784 people living with HIV); and
- **scenario 6:** ART-experienced people living with HIV with suppressed viral load who were switched to DTG monotherapy (four trials, 276 people living with HIV).

The prevalence of acquired INSTI-associated drug resistance mutations was 1.6% by week 48/96 in scenario 3 and 2.9% by week 24/48 in scenario 6. In contrast, the prevalence of INSTI-associated drug resistance mutations among those with failure to suppress viral load was ≤0.1% in the remaining four scenarios. Although more data are needed, the prevalence of acquired DTG-associated resistance may be higher in populations that are not as closely monitored.

The results from eight HIV cohorts, including seven from high-income countries and one from an upper-middle-income country, showed that 4.8% of participants receiving DTG-based ART with unsuppressed viral load had resistance to DTG (Box 5).

In addition, early data are becoming available from standardized cross-sectional HIV drug resistance surveys in low- and middle-income countries. In surveys conducted in Malawi, Mozambique, Uganda and Ukraine, the prevalence of DTG resistance among individuals receiving DTG-based ART with viral non-suppression (≥1000 copies/mL) was higher than anticipated based on clinical trials and ranged from 3.9% to 19.6% (Box 6). The results suggest that the management strategy for people with failure to suppress viral load should focus on expanding access to adherence interventions and that switching regimens could potentially be beneficial for about 10% (Box 6). Further, an increased trend of INSTI resistance among adults receiving DTG-based ART with unsuppressed viral load (>1000 copies/mL) and confirmed DTG exposure has been observed in two national surveys of acquired HIV drug resistance implemented in South Africa in 2021 and 2022 *(51)*. The surveys were implemented in 17 viral load laboratories covering 80% of the population receiving ART in the country. In these surveys, exposure to DTG was assessed using liquid tandem chromatography mass spectrometry. In 2021, INSTI resistance was observed among 2.7% of adults with unsuppressed viral load and detectable DTG levels. In contrast, in 2022, INSTI resistance was detected among 11.1% of adults with unsuppressed viral load and confirmed DTG exposure.

Box 5. Summary of drug resistance results among adults receiving DTG-based ART from the DTG RESIST study

The DTG-RESIST study *(52)* combined data from eight HIV cohorts to examine patterns of drug resistance mutations and identify risk factors for DTG resistance. Eight cohorts from Canada, France, Germany, Italy, the Netherlands (Kingdom of the), South Africa, Switzerland and the United Kingdom contributed data on adults living with HIV who were viraemic on DTG-based ART and underwent genotypic resistance testing.

The analysis included 599 participants who underwent genotypic resistance testing between 22 May 2013 and 20 December 2021. The participants were predominantly men and were living with HIV subtype B. They had been receiving ART for about seven years when starting DTG-based ART; the median year of starting DTG was 2016. Most (94%) study participants were fully susceptible to DTG. Resistance to DTG (low, intermediate or high level according to Stanford HIVdb) was observed for 29 (4.8%) of the participants.

The most commonly detected major drug resistance mutation was R263K (n = 10). Other mutations included G140RS, N155H, Q148HR and E138K. Three people had G118R, which has the strongest impact on susceptibility to DTG.

The risk of DTG resistance was higher for DTG monotherapy (adjusted odds ratio [aOR] 34.1, 95% CI 9.9–117) and DTG plus 3TC dual therapy (aOR 9.2, 95% CI 2.20–38.6) versus triple ART, and in the presence of potential low or low (aOR 5.2, 95% CI 1.3–20.7) or intermediate or high-level (aOR 13.4, 95% CI 4.6–39.7) NRTI resistance. Non-B HIV-1 subtypes were also associated with increased resistance, especially subtype A (aOR 3.1, 0.8–11.6 versus subtype B), but the associations were not statistically significant.

This large international study shows that, although rare, DTG resistance can develop among people with viraemia while taking DTG-containing ART. Although additional studies are warranted, some degree of DTG resistance is anticipated to emerge among people failing to achieve viral suppression while taking DTG-containing therapy, and the risk may be elevated among people with NRTI-resistant virus. Although the evidence regarding subtype differences is tentative, it indicates that non-B subtypes may possibly also be associated with an increased risk of resistance. The study underlines the importance of monitoring the emergence of DTG resistance and maximizing population-level viral suppression.

Box 6. Summary of results of the surveillance of acquired HIV drug resistance to DTG supported by PEPFAR

PEPFAR supports surveillance of acquired DTG resistance in more than a dozen countries, four of which had results available from laboratory and clinic-based surveillance at the time of this report. Two of the four reporting countries (Malawi and Mozambique) conducted clinic-based surveillance in a convenience sample, and two countries (Uganda and Ukraine) conducted nationally representative laboratory-based drug resistance surveillance following the Cyclical Acquired HIV Drug Resistance (CADRE) guidance of the United States Centers for Disease Control and Prevention.

The general CADRE method performs HIV drug resistance testing on remnant samples of viral load specimens collected for routine clinical care that meet defined criteria, including the availability of basic associated demographic data such as ART regimen and duration of ARV drug exposure. In addition, sufficient specimens must be available for HIV drug resistance testing. Broadly, CADRE is aligned with WHO-recommended survey methods.

The results described below are from ongoing analysis and may not represent the final prevalence estimates (Table 4). For the analysis, HIV resistance to DTG was defined as low, intermediate or high-level drug resistance using the Stanford HIV drug resistance database.

Between 2020 and 2021, Malawi implemented a study in 18 high-volume clinics. The study included 1035 adults retested for viral load after initial viral non-suppression while receiving a DTG-based regimen, 79.4% (822 of 1035) resuppressed (viral load <1000 copies/mL). Of the remaining 213 participants with unsuppressed viral loads, the median time since initiation of a DTG-based regimen was 2.5 years (interquartile range: 1.8–3.1). The prevalence of resistance to DTG was 8.6% (95% CI 5.3–11.9).

In Mozambique, between 2021 and 2022, a clinic-based study was conducted at seven high-volume clinical sites in the Gaza province. The study enrolled 717 adults with a high viral load (defined as >1000 copies/mL) after TDF + 3TC + DTG (TLD) transition. Of these, 69.9% (500 of 717) achieved suppression of viral load after an adherence intervention. Among the remaining 217 participants, 24 had insufficient plasma for drug resistance testing; among those with adequate specimen volume, 94.8% (183 of 193) were successfully genotyped. The median time on TLD was 20.1 months. Drug resistance to DTG was present among 8 of 70 (11.4%) people who had suppressed viral load before transition to TLD, 13 of 73 (17.8%) people with previous non-suppressed viral load before transition to TLD and 15 of 40 (37.5%) people with unknown previous viral load status. Overall, 19.6% of the participants (36 of 183; 95% CI 15.1–27.9) had resistance to DTG. Unlike the other studies listed in this section, this study enrolled only treatment-experienced individuals who had transitioned to TLD, which may explain the higher rates of DTG drug resistance, since previous non-adherence may have contributed to the accumulation of drug resistance mutations.

