World Health Organization

HIV DRUG RESISTANCE

HIV DRUG RESISTANCE STRATEGY: 2021 UPDATE

JUNE 2021

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HIV drug resistance strategy, 2021 update

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CONTENTS

Acknowledgements iv

Acronyms and abbreviations iv

1. Introduction 1

2. National action plan on HIV drug resistance 3

3. Quality-of-care indicators: early warning indicators of HIV drug resistance 4

4. Surveillance of HIV drug resistance 6

   4.1 Survey of acquired HIV drug resistance in populations receiving ART 6

   4.2 Survey of pretreatment HIV drug resistance among adults initiating first-line ART 9

   4.3 Survey of pretreatment HIV drug resistance among treatment-naive infants newly diagnosed with HIV 10

   4.4 Survey of HIV drug resistance among PrEP users diagnosed with HIV infection 11

5. HIV drug resistance laboratory network 12

6. HIV drug resistance database 13

7. Disseminating HIV drug resistance information and using data to inform policies 13

8. References 14

Annex 1. Summary of the recommended activities at the country level for assessing and preventing HIV drug resistance 16

Annex 2. Generic budgets 17

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ACRONYMS AND ABBREVIATIONS

ART	Antiretroviral therapy
ARV	Antiretroviral drugs
HIVResNet	HIV Drug Resistance Network
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
PrEP	Pre-exposure prophylaxis

1. INTRODUCTION

Antiretroviral therapy (ART) has been scaled up at an unprecedented rate over the past decade: at the end of June 2020, 26 million people were receiving ART globally. However, the emergence of HIV drug resistance can compromise the effectiveness of antiretroviral (ARV) drugs in reducing HIV incidence and HIV-associated morbidity and mortality[1,2].

Drug-resistant viruses are selected when HIV replicates in the presence of ARV drugs. If HIV drug resistance is not addressed, the drugs used to prevent and treat HIV infection may become ineffective. The 2019 WHO global report on HIV drug resistance showed high prevalence of pretreatment HIV drug resistance to efavirenz and/or nevirapine among adults initiating or reinitiating first-line ART, exceeding 10% in most of the low- and middle-income countries that monitored resistance[3]. In addition, surveys conducted in sub-Saharan African countries showed that more than half of the treatment-naive infants newly diagnosed with HIV carried a virus that was resistant to non-nucleoside reverse-transcriptase inhibitors (NNRTI) and that resistance to nucleoside reverse-transcriptase inhibitors was >10% in more than half the countries surveyed[3]. The high levels of pretreatment HIV drug resistance to NNRTIs highlighted the need to fast-track the transition to dolutegravir-based first-line regimens for adults and children[2,4].

As efforts to scale up ART and pre-exposure prophylaxis (PrEP) continue, and more individuals receive ARV drugs for treating and preventing HIV, a further increase in HIV drug resistance is likely[5-7]. To minimize the emergence and spread of HIV drug resistance, WHO recommends that ART and PrEP programmes be accompanied by measures to monitor the quality of ART and PrEP delivery and the surveillance of HIV drug resistance[8,9].

In 2004, WHO collaborated with HIVResNet, a global network of experts providing technical and strategic advice to WHO on HIV drug resistance, to develop the first strategy for assessing and preventing HIV drug resistance[10]. The strategy was revised in 2012 and in 2015[11-13]. This publication provides a further update of the strategy, which takes into account the lessons learned from implementing the HIV drug resistance surveillance, the implementation of the global action plan on HIV drug resistance[14] and the ongoing scale-up of ART and PrEP programmes, including the transition to new regimens.

