REPORT ON THE GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017–2021

World Health Organization

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CONTENTS

ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
DTG	dolutegravir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
PEPFAR	United States President's Emergency Plan for AIDS Relief
UNAIDS	Joint United Nations Programme on HIV/AIDS

1. INTRODUCTION

The Global Action Plan on HIV drug resistance 2017–2021 provided a comprehensive framework for global and country action and outlined a package of interventions and resources to guide the collective response to HIV drug resistance. The conclusion of this Global Action Plan on HIV drug resistance at the end of 2021 offered an opportunity for WHO to analyse the achievements realised over the preceding five years and identify barriers to the plan's implementation.

The plan's successes, impact and shortfalls were assessed using indicators established in Global Action Plan on HIV drug resistance 2017–2021 and qualitative interviews of key stakeholders at all levels. This report summarizes the findings of the assessment.

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2. BACKGROUND

Antimicrobial resistance is a major global public health threat *(1)*. Minimizing the emergence and transmission of HIV drug resistance is a vital part of the global commitment to address the challenges of antimicrobial resistance *(2)*.

The Global Action Plan on HIV drug resistance 2017–2021 was a five-year framework connecting global and local stakeholders in a coordinated response to HIV drug resistance *(2)*. It articulated the collective and cooperative actions required to prevent, monitor and respond to the global threat posed by HIV drug resistance in populations initiating and receiving antiretroviral therapy (ART).

WHO developed the Global Action Plan on HIV drug resistance 2017–2021 in collaboration with global and national non-state partners, health ministry representatives, researchers, community organizations, civil society and donors. The Global Action Plan on HIV drug resistance 2017–2021 was aligned with the Global Action Plan on antimicrobial resistance adopted by the World Health Assembly in 2015 *(3)* and the Global Health Sector Strategy on HIV 2016–2021 *(4)*.

The Global Action Plan on HIV drug resistance 2017–2021 supported the commitments agreed upon at the United Nations High-Level Meeting on Ending AIDS to establish effective systems to monitor for, prevent and respond to the emergence of drug-resistant HIV among people living with HIV *(2)*.

The goals of the Global Action Plan on HIV drug resistance 2017–2021 were to articulate synergistic actions required to prevent HIV drug resistance from undermining efforts to achieve global targets on health and HIV and to provide the most effective treatment to all people living with HIV, including adults, key populations, pregnant and breastfeeding women, children and adolescents.

The guiding principles of the Global Action Plan on HIV drug resistance were a public health approach, country ownership, sustainable investment, standardized methods to monitor the emergence of HIV drug resistance and comprehensive, coordinated and integrated actions to tackle HIV drug resistance *(2)*.

The Global Action Plan on HIV drug resistance 2017–2021 provided an action framework to be undertaken by countries, global and national partners and WHO structured around strategic objectives **(Fig. 1)** in five key areas: prevention and response, monitoring and surveillance, research and innovation, laboratory capacity and governance and enabling mechanisms.

Fig. 1. **The five strategic objectives of the Global Action Plan on HIV drug resistance 2017–2021**

1 Prevention and response
Implement high-impact interventions to prevent and respond to HIV drug resistance.

2 Monitoring and surveillance
Obtain high-quality data on HIV drug resistance from periodic surveys, while expanding the coverage and quality of routine viral load and HIV drug resistance testing to inform continuous HIV drug resistance surveillance; monitor the quality of service delivery; and collect and analyse data recorded as part of routine patient care for the purpose of evaluating programme performance to prevent HIV drug resistance.

3 Research and innovation
Encourage relevant and innovative research, leading to interventions that will have the greatest public health impact on minimizing HIV drug resistance; and fill existing knowledge gaps on the risk of HIV drug resistance for newer ARV drugs and the impact of service delivery interventions to increase viral load suppression and contain HIV drug resistance.

4 Laboratory capacity
Strengthen laboratory capacity and quality to support and expand the use of viral load monitoring and build capacity to monitor HIV drug resistance in low- and middle-income countries.

5 Governance and enabling mechanisms
Ensure that governance and enabling mechanisms (advocacy, country ownership, coordinated action and sustainable funding) are in place to support action on HIV drug resistance.

Strategic objective 1 articulated the importance of optimized procurement and supply chains for antiretroviral (ARV) drugs and viral load testing reagents and scale-up and use of viral load testing to maximize population-level viral load suppression among people receiving ART. In addition, strategic objective 1 highlighted the importance of adequate adherence support and the appropriate use of recommended ARV drugs. In addition, the Global Action Plan on HIV drug resistance 2017–2021 articulated how countries should develop plans to respond to rising levels of HIV drug resistance, including the transition to dolutegravir (DTG)-based first-line ART.

Strategic objective 2 supported the collection and analysis of data from nationally representative HIV drug resistance surveys and the collection and analysis of early warning indicators of HIV drug resistance, a subset of globally recommended quality of care indicators predictive of viral load suppression or HIV drug resistance in populations receiving ART *(2, 5)*.

Strategic objective 3 encouraged relevant and innovative research designed to close identified knowledge gaps related to the risk of HIV drug resistance for newer ARV drugs and to identify service delivery interventions that would increase viral load suppression and minimize the emergence and transmission of HIV drug resistance.

Strategic objective 4 supported strengthening the laboratory capacity for HIV drug resistance genotyping for surveillance in low- and middle-income countries, facilitating in-country capacitation for HIV drug resistance testing for surveillance and providing support for drug resistance testing in WHO-designated regional and specialized laboratories for countries without HIV drug resistance testing capacity. In addition, strategic objective 4 underscored the need to strengthen the WHO HIV drug resistance laboratory network capacity to conduct resistance testing using dried blood spots and sequence the integrase region of the HIV-1 pol gene.

Strategic objective 5 defined governance and the enabling mechanisms of advocacy, country ownership, coordinated action and sustainable funding that were in place to initiate and sustain actions to address HIV drug resistance. In addition, strategic objective 5 emphasized integrating HIV drug resistance prevention, monitoring and response into long-term HIV programme planning and funding and linking it to national antimicrobial resistance strategies.

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3. PROGRESS ON HIV DRUG RESISTANCE PREVENTION AND RESPONSE

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STRATEGIC OBJECTIVE 1:
Implement high-impact interventions to prevent and respond to HIV drug resistance.

3.1 Prevention of HIV drug resistance

Prevention of HIV drug resistance is a critical component of any national AIDS programme. It is achieved by using WHO-recommended ARV drugs, optimizing ART service delivery and eliminating programmatic gaps to deliver ARV drugs in ways that minimize treatment interruptions and maximize adherence.

Opportunities for clinics and ART programmes to minimize the possible emergence of HIV drug resistance may be identified through routine monitoring of programme quality indicators associated with treatment failure and drug resistance. Early warning indicator results provide clinic and programme managers with data about how their clinics perform compared with national means and with international targets to prevent the emergence of HIV drug resistance.

WHO's response

- In 2019, WHO published a technical brief for maintaining and improving the quality of care within HIV clinical services *(6)* to guide the implementation of high-quality HIV services through approaches to policy, strategy and service delivery, to suggest considerations for selecting measures of high-quality services and to provide case examples of quality management in HIV services in low- and middle-income countries.

- In 2021, WHO and Project ECHO, in partnership with the WHO Quality of HIV Care Global Technical Working Group, initiated a collaboration to host a webinar series bringing together health policy-makers, national programme managers, health-care providers, donors and partners in interventions on HIV and people living with HIV *(7)*. An overall goal was to stimulate discussions between various stakeholders and share best practices and lessons learned to improve the quality of care and life of people living with HIV. Webinars have been held on community-led monitoring and how it can contribute to improved access to medicines, including preventing ARV drug stock-outs and improving the quality of life for people living with HIV. These webinars emphasize the need for high-quality HIV care services along the entire cascade. They have featured locally led initiatives to maximize the quality of service delivery, all of which directly or indirectly maximize population-level HIV viral suppression, thereby minimizing the preventable emergence and transmission of drug-resistant HIV.

- Action briefs detailing initiatives in different countries to improve the quality of HIV care delivered to people living with HIV were released on the WHO Global Learning Laboratory for Quality Universal Health Coverage in 2021 (https://www.who.int/news/item/09-12-2021-quality-of-hiv-care-from-guidance-to-implementation). These briefs focus on quality assurance and improvement applied to HIV programmes, their results and what was learned from implementation experiences.

Countries' response

- This report summarizes the outcomes of monitoring quality-of-care indicators associated with the emergence of HIV drug resistance in countries with a high burden of HIV infection from 2017 to 2021 *(8)*. During this period, 44 of 45 WHO focus countries reported data on ART programme quality-of-care indicators through the UNAIDS Global AIDS Monitoring system *(9)*. Where available, viral load suppression data from the United States President's Emergency Plan for AIDS Relief (PEPFAR) population health indicator survey were used. Country performance for each indicator was classified using targets established for WHO early warning indicators of HIV drug resistance. To provide as minimally biased estimates as possible, only data from countries reporting nationally representative data or data derived from ≥70% of all ART clinics in the country are summarized below. Note that not all countries reported data on each of the outcome indicators, and this is reflected in the variability of the denominators. Data on how well countries retain people receiving ART 12 months after initiation were generally scarce or infrequently reported. In 2019, the retention indicator was revised to total attrition on ART, which has since been incorporated into WHO's indicator guidance and monitoring tools. However, the attrition indicator has not yet been incorporated into Global AIDS Monitoring; thus, the data are reported below for only 2017 and 2018.

  - Adults: the proportion of countries with data was 31% (14 of 45) in 2017, rising to 47% (21 of 45) in 2018. The proportion of countries meeting the target of >85% of adults retained on ART after 12 months was 36% (5 of 14) in 2017 and 29% in 2018 (6 of 21).

  - Children: the proportion of countries with data was 31% (14 of 45) in both 2017 and 2018. The proportion of countries meeting the target >85% of children retained on ART was 29% (4 of 14) in 2017, rising to 43% in 2018 (6 of 14).

- **Viral load testing coverage**

  - Adults: the proportion of countries reporting data on viral load testing coverage was 69% (31 of 45) in 2017, 91% (41 of 45) in 2018, 78% (35 of 45) in 2019, 67% (30 of 45) in 2020 and 56% (25 of 45 in 2021. The proportion of countries achieving the target for viral load testing coverage of ≥70% of adults receiving ART having at least one viral load test annually was 32% (10 of 31) in 2017, 41% (17 of 41) in 2018 and rising to 43% (15 of 35) in 2019. However, in 2020 the proportion dropped to 37% (11 of 30) and rose modestly to 40% (10 of 25) in 2021. The decrease in viral load testing coverage in 2020 may have been due to disruption in patient care or viral load testing reagent supply chain challenges because of the global COVID-19 pandemic.

○ Children: the proportion of countries with data on viral load testing coverage was 42% (19 of 45) in 2017, 64% (29 of 45) in 2018 and 2019, 51% (23 of 45) in 2020 and dropping to 29% (13 of 45) in 2021. The proportion of countries achieving the target for viral load testing coverage ≥70% of children receiving ART receiving at least one viral load test annually was 37% (7 of 19) in 2017, 38% (11 of 29) in 2018, increasing to 59% (17 of 29) in 2019 but dropping to 43% (10 of 23) in 2020 with a rebound to 77% (10 of 13) in 2021. For adults, the decrease in viral load testing coverage in 2020 may have been due to disruption in patient care or viral load testing reagent supply chain challenges because of the global COVID-19 pandemic, as highlighted in other reports.

- **Viral load suppression.** Viral suppression was only assessed among countries reporting levels of viral load testing coverage ≥70% or a nationally representative estimate.

  ○ Adults: The proportion of countries with available data was 36% (16 of 45) in 2017, 24% (11 of 45) in 2018, 27% (12 of 45) in 2019, 29% (13 of 45) in 2020 and 20% (9 of 45) in 2021. The proportion of countries achieving the target ≥90% of adults receiving ART having a viral load testing documenting viral load ≤1000 copies/ml was 25% (4 of 16) in 2017, 55% (6 of 11) in 2018, 50% (6 of 12) in 2019, 69% (9 of 13) in 2020 and 78% (7 of 9) in 2021.