In Ukraine, between 2020 and 2021, 686 specimens from people with unsuppressed viral load while on any ART regimen were subject to HIV drug resistance testing following CADRE guidance. Of the 686 specimens, 594 were successfully sequenced and the overall weighted prevalence of DTG resistance was 3.7% (95% CI 1.7–5.7). Among those on a DTG-containing regimen (366 individuals), the weighted prevalence of DTG resistance was 6.6% (95% CI 2.3–10.9).

In Uganda, between 2021 and 2022, laboratory-based surveillance was implemented following the CADRE method using remnant samples from people receiving a DTG-based regimen, most commonly TLD, with viral load ≥1000 copies/mL. Among 857 remnant samples tested, 400 were from children (<15 years) and 457 adults (≥15 years). The median time on a DTG-based regimen for children and adults was 15.5 months (interquartile range 11–22) and 18 months (interquartile range 13–27), respectively. The weighted prevalence estimates of DTG resistance were 6.6% (95% CI: 3.5–9.6) for children and 3.9% (95% CI: 0.7–7.1) for adults.

Taken together, these data suggest that (1) most people receiving DTG-based regimens do not have resistance to DTG at the time of failure to suppress viral load (second unsuppressed viral load and at least nine months of DTG drug exposure); nevertheless, prevalence estimates are higher than what would have been expected based on clinical trials; (2) the management strategy for people with unsuppressed viral load on DTG-based regimens should stress expanded access to high-quality and evidence-based adherence interventions; (3) switching regimen could potentially benefit about 1 in 10 people; (4) treatment-experienced people transitioned to DTG-based regimens may have higher levels of DTG resistance than everyone receiving DTG-based regimens experiencing unsuppressed viral load. Finally, drug resistance surveillance efforts may help to inform policy-makers which populations could benefit from drug resistance testing for clinical management.

Several more PEPFAR-supported countries are in the data collection or testing stage, and the results from multicountry analysis are anticipated to have sufficient power to further delineate the risk factors and patterns of drug resistance emergence among individuals exposed to DTG-based regimens.

Despite the information gained from surveys, important questions remain and include the characterization of clinical outcomes for people with DTG resistance if they are switched to a protease inhibitor–based regimen, which incurs a higher pill burden, as opposed to continual expectant management on a DTG-containing regimen. Finally, the clinical significance of individual DTG-associated drug resistance mutations and their association with viral outcomes requires additional study.

Table 4. HIV drug resistance to DTG among adults receiving DTG-based ART in PEPFAR-supported surveys, 2020–2022

Country	Method	Sample size genotyped	Inclusion criteria	Year of sample collection	Prevalence of DTG resistance
Uganda	Laboratory-based	457 (255 amplified)	• At least nine months on a DTG-based regimen • Dried blood spots or plasma test with viral load ≥1000 copies/mL • ≥15 years of age	2021–2022	3.9%[a]
Ukraine	Laboratory-based	366 (315 amplified)	• At least nine months on a DTG-based regimen • Plasma viral load ≥1000 copies/mL • >18 years of age	2020–2021	6.6%[a]
Mozambique	Clinic-based	193 (183 amplified)	• Treatment-experienced people transitioned to TLD experienced persistent failure to suppress viral load (viral load >1000 copies/mL) • >18 years of age	2021–2022	19.6%
Malawi	Clinic-based	213 (212 amplified)	• At least nine months on a DTG-based regimen • Viral load ≥1000 copies/mL • ≥15 years of age	2020–2021	8.6%[a]

At the time of protocol development, the transition to TLD roll-out was just beginning in Ukraine; however, 53.8% of the specimens successfully sequenced were from people receiving a DTG-based regimen. HIV resistance to DTG was defined as low, intermediate or high-level drug resistance using the Stanford HIV drug resistance database. Prevalence accounts for specimens with drug resistance-associated mutations to DTG, divided by the denominator of all samples successfully amplified.

[a] Weighted analysis. In the case of Uganda, the weighted analysis was conducted by adjusting for genotyping failure using a propensity score model.

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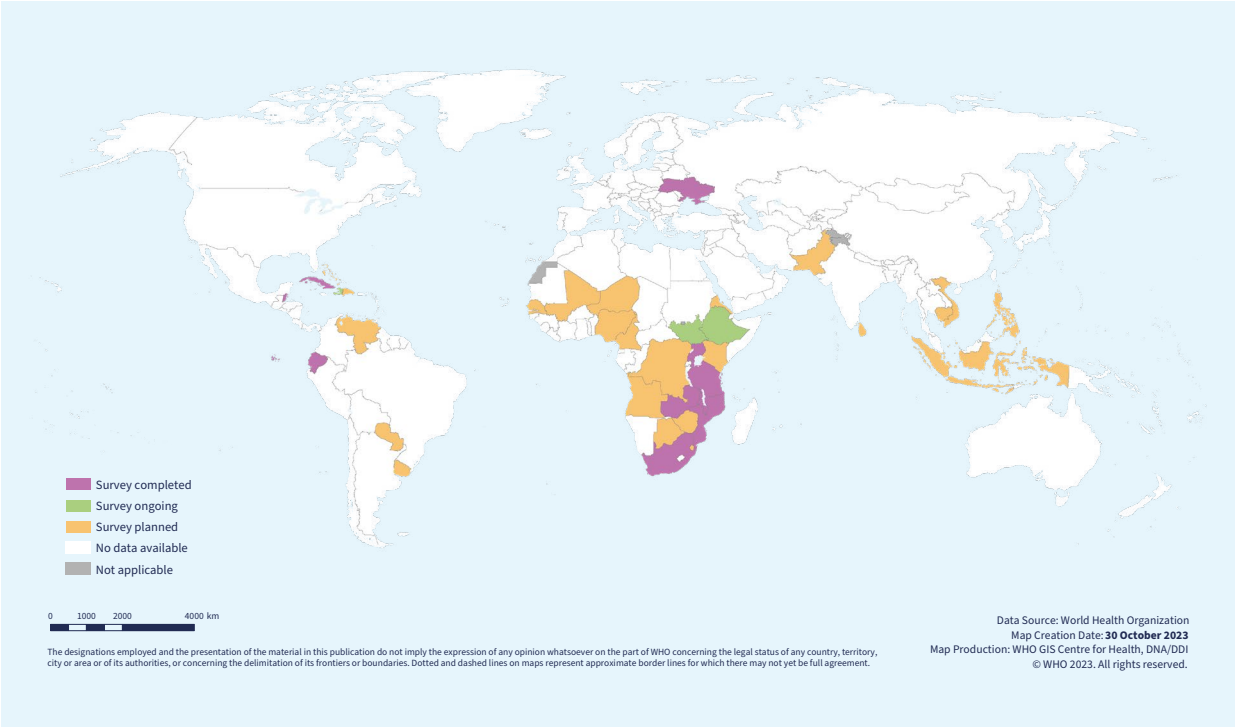
WHO recommends that countries scaling up DTG-containing ART conduct routine drug resistance surveillance to obtain information about the prevalence and patterns of acquired DTG resistance *(3,10–12)*. Given the evolving science on what would be considered concerning (or high) population levels of DTG-resistant HIV, how signals of acquired DTG-resistant HIV detected using this or other survey methods would potentially motivate guideline changes to promote alternate regimens is speculative. Thus, WHO does not currently suggest thresholds of DTG resistance above which it recommends specific actions at the country level. However, nationally, surveys should conclude with conversations within and between ART programmes and WHO to define the programmatic and public health implications of survey results in the context of the most up-to-date science. Finally, when available, the aggregate analysis of survey results from various countries will be valuable globally as the basis of WHO recommendations for drug-switching strategies for people for whom DTG-based ART has failed.