This publication at a glance

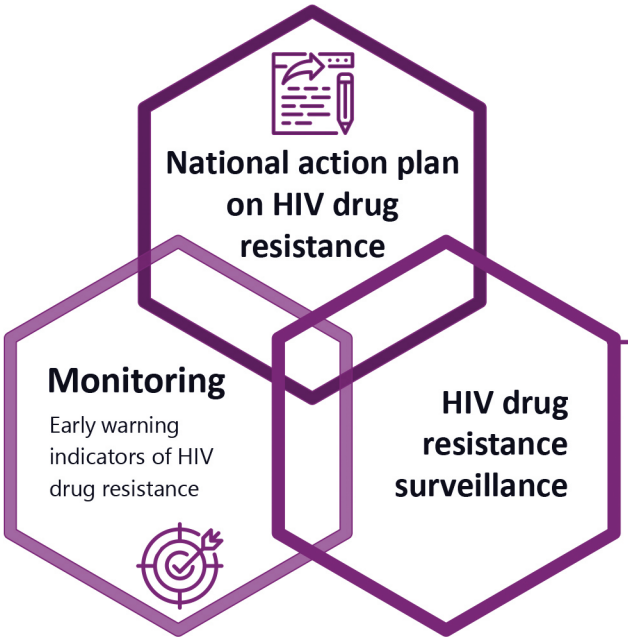
This publication provides an overview of the core set of WHO-recommended activities at the country level, with the aim of supporting programme planning and budgeting (Fig. 1 and Annex 1) and informing the preparation of grant proposals.

The core activities on HIV drug resistance recommended by WHO are:

- developing and implementing the national action plan on HIV drug resistance;
- monitoring the quality-of-care indicators associated with and predicting HIV drug resistance (also known as early warning indicators of HIV drug resistance); and
- implementing HIV drug resistance surveys, including:
  - surveys of acquired HIV drug resistance among populations receiving ART (adults and children);
  - surveys of pretreatment HIV drug resistance among treatment-naive infants newly diagnosed with HIV;
  - surveys of pretreatment HIV drug resistance among adults initiating first-line ART; and
  - surveys of HIV drug resistance among users of PrEP diagnosed with HIV.

This publication also briefly summarizes the purpose and structure of the HIV Drug Resistance Laboratory Network, the WHO HIV drug resistance database and the recommendation on timely dissemination and use of HIV drug resistance survey data at the country level.

Fig. 1 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

What is new in the 2021 HIV drug resistance strategy?

- Updated list of early warning indicators
- WHO recommends updated methods for the survey of acquired HIV drug resistance
- WHO recommends a new survey method for countries scaling up pre-exposure prophylaxis
- To monitor resistance to integrase inhibitors, including dolutegravir, WHO recommends genotyping the HIV integrase region (in addition to the reverse-transcriptase and protease regions) in all specimens collected in surveys of pretreatment or acquired HIV drug resistance.

2. NATIONAL ACTION PLAN ON HIV DRUG RESISTANCE

What is the global action plan on HIV drug resistance?

In 2017, WHO launched a comprehensive global action plan on HIV drug resistance outlining strategic objectives and key actions for countries and global stakeholders to prevent, monitor and respond to HIV drug resistance at the global and country levels and to protect the ongoing progress towards achieving the global targets for epidemic control by 2030[14,15]. The global action plan on HIV drug resistance has five strategic areas of work: (1) prevention and response; (2) monitoring and surveillance; (3) research and innovation; (4) laboratory capacity; and (5) governance and enabling mechanisms.

Why should countries develop a national action plan on HIV drug resistance?

A national action plan on HIV drug resistance will provide a framework for concrete action to minimize and contain HIV drug resistance at the country level and is expected to guide the delivery of critical activities aimed to protect the investments and progress made by ART programmes in countries.

How should countries develop and implement the national action plan on HIV drug resistance?

WHO recommends that countries develop a five-year national action plan on HIV drug resistance aligned to the five strategic objectives outlined in the global action plan on HIV drug resistance. The early warning indicators and the surveillance of HIV drug resistance – components of the core set of WHO-recommended activities described in the following sections – should be included as part of the strategic objective of monitoring and surveillance.

The framework for action on HIV drug resistance needs to be adapted at the national level, including an implementation time frame, milestones, key indicators and funding plan. The national action plan on HIV drug resistance should be integrated into the national HIV strategic plan and national antimicrobial resistance plan. Countries are encouraged to implement, in collaboration with relevant partners, the services and actions given priority in the national action plan to prevent, monitor and respond to HIV drug resistance and to use data to inform national ARV drug policies and guidelines. Countries should revise annually the level of accomplishments according to predefined milestones, evaluate the constraints encountered and, if needed, set new priorities for action.