  ○ Children: the proportion of countries with available data was 16% (7 of 45) in 2017, 22% (10 of 45) in 2018, 38% (17 of 45) in 2019 and 18% (8 of 45) in both 2020 and 2021. The proportion of countries achieving the target of ≥90% of children receiving ART having a viral load test documenting viral load test result ≤1000 copies/ml was comparatively lower in children than adults, with only 14% (1 of 7) of countries achieving the target in 2017, 20% (2 of 10) in 2018, 18% (3 of 17) in 2019, 38% (3 of 8) in 2020 and 25% (2 of 8) in 2021.

- **Drug stock-outs.** Data on ARV drug stock-outs were reported for the years 2017–2020. As of 2021, the indicator is being updated to reflect community-based and multimonth dispensing approaches.

  ○ Adults: the proportion of countries with available data was 67% (30 of 45) in 2017 and 2018, dropping 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 of routinely dispensed ARV drugs was 50% (15 of 30) in 2017 and 2018 (15 of 30), 54% in 2019 (13 of 24) and 50% (13 of 26) in 2020.

○ Children: the proportion of countries with available data was 67% (30 of 45) in 2017 and 2018, 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 of routinely dispensed ARV drug formulations for children was 53% (16 of 30) in 2017, 50% in 2018 (15 of 30), 54% in 2019 (13 of 24) and 50% (13 of 26) in 2020.

- **Proportion of people switching to second-line ART** is a proxy measure of how well a country uses viral load to identify people for whom first-line ART is failing and switching them to a second-line regimen, thereby preventing the emergence and possible transmission of drug-resistant virus.

  ○ Adults: the proportion of countries reporting data was 62% (28 of 45) in 2017, 56% (25 of 45) in 2018 and 2019, 62% (28 of 45) in 2020 and 64% (29 of 45) in 2021. The proportion of countries achieving the target of having at least 5% of adults receiving a second-line ART regimen was 43% (12 of 28) in 2017, 36% (9 of 25) in 2018 and 2019 and 46% (13 of 28) in 2020 and 45% (13 of 29) in 2021.

  ○ Children: the proportion of countries reporting data was 56% (25 of 45) in 2017, 51% (23 of 45) in 2018, 56% (25 of 45) in 2019 and 2020 and 60% (27 of 45) in 2021. The proportion of countries that achieved the target of having at least 5% of children receiving ART receiving a second-line regimen was 76% (19 of 25) in 2017, 65% (15 of 23) in 2018, 80% (20 of 25) in 2019 and 2020 and 74% (20 of 27) in 2021. The high proportion of children receiving second-line treatment may reflect the use of protease inhibitors (PI) as first-line ART among children, with countries reporting this as second-line ART.

Overall, reporting indicators **(Table 1)** from countries remain suboptimal, clearly underscoring a need to strengthen national and regional data reporting systems for globally relevant indicators. The performance of programmatic quality indicators **(Table 2)** also remained suboptimal in most countries during the reporting period, especially for children, and was below the 2021 targets established in the Global Action Plan on HIV drug resistance 2017–2021 **(Annex 1)**. These findings underscore the need for proactive approaches to improving the quality of HIV treatment and care services to minimize the emergence of preventable drug-resistant HIV. Published examples from countries documenting clinic and programme changes implemented in response to early warning indicators monitoring include Cameroon, Ethiopia, Uganda and Zimbabwe *(10-13)*. Examples of quality improvements included strategies to strengthen data completeness and reporting, optimized ARV drug dispensing practices to follow global guidance, support for patient adherence to therapy and minimalization of classification of lost to follow up through enhanced documentation of clinic transfers.

Table 1. Proportion of focus countries reporting data on quality-of-care indicators, 2017–2021 (n = 45)

Population	Year	Retention on ART 12 months after ART initiation		Viral load testing coverage			Viral load suppression			Drug stock-outs			Proportion of patients switched to second-line ART	
		n	%	n	%		n	%		n	%		n	%
Adults	2017	14	31	31	69		16	36		30	67		28	62
	2018	21	47	41	91		11	24		30	67		25	56
	2019			35	78		12	27		24	53		25	56
	2020			30	67		13	29		26	58		28	62
	2021			25	56		9	20					29	64
Children	2017	14	31	19	42		7	16		30	67		25	56
	2018	14	31	29	64		10	22		30	67		23	51
	2019			29	64		17	38		24	53		25	56
	2020			23	51		8	18		26	58		25	56
	2021			13	29		8	18					27	60

Table 2. Proportion of focus countries meeting targets of excellent performance on quality-of-care indicators, 2017–2021

Population	Year	Retention on ART 12 months after ART initiation		Viral load testing coverage			Viral load suppression			Drug stock-outs			Proportion of patients switched to second-line ART	
		n/N	%	n/N	%		n/N	%		n/N	%		n/N	%
Adults	2017	5/14	36	10/31	32		4/16	25		15/30	50		12/28	43
	2018	6/21	29	17/41	41		6/11	55		15/30	50		9/25	36
	2019			15/35	43		6/12	50		13/24	54		9/25	36
	2020			11/30	37		9/13	69		13/26	50		13/28	46
	2021			10/25	40		7/9	78					13/29	45
Children	2017	4/14	29	7/19	37		1/7	14		16/30	53		19/25	76
	2018	6/14	43	11/29	38		2/10	20		15/30	50		15/23	65
	2019			17/29	59		3/17	18		13/24	54		20/25	80
	2020			10/23	43		3/8	38		13/26	50		20/25	80
	2021			10/13	77		2/8	25					20/27	74

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

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3.2 Responses to high levels of pretreatment HIV drug resistance

The action framework of the Global Action Plan on HIV drug resistance 2017–2021 stressed the importance that WHO ensured normative guidance on the use of ARV drugs for prevention and treatment was regularly updated, incorporating emerging evidence on resistance to new drug classes. Also, researchers were asked to generate evidence regarding which public health interventions have the most significant impact in preventing and responding to HIV drug resistance, to be used for national and global decision-making. In addition, countries were encouraged to periodically review and update national policies and protocols on using ARV drugs for HIV prevention and treatment based on WHO guidelines and the need to respond promptly to rising levels of HIV drug resistance.

Researchers' response

In 2017, a modelling study predicted that failure to act on increasing levels of pretreatment HIV drug resistance to non-nucleoside reverse-transcriptase inhibitor (NNRTI) drugs would lead to 5.7% more people dying from AIDS-related causes, 3.5% more people acquiring HIV infection and a 2.0% increase in expenditure for ART programmes during the following five years *(14)*.

WHO's response

In 2016, WHO published guidance to support countries to respond to high levels (≥10%) of NNRTI pretreatment resistance *(15)*. The guidance emphasized accelerated transition to non-NNRTI-based ART (integrase inhibitor-based treatment) and, in settings where the transition was not feasible, the guidance suggested considering an individual HIV drug resistance test, if feasible, to guide the selection of optimal regimens among people initiating or reinitiating treatment. In 2018, WHO issued interim guidelines recommending DTG-containing ART as the preferred first-line treatment in adolescents and adults, and the 2021 guidelines update extends the recommendation to use for children ≥3 kg and ≥4 weeks of age *(16)*.

Countries' response

- **Pretreatment HIV drug resistance, prevalence of NNRTIs ≥10%**. Between 2014 and 2021, 26 of 35 countries implementing surveys of pretreatment HIV drug resistance reported NNRTI resistance levels exceeding 10% *(17)*. All 26 countries have adopted and implemented DTG-based first-line ART. The 2021 target established in the Global Action Plan on HIV drug resistance 2017–2021 was that 100% of countries responded to HIV drug resistance through adjusting programmes or revising national ART guidelines; therefore, the target was successfully achieved **(Annex 1)**.

- **High levels of HIV resistance to NNRTI drugs among infants newly diagnosed with HIV**. Between 2012 and 2020, 11 countries in Africa reported data to WHO on levels of HIV drug resistance in infants less than 18 months of age and ART naive *(17)*. Levels of resistance to efavirenz + nevirapine were very high, exceeding 50% in most countries, underscoring the urgent need to transition to WHO-recommended non-NNRTI-containing regimens for young children. These 11 countries adopted lopinavir + ritonavir as the preferred first-line regimen. Further, these countries are also shifting towards using DTG for infants ≥3 kg and ≥4 weeks of age following the current WHO recommendations.

- **Adoption of DTG-based ART as the preferred first-line regimen**. The number of countries adopting DTG as part of the preferred first-line ART has steadily increased. As of July 2022, 108 countries (88% of 123 reporting countries) had transitioned to DTG as part of the preferred first-line ART for adults and adolescents **(Map 1)**. Also, 60 countries (55% of 110 reporting countries) had adopted DTG-based antiretroviral therapy as part of the preferred first-line regimen for infants and children **(Map 2)**.