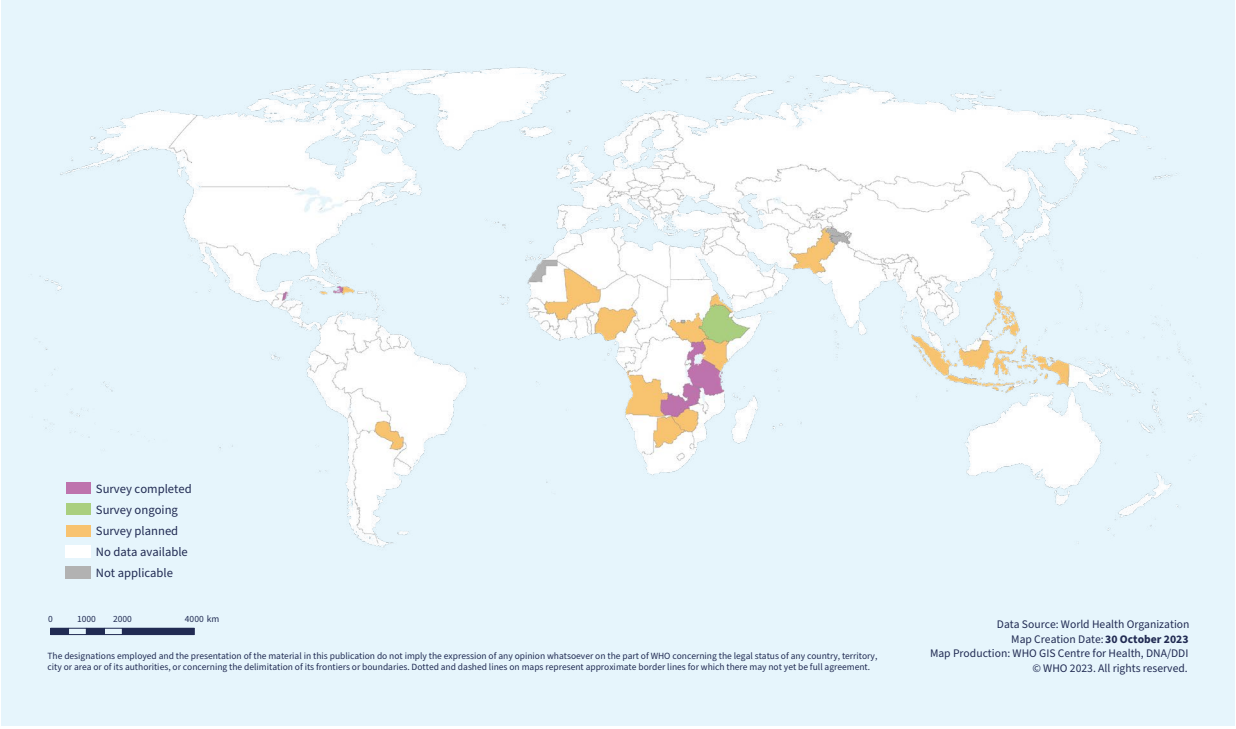
> WHO advises drug resistance surveillance to monitor the emergence of potential DTG resistance during roll-out.

As of July 2023, only 10 countries had finalized the implementation of acquired HIV drug resistance surveys among adults receiving DTG-based ART with viral load ≥1000 copies/mL; three surveys are ongoing and 24 surveys are planned (Map 1). In addition, only six countries had implemented surveys of acquired HIV drug resistance among children and adolescents receiving DTG-based ART with unsuppressed viral load; one survey is ongoing and 14 surveys are planned (Map 2). Although the emergence of acquired DTG resistance is anticipated to be low due to its high genetic barrier to drug resistance (53), early reported signals of up to 19% suggest that DTG resistance is occurring at higher than anticipated rates. This finding greatly amplifies the urgent need to implement standardized surveys in multiple countries and across regions. Further characterization of the prevalence and patterns of DTG resistance and their associated clinical determinants will provide an enhanced understanding of likely trends in acquired DTG resistance. Moreover, results from standardized country-level surveys will also inform modelling work predicting future trends of acquired DTG resistance. WHO strongly encourages countries scaling up and maintaining populations on DTG-based ART to routinely implement surveys of acquired HIV drug resistance using WHO-recommended methods *(10–12)*.

Map 1. Implementation of acquired HIV drug resistance surveys among adults receiving dolutegravir-based antiretroviral therapy with viral load ≥1000 copies/ml, 2019-2023



Map 2. Implementation of acquired HIV drug resistance surveys among children and adolescents receiving dolutegravir-based antiretroviral therapy with viral load ≥1000 copies/ml, 2019-2023



Chapter 5

Assessment of programme quality indicators associated with the emergence of HIV drug resistance

Many factors are associated with the emergence of HIV drug resistance. These include viral factors (for example, subtype, replication capacity and pre-existing polymorphisms) and drug-related factors (for example, drug potency, pharmacokinetics, drug–drug interactions, drug tolerability and genetic barriers to the selection of resistance). There are also other factors, such as adherence, drug stock-outs, attrition of individuals from ART and the use of viral load testing to identify people with failure to suppress viral load, followed by a prompt regimen switch if indicated. Although viral and drug-related factors are often beyond the control of public health or programme action, monitoring programme factors associated with HIV drug resistance can alert ART programmes to situations that may favour the emergence of HIV drug resistance or failure to suppress viral load at the population level.

The early warning indicators of HIV drug resistance are a set of standard quality-of-care indicators used to assess whether ART programmes deliver services of sufficient quality to minimize the emergence of HIV drug resistance. The early warning indicators use standardized definitions that have evolved over time as programmes mature and public health actions are refined. Monitoring early warning indicators is useful to identify gaps in service delivery that can be corrected at the clinic or programme level to minimize the risk of resistance and optimize overall programme performance. The findings from monitoring early warning indicators can be used to identify the clinics that most urgently need support or resources and to address the most pressing gaps in service delivery.

