ACTION PLAN

GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017–2021

2018 PROGRESS REPORT

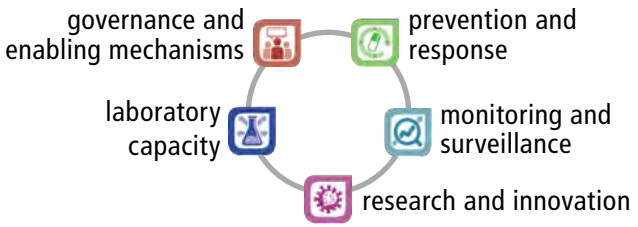
JULY 2018

HIV DRUG RESISTANCE

EXECUTIVE SUMMARY

The rise in antimicrobial resistance is a growing global health concern that requires collective and coordinated action. Minimizing the emergence and transmission of drug-resistant HIV is a critical aspect of the global response to antimicrobial resistance. Increasing prevalence of HIV drug resistance to commonly used antiretroviral drugs poses a threat to the HIV response, with the potential to fuel an increase in HIV incidence, mortality and treatment costs if not adequately addressed.

In 2017, WHO and partners jointly developed and launched a comprehensive five-year Global Action Plan on HIV drug resistance (2017–2021), which outlines key actions for country and global stakeholders to prevent, monitor and respond to HIV drug resistance and to protect the ongoing progress towards achieving the global targets for epidemic control by 2030. The Global Action Plan has five strategic objectives:



This report summarizes the progress in implementing the Global Action Plan achieved during the first year (2017 to 2018) and the remaining challenges, with specific focus on 45 countries accounting for more than 85% of the total burden of HIV infection.

ADVANCEMENTS ON THE GLOBAL ACTION PLAN

- ✔ improved uptake of HIV drug resistance surveillance, better awareness of the relevance of HIV drug resistance and increased commitment by countries and donors to measuring HIV drug resistance;
- ✔ incorporating integrase inhibitor resistance testing in surveillance activities in anticipation of dolutegravir use in low- and middle-income countries;
- ✔ progress by the global research community in addressing critical research gaps related to HIV drug resistance; and
- ✔ positive advances in community engagement in tackling HIV drug resistance and awareness of the link between HIV drug resistance and the quality of care.

AREAS FOR FURTHER ACTION

- Need for further improvement in in the quality of care to attain the set targets of the Global Action Plan for retention in treatment, viral load testing coverage, viral load suppression, antiretroviral drug stock-outs and appropriate use of second-line antiretroviral therapy;
- need for increased visibility of the reporting and use of quality-of-care indicators;
- need for timely response to documented high levels of pretreatment drug resistance; and
- need to strengthen links between HIV drug resistance and other global health policy priorities, including antimicrobial resistance and universal health coverage.