Who should develop the national action plan on HIV drug resistance at the country level?

Health ministries should develop national action plans on HIV drug resistance through a consultative process with input from national stakeholders (people living with HIV and their communities, community-based and civil society organizations, nongovernmental organizations, academia, United Nations programmes and agencies, national or international implementing partners and donors) to increase awareness, advocacy, political and programmatic commitment and resource allocation to tackle HIV drug resistance.

What is the cost of developing a national action plan on HIV drug resistance?

A generic cost estimate of the process to develop a national action plan on HIV drug resistance is US$ 23 500 (Annex 2, Table A1).

What tools and guidance are available to support countries to develop a national action plan on HIV drug resistance?

- Global action plan on HIV drug resistance: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/global-action-plan-and-strategy-on-hiv-drug-resistance
- WHO HIV drug resistance webpage: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance

3. QUALITY-OF-CARE INDICATORS: EARLY WARNING INDICATORS OF HIV DRUG RESISTANCE

What are early warning indicators?

The early warning indicators are a set of standard quality-of-care indicators used to assess whether ART programmes deliver services with the quality required to minimize the emergence of HIV drug resistance. Early warning indicators use standardized definitions, which have evolved over time as programmes mature and public health actions are refined (Table 1).

What is new in the monitoring of early warning indicators?

The updated list of early warning indicators is included in Table 1 and is described in the 2020 WHO consolidated HIV strategic information guidelines[16,17].

Although four indicators remain unchanged (viral load testing coverage, ARV medicine stock-out, ART adherence proxy and appropriate switch to second-line ART), the updated list includes three new indicators.

- **Total attrition from ART.** This indicator measures progress towards promoting retention receiving ART and mitigating loss: that is, ART attrition[16]. The total attrition from ART indicator replaces the previously used indicator of retention at 12 months receiving ART.
- **People living with HIV who have suppressed viral load.** This indicator measures clinical outcomes of people receiving ART regardless of when they initiated ART[16] and replaces the previously used indicator of viral load suppression at 12 months after initiating ART.
- **Appropriate second viral load test.** This indicator measures the extent to which people living with HIV with non-suppressed viral load receive appropriate follow-up viral load testing to check whether they have suppressed viral loads.[16]

Why should countries monitor early warning indicators of HIV drug resistance?

WHO recommends assessing whether ART programmes deliver services with the quality required to minimize the emergence of HIV drug resistance. Monitoring early warning indicators is useful to identify gaps in service delivery, for which corrective action may be taken at the ART clinic or programme level to optimize overall programme performance. Findings from monitoring early warning indicators can be used to identify the clinics most in need of support or resources and to address the most pressing gaps in service delivery. Additionally, exploring differences in performance between clinics can lead to documentation and sharing of best practices within countries. The global action plan on HIV drug resistance provide examples of public health actions to respond to suboptimal performance quality-of-care indicators[14], including:

- implementing interventions to improve ART adherence linked to improved suppression of viral loads;
- advocating high levels of coverage for viral load testing;
- implementing a process to ensure prompt switch to second-line ART when indicated;
- strengthening communication and integration between pharmacy and clinic records to identify people at risk of HIV drug resistance because of missed pill pickups; and
- supporting and strengthening supply chain management.

How should early warning indicators be monitored?

Early warning indicators monitoring should be integrated into routine monitoring and evaluation systems of ART programmes, to minimize costs and strengthen existing data collection and reporting processes. Monitoring of early warning indicators uses scorecarding, which facilitates understanding of clinic and programme performance at a glance. The performance at the local and national levels is categorized in three strata (a colour-based scorecard system) in which red signals situations that require corrective action, amber a fair performance (not yet at the desired level) and green signals excellent performance (achieving the desired level) (Table 1). The grey classification is applied in situations in which performance cannot be established since more than 30% of the data are missing.