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> Preventing HIV drug resistance is crucial for ART programme success. Monitoring quality indicators associated with resistance prevention helps to identify quality gaps, leading to improved clinic and programme service delivery.

5.1 Key findings: country-level assessment

Between 2017 and 2022, 44 of 45 WHO focus countries[1] reported data on quality indicators through the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global AIDS Monitoring system (Table 5). Where available, viral load suppression data from the PEPFAR population health indicator survey were used. The targets for the country-level programmatic quality indicators are classified based on the targets for clinic-level WHO early warning indicators of HIV

1. The 45 WHO focus countries with a high burden of HIV infection are: tier 1 (more than 60% of the global disease burden): Cameroon, Democratic Republic of the Congo, India, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, United Republic of Tanzania, Uganda, Zambia and Zimbabwe. Tier 2 (an additional 20–30% of the global disease burden): Angola, Botswana, Brazil, Cambodia, Chad, China, Côte d’Ivoire, Dominican Republic, Eswatini, Ethiopia, Ghana, Guatemala, Islamic Republic of Iran, Jamaica, Lesotho, Malawi, Malaysia, Mali, Mexico, Morocco, Myanmar, Namibia, Papua New Guinea, Somalia, Sudan, South Sudan, Thailand, Ukraine and Viet Nam.

drug resistance (3). To provide as minimally biased estimates as possible, only data from countries reporting nationally representative data or data from ≥70% of all ART clinics in the country are summarized below.

Retention 12 months after ART initiation. Data on people retained on ART 12 months after initiation were generally scarce or inadequately reported. The proportions of countries with classifiable information were 49% (22 of 45) in 2017 and 56% (25 of 45) in 2018. The proportion of countries meeting the target of ≥85% retained on ART 12 months after ART initiation was 27% (6 of 22) in 2017 and 20% in 2018 (5 of 25). In 2020, the retention indicator was substituted in favour of total attrition on ART, which has been incorporated into WHO's indicator guidance and monitoring tools *(3,54,55)*.

Viral load testing coverage. The proportions of countries reporting levels of viral load testing coverage were 64% (29 of 45) in 2017, 89% (40 of 45) in 2018, 78% (35 of 45) in 2019, 62% (28 of 45) in 2020, 56% (25/45) in 2021 and 52% (23/45) in 2022. The proportions of countries achieving the target of ≥70% of eligible individuals on treatment receiving at least one annual viral load test were 31% (9 of 29) in 2017, 40% (16 of 40) in 2018, 43% (15 of 35) in 2019 and 28.5% (8 of 28) in 2020. From 2021, the target was changed to ≥95%. The proportions of countries achieving the revised target of ≥95% were 4% (1 of 25) in 2021 and 17% (4 of 23) in 2022. The decline in viral load testing coverage from 2021 resulted from the change in targets according to the revised targets for early warning indicators.

Viral load suppression. Viral load suppression was only assessed among countries reporting viral load testing coverage ≥70% or a nationally representative estimate. The proportions of reporting countries with data meeting these inclusion criteria were 33% (15 of 45) in 2017, 36% (16 of 45) in 2018, 33% (15 of 45) in 2019, 22% (10 of 45) in 2020, 24% (11 of 45) in 2021 and 24% (11 of 45) in 2022. The proportions of countries reporting ≥90% of people receiving ART achieving viral suppression were 33% (5 of 15) in 2017, 50% (8 of 16) in 2018, 67% (10 of 15) in 2019, 80% (8 of 10) in 2020, 75% (9 of 12) in 2021 and 82% (9 of 11) in 2022.

Drug stock-outs. Data on drug stockouts were reported for the years 2017–2020 but are being revised from 2021 to reflect community-based and multimonth dispensing approaches. The proportion of countries reporting was 67% (30 of 45) in 2017 and 2018 and dropped to 53% (24 of 45) in 2019 and 58% (26 of 45) in 2020. The proportion of countries meeting the target of zero drug stock-outs was 50% (15 of 30) in 2017 and 2018, 54% in 2019 (13 of 24) and 50% (13 of 26) in 2020.

The proportion of people switched to second-line ART is a proxy measure of how well a country uses viral load to identify failures and switch them timely to prevent emergence and accumulation of resistance: The proportions of countries reporting this indicator were 64% (29 of 45) in 2017 and 2018, 62% (28 of 45) in 2019, 56% (25 of 45) in 2020 and 64% (29 of 45) in both 2021 and 2022. The proportions of countries that achieved the target of having at least 5% of people on a second-line ART regimen were 45% (13 of 29) in 2017, 38% (11 of 29) in 2018, 50% (14 of 28) in 2019, 56% (14 of 25) in 2020 and 41% (12 of 29) in both 2021 and 2022.

Taken as a whole, the results suggest the need for a proactive approach to improving the quality of HIV treatment and care services to minimize the emergence of preventable HIV drug resistance. In addition, data reporting systems also need to be strengthened to ensure that all countries can monitor and report on quality-of-care indicators and ultimately use the data to improve the quality of HIV service delivery and the prevention of HIV drug resistance.

> “
>
> Quality-of-care indicator data highlight a need to significantly improve the quality of HIV care and treatment and a need to strengthen data use and reporting.

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Table 5. Countries with a high burden of HIV infection meeting targets for the quality-of-care indicators associated with the emergence of HIV drug resistance among adults, 2017–2022

	Retention on ART at 12 months[b]		Viral load testing coverage[c]						Viral load suppression[d]						ARV drug stock-out				Proportion of people receiving second-line ART					
	2017	2018	2017	2018	2019	2020	2021	2022	2017	2018	2019	2020	2021	2022	2017	2018	2019	2020	2017	2018	2019	2020	2021	2022
Angola																								
Botswana																								
Brazil																								
Cambodia																								
Cameroon[a]																								
Chad																								
China																								
Côte d'Ivoire[a]																								
Democratic Republic of the Congo																								
Dominican Republic																								
Ethiopia																								
Eswatini																								
Ghana																								
Guatemala																								
Haiti																								
India																								
Indonesia																								
Iran (Islamic Republic of)																								
Jamaica																								
Kenya																								
Lesotho[a]																								
Malawi																								
Malaysia																								
Mali																								
Mexico																								
Morocco																								
Mozambique[a]																								
Myanmar																								
Namibia[a]																								
Nigeria																								
Pakistan																								
Papua New Guinea																								
Philippines																								
Russian Federation																								
Somalia																								
South Africa																								
South Sudan																								
Sudan																								
Thailand																								
Uganda[a]																								
Ukraine																								
United Republic of Tanzania																								
Viet Nam																								
Zambia																								
Zimbabwe[a]																								

Sources: AIDSInfo, UNAIDS/WHO Global AIDS Monitoring tool and WHO AIDS Medicines and Diagnostics Survey on the use of ARV medicines and laboratory technologies and implementation of WHO-related guidelines.