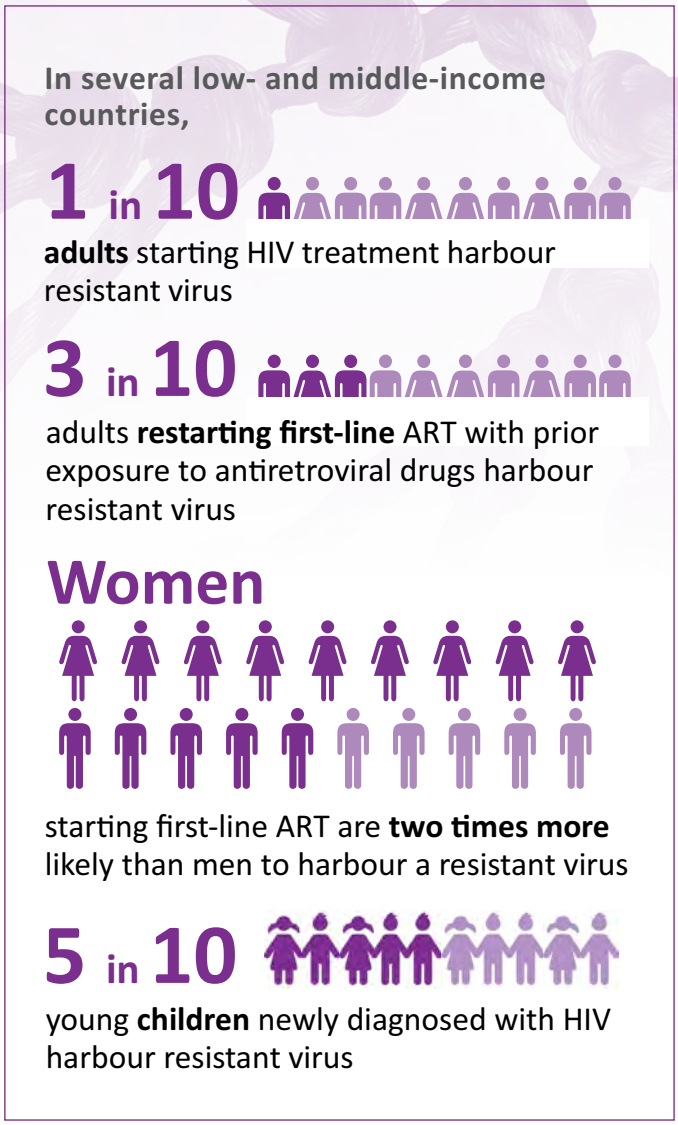
CONCLUSIONS

An effective response to HIV drug resistance requires a long-term multi-partner effort working at different levels across a range of sectors. The Global Action Plan on HIV drug resistance is a five-year plan offering the global community a framework for concerted action. One year has passed, and several examples of positive results have been achieved. Over the next four years, continued and greater engagement is required to maximize these efforts to fully achieve the goals of the Global Action Plan.

World Health Organization

INTRODUCTION

FIG. 1.
High levels of pretreatment HIV drug resistance to efavirenz/nevirapine



The *WHO HIV drug resistance report 2017 (1)* documents that, in several low- and middle-income, more than **1 in 10 adults** starting antiretroviral therapy had HIV that was already resistant to efavirenz or nevirapine, the most commonly used first-line antiretroviral drugs[1] **(Fig. 1)**.

In these settings, **women are two times more likely than men** to carry virus with pretreatment resistance, posing a significant challenge to the elimination of mother-to-child transmission of HIV (PMTCT) and to maternal and child health outcomes *(1)*.

One in five people starting first-line treatment reports previous exposure to antiretroviral drugs (such as PMTCT-exposed women or people restarting first-line treatment after a period of treatment interruption). This group is **three times more** likely to harbor virus with pretreatment resistance to efavirenz or nevirapine than antiretroviral-naive individuals *(1)*.

Children represent a very vulnerable population: **one out of two children** newly diagnosed with HIV is infected with virus harbouring resistance to efavirenz and nevirapine,[1] thus at high risk of suboptimal treatment *(2)*. HIV drug resistance among people starting or restarting antiretroviral therapy (pretreatment HIV drug resistance) has been increasing annually after the roll-out of antiretroviral therapy.

By the end of 2017, 21 million people were receiving life-saving antiretroviral therapy. A further 15.8 million are expected to start treatment in accordance with the WHO "treat all" recommendation, resulting in 36.7 million people who must be successfully maintained on lifelong treatment. Achieving high HIV testing access (at least 90% of all people living with HIV) and treatment coverage (at least 90% of the people who know their HIV-positive status) coupled with high levels of viral load suppression (at least 90% of the people receiving treatment) should lead to eliminating HIV as a public health threat by 2030.