In countries in which the early warning indicators are not systematically and routinely collected in all clinics or the quality of the routinely available data is poor or unreliable, early warning indicators may be monitored through a special survey targeting a nationally representative sample of clinics. This approach will generate a reliable overview of a national programme's performance. Annex 2.4.6 of

Table 1. WHO-recommended quality-of-care indicators: early warning indicators of HIV drug resistance

Reference number[a]	Name	Description	Performance strata Green: good Amber: fair Red: poor
AV.2	Total attrition from ART	Number and percentage of people living with HIV reported to be receiving ART at the end of the last reporting period and/or newly initiating ART during the current reporting period who were not receiving ART at the end of the reporting period	Green: <15%
			Amber: 15–25%
			Red: >25%
AV.3	People living with HIV who have suppressed viral load	Percentage of people living with HIV receiving ART (for at least six months) who have viral suppression (defined as viral load <1000 copies/mL)	Green: ≥90%
			Amber: 80 to <90%
			Red: <80%
AV.6	Viral load testing coverage	Percentage of people receiving ART (for at least six months) with viral load test results	Green: >95%
			Amber: 85–95%
			Red: <85%
AV.8	Appropriate second viral load test	Percentage of people receiving ART with viral load ≥1000 copies/mL who received a follow-up viral load test within six months after enhanced adherence counselling	Green: ≥90%
			Red: <90%
AV.10	ARV medicine stock-out	Percentage of months with any day(s) of stock-out of any routinely dispensed ARV drug during the reporting period (12 months)[b]	Green: 0%
			Red: >0%
AV.11	ART adherence proxy (ARV drug refills)	Percentage of people receiving ART who pick-up all prescribed ARV drugs on time (no more than two days late at the first drug pickup after a defined baseline pickup)	Green: >90%
			Amber: 80–90%
			Red: <80%
AV.14	Appropriate switch to second-line ART	Percentage of people with confirmed viral load ≥1000 copies/mL who switch to second-line ART within 90 days of the confirmatory viral load test result of ≥1000 copies/mL	Green: 100%
			Red: <100%

a WHO consolidated HIV strategic information guidelines[16,17].

b The WHO consolidated HIV strategic information guidelines[16,17] describe the indicator ARV medicine stock-out as an above-site indicator as follows: percentage of ART sites that had stock-outs of any ARV drugs during the reporting period.

the WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance provides more detail on the overall recommended primary (clinic) and secondary (patient record) sampling methods, abstraction and reporting for early warning indicators[18].

How frequently should early warning indicators be monitored?

WHO recommends that early warning indicators be monitored annually. Annual monitoring of early warning indicators enables degrees of improvement or decline over time to be measured, both within and between clinics.

What is the cost of monitoring early warning indicators?

The monitoring of early warning indicators should be integrated into the routine monitoring and evaluation systems of ART programmes, leveraging the existing data collection and reporting processes and resources. In countries in which early warning indicators are not integrated into routine monitoring systems, the generic estimated cost for the early warning indicators data abstraction, analysis and report production is about US$ 54 000 (Annex 2, Table A2). All figures should be adapted to reflect the local context and costs. Abstraction costs will vary depending on the number and location of facilities to monitor, the size of the patient population, whether records are paper- or electronic-based and ultimately whether abstraction is integrated with other routine monitoring activities.

What tools and guidance are available to support countries in monitoring early warning indicators?

- WHO consolidated HIV strategic information guidelines: https://www.who.int/publications/i/item/9789240000735
- WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance, Annex 2.4.6: https://www.who.int/hiv/pub/guidelines/WHO_Consolidated_Guidelines_Annexes_2.4.6.pdf?ua=1
- WHO HIV drug resistance webpage, prevention of HIV drug resistance: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/prevention

WHO plans to update the early warning indicators extraction tools.

4. SURVEILLANCE OF HIV DRUG RESISTANCE

Performing surveillance of HIV drug resistance provides countries with evidence that can be used to optimize patient and population-level treatment outcomes. This section describes how high-quality data should be obtained from periodic nationally representative HIV drug resistance surveys among various populations.