[a] Viral load suppression data (from seven countries in different years) were obtained from a population health impact survey supported by PEPFAR.

[b] Countries' datasets were included if they comprise ≥70% of the people newly initiating ART or <70% but reported to be nationally representative.

[c] The data originated from countries responding with the proportion of people receiving ART who received a viral load test in the 12-month period. Countries' datasets were included if data were collected from everyone receiving ART or from a nationally representative data set. However, the results may overestimate viral load testing coverage in countries in which viral load testing coverage is estimated based on the number of tests done and thus may not be able to account for multiple tests per person.

[d] Countries' datasets were included if viral load testing coverage was ≥70%; or <70% and reported to be nationally representative

Data not available Data reported but not national representative or ≥70% of eligible population

Excellent performance: targets for retention at 12 months (>85%), viral load testing coverage (≥70% until 2020 and ≥95% from 2021 onwards), viral load suppression (≥90%), drug stock-outs (0%), proportion of people receiving second-line ART (≥5%)

Fair performance: targets for retention at 12 months (75-85%), viral load testing coverage (85- <95% from 2021 onwards), viral load suppression (80-<90%)

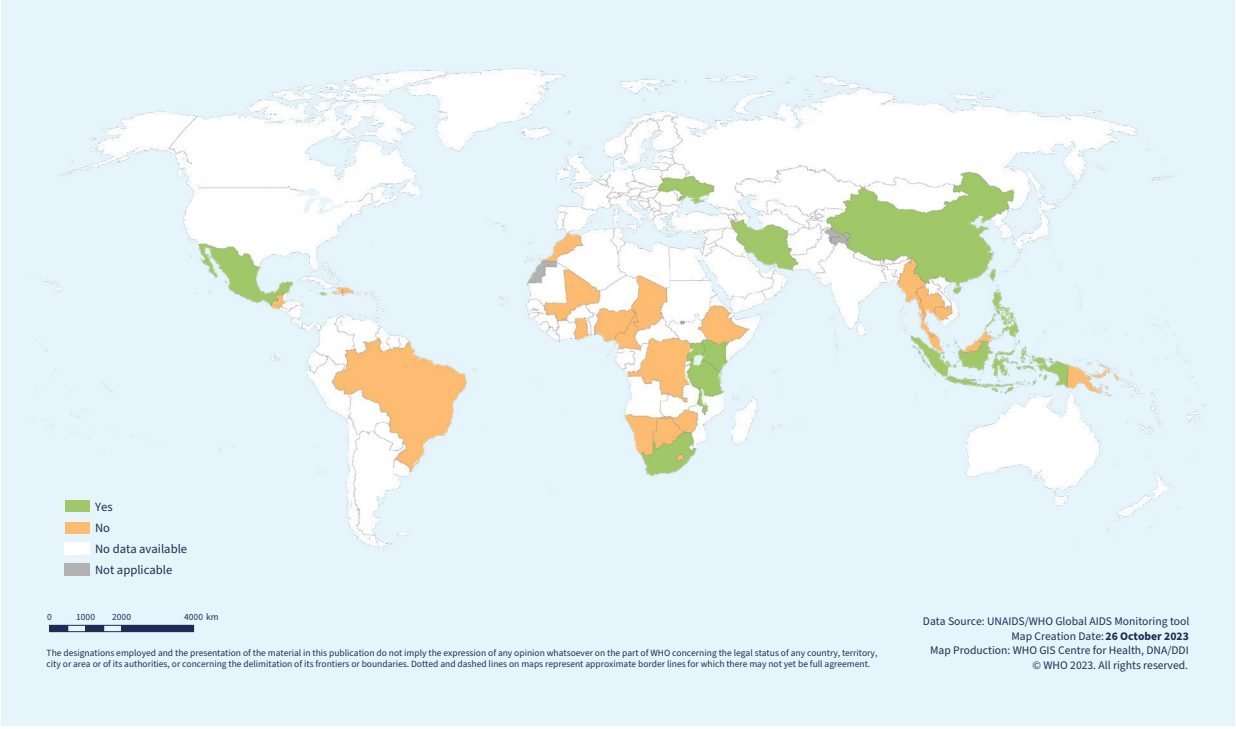
Unsatisfactory performance: retention (<75%), viral load testing coverage (<70%), viral load testing coverage (≥85% from 2021 onwards) viral load suppression (<80%), drug stock-outs (>0%), proportion of people receiving second-line ART (<5%)

5.2 Key findings: monitoring quality-of-care indicators at the clinic level

Map 3 shows countries that reported implementing the monitoring of early warning indicators at the clinic level in 2022. In 2022, 12 of the 45 WHO HIV focus countries reporting data indicated either conducting ad hoc surveys of early warning indicators or had integrated the data collection for early warning indicators into routine monitoring and evaluation systems following WHO recommendations. Among the countries reporting clinic-level early warning indicators data in 2022, 92% (11 of 12) had integrated early warning indicators into routine monitoring and evaluation systems following the WHO recommendations.

Integrating early warning indicators into routine clinic and programme monitoring and evaluation systems, followed by rapid investigation of gaps in service delivery and appropriate data-driven and community-centred response to suboptimal performance, is foundational to preventing HIV drug resistance and maximizing population-level suppression of viral load.

Map 3. Countries monitoring clinic-level early warning indicators of HIV drug resistance in 2022 among the 45 high-burden countries



Chapter 6

Conclusion

Introducing DTG-containing ART regimens for treating HIV infection affords a great opportunity to significantly improve the lives of millions of people living with HIV around the world. Similarly, should the introduction of CAB-LA for preventing HIV be scaled up, it will likely greatly decrease incident HIV infections. However, as witnessed with other ARV drug classes, drug resistance to INSTIs can and will emerge. In high-income countries, HIV drug resistance testing of individuals is often used to tailor regimen selection and predict treatment response. However, in most if not all resource-limited settings, HIV drug resistance testing is not routinely available for individual management, and this is currently not recommended by WHO. Even with recent technological advancements, HIV drug resistance testing is unlikely to be routinely available for millions of people in the near future. Further, the limited availability of alternative regimens restricts treatment change based on test results. HIV drug resistance remains a threat to the long-term ART effectiveness, and the absence of accessible HIV drug resistance testing for individual care necessitates that these efforts be intensified to optimize population-based HIV treatment outcomes and to minimize the preventable emergence and transmission of drug-resistant HIV. Unless carefully monitored and contained, the emergence and possible transmission of DTG-resistant HIV has the potential to greatly reduce the efficacy of currently recommended regimens.