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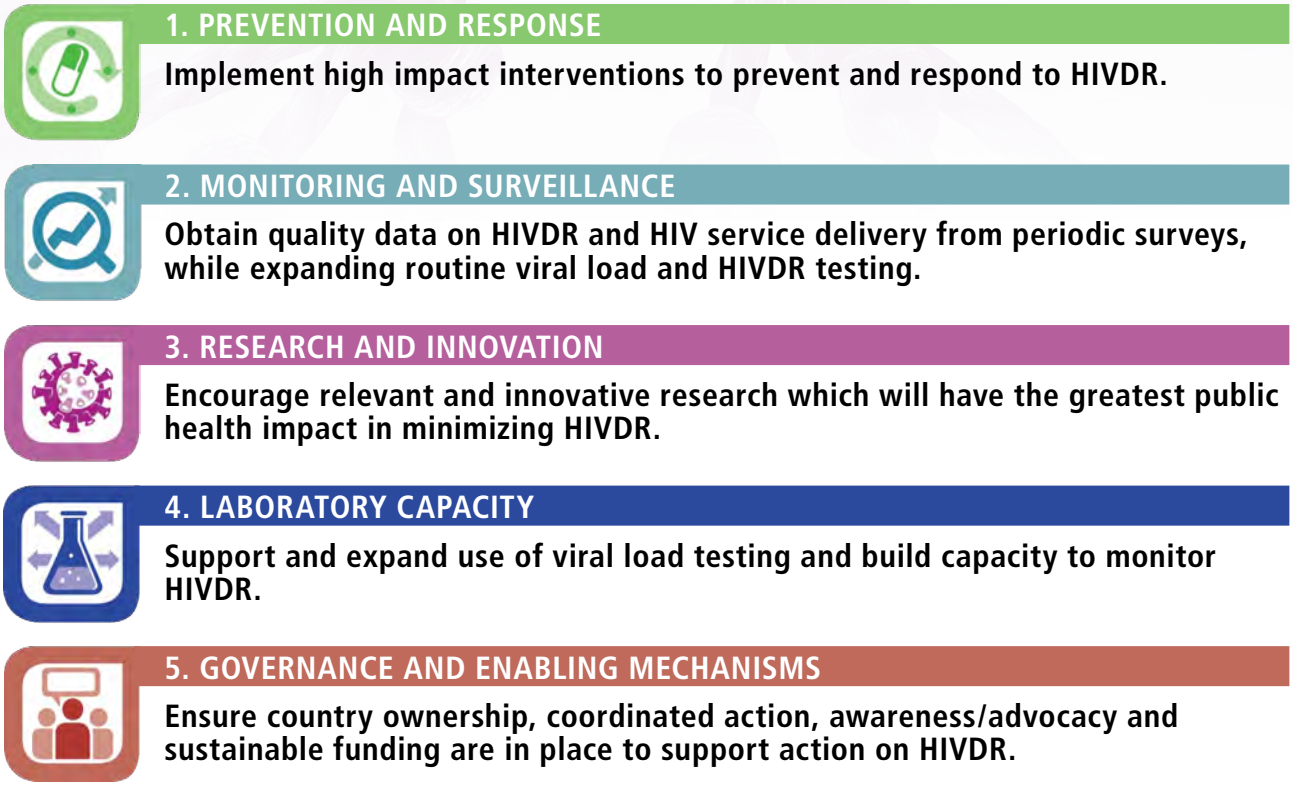
[1] As of end of 2016, efavirenz and nevirapine were used in 86% and 14% of adults, and 29% and 47% of children on first-line HIV treatment, respectively (Clinton Health Access Initiative. ARV Market Report: The State of the Antiretroviral Drug Market in Low- and Middle-Income Countries, 2016–2021. 2017 https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final.pdf (accessed July 07, 2018).

In 2017, WHO and partners jointly developed and launched a comprehensive five-year **Global Action Plan** *(3)* that articulates key synergistic actions for countries and stakeholders to prevent, monitor and respond to HIV drug resistance **(Fig. 2)**.

This report summarizes the current progress in implementing the Global Action Plan on HIV drug resistance, one year after the initial launch, and specifically focuses on 45 WHO focus countries for HIV, which account for more than 85% of the global burden of HIV infection.[2]

FIG. 2.
Global Action Plan on HIV drug resistance (HIVDR) and its five Strategic Objectives



[2] Angola, Botswana, Brazil, Cambodia, Cameroon, Chad, China, Côte d'Ivoire, Dominican Republic, Democratic Republic of the Congo, Ethiopia, Ghana, Guatemala, Haiti, India, Indonesia, Islamic Republic of Iran, Jamaica, Kenya, Lesotho, Malawi, Malaysia, Mali, Mexico, Morocco, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Somalia, South Africa, South Sudan, Sudan, Eswatini (Swaziland), Thailand, Uganda, Ukraine, United Republic of Tanzania, Viet Nam, Zambia and Zimbabwe.

PROGRESS ON HIV DRUG RESISTANCE PREVENTION AND RESPONSE

Preventing resistance emergence

Preventing HIV drug resistance is critical for the success of any HIV treatment programme and is achieved by optimizing the quality of antiretroviral therapy services and eliminating programmatic gaps along the cascade of HIV treatment. These gaps are identified by routinely monitoring programme quality indicators that are associated with the emergence of preventable resistance: retention on treatment, adherence to HIV treatment, viral load testing coverage, viral load suppression, timely switch to second-line antiretroviral therapy and antiretroviral drug stock-outs.