Map 1. Adoption of DTG-based regimen as the preferred first-line ART in the national guidelines for adults and adolescents, July 2022
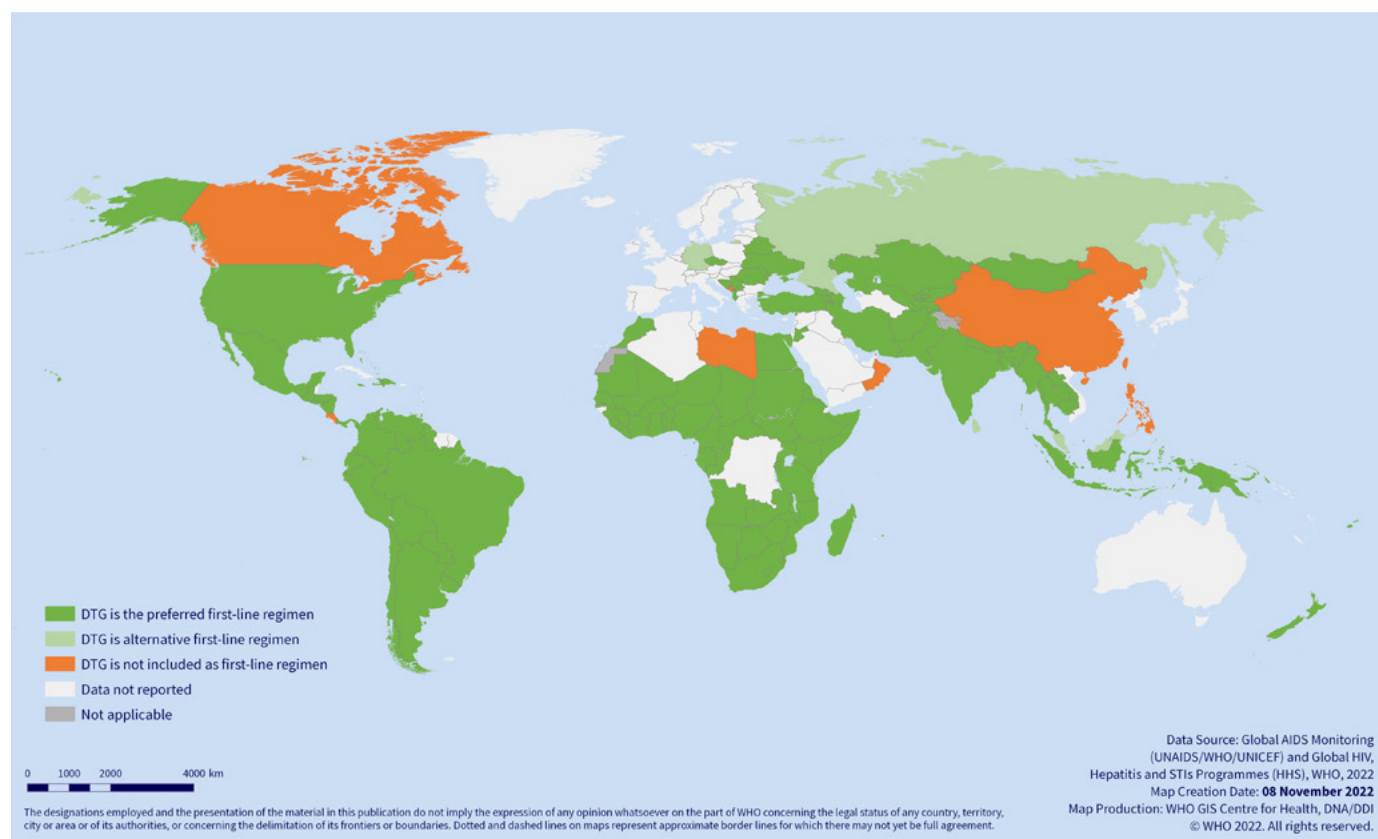
Map 2. Adoption of DTG-based regimen as the preferred first-line ART in the national guidelines for infants and children living with HIV, July 2022
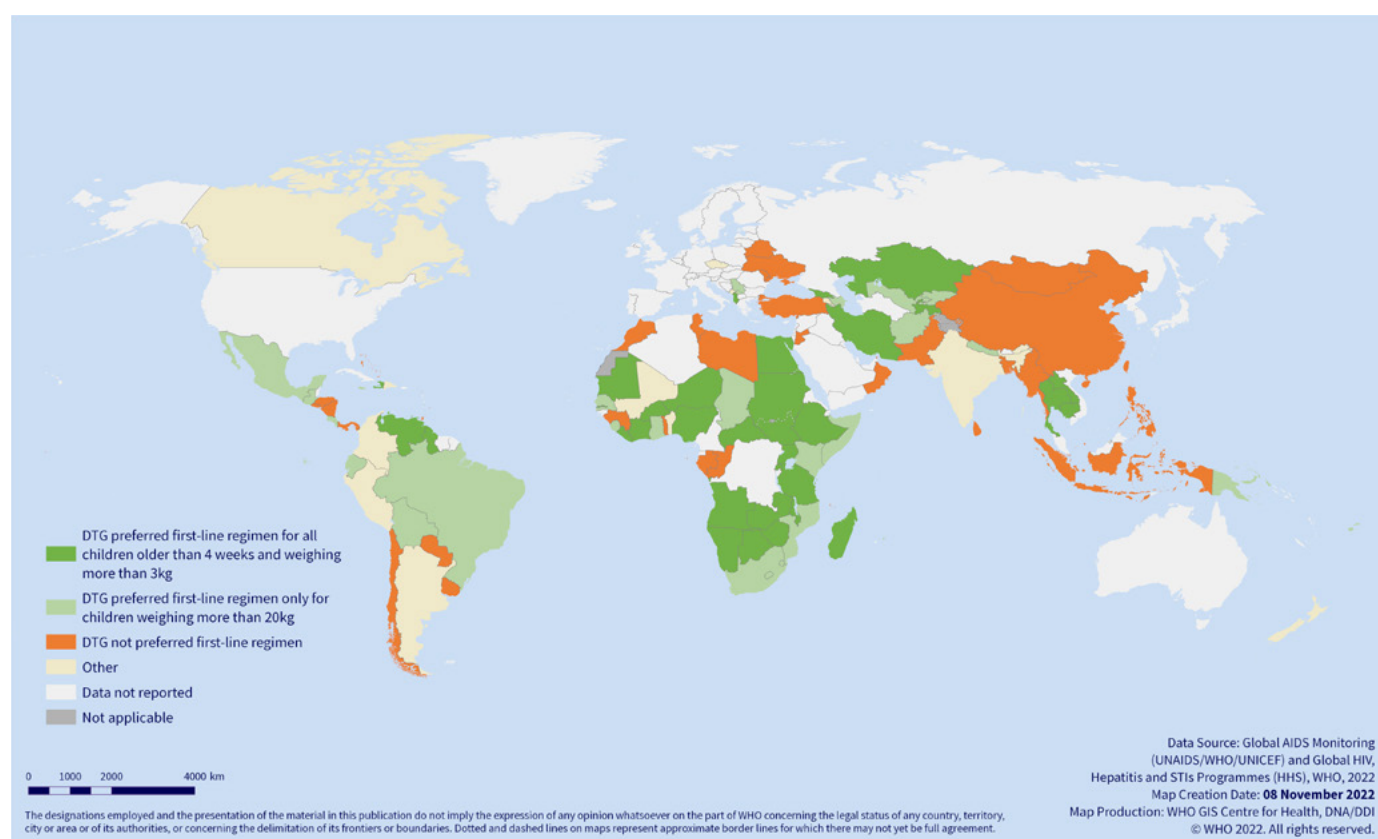
4. PROGRESS ON MONITORING AND SURVEILLANCE

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STRATEGIC OBJECTIVE 2:

Obtain quality data on HIV drug resistance from periodic surveys, while expanding the coverage and quality of routine viral load and HIV drug resistance testing to inform continuous HIV drug resistance surveillance; monitor quality of service delivery and collect and analyse data recorded as part of routine patient care for the purpose of evaluating programme performance to prevent HIV drug resistance.

4.1 HIV drug resistance surveillance

The action framework of the Global Action Plan on HIV drug resistance 2017–2021 articulated WHO's role in developing guidelines for HIV drug resistance surveillance and monitoring and supporting countries in conducting HIV drug resistance surveillance and monitoring. WHO was also responsible for strengthening the HIV drug resistance surveillance data repository and management. In addition, WHO was asked to report global and regional levels of HIV drug resistance and trends regularly.

Countries were encouraged to implement periodic nationally representative surveys to estimate the prevalence of drug-resistant HIV and to disseminate HIV drug resistance survey results in the country and to WHO for timely public health assessment.

WHO's response

- **HIV drug resistance surveillance methods.** To assist countries with HIV drug resistance surveillance, new standardized methods and operational toolkits were developed, including:

  - HIV drug resistance surveillance in countries scaling up pre-exposure prophylaxis *(18)*;

  - Laboratory-based survey of acquired HIV drug resistance using remnant viral load specimens *(19)*;

  - Clinic-based survey of acquired HIV drug resistance *(20)*; and

  - Sentinel surveillance of acquired HIV resistance in populations receiving ART *(21)*.

- **HIV drug resistance database.** WHO has developed an HIV drug resistance database as a global repository of HIV drug resistance survey data, which includes deidentified individual-level epidemiological information linked to HIV genome sequences. The database has four main purposes: (1) quality assurance of epidemiological and sequence data; (2) to ensure standardized interpretation of resistance by linking to the most recent algorithm for interpreting these data; (3) to support the dissemination of data for global reporting; and (4) to provide a long-term, secure repository for data on resistance to HIV drugs.

- **HIV drug resistance strategy.** The WHO-recommended HIV drug resistance surveillance, monitoring and response strategy was updated in 2021 in response to changing country needs, evolving science and the introduction of new ARV drugs for the prevention and treatment of HIV *(22)*. The 2021 update of the strategy included new survey methods of acquired HIV drug resistance, focusing on DTG resistance and new survey methods for countries scaling up PrEP *(18)*.

- **HIV drug resistance reports.** WHO promotes the dissemination and sharing of health data to advance public health by permitting analysis that enables the fullest possible understanding of health challenges to help to develop new solutions and ensure that decisions are based on the best available evidence. From 2017 to 2021, WHO produced three global reports and maps on HIV drug resistance prevalence and trends based on the information shared by countries *(17, 23, 24)*. The target established in the monitoring framework for the Global Action Plan on HIV drug resistance 2017–2021 **(Annex 1)** was therefore achieved (two WHO reports published by 2021).

- **Country support to conduct HIV drug resistance surveillance:** From 2017 to 2021, WHO provided technical assistance to 81 countries for the surveillance of HIV drug resistance **(Map 3)**. Based on countries' requests, WHO facilitated the development of protocols, training and surveys implementation, database use, data quality assurance, analysis and interpretation and country reports drafting and dissemination.

Map 3. Country support and technical assistance provided by WHO for the surveillance of HIV drug resistance, 2017–2021
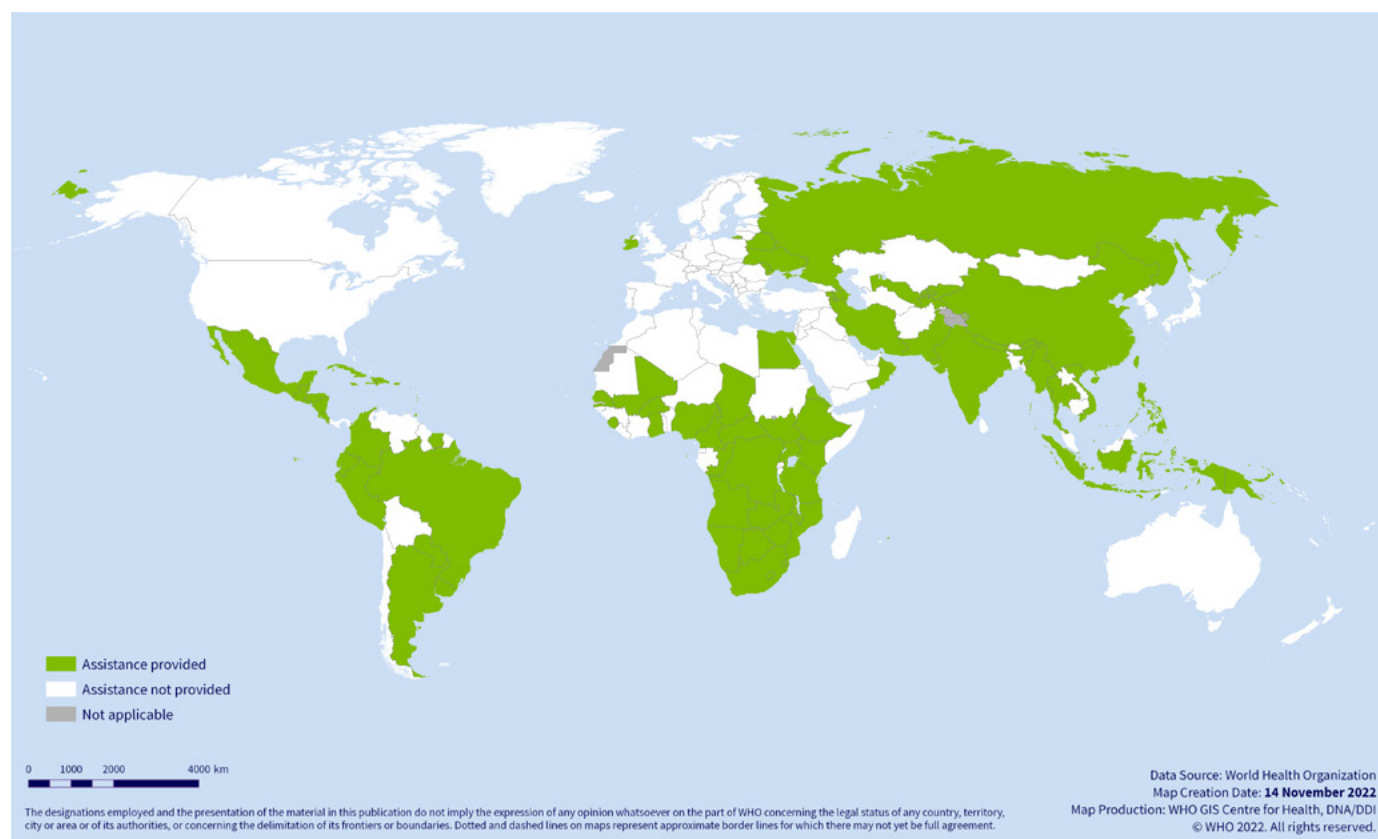
Countries' response

Substantial progress in survey implementation has been achieved since 2014, with 56 countries implementing 139 surveys. Between 2017 and 2021, 106 surveys were implemented in 43 countries versus 33 surveys in 23 countries between 2014 and 2016 **(Map 4)**.

- Thirty-nine pretreatment drug resistance surveys were implemented in 38 countries between 2017 and 2021 versus 17 surveys in 17 countries between 2014 and 2016.

- Six surveys of HIV drug resistance among treatment-naive infants were implemented in six countries between 2017 and 2021 (some recent surveys have not been finalized) versus four surveys in four countries between 2014 and 2016.

- Sixty-one surveys of acquired HIV drug resistance were implemented in 30 countries between 2017 and 2020 versus 12 surveys in seven countries between 2014 and 2016.