What is new in HIV drug resistance surveillance?

- Surveillance of acquired HIV drug resistance: WHO has developed a new laboratory-based method and has updated the standard clinic-based method.
- WHO recommends a new survey method for countries scaling up PrEP.
- WHO recommends genotyping the HIV integrase region, in addition to the reverse-transcriptase and protease regions, in all specimens collected in surveys of pretreatment or acquired HIV drug resistance.

4.1 Survey of acquired HIV drug resistance in populations receiving ART

What is new in acquired HIV drug resistance surveillance?

- WHO has developed a new laboratory-based method and has updated the standard clinic-based method.
- Recommendation to genotype the HIV integrase region in addition to the reverse-transcriptase and protease regions.
- Recommendation to perform two surveys simultaneously: among children and adolescents and among adults.

What is the purpose of this survey?

The survey of acquired HIV drug resistance provides critical information to assess the performance of ART programmes in achieving viral load suppression targets and describes resistance patterns in populations receiving ART to inform the selection of second-line and potentially third-line regimens.

What is the target population?

Adults, adolescents and children receiving ART.

Are children and adults aggregated together in the same survey sampling?

Because the prevalence of acquired HIV drug resistance and the public health actions are likely to be different for adults and children, the two populations should be assessed separately in simultaneous surveys with separate sample sizes. The sampling methods will be identical for the two groups.

What survey methods is WHO recommending?

WHO recommends two alternative survey methods to monitor population-level acquired HIV drug resistance. A newly developed laboratory-based approach leveraging remnant viral load specimens conducts HIV drug resistance testing on a random sample of remnant viral load specimens with viral load ≥1000 copies/mL routinely collected for patient management and stored in national viral load testing laboratories.

A clinic-based approach uses a method known as a two-stage cluster design in which a sample of clinics is first selected from a list of all clinics dispensing ART in the country. In the second stage, a sample of eligible patients is recruited from each of the selected clinics. The patients included in the survey will have blood specimens collected for viral load testing. Specimens with a viral load ≥1000 copies/mL will be genotyped to assess HIV drug resistance.

Which survey method should be used in countries?

The selection of the survey method depends on country readiness to implement one or the other survey approach. Countries should self-assess for readiness using the framework described in the WHO concept note and summarized in Fig. 2[19].

How frequently should this survey be repeated?

Every three years.

4.1.1 Laboratory-based survey of acquired HIV drug resistance using remnant viral load specimens

What is new in this survey?

- The specimens are collected in the context of routine viral load monitoring and stored in national viral load testing laboratories.
- Separate estimates of viral load suppression and HIV drug resistance among eligible individuals receiving dolutegravir-containing regimens and among eligible individuals receiving non-dolutegravir-containing regimens.
- Recommendation to genotype the HIV integrase region in addition to the reverse-transcriptase and protease regions.
- Recommendation to perform two surveys simultaneously: among children and adolescents and among adults.

What are the survey outcomes?