All 45 focus countries reported data in 2018 to WHO/UNAIDS[3] based on 2016–2017 cohorts. Overall information was variably reported, with the percentage of missing data ranging from 16% to 40% for the various indicators.

Table 1 summarizes the proportion of countries achieving the targets for the programme quality indicators related to HIV drug resistance in 2017. These results can be considered as baseline information to evaluate and assess future trends.

TABLE 1.
Programme quality indicators associated with HIV drug resistance (HIVDR) and associated targets

Programme quality indicator for HIVDR	Indicator target	Proportion of focus countries achieving indicator target as of 2017[a]
Antiretroviral drug stock-outs	**Zero** antiretroviral drug stock-outs during a 12-month period	14 of 27 (52%)
Retention on antiretroviral therapy[b]	≥**85%** of people living with HIV retained on antiretroviral therapy 12 months after initiation	8 of 26 (31%)
Viral load testing coverage[c]	≥**90%** of people on antiretroviral therapy receiving at least one routine viral load test in a year	3 of 31 (10%)
Viral load suppression[d]	≥**90%** viral load suppression among people on antiretroviral therapy with a viral load test result available	4 of 14 (29%)
Use of second-line antiretroviral therapy regimens	At least **5%** of people receiving second-line antiretroviral therapy	13 of 28 (46%)

[a] Source: UNAIDS/WHO Global AIDS Monitoring tool 2018 (section 1.3 and 1.4) and WHO/AIDS Medicines and Diagnostics Survey on the use of ARV medicines and laboratory technologies and implementation of WHO Related Guidelines 2018. Overall, 60–84% of the 45 HIV focus countries contributed data for each indicator; countries' dataset that did not meet the minimum criteria were excluded (as described in b,c,d).
[b] Countries' datasets were included if comprise ≥70% of people newly initiated on antiretroviral therapy; or <70% but reported to be nationally representative.
[c] Data came from countries responding with the proportion of people on treatment who received a viral load test in the 12 months period. Countries' datasets were included if collected from all patients on ART or from a national representative data set. The results may however have been overestimated in countries where reporting did not account for multiple tests per patient
[d] Countries' datasets were included if viral load testing coverage was ≥70% or <70% but reported to be nationally representative

[3] Reported in 2018 through (1) UNAIDS/WHO Global AIDS Monitoring tool: online tool for monitoring the 2016 United Nations Political Declaration on Ending AIDS; and (2) WHO/AIDS Medicines and Diagnostics Survey on the use of ARV medicines and laboratory technologies implementation of WHO Related Guidelines

Based on the data reported by countries to WHO/UNAIDS few countries had achieved the indicator targets in 2017 **(Table 1)**. Specifically, **52%** of the countries reported *zero* antiretroviral drug stock-outs, **31%** reported ≥85% retention on treatment, **10%** reported ≥90% viral load testing coverage and **29%** reported viral load suppression ≥90%. Finally, a low rate of switching to second-line antiretroviral therapy is also a challenge in most low- and middle-income countries. Although about 10–20% of people have documented elevated viral load while receiving first-line antiretroviral therapy *(4)* and may need to switch to second-line regimens, only **46%** of countries had at least 5% of the people receiving antiretroviral therapy on a second-line regimen, which indicates a suboptimal use of available treatment options. These findings highlight important programmatic gaps suggesting the need for a proactive approach to improving the quality of HIV treatment and care services in order to minimize the emergence of preventable HIV drug resistance.

Some countries are already taking important steps to address programme gaps **(Box 1)**. It is critical that antiretroviral therapy programmes develop national frameworks for improving quality to enable them to effectively respond to challenges in programme implementation. Such a framework should incorporate quality improvement approaches to assess clinic functioning and introduce locally sustainable solutions to complex problems, including stronger systems for drug procurement and supply chain, increased use of viral load testing and differentiated care models to maximize adherence and retention. Finally, increased community engagement is essential to monitor the quality of antiretroviral therapy delivery and prevent the emergence of HIV drug resistance.

BOX 1.