Map 4. Implementation of national HIV drug resistance surveys, 2004–2021
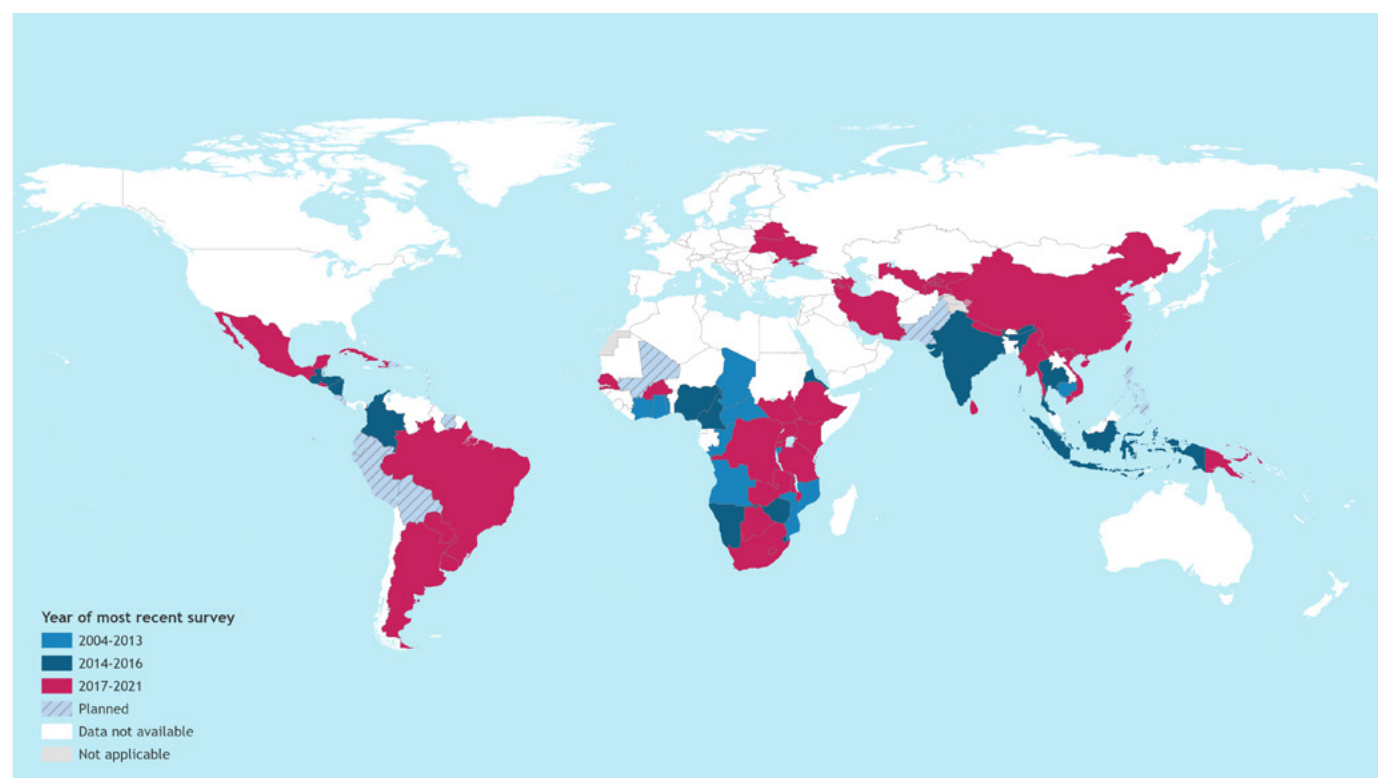
Year of most recent survey
- 2004-2013
- 2014-2016
- 2017-2021
- Planned
- Data not available
- Not applicable

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: WHO GIS Centre for Health, DNA/DDI

Map Creation Date: **12 October 2021**

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4.2 Monitoring early warning indicators of HIV drug resistance at the clinic level

WHO's response

WHO recommends that programmes routinely monitor the quality-of-care indicators known as early warning indicators of HIV drug resistance at the national and clinical levels. Routine monitoring of quality-of-care indicators and response to suboptimal performance form the foundation of HIV drug resistance prevention and link WHO-recommended surveillance of HIV drug resistance to programmatic interventions designed to minimize it.

The early warning indicators use standardized definitions, which have evolved as programmes mature and public health actions are refined. A consultative process led by WHO was used to update the indicators included in the 2020 WHO consolidated HIV strategic information guidelines *(25)*. The most up-to-date early warning indicators for HIV drug resistance were included in the WHO HIV drug resistance surveillance, monitoring and response strategy updated in 2021 *(22)*.

Countries' response

Between January 2018 and December 2021, 51% (23 of 45) of the 45 countries with a high burden of HIV infection reporting data to the UNAIDS Global AIDS Monitoring system monitored programme early warning indicators

associated with HIV drug resistance at the clinic-level. The proportion of countries implementing early warning indicators monitoring and reporting data declined from 36% (8 of 22) in 2018 to 29% (8 of 28) in 2019, 28% (9 of 32) in 2020 and 21% (6 of 28) in 2021. The target established in the monitoring framework for the Global Action Plan on HIV drug resistance 2017–2021 **(Annex 1)** was therefore not achieved (≥90% of the 45 WHO focus countries monitored the early warning indicators in 2021).

The decline in indicator monitoring and reporting highlights a need for increased advocacy of the importance of frequent quality-of-care indicator monitoring and prompt response to suboptimal performance to improve the quality of service delivery at the clinic and programmatic levels.

Integration of early warning indicators into the routine clinic and programme monitoring and evaluation systems, followed by rapid investigation and response to suboptimal performance, may increase early warning indicators monitoring and enable clinics and programmes to close gaps in service delivery. As of 2021, 75% (18 of 24) of countries reporting data have integrated early warning indicators into routine monitoring and evaluation systems in accordance with the WHO recommendations. However, many countries still need to report data.

5. PROGRESS IN RESEARCH AND INNOVATION

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STRATEGIC OBJECTIVE 3:

Encourage relevant and innovative research, leading to interventions that will have the greatest public health impact on minimizing HIV drug resistance; fill existing knowledge gaps on the risk of HIV drug resistance for newer ARV drugs and the impact of service delivery interventions to increase viral load suppression and contain HIV drug resistance.

Relevant and innovative research is vital to address knowledge gaps and create interventions that significantly minimize HIV drug resistance. The Global Action Plan on HIV drug resistance 2017–2021 tasked WHO to convene a research priority-setting process in collaboration with research institutions and expert networks. Also, researchers were encouraged to address the research gaps related to HIV drug resistance.

WHO's response

In 2017, WHO convened an expert meeting to identify research gaps and areas of innovation for prevention, monitoring and addressing concerns on HIV drug resistance. Overall, the group identified priority gaps grouped around three main themes: (1) epidemiological and clinical, (2) virological and (3) innovative technologies with a specific focus on the transition to DTG-based ART **(Table 3)**.

Research topics considered the highest priority within the five-year plan were ranked as tier 1. Topics deemed less critical over the next five years were ranked as tier 2.

Researchers' response

The monitoring framework for the Global Action Plan on HIV drug resistance 2017–2021 defined the research and innovation indicator target as ≥50% of research gaps identified by the expert meeting convened by WHO in 2017 should have at least one investigation planned or initiated. The research community addressed all but two of the gaps identified by the expert meeting convened by WHO in 2017 **(Table 3)**. Therefore, the target was exceeded, with 92% of the identified research gaps related to HIV drug resistance being addressed by the research community by the end of 2021 **(Annex 1)**.

Table 3. Summary of progress in addressing research gaps related to HIV drug resistance

Epidemiology and clinical aspects		
•	Effect of pre-existing resistance to the nucleoside reverse-transcriptase inhibitor (NRTI) backbone on the efficacy of DTG-based ART	✓
•	Levels of viral suppression and prevalence and pattern of HIV drug resistance mutations among people for whom DTG-based ART is failing in low- and middle-income countries	✓
•	Cost–effectiveness of individualized HIV drug resistance testing for people for whom a boosted PI or DTG-based regimen is failing to minimize unnecessary switches to subsequent lines	✓
•	HIV drug resistance emerging in programmes scaling up PrEP	✓
•	Impact of K65R/M184V mutations on the efficacy of tenofovir disoproxil fumarate (TDF)- and emtricitabine (FTC)-based PrEP	✓
•	Validated local, inexpensive and sustainable corrective actions to minimize the emergence and transmission of preventable drug-resistant HIV	—
•	Clinical impact of raltegravir-based ART among children infected with NRTI-resistant HIV	✓
•	Clinical impact of DTG administered twice daily among children for whom raltegravir-based ART is failing	✓
•	Optimal viral load switching algorithm to minimize the emergence of resistance	✓
•	Simple algorithm for interpreting HIV drug resistance for use by caregivers	✓
•	Efficacy of DTG administered twice daily as a strategy to increase the potency of the regimen among individuals with partly active NRTI backbone	✓
•	Levels of viral suppression and acquired HIV drug resistance among people receiving second-line boosted PIs in low- and middle-income countries, with particular focus on atazanavir + ritonavir	✓
•	Response of TDF, lamivudine and DTG in populations at high risk of suboptimal adherence (such as adolescents) and among people coinfected with tuberculosis and HIV	✓
•	Clinically significant thresholds of low-abundance NNRTI-resistant variants	✓
•	Cost–effectiveness analysis tools for use in countries for financing and advocacy of optimized treatment	✓
Virological aspects		
•	Correlation of genotype-phenotype and clinical significance for all mutations	✓
•	List of transmitted integrase inhibitor mutations	✓
•	Minimum set of mutations for PIs, reverse-transcriptase inhibitors and integrase inhibitors for clinical purposes for point-mutation technology	—
•	Impact of novel drug delivery methods (such as long-acting drug formulations) on the selection of HIV drug resistance	✓
Innovative technologies		
•	Simple and affordable point-of-care HIV drug resistance assays	✓
•	Inexpensive, simple, easy-to-interpret tests that combine viral load and HIV drug resistance testing that can be used to minimize unnecessary switches to subsequent regimens	✓
•	Simple and affordable next-generation sequencing bioinformatics algorithms	✓
•	Newer collection matrices for HIV drug resistance testing	✓
•	Affordable, simple and easy-to-use point-of-care tests to measure drug levels to distinguish people for whom treatment is failing because of poor adherence versus resistance	✓

Methods: rapid assessment of research question implementation among the research community and review of published literature. Research topics considered the highest priority within the five-year plan were ranked as tier 1. Topics deemed less critical over the next five years were ranked tier 2.

• Tier 1 research question   • Tier 2 research question   ✓ Research currently undergoing   — No evidence that research is being conducted

6. PROGRESS IN STRENGTHENING LABORATORY CAPACITY

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STRATEGIC OBJECTIVE 4:
Strengthen laboratory capacity and quality to support and expand use of viral load monitoring and build capacity to monitor HIV drug resistance in low- and middle-income countries.

6.1 HIV viral load testing

Early identification of patients experiencing failure to suppress viral loads and their appropriate management reduces the risk of emergence, accumulation and transmission of drug resistance variants. It ensures good treatment response and the prevention of onward HIV transmission. For this reason, expanding access and optimal use of viral load testing is a critical measure for preventing HIV drug resistance.

The action framework of the Global Action Plan on HIV drug resistance 2017–2021 included WHO's technical assistance to countries to generate quality-assured viral load test results. Also, countries were encouraged to ensure the availability of high-quality viral load testing, including prompt reporting and the use of results for clinical care.