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Annex

Fig. A1 summarizes the proportion of previous exposure to ARV drugs among adults initiating ART that was assessed in 30 surveys, including data from seven countries that were not included in the 2021 WHO report on HIV drug resistance. The percentage of ART initiators with previous exposure to ARV drugs varied widely across countries, with Uganda reporting only 1.2% (95% CI 0.4–3.7%) of survey participants having previous ARV drug exposure and Haiti reporting 99.3% (95% CI 95.1–99.9%) having previous ARV drug exposure.

Since the publication of the latest WHO report on HIV drug resistance in 2021, 10 additional countries have shared their pretreatment HIV drug resistance survey data with WHO. Similar to previous reports, the prevalence of HIV drug resistance to NVP or EFV was notably greater among ART initiators who had previously been exposed to ARV drugs than among those not exposed (Fig. A2). Overall, of the 40 surveys submitted to WHO, 26 reported levels of NVP or EFV drug resistance exceeding 10% among adults starting first-line ART (Fig. A3).

In January 2021, the United States Food and Drug Administration approved the use of long-acting CAB + rilpivirine (CAB + RPV LA) ART for people living with HIV. CAB + RPV LA is not a currently WHO-recommended treatment option. The role, opportunities and challenges of the CAB + RPV LA ART regimen in the context of existing and future oral regimens was discussed during the Fourth Conference on Antiretroviral Drug Optimization in 2021 *(1)*.

After careful consideration, the Conference concluded that, although CAB + RPV LA certainly demonstrates promising potential, it may not be the most optimal long-term solution for implementation in low- and middle-income countries. Nevertheless, the Conference also concluded that implementation science studies on the delivery of CAB + RPV LA in low- and middle-income countries are necessary, acknowledging that the context varies in low- and middle-income countries and that introducing long-acting products will require tailored approaches that consider their unique needs and available resources. In this report, Fig. A4 presents the historical data from nationally representative surveys of pretreatment HIV drug resistance to RPV. The levels of pretreatment RPV resistance among individuals initiating ART without previous exposure to ARV drugs ranged from 0.0% (95% CI 0.0–9.4%) in Tajikistan in 2016 to a high of 16.6% (95% CI 11.2–24.0%) in Eswatini. These data suggest that, if RPV were to be used in combination with CAB as a long-acting ART, pretreatment HIV drug resistance testing would be needed as part of the implementation science studies in some settings to identify those without RPV drug resistance because pretreatment RPV drug resistance mutations are a risk factor for failure to suppress viral load among people treated with CAB + RPV LA *(2,3)*.

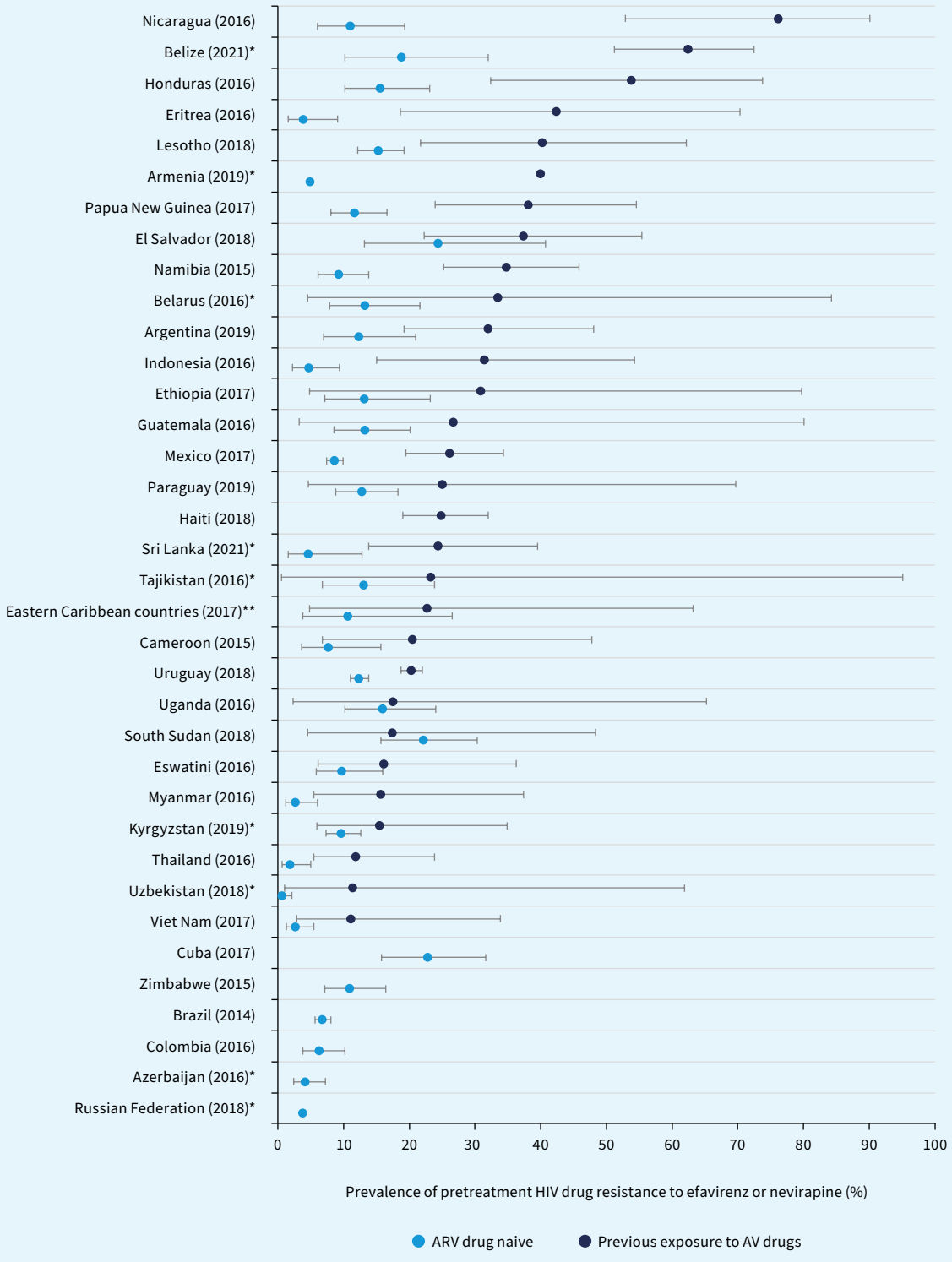
Fig. A1. Proportion of adults initiating ART and reporting previous ARV drug exposure, 2014–2021