Antiretroviral therapy programme in Cameroon responds to programme quality gaps

WHO recommends that programmes routinely monitor a minimum set of quality indicators associated with the emergence of preventable HIV drug resistance (early warning indicators). Recognizing the need to minimize the emergence and transmission of HIV drug resistance, Cameroon has conducted five rounds of monitoring of the early warning indicators in 10–50 clinics since 2008. When each round was completed, national and clinic-level recommendations were developed and implemented based on the findings.

In 2017, an investigation was carried out by the national programme in a subset of antiretroviral therapy clinics[4] to assess the impact of recommendations generated as a result of monitoring early warning indicators. Messaging on adherence to antiretroviral therapy provided by social workers substantially increased on-time pill pick-up in some clinics, with adherence improving from a range of 10–51% in year 1 to 91–100% by year 4. This improvement is especially important given the limited viral load testing coverage in the country. In addition, 100% of the people receiving treatment were given appropriate triple-drug combinations in all five rounds.

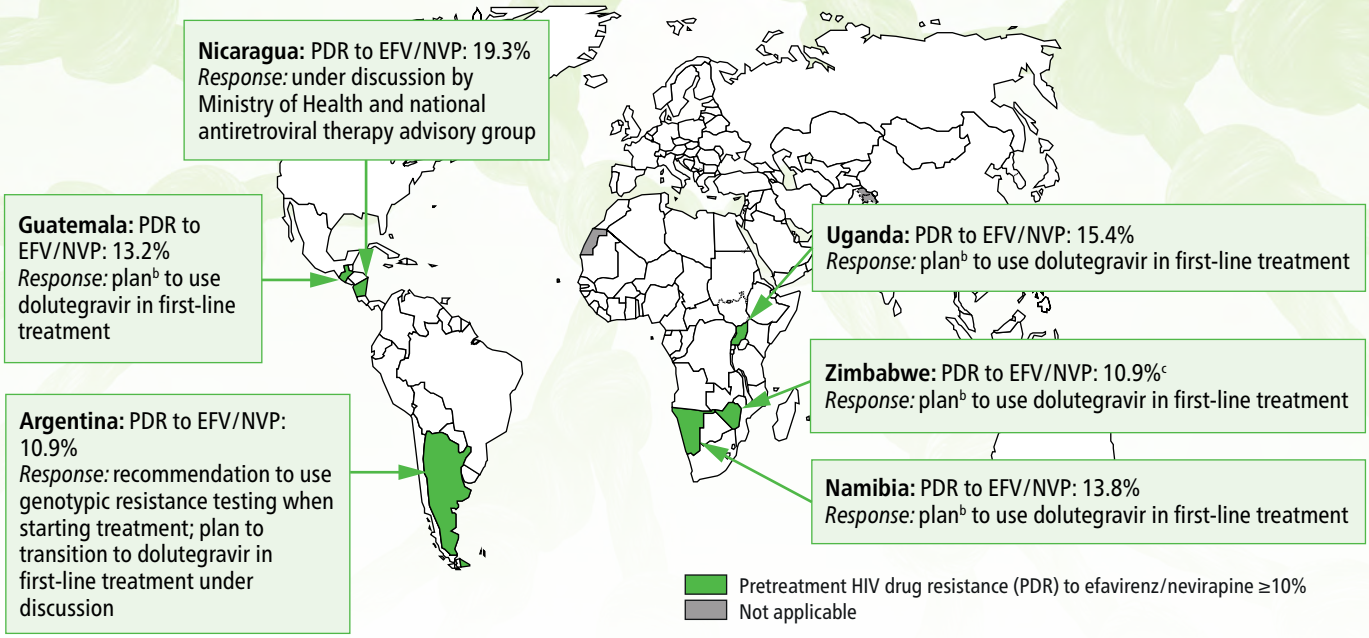
Countries' responses to high levels of pretreatment drug resistance

WHO 2017 guidelines *(5)* recommend that, in countries in which the prevalence of pretreatment HIV drug resistance to efavirenz or nevirapine is ≥10%, an alternative first-line regimen that does not contain non-nucleoside reverse-transcriptase inhibitors (NNRTI) such as efavirenz or nevirapine, should be urgently considered. If this is not feasible, using HIV drug resistance testing to guide the selection of an optimal regimen for people starting treatment can be considered *(5)*.

In 2017, **6 of 11 countries** implementing national HIV drug resistance surveys (Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe) reported a prevalence of pretreatment HIV drug resistance to efavirenz or nevirapine exceeding 10%. **Fig. 3** shows the policy changes made by these countries in response to the high levels of pretreatment HIV drug resistance.