WHO's response

To assist countries to generate quality-assured viral load test results, WHO published the following guidance from 2017 to 2021:

- Technical update: considerations for developing a monitoring and evaluation framework for viral load testing: collecting and using data for scale-up and outcomes (26);
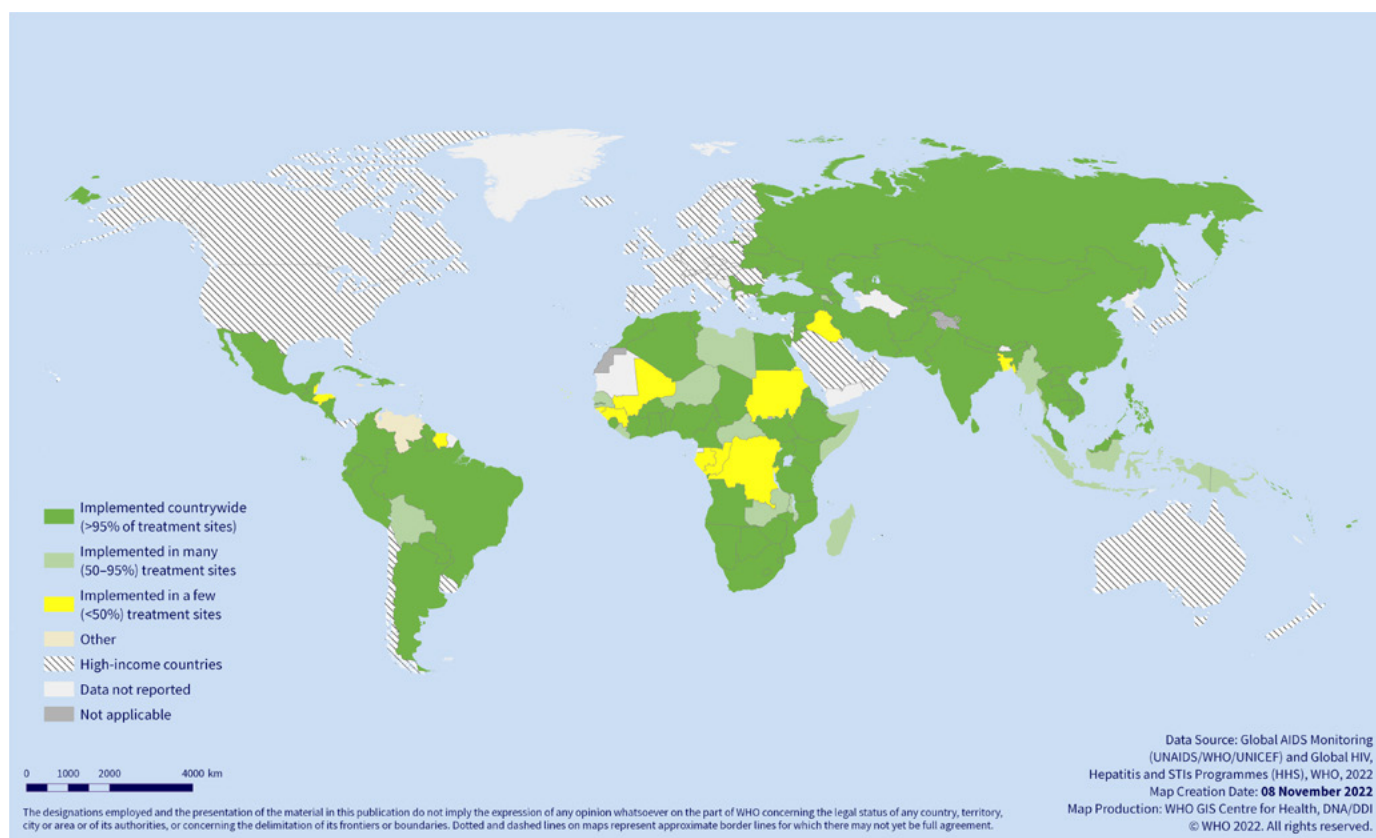
- Toolkit: HIV molecular diagnostics toolkit to improve access to viral load testing and infant diagnosis: HIV treatment and care (27); and

- Module for assessing and strengthening the quality of viral load testing data within HIV programmes and patient monitoring systems: implementation tool (28).

Countries' response

Majority of the countries within low- and middle-income countries have a nation-wide policy for routine viral load monitoring for adults and adolescents, with 74% (91 of 123) reporting implementation in >95% of clinic sites; of the remainder, almost half (47%, 15 of 32) reported implementation in many (50–95%) treatment sites **(Map 5)**.[1]

Nevertheless, viral load testing coverage remains suboptimal among the 45 HIV high-burden countries reporting data to WHO; 88% (22 of 25) had viral load testing coverage below 90% in 2021. Moreover, 32% of the countries reported ≤50% viral load testing coverage in 2021. This is, however, a slight improvement from 2018, 2019, and 2020 where 40%, 34% and 36% of the countries reported viral load testing coverage of ≤50%. More efforts are, however, needed to ensure universal access and effective utilization of viral load tests in low- and middle-income countries.

Map 5. National policy on routine viral load testing for monitoring ART and implementation status among adults and adolescents living with HIV in low- and middle-income countries, July 2022[2]

Implemented countrywide (>95% of treatment sites)

Implemented in many (50–95%) treatment sites

Implemented in a few (<50%) treatment sites

Other

High-income countries

Data not reported

Not applicable

0   1000   2000   4000 km

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global AIDS Monitoring (UNAIDS/WHO/UNICEF) and Global HIV, Hepatitis and STIs Programmes (HHS), WHO, 2022
Map Creation Date: **08 November 2022**
Map Production: WHO GIS Centre for Health, DNA/DDI
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[1] Low and middle-income countries defined by the World Bank income categorisation.

[2] The map illustrates reported country policy but not necessarily compliance to stated policy.

6.2 HIV drug resistance testing

High-quality HIV drug resistance testing is critical for the surveillance of HIV drug resistance at a population level. Therefore, the action framework of the Global Action Plan on HIV drug resistance 2017–2021 encouraged countries to designate a laboratory for HIV drug resistance testing, build capacity and apply for membership in the WHO HIVResNet Laboratory Network. In addition, the framework underscored the importance of expanding and strengthening the capacity of the WHO HIVResNet Laboratory Network to conduct resistance testing to newer drug classes, including integrase inhibitors, and to use field-friendly specimens such as dried blood spots.

WHO's response

The WHO HIVResNet Laboratory Network performs drug resistance testing for countries implementing HIV drug resistance surveillance. The WHO HIVResNet Laboratory Network supports HIV drug resistance surveillance by providing accurate and timely genotyping results that meet WHO specifications. Its objectives are to ensure the proper collection, handling, shipment and storage of specimens and the availability of quality-assured HIV genotyping laboratory services producing comparable and reliable results at the national, regional and global levels.

The WHO HIVResNet HIV drug resistance laboratory operational framework, originally published in 2017 *(29)*, described how designated HIVResNet Laboratory Network laboratories functioned to support national, regional and global HIV drug resistance surveillance in a standardized format according to WHO specifications.

The WHO HIV drug resistance laboratory operational framework was updated in 2020 *(30)* to reflect technical and strategic developments, including consideration of next-generation sequencing methods, updates to the standard operating procedures for post-testing quality assurance of HIV sequence data related to integrase and recommendations for assay validation.

The third edition of the WHO manual for HIV drug resistance testing using dried blood spots was published in 2020 *(31)*. It provides current best practice recommendations for laboratory HIV drug resistance testing using dried blood spots.

To expand the number of WHO-designated laboratories for HIV drug resistance testing in low- and middle-income countries, WHO provided training, mentoring and capacity building of laboratory personnel, guidance on appropriate HIV drug resistance testing standard procedures and quality control. Also, WHO facilitated the participation of the WHO-designated laboratories in a WHO-recognized external quality assurance programme. Finally, WHO performed the evaluation and designation process following the HIV drug resistance laboratory operational framework.

WHO is steering a diagnostic testing agenda for the future development of affordable HIV drug resistance tests for individual patient management in specific use cases in low- and middle-income countries. This initiative follows the increased use of HIV drug resistance testing for individual patient monitoring in low- and middle-income countries. Among 34 countries with a high burden of HIV reporting data to WHO, 23 (68%) have a policy recommending HIV drug resistance testing for individual patient management.

To support this diagnostic agenda, WHO convened a series of consultations between July 2021 and November 2022 to develop a target product profile for HIV drug resistance tests for patient management in low- and middle-income countries. The target product profile is expected to be completed in 2023.
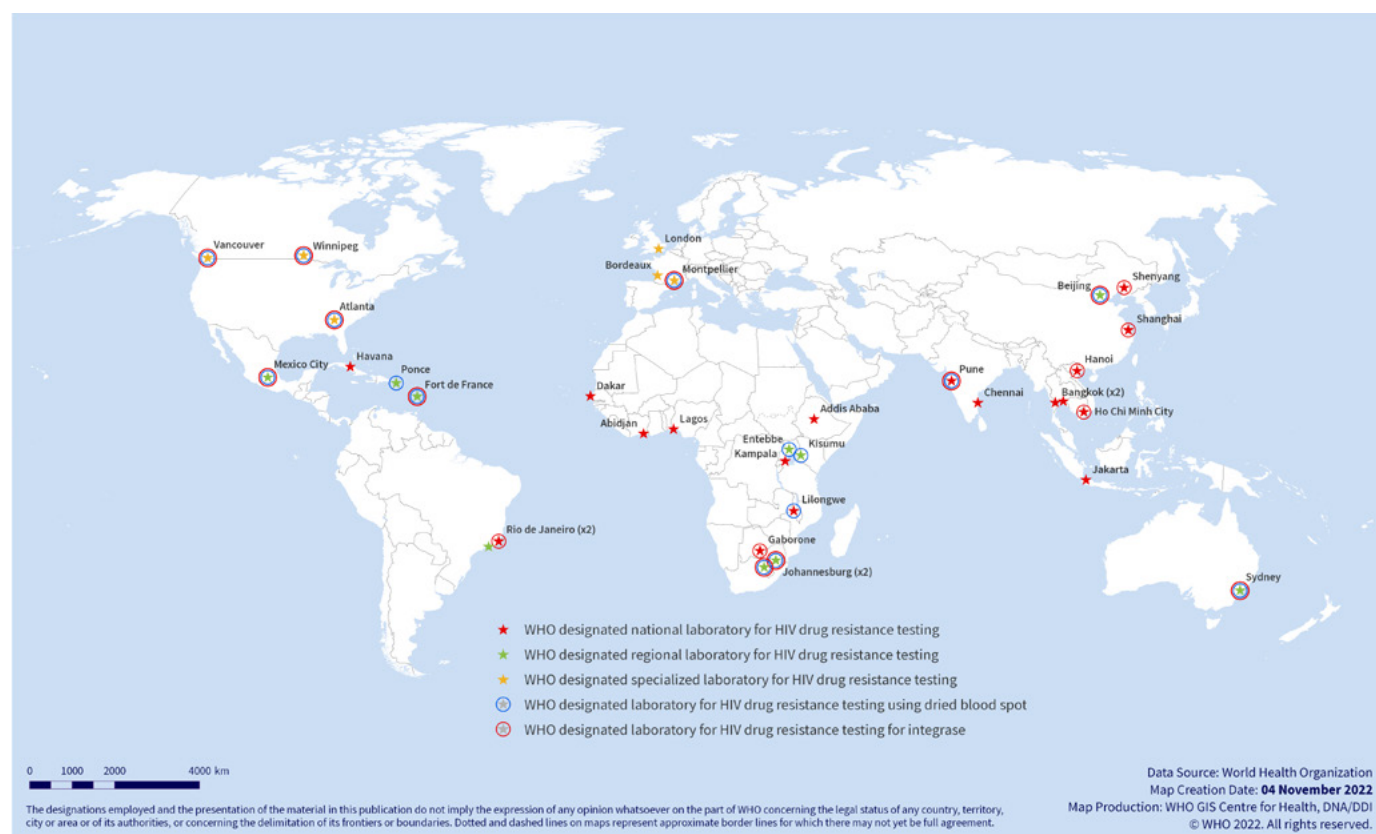
WHO HIVResNet's response

The WHO HIVResNet HIV drug resistance laboratory operational framework classifies the laboratories into national, regional and specialized. National laboratories perform HIV drug resistance testing for surveys in their country. Regionally designated laboratories perform testing for surveys within their region for countries without nationally designated laboratories. Specialized laboratories perform genotyping for any country, support WHO in technical assistance and support drug resistance testing when needed.