Country (year)	Previous ARV drug exposure (%)	Type of previous ARV drug exposure			
		PMTCT (%)	ART (%)	Other (%)	Unknown (%)
Haiti (2018)	99.3	0.6	99.2	0.2	0.0
Belize (2021)*	70.5	3.0	97.0	0.0	0.0
Eastern Caribbean countries (2017)	42.3	59.1	4.5	0.0	36.4
Uruguay (2018)	35.6	1.3	79.8	1.3	17.6
Honduras (2016)	26.3	7.9	90.8	0.0	1.3
Argentina (2019)	23.8	8.0	83.6	1.7	6.7
Papua New Guinea (2017)	20.9	0.0	98.7	0.0	1.3
El Salvador (2018)	20.3	1.7	100.0	0.0	0.0
Thailand (2016)	18.1	24.9	75.1	0.0	0.0
Sri Lanka (2021)*	18.2	0.0	92.5	0.0	7.5
Namibia (2015)	18.0	23.2	76.8	0.0	0.0
South Sudan (2018)	16.4	2.3	11.1	0.0	88.9
Kyrgyzstan (2019)*	15.1	0.0	100.0	0.0	0.0
Tajikistan (2016)*	13.6	0.0	100.0	0.0	0.0
Nicaragua (2016)	12.3	38.1	9.5	4.8	47.6
Indonesia (2016)	12.0	0.0	99.5	0.5	0.0
Eswatini (2016)	10.7	60.6	16.1	0.0	23.3
Eritrea (2016)	8.6	0.0	100.0	0.0	0.0
Myanmar (2016)	8.4	13.2	76.4	10.1	0.3
Cameroon (2015)	7.8	47.4	24.0	28.6	0.0
Mexico (2017)	7.4	0.0	97.1	2.9	0.0
Viet Nam (2017)	7.0	30.9	69.1	0.0	0.0
Uzbekistan (2018)*	5.9	66.7	33.3	0.0	0.0
Ethiopia (2017)	5.8	30.8	1.6	0.0	67.5
Lesotho (2018)	5.3	24.0	70.0	1.6	4.4
Belarus (2016)*	3.9	0.0	100.0	0.0	0.0
Paraguay (2019)	3.8	0.0	100.0	0.0	0.0
Armenia (2019)*	3.5	0.0	100.0	0.0	0.0
Guatemala (2016)	2.8	12.0	0.0	0.0	88.0
Uganda (2016)	1.2	8.1	59.9	0.0	32.0

The figure shows the proportion of adults initiating ART and reporting previous exposure to ARV drugs and the proportional distribution of the type of exposure to ARV drugs in 30 countries reporting data to WHO between 2014 and 2021. The Eastern Caribbean countries is a multicountry survey carried out in Antigua and Barbuda, Dominica, Grenada, Saint Kitts and Nevis, Saint Lucia and Saint Vincent and the Grenadines. The data from Sri Lanka were obtained from Elwitigala et al. (4). Data not included in previous reports are marked with an asterisk (*).

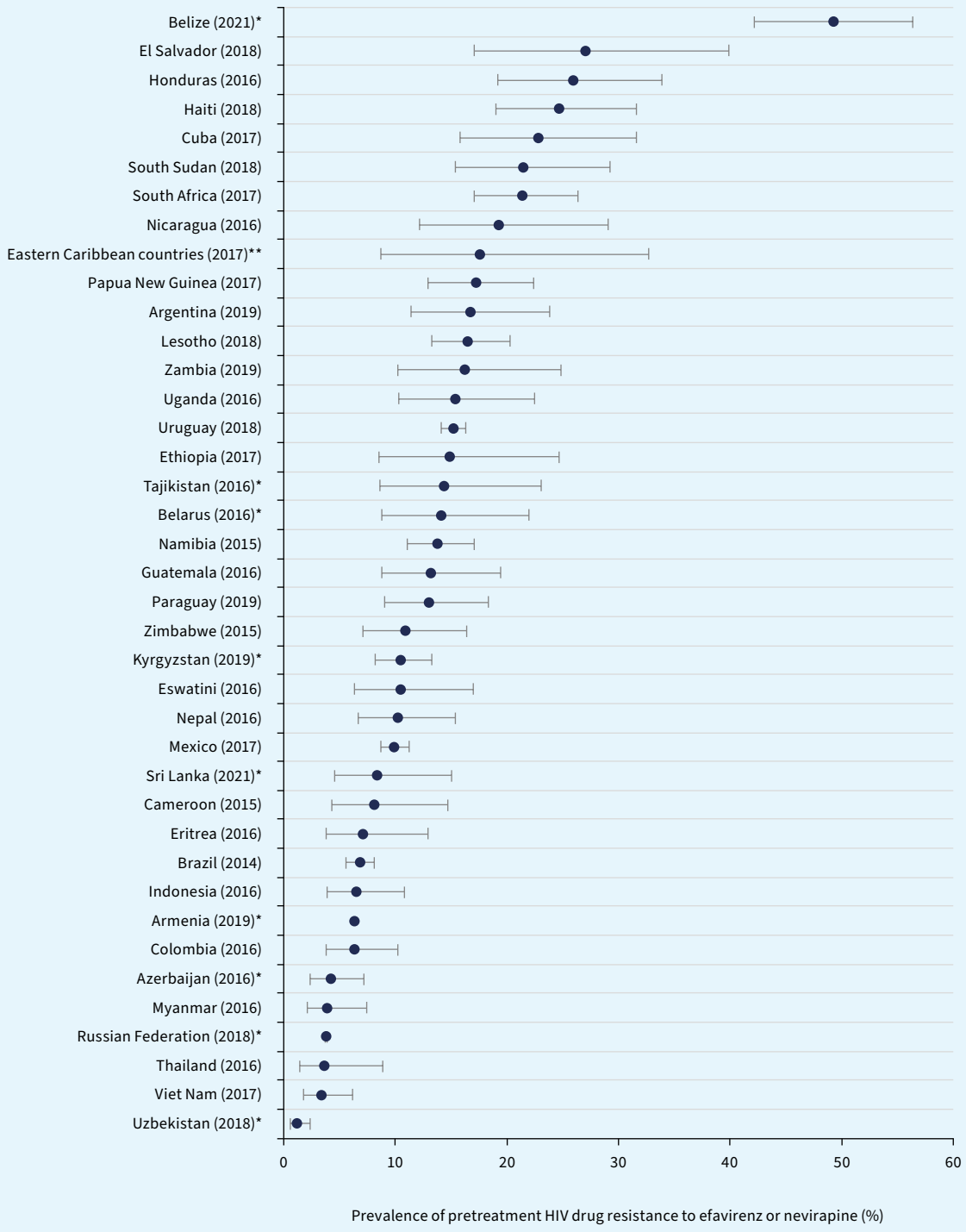
ARV: antiretroviral drugs; ART: antiretroviral therapy; PMTCT: prevention of mother-to-child transmission.