[4] National report on early warning indicators of HIV drug resistance, Cameroon. 2018.

FIG. 3.
Response to levels of pretreatment HIV drug resistance (PDR) to efavirenz/nevirapine (EFV/NVP) at or above 10% among people initiating first-line antiretroviral therapy: uptake of WHO recommendations[a]



[a] Guidelines on the public health response to pretreatment HIV drug resistance. Geneva: World Health Organization; 2017.
[b] Transition plan to use dolutegravir has been delayed or under revision due to safety concerns for infants born to women who are on dolutegravir at time of conception.
[c] Only ARV drug naive starting first-line antiretroviral therapy were included.

One alternative drug in first-line for use in countries with high levels of NNRTI pretreatment HIV drug resistance is dolutegravir (DTG), an integrase inhibitor, in combination with two nucleoside reverse-transcriptase inhibitors (NRTIs). Given the advantages of DTG compared to NNRTI, and its recent availability as a low-cost fixed-dose combination of tenofovir, lamivudine and DTG in 92 low- and middle-income countries, many countries made plans to transition to DTG in first-line antiretroviral therapy.

The transition plan to use DTG in first-line HIV treatment was accelerated in countries with high levels of pretreatment HIV drug resistance. However, recent findings from an observational study in Botswana on the use of DTG among women at the time of conception signalled the potential association between DTG use and neural tube defects among children *(6)*. As a result, the accelerated roll-out of DTG has slowed in some countries as more information on the signal of risk is obtained. Other countries implemented policy changes in response to high levels of pretreatment resistance, even if the prevalence was below the recommended 10% threshold for public heath action.

In Mexico, for example, where a national prevalence of pretreatment resistance was 9.2% (14.8% in women), resistance testing was recommended for children and adolescents starting HIV treatment and in pregnant women with prior exposure to antiretroviral drugs.

Brazil had been an early adopter of DTG and had a prevalence of resistance to NNRTI measured in naive individuals of 6.8%. Following the recent safety concerns associated with DTG, the use of HIV drug resistance testing has been recommended for all individuals of child bearing potential starting HIV treatment and not using an effective contraceptive method (intrauterine device or hormone implant) to select the most suitable regimen.

PROGRESS ON HIV DRUG RESISTANCE MONITORING AND SURVEILLANCE

HIV drug resistance surveillance

WHO recommends periodic nationally representative surveys to inform the emergence and transmission of HIV drug resistance **(Box 2)**, provide data to support the selection of optimal antiretroviral therapy in a country and measure the extent to which the emergence and transmission of drug-resistant virus are minimized through programme practices and antiretroviral stewardship.

HIV drug resistance has emerged to all antiretroviral drugs developed to date, including DTG, and resistance surveillance should therefore be conducted routinely regardless of the regimen used.

To assist countries in implementing surveys, standardized guidance, operational toolkits and a database to support countries and genotyping laboratories in the quality assurance of epidemiological and sequence data are available (7).

BOX 2.
WHO's guidance on nationally representative HIV drug resistance survey: purpose and public heath use

Pretreatment drug resistance: assess resistance present at the time of initiating antiretroviral therapy to support a country's choice of recommended regimens for first-line antiretroviral therapy and pre- and post-exposure prophylaxis.

Acquired drug resistance: assess resistance among people receiving treatment to guide the selection of second- and third-line regimens, monitor practices in switching treatment and inform national estimates of viral load suppression.

Resistance among HIV infected, treatment-naive infants: assess resistance among infants less than 18 months old, who have not started treatment, to support the selection of first-line antiretroviral therapy and the composition of subsequent regimens.

WHO recommends to repeat pretreatment and acquired HIV drug resistance surveys every 3 years, and surveys in infants every 5 years.

Upcoming WHO's guidance on HIV drug resistance surveillance

As viral load testing coverage increases in countries, the prevalence of acquired drug resistance can be estimated by genotyping remnant viral load specimens from people with viral non-suppression routinely collected at the central laboratory level. This approach offers an alternative to a standard acquired drug resistance survey in countries with optimal viral load testing coverage and data system; WHO is developing guidance for implementation.