As of November 2022, the WHO HIVResNet Laboratory Network includes 35 laboratories worldwide **(Map 6)**, 18 national laboratories, 10 regional laboratories, and seven specialized laboratories. Fifteen laboratories have the capacity for genotyping from dried blood spot specimens. The monitoring framework for the Global Action Plan on HIV drug resistance 2017–2021 defined the research and innovation indicator target as ≥70% of the regional and specialized laboratories have the capacity for HIV drug resistance testing using dried blood spot specimens by 2021 **(Annex 1)**. As of 2021, 76% of regional and specialized laboratories have the capacity for HIV drug resistance testing using dried blood spots, and this target was therefore achieved.

WHO is also advocating for increasing capacity within the WHO HIVResNet Laboratory Network to expand capacity to test for integrase inhibitor resistance to support drug resistance surveillance of people receiving a DTG-based regimen. To date, 17 WHO HIVResNet Laboratory Network members have validated a genotypic assay for integrase **(Map 6)**, with several others expected to complete the validations before the end of 2022.

Map 6. WHO HIVResNet Laboratory Network, November 2022

★ WHO designated national laboratory for HIV drug resistance testing
★ WHO designated regional laboratory for HIV drug resistance testing
★ WHO designated specialized laboratory for HIV drug resistance testing
◉ WHO designated laboratory for HIV drug resistance testing using dried blood spot
◉ WHO designated laboratory for HIV drug resistance testing for integrase

Data Source: World Health Organization
Map Creation Date: **04 November 2022**
Map Production: WHO GIS Centre for Health, DNA/DDI
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7. PROGRESS ON BUILDING SUSTAINABLE GOVERNANCE AND ENABLING MECHANISMS

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STRATEGIC OBJECTIVE 5:
Ensure that governance and enabling mechanisms (advocacy, country ownership, coordinated action and sustainable funding) are in place to support action on HIV drug resistance.

7.1 Advocacy and awareness

Awareness of the HIV drug resistance burden among policy-makers, health-care workers, communities, patients and civil society is critical in combatting the emergence and spread of HIV drug resistance. The action framework of the Global Action Plan on HIV drug resistance 2017–2021 highlighted the need to effectively communicate the importance of combatting HIV drug resistance with different audiences, to increase HIV drug resistance awareness and commitment. The Global Action Plan on HIV drug resistance 2017–2021 stressed the need to build community engagement and literacy for preventing and responding to HIV drug resistance.

WHO's response

WHO has been using avenues such as World Antimicrobial Awareness Week *(32)* and Global Antimicrobial Resistance and Use Surveillance System reports *(33)* for increased HIV drug resistance awareness and advocacy. In addition, WHO has developed infographics and video clips to simplify HIV drug resistance messaging, which are available on the WHO HIV drug resistance website.

Community organizations and civil society response

In 2018, WHO, the Joep Lange Institute, Aidsfonds and the Partnership to Inspire, Transform and Connect the HIV response (PITCH) met in The Hague, Netherlands, with civil society advocates, community representatives, health practitioners, researchers and policy-makers to define the building blocks of a bold advocacy strategy to promote the implementation of the Global Action Plan *(34)*. Overall, the meeting affirmed the critical role of the community and civil rights groups in preventing and monitoring HIV drug resistance and identified ways to engage them by:

- more strongly emphasizing that HIV drug resistance is a quality-of-care concern that requires community engagement to monitor and address;

- developing quality indicators and a framework to guide community responses;

- increasing HIV drug resistance awareness by developing simplified, evidence-informed messaging, including coordinated audience-specific messaging at critical events and through social media; and

- benchmarking countries and regions based on their quality-of-care indicators to trigger community engagement in supporting quality improvement processes and stimulating advocacy actions.

In 2021, UNAIDS developed a guide for establishing community-led monitoring of HIV services that countries can leverage to implement the recommendations from the meeting in The Hague *(34, 35)*.

7.2 Funding HIV drug resistance activities

Establishing sustainable funding mechanisms is critical to support HIV drug resistance prevention and monitoring activities in low- and middle-income countries. The action framework of the Global Action Plan on HIV drug resistance 2017–2021 encouraged global partners to mobilize funding to support strategies to prevent, respond to and monitor HIV drug resistance at the global, national and local levels.

Global partners' response

The Global Fund to Fight AIDS, Tuberculosis and Malaria and PEPFAR have committed to funding HIV drug resistance surveillance activities in countries. They have committed to strengthening health-care systems and building laboratory capacity to achieve universal viral load testing coverage. A review of Global Fund grants shows that, between 2015 and 2017, 24 countries received support for HIV drug resistance prevention, monitoring and response, totalling about US$ 4.7 million. Most of this support funded HIV drug resistance surveys. Between 2018 and December 2021, 22 countries reported Global Fund support to implement 42 HIV drug resistance surveys.

In 2021–2022, PEPFAR supported the implementation of laboratory-based surveys of acquired HIV drug resistance surveillance in 16 countries.

Both the Global Fund and PEPFAR have committed to support countries to prevent and monitor the emergence of integrase inhibitor drug resistance as countries transition to DTG-based regimens as a means of ensuring the durability of these regimens and as part of global efforts to end the AIDS epidemic as a public health threat by 2030.

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7.3 Coordinata, integration, alignment and country ownership

The action framework of the Global Action Plan on HIV drug resistance 2017–2021 highlighted WHO's role in ensuring continual dialogue between academia, country programmes, policy-makers and donors on HIV drug resistance. Also, countries were encouraged to develop a five-year national action plan on HIV drug resistance, with milestones and a funding plan, based on the Global Action Plan on HIV drug resistance 2017–2021 and adapted to the local context. Global partners were encouraged to support the implementation of all elements of the Global Action Plan on HIV drug resistance.

WHO's response

- **WHO HIVResNet.** WHO has brought together organizations and experts working in HIV drug resistance to form WHO HIVResNet. It is a network of international experts, including researchers, laboratorians, implementing partners and members of civil society, established in 2004 to support and provide technical advice to WHO on activities to prevent, monitor and respond to HIV drug resistance, optimize the use of resistance testing and support policies related to optimal ART selection *(36)*. WHO HIVResNet is governed by a Steering Group and organized into five thematic working groups reporting to WHO **(Fig. 2)**. WHO meets with the working groups when needed and annually convenes a meeting with all WHO HIVResNet to promote the dialogue on HIV drug resistance challenges and the progress to address them. The WHO HIVResNet meeting reports are available at the WHO HIV drug resistance website *(36)*.
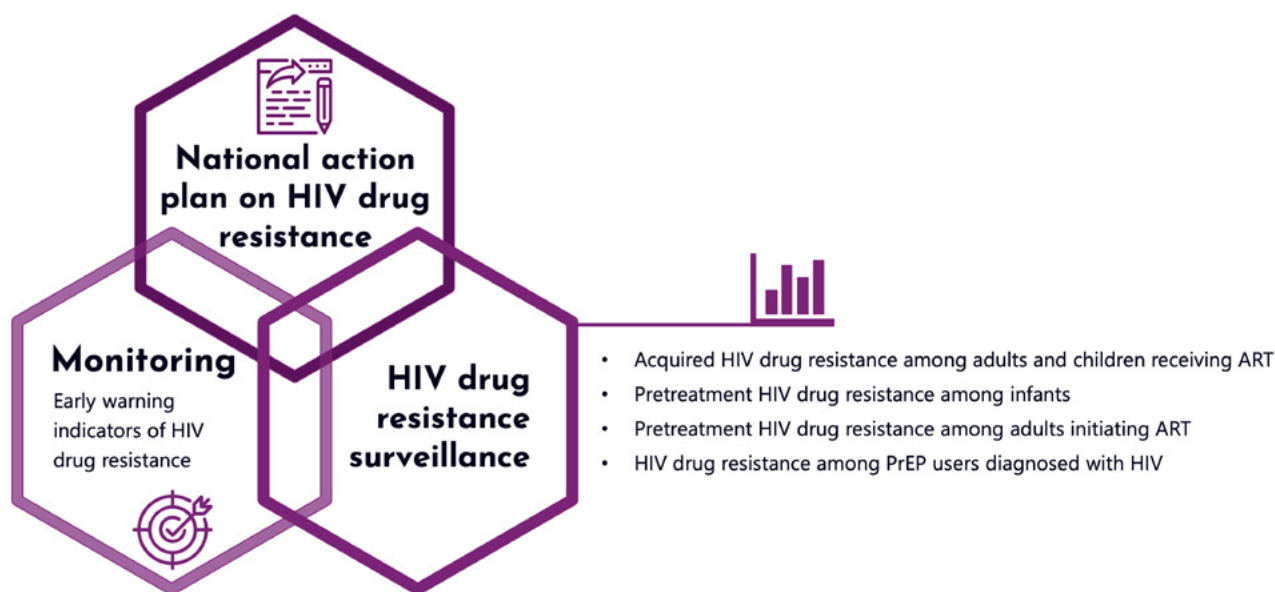
Fig. 2. WHO HIVResNet structure
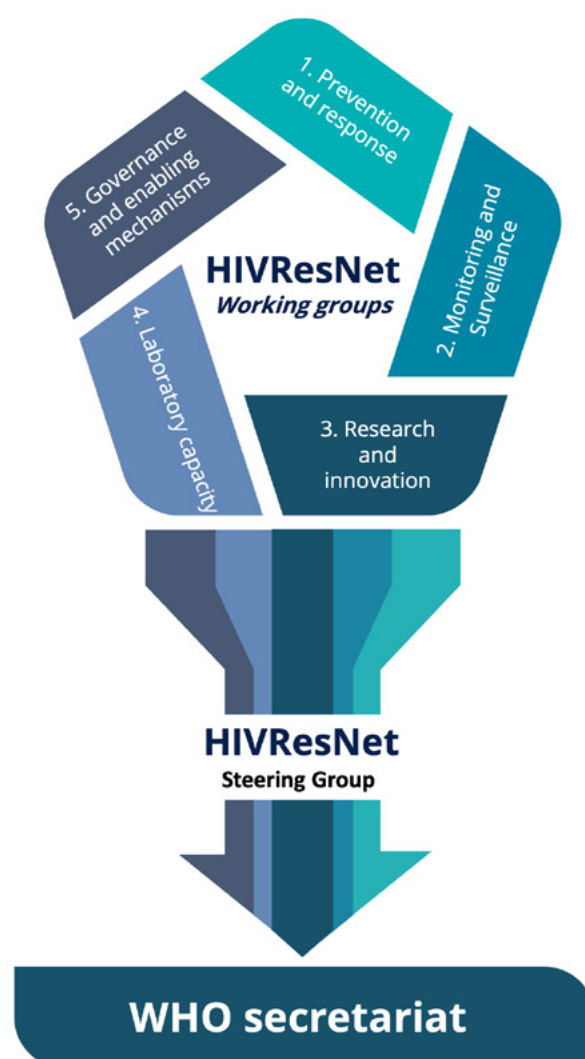
- **HIV drug resistance strategy.** The WHO-recommended HIV drug resistance surveillance, monitoring and response strategy updated in 2021 articulated the core set of WHO-recommended activities at the country level to support programme planning and budgeting and inform the preparation of grant proposals **(Fig. 3)**.

One core recommended activity was developing national action plans on HIV drug resistance. The guidance included how countries should develop and implement the national action plan on HIV drug resistance, who should lead the process and a generic budget to develop the national action plan on HIV drug resistance *(22)*.

Fig. 3. HIV drug resistance strategy: recommended core set of activities in countries

- Acquired HIV drug resistance among adults and children receiving ART
- Pretreatment HIV drug resistance among infants
- Pretreatment HIV drug resistance among adults initiating ART
- HIV drug resistance among PrEP users diagnosed with HIV

- **Country support to develop a five-year national action plan on HIV drug resistance.** From 2017 to 2021, WHO provided technical assistance to 17 countries to develop and review their national action plan on HIV drug resistance, including 12 in the African Region, four in the Region of the Americas and one in the Western Pacific Region.

Countries' response

Governance and ownership of HIV drug resistance prevention, monitoring and response are critical elements of a well-functioning ART programme. WHO recommends that countries integrate national action plans on HIV drug resistance into their broader HIV response and plans to strengthen the public health sector.

The number of WHO focus countries with a national action plan on HIV drug resistance ranged from 46% (13 of 28 focus countries reporting data to WHO) in 2018 to 64% (25 of 39 focus countries reporting data to WHO) in 2020, suggesting in-country commitment and multistakeholder engagement.