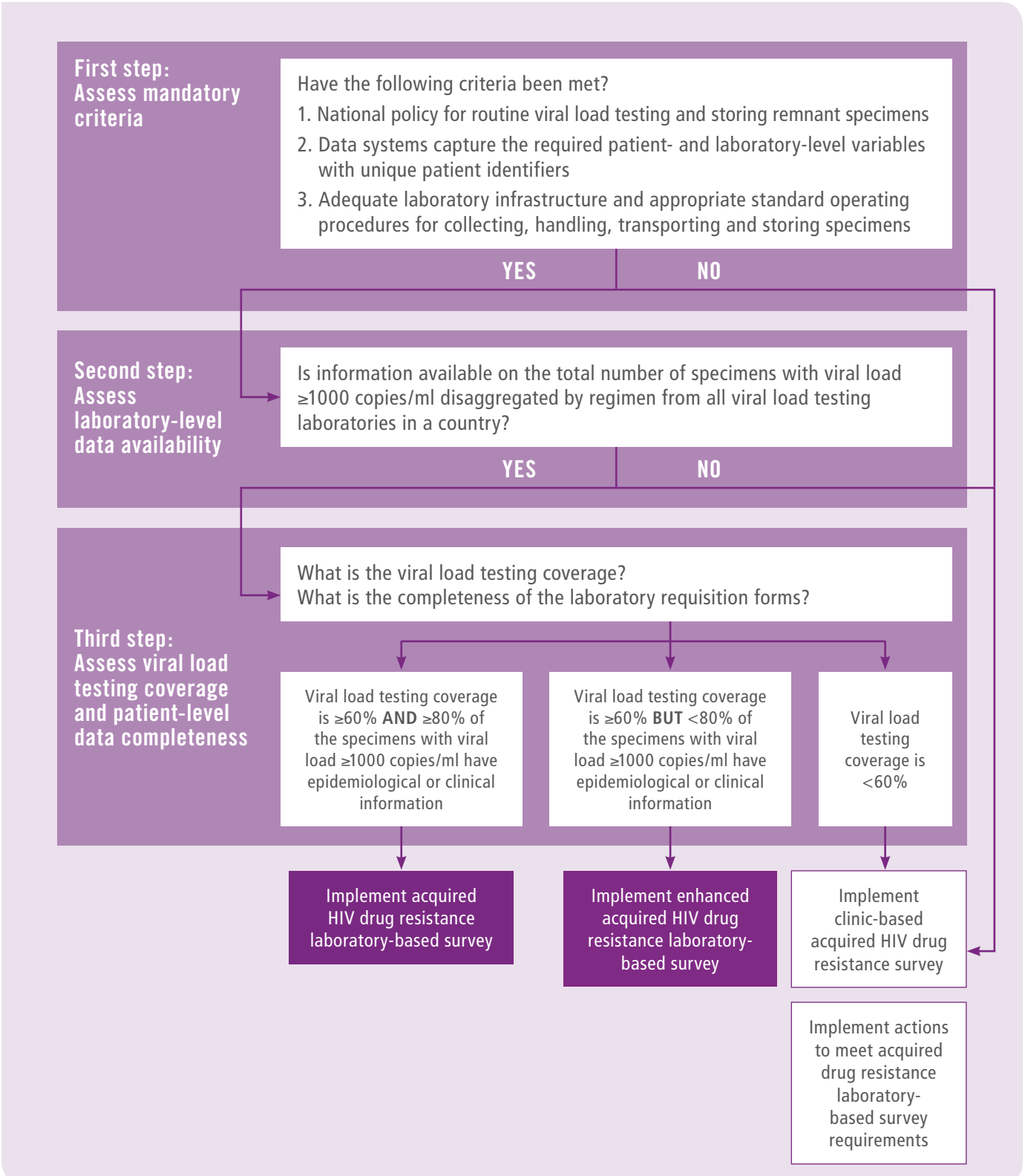
Estimates of the prevalence of viral load suppression and HIV drug resistance in the following subgroups:

- adults and children receiving a dolutegravir-containing ART regimen;
- adults and children receiving a non-dolutegravir-containing ART regimen; and
- adults and children receiving ART, regardless of ART regimen.

What are the advantages of this survey method compared with the clinic-based approach?

- Reduced cost
- Simpler to implement
- Provides an ongoing impetus to support viral load scale-up and strengthening of data systems to optimize patient care
- Sampling from among those with viral non-suppression increases the precision of the drug resistance outcome

Fig 2. Selection of survey method for the surveillance of acquired HIV drug resistance



What is the survey method?

HIV drug resistance testing is conducted on a random sample of remnant viral load specimens collected from people with viral non-suppression (defined as viral load ≥1000 copies/mL) in the context of routine viral load monitoring and stored in national viral load testing laboratories[19]. The number of specimens to be selected for genotyping from each viral load laboratory is proportional to the number of remnant specimens with viral load ≥1000 copies/mL collected during the defined survey period in each viral load laboratory. Specimens are sampled using systematic sampling. HIV drug resistance is predicted using the Stanford HIVdb algorithm[20,21].