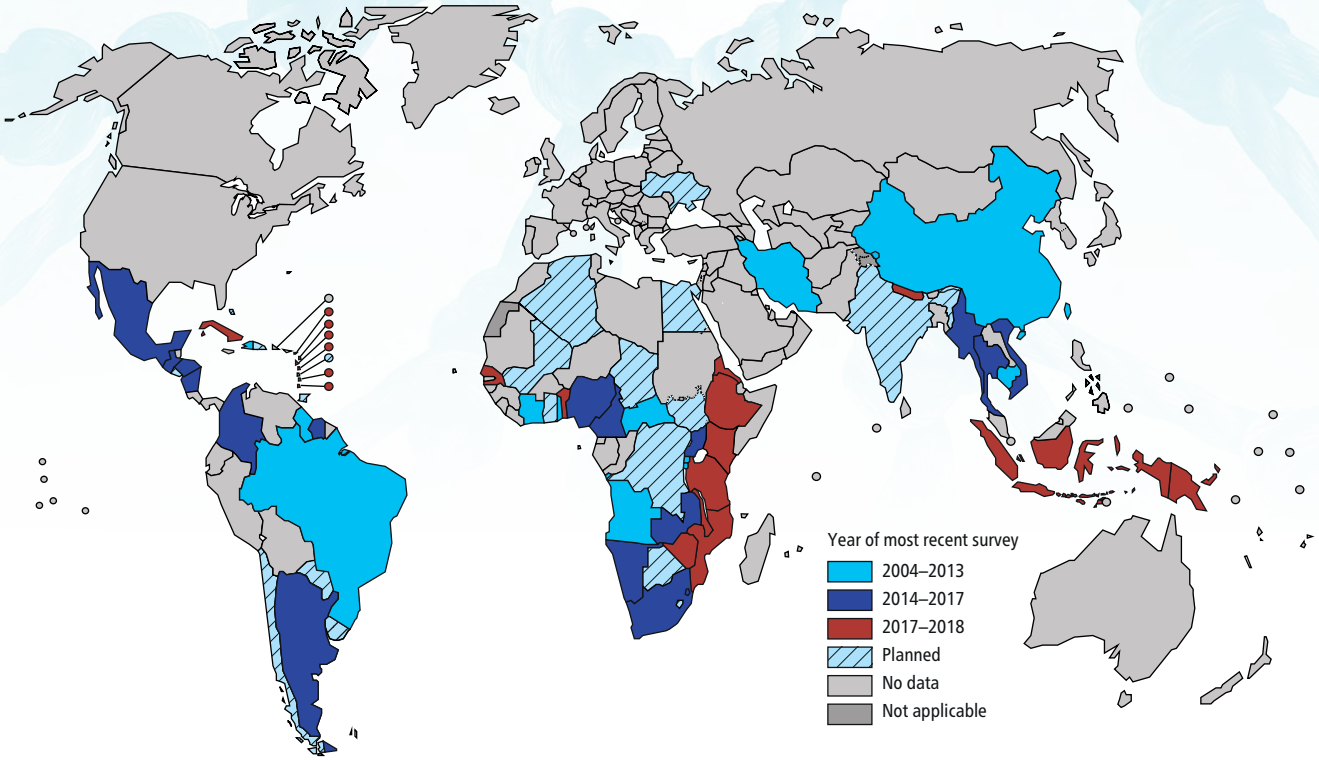
Pre-exposure prophylaxis (PrEP) is an effective approach to prevent HIV infection by using antiretroviral drugs. Resistance can emerge as a result of poor adherence to PrEP without frequent repeat HIV testing. WHO is developing guidance for countries to monitor resistance emerging from PrEP.

Progress in survey implementation

Since 2004, 271 surveys have been implemented in 69 countries. Substantial progress in implementing surveys has been achieved in this period **(Fig. 4)**.

Between 2017 and 2018, 20 WHO-recommended pretreatment HIV drug resistance surveys and nine acquired drug resistance surveys were initiated in 20 countries, and an additional 28 countries plan to conduct surveys in 2018 **(Fig. 5)**. Of the 45 HIV focus countries, 47% have implemented at least one of the recommended HIV drug resistance surveys over the previous three years. The survey results will be reported in the next WHO HIV drug resistance report.

FIG. 4.
Implementation of WHO recommended HIV drug resistance surveys, 2004–2018



Progress in routine monitoring of program quality indicators