The target established in the monitoring framework for the Global Action Plan on HIV drug resistance 2017–2021 **(Annex 1)** was 100% of 45 WHO focus countries reporting data with HIV drug resistance strategy up to date by 2021. Therefore, this Global Action Plan on HIV drug resistance 2017–2021 target was not achieved.

Global partners' response

The Global Fund, United States Centers for Disease Control and Prevention and other international partners provided financial and technical support for developing and implementing national action plans on HIV drug resistance, including updating ARV guidelines for HIV prevention and treatment, implementing HIV drug resistance surveys, enhancing the quality of care, strengthening laboratory systems to ensure quality-assured viral load testing and HIV drug resistance genotyping, analysing data and interpreting public health.

8. QUALITATIVE INFORMATION OBTAINED FROM KEY STAKEHOLDER INTERVIEWS ABOUT THE GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017–2021

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8.1 Qualitative interview methods

Individual and small-group semistructured interviews were conducted with 62 key stakeholders from 36 institutions and 20 countries between March and June 2022 (Annex 2). A background briefing note was prepared and circulated before each interview.

The key stakeholder interviews were conducted with the objective of understanding and documenting the perspectives of key stakeholders on:

- the utility, impact and challenges of the Global Action Plan on HIV drug resistance 2017–2021 in preventing, monitoring, and responding to HIV drug resistance;

- the goals, structure and organization of a future global action plan 2023–2030; and

- an integrated global action plan on drug resistance for HIV, viral hepatitis and sexually transmitted infections.

In addition to interviews, two virtual large-group discussions were conducted with viral hepatitis and sexually transmitted infection content experts. The outcomes of the discussions are summarized below.

8.2 Interviewees' perspectives: Global Action Plan on HIV drug resistance 2017-2021

Key themes are described for each strategic objective. Priority research questions identified by the interviewees to be addressed in a future global action plan are summarized.

HIV drug resistance prevention and response

Concerning the prevention of and response to HIV drug resistance, the consensus of the interviewees was that the Global Action Plan on HIV drug resistance 2017–2021 had affected global HIV drug resistance prevention and response during its lifespan. In particular, interviewees cited the value of the Global Action Plan on HIV drug resistance 2017–2021 in stimulating countries and implementing partners to use HIV drug resistance surveys results in developing national and global normative guidance for using ARV drugs for HIV treatment and prevention. A clear and frequently cited example of success was how the Global Action Plan on HIV drug resistance 2017–2021 catalysed the global dialogue around the transition from NNRTI-based first-line ART to DTG-based ART. Data generated through the standardized surveys documented increasing levels of NNRTI resistance in numerous countries and helped to propel the global shift from NNRTI-based ART to DTG-based treatment. Between 2014 and 2021, 21 surveys of pretreatment drug resistance from 26 reported levels of resistance to nevirapine or efavirenz exceeding 10%. By 2021, all 26 countries had initiated the transition to DTG-based first-line ART *(15)*.

In terms of future priorities, interviewees expressed the view that WHO and partners should continue to conduct the important HIV drug resistance prevention and response activities as they did in 2017–2021, with any adaptations that may be needed in the era of tenofovir, lamivudine and DTG.

HIV drug resistance surveillance

Interviewees affirmed WHO's pivotal role in developing high-quality guidance for the surveillance monitoring of HIV drug resistance and the perceived impact of the Global Action Plan on HIV drug resistance 2017–2021 on raising awareness of the need to implement nationally representative HIV drug resistance surveys to inform the selection of optimal ART regimens. Specifically, the Global Action Plan on HIV drug resistance 2017–2021 stimulated the implementation of pretreatment HIV drug resistance surveys among adults and infants, with the results supporting the accelerated global transition to DTG-based ART for all people living with HIV.

Regarding future priorities, the consensus was that surveys of HIV drug resistance should continue, especially surveys focused on HIV drug resistance among people experiencing treatment failure while receiving DTG-based ART. Experts noted that such surveys would be especially critical since the prevalence of DTG resistance in populations failing DTG-based ART in low- and middle-income countries remains uncertain. However, interviewees commented on the substantial time lag between survey implementation and reporting, which lessens the impact of WHO-recommended surveys on decision-making. This fundamental challenge needs to be addressed in a future global action plan. In addition, interviewees suggest that consideration be given to developing surveys using sentinel methods to complement more extensive nationally representative surveys. Sentinel surveys could be designed with smaller sample sizes and yield rapid, programmatically actionable information on acquired DTG resistance in populations experiencing treatment failure.

In addition, since an increasing number of countries perform HIV drug resistance testing for clinical management, there was a consensus that guidance on responsibly aggregating available deidentified person-level HIV drug resistance genotypes and demographic information could be used for programme decision-making. A framework would need to be developed to assess the quality, completeness, accuracy and consistency of HIV drug resistance testing data obtained during routine clinical care. Minimum criteria to define populations could be developed, so the aggregate analysis would provide a cumulative and expanding understanding of DTG drug resistance, including its prevalence, patterns and determinants.

Leveraging next-generation sequencing infrastructure and data sharing and reporting archetypes developed during the COVID-19 pandemic (Box 1) should be strongly considered in a future gap on HIV drug resistance and could facilitate an enhanced and more timely global understanding of the emerging prevalence and patterns of HIV drug resistance in the DTG era. Greater use of next-generation sequencing for HIV drug resistance surveillance in the future may produce similar benefits for HIV programmes and global public health guidance as observed with SARS-CoV-2.

Box 1. The COVID-19 pandemic strengthened surveillance capacity

Concerning future WHO surveillance strategies, interviewees noted numerous examples of rapid genotyping, reporting of results and data sharing for public health decision-making during the COVID-19 pandemic. There was a consensus that the pandemic led to the expansion of next-generation sequencing capacity in several low- and middle-income countries, which could be leveraged to strengthen future global HIV drug resistance surveillance plans. Moreover, the COVID-19 pandemic accelerated the integration of genomics into public health, with the rapid sequencing of the SARS-CoV-2 virus and evolving viruses with sequence information available in the public domain within weeks for policy-makers to make decisions *(37, 38)*.

In particular, interviewees noted that HIV drug resistance data are often slowly shared globally, if at all, and lessons can be learned from other diseases and surveillance networks. The Global Initiative on Sharing Avian Influenza Data (GISAID) Initiative is one such example. GISAID promotes the rapid sharing of data from all influenza viruses and SARS-CoV-2 *(39)*. Data sharing includes genetic sequence and related clinical and epidemiological data associated with human viruses and geographical and species-specific data associated with avian and other animal viruses to help researchers understand how viruses evolve and spread during epidemics and pandemics *(39)*. GISAID facilitates the rapid sharing of data by overcoming hurdles and restrictions that discourage or prevent sharing of virological data before formal publication. The Initiative ensures free and open access to data within the GISAID platform for all individuals who agree to identify themselves and agree to uphold the GISAID sharing mechanism governed through its database access agreement *(39)*. WHO and partners may learn from the key principles of GISAID in terms of full agreement of all GISAID partners to share data and publish data promptly while acknowledging the source of the data.

Monitoring early warning indicators of HIV drug resistance

Countries highly value the routine monitoring of early warning indicators of HIV drug resistance because they collect facility-level information and document individual clinic-level and overall HIV programme performance in achieving quality service delivery over time and in a standardized and reproducible way. In addition, early warning indicators provide simple, at-a-glance performance strata, supporting local, district and national assessments and identifying areas of programmatic weakness that can be strengthened through appropriate local or national quality-of-care interventions.

Despite the overall positive consensus on the clinic and programme-level value of routine early warning indicators monitoring, especially if integrated into overall quality improvement initiatives, interviewees queried whether early warning indicators of HIV drug resistance, as currently defined, remained relevant in the era of DTG. Early warning indicators of HIV drug resistance were introduced in 2006, with definitions revised in 2011 after a systematic review

of the literature using the GRADE method, with targets established using a mixed-methods (normative and criterion referencing) approach *(40)*.

Although early warning indicators definitions have been recently updated to align with global strategic information guidance and targets have been adjusted, neither the targets nor the definitions have benefitted from a systematic review focusing on populations receiving DTG-containing regimens. Due to DTG's high genetic barrier to the selection of drug resistance–associated mutations, the early warning indicators definitions and targets established and validated for NNRTI-based therapies in 2011 may no longer be associated with population-level viral load suppression (HIV drug resistance prevention) or the emergence of possible HIV drug resistance *(41, 42)*. Should WHO retain early warning indicators of HIV drug resistance in the future, they would benefit from a similar revision as completed in 2011. Also, the early warning indicators should be more fully integrated into routine monitoring and evaluation systems at the country level and more fully integrated into global normative guidance for strategic information and quality of care. Finally, to realize their full potential, early warning indicators should be accompanied by tool kits for action at the clinic and national programme levels to facilitate rapid data-informed intervention to optimize care.

Research and innovation

Overall, interviewees concurred that the Global Action Plan on HIV drug resistance 2017–2021 had reliably given priority to research questions at the time of its publication and that the document helped to stimulate research into critical public health and HIV programme–related HIV drug resistance questions. WHO's convening role in establishing the research agenda was broadly acknowledged as necessary for future HIV drug resistance work. Some interviewees suggested that WHO should guide development demonstration projects of new regimens (such as long-acting injectable PrEP) to ensure that critical public health questions related to HIV drug resistance are embedded into these studies to the extent possible. Such integration could enable more timely drug resistance information and lead to more rapid and evidence-based recommendations on HIV drug resistance concerns. Box 2 summarizes public health HIV drug resistance research questions identified during the interviews

Box 2. HIV drug resistance research questions to be considered for inclusion in a future global action plan on HIV drug resistance

HIV resistance to integrase inhibitors

- How quickly (if at all) will DTG resistance emerge in populations experiencing treatment failure, and what are the epidemiological determinants of DTG resistance in this context?

- What are the population-level determinants of the emergence of integrase inhibitor resistance among people for whom DTG-based ART is failing?

- What are the potential mechanisms of HIV resistance to integrase inhibitors?

- Does the presence of DTG resistance always equate to clinical failure?

- What are the optimal ART regimens for use in the setting of DTG resistance in adults and children?

Long-acting ARV drugs for HIV treatment and prevention

- What is the potential impact of long-acting cabotegravir PrEP failure (and resistance selection) on subsequent DTG-based ART?

- Is the required enhanced surveillance of HIV drug resistance emergence during the drug tail period observed in long-acting ARV drug formulations?

- What is the role of modelling HIV drug resistance in the era of integrase inhibitors, and what concerns exist regarding cross-resistance to DTG among people testing positive for HIV after receiving long-acting cabotegravir PrEP?

- What is the optimal approach for resistance monitoring and surveillance for new ARV drug products, including long-acting formulations, to be undertaken?

PrEP

- Is enhanced surveillance of HIV resistance to ARV drugs used for PrEP required?

- What role will oral or long-acting injectable PrEP and PrEP roll-out have in potentially fuelling population-level resistance?

HIV drug resistance testing

- What is the role of next-generation sequencing in HIV drug resistance surveillance?

- When is HIV drug resistance testing in clinical practice for patient care most useful and necessary?

- What is the role of possible future point-of-care, or near point-of-care, integrase inhibitor drug resistance testing?

Other areas of work

- What HIV drug resistance studies are needed among children?

- How should HIV drug resistance surveillance be given priority for key populations, adolescents and pregnant and breastfeeding women?

- Should the traditional concept of third-line and salvage regimens be replaced by individual HIV drug resistance testing and individualized third-line or salvage regimen composition?

Laboratory capacity

The WHO HIVResNet Laboratory Network has been successful in building sustained country capacity to monitor HIV drug resistance. Interviewees reported that the Global Action Plan on HIV drug resistance 2017–2021 was effective and valued by stakeholders because it supported the ongoing establishment of a robust laboratory network providing high-quality HIV drug resistance test results for countries conducting national HIV drug resistance surveys.