Fig. A2. Prevalence of pretreatment HIV drug resistance to EFV or NVP among adults initiating ART by previous exposure to ARV drugs, 2014–2021



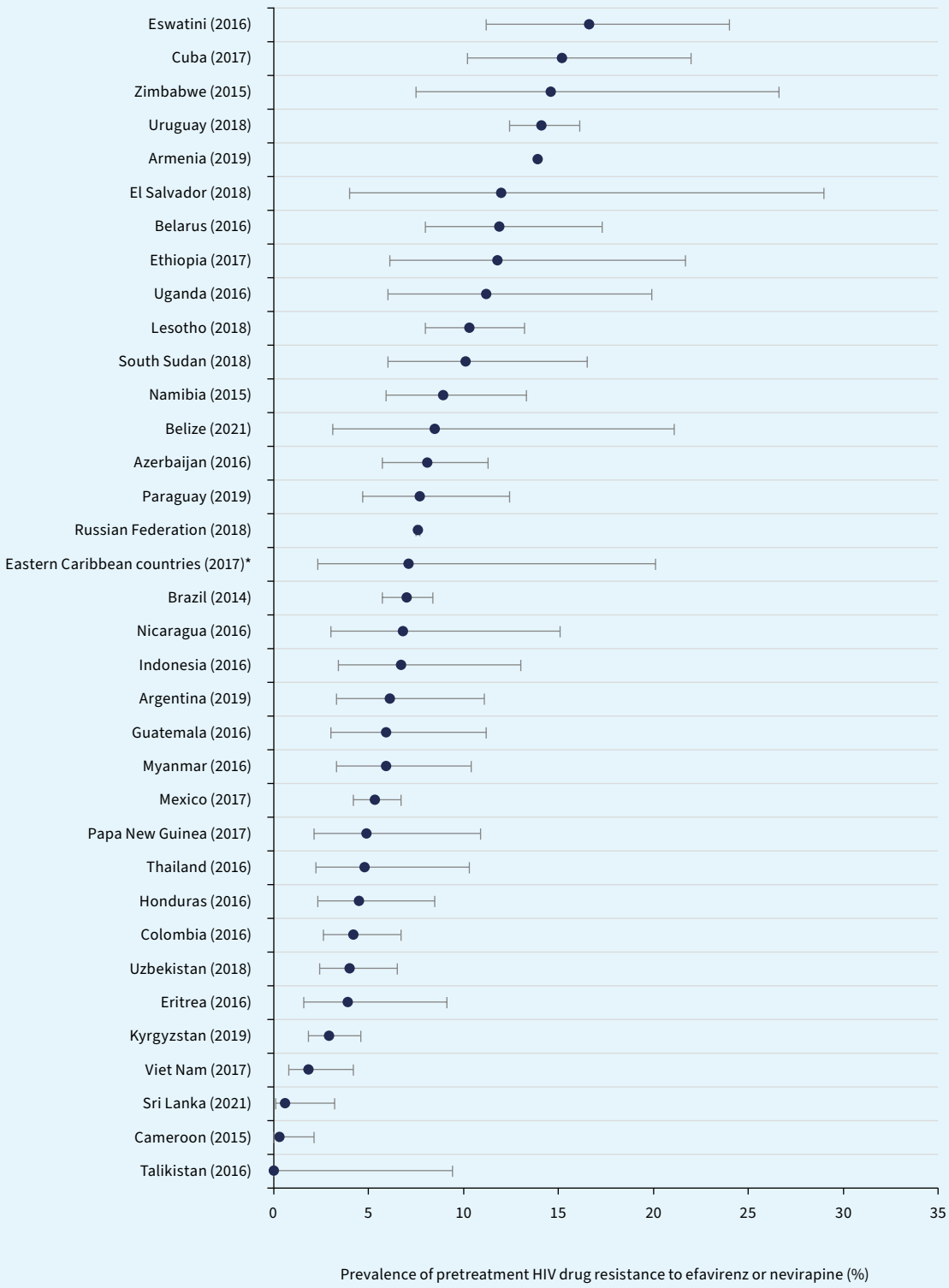
The figure shows the study design–weighted prevalence and 95% confidence interval (error bars) of pretreatment HIV drug resistance to EFV or NVP among adults initiating ART, with or without previous exposure to ARV drugs, in countries reporting data to WHO between 2014 and 2021. In all countries, pretreatment HIV drug resistance estimates are generated from nationally representative surveys using standard WHO survey methods. In six countries (Azerbaijan, Brazil, Colombia, Cuba, Russian Federation and Zimbabwe), only individuals initiating ART without previous exposure to ARV drugs were included in the pretreatment HIV drug resistance surveys. HIV drug resistance was defined as the presence of a penalty score ≥15 using the Stanford HIVdb algorithm. The data from Sri Lanka were obtained from Elwitigala et al. *(4)*. Data not included in previous reports are marked with an asterisk (*). The Eastern Caribbean countries are shown in aggregate because a multicountry survey was conducted in Antigua and Barbuda, Dominica, Grenada, Saint Kitts and Nevis, Saint Lucia and Saint Vincent and the Grenadines (**).

Fig. A3. Prevalence of pretreatment HIV drug resistance to EFV or NVP among adults initiating ART, 2014–2021



The figure shows the study design–weighted prevalence and 95% confidence interval (error bars) of pretreatment HIV drug resistance to EFV or NVP among adults initiating (or reinitiating) ART in countries reporting data to WHO between 2014 and 2021. In all countries, pretreatment HIV drug resistance estimates are generated from nationally representative surveys using standard WHO survey methods, except in South Africa, where pretreatment HIV drug resistance estimates are generated from a national household survey. In six countries (Azerbaijan, Brazil, Colombia, Cuba, Russian Federation and Zimbabwe), only individuals initiating ART without previous exposure to ARV drugs were included in the pretreatment HIV drug resistance surveys. HIV drug resistance was defined as the presence of a penalty score ≥15 using the Stanford HIVdb algorithm. The data from Sri Lanka were obtained from Elwitigala et al. *(4)*. Data not included in previous reports are marked with an asterisk (*). The Eastern Caribbean countries are aggregated because a multicountry survey was carried out in Antigua and Barbuda, Dominica, Grenada, Saint Kitts and Nevis, Saint Lucia and Saint Vincent and the Grenadines (**).

Fig. A4. Prevalence of pretreatment HIV drug resistance to RPV among adults initiating ART without previous exposure to ARV drugs, 2014–2021



The figure shows the study design–weighted prevalence and 95% confidence interval (error bars) of pretreatment HIV drug resistance to RPV among adults initiating ART without previous exposure to ARV drugs in countries reporting data to WHO between 2014 and 2021. In all countries, pretreatment HIV drug resistance estimates are generated from nationally representative surveys using standard WHO survey methods. The Eastern Caribbean countries are aggregated because a multicountry survey was carried out in Antigua and Barbuda, Dominica, Grenada, Saint Kitts and Nevis, Saint Lucia and Saint Vincent and the Grenadines (*). HIV drug resistance was defined as the presence of a penalty score ≥15 using the Stanford HIVdb algorithm. The data from Sri Lanka were obtained from Elwitigala et al. *(4)*.

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