- **Participating sites:** all viral load testing laboratories in a country.[a]
- **Specimen selection:** remnant specimens (plasma or dried blood spots) with viral load ≥1000 copies/mL collected from people receiving ART as part of routine clinical care. Only the first specimen obtained from an individual in the survey period is eligible. Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance (22,23).
- **Sample size:** the required sample size ranges from 465 to 657 eligible specimens with viral load ≥1000 copies/mL, depending on the proportion of individuals receiving dolutegravir-based ART. WHO developed a sample size calculator in which countries can specify their own population sizes to obtain a country-specific sample size.
- **Key variables to collect:** (1) the name of the viral load testing laboratory, (2) a unique patient identifier, (3) date of birth or age and (4) current ART regimen.
- **Survey duration:** three months.

In addition, deidentified patient-level information linked to all viral load tests regardless of viral load results during the three-month survey period is abstracted to estimate viral load suppression overall and by regimen.

Which countries should implement this survey method?

WHO recommends using a readiness assessment framework described in a concept note[19] (summarized in Fig. 2) to assess country readiness to implement this survey method. Briefly, countries must assess their readiness to implement this survey method by assessing the following criteria:

- the existence of national policies establishing routine viral load testing and storage of remnant specimens;
- data systems enabling viral load testing coverage to be estimated;
- adequate laboratory infrastructure enabling specimen storage at <20°C;
- required availability of laboratory-level data: total number of eligible case specimens disaggregated by dolutegravir-containing and non-dolutegravir-containing ART regimens;
- national viral load testing coverage ≥60%, excluding viral load testing performed at the point of care; and
- the availability of required patient-level data must be ≥80%: unique patient identifier, date of birth or age and current ART regimen.

In countries where viral load testing coverage is ≥60% but the availability of required patient-level data is <80%, an enhanced lab-based survey approach should be used, in which ART clinics within each viral load testing laboratory catchment area are randomly sampled and eligible case specimens are randomly sampled from the selected clinics only[19]. Each sampled clinic should receive intensive support to ensure that all viral load specimens are sent to the laboratory along with completed requisition forms.

What is the cost of implementing this survey?

Assuming a sample size of 539 specimens and genotyping costs of US$ 150 per specimen, the generic estimated budget for a survey of adults is about US$ 157 450 (Annex 2, Table A3). If simultaneous surveys are carried out among adults and children (assuming a sample size of 368 specimens for children), the generic estimated budget is about US$ 212 650 (Annex 2, Table A4).

What tools and guidance are available to support countries to implement this survey?

- *Laboratory-based survey of acquired HIV drug resistance using remnant viral load specimens*[19] and implementation toolkit: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art
- Online sample size calculators:
  - For countries with viral load coverage ≥60% and required survey variables availability ≥80%: https://worldhealthorg.shinyapps.io/ADR_LabBasedMethod
  - For countries with viral load coverage ≥60% but availability of required survey variables <80%: https://worldhealthorg.shinyapps.io/ADR_LabBasedMethod_2

a Ideally, all viral load laboratories in a country participate. However, in countries with many viral load laboratories (such as more than 10), a viral load laboratory or a combination of laboratories can be dropped from the sampling frame if they have <10% of potential case specimens during a defined 3-month survey period.

4.1.2 Clinic-based survey of acquired HIV drug resistance

What is new in this survey?

- The survey population includes individuals receiving ART, regardless of the time they have received ART (previous methods recommended two separate samples: people receiving ART for 12 (±3) months and people receiving ART for ≥48 months).
- Separate estimates of viral load suppression and HIV drug resistance among eligible individuals receiving dolutegravir-containing regimens and among eligible individuals receiving non-dolutegravir-containing regimens.
- Recommendation to genotype the HIV integrase region in addition to the reverse-transcriptase and protease regions.
- Recommendation to perform two surveys simultaneously: among children and adolescents and among adults.

What are the survey outcomes?

Estimates of the prevalence of viral load suppression and HIV drug resistance in the following subgroups:

- adults and children receiving a dolutegravir-containing ART regimen;
- adults and children receiving a non-dolutegravir-containing ART regimen; and
- adults and children receiving ART, regardless of ART regimen.