Looking to the future, some interviewees suggested a need for WHO to clarify its designation criteria for laboratories using next-generation sequencing and support the development of standardized platforms for cleaning and analysing HIV drug resistance genotypic data generated by next-generation sequencing. Also, interviewees suggested that WHO should emphasize the use of new technologies and stimulate the development of forward-thinking and novel ones. Additionally, special consideration could be given to developing and using high-throughput centralized regional laboratories to improve efficiency and lower costs by testing at scale. However, such a shift in approach may introduce new challenges for specimen transport, data ownership and timely reporting of results.

Governance and enabling mechanisms

Stakeholders endorsed that the Global Action Plan on HIV drug resistance 2017–2021 delineated the tasks and responsibilities of the stakeholders at different levels. It facilitated narratives between stakeholders and donors, informed regional and national plans for preventing and monitoring HIV drug resistance and provided a framework for integrating HIV drug resistance plans into broader HIV and health sector strategies. Notably, at the global level, the Global Action Plan on HIV drug resistance 2017–2021 facilitated the integration of HIV drug resistance into the broader context of prevention, treatment and care. For example, in 2021, WHO HIVResNet and the resistance agenda were integrated into the Conference on Antiretroviral Therapy Optimization (CADO-4) and the Paediatric Antiretroviral Drug Optimization (PADO-5) meetings.

Interviewees reported that the structure of the five working groups of the Global Action Plan on HIV drug resistance 2017–2021, one related to each strategic objective, was complex and that the working group structure, scope and terms of reference need to be re-evaluated if they are to continue. One possible way to simplify the structure would be to reorganize WHO HIVResNet along the lines of CADO and PADO – creating integrated adult, children and adolescent working groups with cross-cutting content experts in each group to oversee the direction of future strategic priority areas.

In terms of governance at the secretariat level, one challenge articulated by interviewees was that WHO currently leads all five workstreams and is insufficiently resourced to do so. Moreover, working groups are all voluntary and lack funding to operationalize terms of reference. WHO may consider exploring whether new funding opportunities may emerge by assigning the responsibility for chairing some or all working groups to other institutions, such as through designated WHO collaborating centres on HIV drug resistance or through regional centres of excellence or partners.

Looking to the future, stakeholders endorsed a need for WHO to provide more frequent communication. There was unanimous agreement that there should be greatly enhanced community partnerships and involvement of people living with HIV and civil society in developing the development of a future global action plan on HIV drug resistance. In addition, community members should be involved in developing global, regional and national HIV drug resistance surveillance, monitoring and response plans to give voice to community concerns, raise awareness of HIV drug resistance and support the development of culturally appropriate messaging around the links between quality of care, viral load suppression at the population level and preventing HIV drug resistance. Finally, all stakeholders endorsed that comprehensive and inclusive consultations will be required for a successful new global action plan on HIV drug resistance.

8.3 Interviewees' perspectives: Global action plan on HIV drug resistance 2023–2030

The planning for a future global action plan on HIV drug resistance 2023–2030 coincides with the global transition to DTG-based treatments and the rollout of long-acting ARV drugs for treatment and prevention. Interviewees stated that it would be necessary for WHO and partners to define the current key HIV drug resistance-related epidemiological and public health questions, anticipate future questions and identify optimal methods to answer them, whether by research, surveillance or a hybrid of the two. In parallel, WHO and WHO HIVResNet should review the lessons learned from this landscaping review and evaluate lessons from other WHO groups, such as the CADO and PADO groups and the WHO Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP) in terms of structure, working modalities, reporting, governance and funding.

Many interviewees underscored the ongoing importance of adequate and sustained funding for HIV drug resistance monitoring and surveillance activities and future normative guidance development for supporting the WHO HIVResNet Laboratory Network. To date, in-country surveys have been mainly funded by donors, and countries have largely not stepped up to incorporate the costs of implementing HIV drug resistance surveys into national HIV care and treatment budgets. Moreover, governments have often struggled to incorporate funding for HIV drug resistance prevention, surveillance and response activities into Global Fund and PEPFAR country and regional operating plans because of competing priorities. PEPFAR and Global Fund remain major donors, and other sustainable modes of funding should be explored and secured in the future. Creative ways to engage national governments to set aside a percentage of their national budget for resistance prevention, monitoring and response efforts must be realized. To facilitate the future commitment of donors and implementing partners, they will need to be involved in planning a future global action plan to ensure that ongoing and new activities are funded. Finally, the concept of an integrated global action plan for HIV, viral hepatitis and sexually transmitted infections may open new funding opportunities.

9. CONCLUSION

The goals of the Global Action Plan on HIV drug resistance 2017–2021 were to articulate synergistic actions required to prevent HIV drug resistance from undermining efforts to achieve global targets on health and to ensure the ongoing efficacy and durability of the available ARV drugs used for prevention and for people living with HIV. Following review of progress in each of the five strategic objectives and interviews with key stakeholders from 36 institutions and 20 countries, the Global Action Plan on HIV drug resistance has been largely successful in achieving these central goals, even though specific indicator outcomes established in 2017 generally were not achieved.

Overall, the performance of programmatic quality indicators remained suboptimal in most countries reporting data during the period of the Global Action Plan on HIV drug resistance 2017–2021, especially among children. These findings underscore the need for proactive approaches to improving the quality of HIV treatment and care services to minimize the emergence of preventable drug-resistant HIV. The reporting of indicator data from countries remains suboptimal, underscoring a need to strengthen national and regional data reporting systems for globally relevant indicators.

The stakeholders interviewed endorsed that the Global Action Plan on HIV drug resistance 2017–2021 clearly delineated the tasks and responsibilities of the stakeholders, facilitated narratives with stakeholders and donors and informed regional and national plan development. Notably, the Global Action Plan on HIV drug resistance 2017–2021 facilitated the integration of HIV drug resistance into the broader context of prevention, treatment and care, especially more recently in 2021 with the inclusion of WHO HIVResNet in CADO-4 and PADO-5 meetings.

In the next global action plan, it will be important to learn from the feedback received from the broad consultative process undertaken in this review of the Global Action Plan on HIV drug resistance 2017–2021, consult with partners in developing and designing the new global action plan and implement a robust monitoring and evaluation plan that starts with global action plan initiation, enabling WHO, countries and other implementing partners to respond and course correct.

Given current global efforts to integrate health services under the umbrella of universal health coverage, the environment is conducive to development of a global action plan unifying drug resistance for HIV, viral hepatitis and sexually transmitted infections. The success of a future global action plan unifying HIV, viral hepatitis and sexually transmitted infections will require robust and sustained public health surveillance, strong country engagement and ownership, a willingness to share data in real time and greatly enhanced community engagement in the conceptualization and implementation.

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The 45 WHO Focus Countries with High HIV Burden are:
Tier 1 (over 60% of 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, Zimbabwe.
Tier 2 (additional 20-30% of 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, Viet Nam.

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ANNEX 1. MONITORING FRAMEWORK AND OUTCOMES FOR THE GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017–2021

Areas of work		2021 indicator target	2021 indicator outcome
1. Prevention and response	ARV drug stock-outs	**<15%** of countries reporting **any** ARV drug stock-out during a 12-month period (among the 45 WHO focus countries reporting data)	Adults: 50% (13 of 26)
			Children: 50% (13 of 26)
	Retention on ART[a]	**>90%** of countries reporting **>85%** retention on treatment at a defined time point (among the 45 WHO focus countries reporting data)	Adults: 29% (6 of 21)
			Children: 43% (6 of 14)
	Viral load testing coverage	**≥50%** of countries achieving **≥70%** viral load coverage: people receiving ART having a 12-month viral load test result available in their medical record (among the 45 WHO focus countries reporting data)	Adults: 40% (10 of 25)
			Children: 77% (10 of 13)
	Viral load suppression	**≥90%** of countries reporting viral load suppression of **≥90%** among people receiving ART with a viral load test result available (among the 45 WHO focus countries reporting data)	Adults: 78% (7 of 9)
			Children: 25% (2 of 8)
	Use of second-line ART regimens	**≥80%** of countries report having at least **5%** of people receiving second-line ART (among the 45 WHO focus countries reporting data)	Adults: 45% (13 of 29)
			Children: 74% (20 of 27)
	National response to HIV drug resistance	**100%** of countries responding to HIV drug resistance through programme adjustments and/or revising national ART guidelines	Adults: 100% (26 of 26)[b]
			Children: 100% (11 of 11)[c]
2. Monitoring and surveillance	Surveillance	**100%** of countries conducting and reporting on HIV drug resistance surveillance (among the 45 WHO focus countries reporting data in the last 3 years)	57% (12 of 21)
	Early warning indicators relevant for HIV drug resistance	**≥90%** of countries assessing early warning indicators for HIV drug resistance at a clinic-level (among the 45 WHO focus countries)	21% (6 of 28)
	Global report on HIV drug resistance	**Two** WHO reports published by 2021	Three WHO reports published in 2017, 2019 and 2021
3. Research and innovation	Implementation of HIV drug resistance-–related research established in the Global Action Plan on HIV drug resistance	**One** position paper on priority HIV drug resistance research questions	Research questions published in the 2018 Global Action Plan report
		≥50% of research questions defined in the Global Action Plan have been planned or initiated	92% (22 of 24) of the HIV drug resistance research questions identified are being addressed
4. Laboratory capacity	Expansion of HIV drug resistance testing laboratories	**≥70%** of WHO HIVResNet regional and specialized labs designated for HIV drug resistance using DBS	76% (13 of 17) of regional and specialized laboratories with the capacity for DBS testing
5. Governance and enabling mechanism	Mobilization of resources to implement the Global Action Plan	**100%** of WHO HIV focus countries including HIV drug resistance activities in funding proposals to Global Fund and PEPFAR, other sources or country health budgets	Data unavailable
	Mobilization of resources to coordinate, monitor and support the Global Action Plan's implementation	**100%** of WHO HIV focus countries having **100%** budget for HIV drug resistance activities	Data unavailable
	National HIV drug resistance strategy	**100%** of countries with HIV drug resistance strategy up to date (among the 45 WHO focus countries reporting data)	64% (23 of 36)

[a] Represents 2018 data. From 2019 onwards, the retention indicator was revised to "total attrition on ART", which has since then been incorporated into WHO's indicator guidance and monitoring tools, but countries had not yet started reporting by the end of 2021.

[b] Countries that reported to WHO having pretreatment drug resistance to non-nucleoside reverse transcriptase inhibitors of ≥10%.

[c] Countries that reported to WHO data on HIV drug resistance survey among infants <18 months.

Data sources: Global AIDS Monitoring, WHO surveys, reports received from countries and Global Fund and PEPFAR reports.

ANNEX 2. WHO AND PARTNER ORGANIZATIONS INTERVIEWED, BY WHO REGION

Institution	WHO region
WHO headquarters	Headquarters
WHO regional offices	African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, Western Pacific Region
WHO HIVResNet Steering Group chairs	African Region, Region of the Americas, Western Pacific Region
WHO HIVResNet working group co-chairs	African Region, Region of the Americas, European Region
WHO HIVResNet Laboratory Network	African Region, Region of the Americas
National Health Laboratory Service, South Africa	African Region
Ministry of Health, Kenya	African Region
Ministry of Health, Uganda	African Region
Wits Reproductive Health and HIV Institute, University of Witwatersrand	African Region
HIV treatment advocates network (AfroCab)	African Region
International Treatment Preparedness Coalition	African Region
Ministry of Health, Uganda	African Region
Global Fund to Fight HIV, Tuberculosis and Malaria	European Region
National Haemophilia Center, Israel	European Region
French National Institute of Health and Medical Research (Inserm)	European Region
Institute for AIDS Research (IrsiCaixa), Spain	European Region
University College London	European Region
Partners in Health	Region of the Americas
United States Centers for Disease Control and Prevention	Region of the Americas
United States Agency for International Development	Region of the Americas
Johns Hopkins University	Region of the Americas
Columbia university	Region of the Americas
University of California, San Francisco	Region of the Americas
University of California, Los Angeles	Region of the Americas
Harvard University	Region of the Americas
University of Pittsburgh	Region of the Americas
Oswaldo Cruz Foundation (Fiocruz), Brazil	Region of the Americas
Data First Consulting	Region of the Americas
AIDS Healthcare Foundation	Region of the Americas
Elizabeth Glaser Pediatric AIDS Foundation	Region of the Americas
Chennai Antiviral Research and Treatment	South-East Asia Region

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