What is the survey method?

This survey uses a method known as a two-stage cluster design. In the first stage, clinics are sampled from a list of all clinics dispensing ART in the country using probability proportional to the proxy size method. In the second stage, a fixed sample of eligible patients is consecutively recruited from each of the selected clinics. The patients included in the survey will have blood specimens collected for viral load testing. Specimens with a viral load ≥1000 copies/mL will be genotyped, and HIV drug resistance is predicted using the Stanford HIVdb algorithm[20,21].

- **Participating sites:** clinics providing ART
- **Sample size:** depending on the proportion of individuals on dolutegravir-based ART, the required sample size ranges from 715 to 1480. WHO developed applications in which countries can specify their own population sizes to obtain a country-specific sample size (see the implementation toolkit that is available to support countries to implement this survey).
- **Participant eligibility criteria:** (1) provide informed consent, (2) diagnosed with HIV and (3) currently receiving ART for at least three months
- **Key variables to collect include:** (1) a unique patient identifier, (2) date of birth or age, (3) gender and (4) ART history
- **Specimens:** plasma or dried blood spots. Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance[22,23].
- **Survey duration:** patients are enrolled over a three-month period.

Which countries should implement this survey method?

Countries unable to implement laboratory-based acquired HIV drug resistance surveys (subsection 4.1.1) are encouraged to implement the clinic-based acquired HIV drug resistance survey[19].

What is the cost of implementing this survey?

To estimate the cost of a clinic-based acquired HIV drug resistance survey, the following six main budget categories should be considered: protocol development and training, survey coordination, site support visits, laboratory (such as shipping specimens, viral load testing and cost of genotyping), technical support (such as adapting the protocol and analysis), and producing, printing and disseminating a report. Assuming a sample size of 900 adults enrolled in 30 sites, and viral load and genotyping costs of US$ 60 and US$ 150 per specimen, respectively – the generic estimated budget is about US$ 272 350 (Annex 2, Table A5). If simultaneous surveys are carried out among adults and among children and adolescents (assuming a sample size of 1200 children and adolescents), the generic estimated budget for both surveys is about US$ 398 950 (Annex 2, Table A6).

What tools and guidance are available to support countries to implement this survey?

- *Clinic-based survey of acquired HIV drug resistance* and implementation toolkit: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art
- Online sample size calculator: https://worldhealthorg.shinyapps.io/ADR_ClinicBasedMethod/

4.2 Survey of pretreatment HIV drug resistance among adults initiating first-line ART

What is new in the pretreatment HIV drug resistance survey?

As countries are transitioning to dolutegravir-based first-line ART, WHO recommends genotyping the integrase region in addition to the reverse-transcriptase and protease regions.

What is the purpose of this survey?

The survey of pretreatment HIV drug resistance in populations initiating first-line ART is relevant to inform the choice of nationally recommended first-line ART regimens and regimens used for pre- and post-exposure prophylaxis[24].

What are the survey outcomes?

- The prevalence of previous ARV drug exposure
- The prevalence of HIV drug resistance in the following subgroups:
  - Adults initiating ART, regardless of previous ARV drug exposure
  - Adults initiating ART with previous ARV drug exposure
  - Adults initiating ART without previous ARV drug exposure

What is the survey method?

This cross-sectional survey uses a method known as a two-stage cluster design. In the first stage, at least 15 clinics are sampled from a list of all clinics dispensing ART in the country using the probability proportional to size or probability proportional to proxy size method. In the second stage, a fixed sample of eligible patients is recruited from each of the selected clinics[24]. The specimens collected are genotyped and HIV drug resistance is predicted using the Stanford HIVdb algorithm[20,21].

- **Target population:** adults initiating first-line ART, regardless of previous exposure to ARV drugs.
- **Participating sites:** clinics providing ART
- **Sample size:** the required sample size is 345. WHO developed applications in which countries can specify their own population sizes to obtain a country-specific sample size.
- **Participant eligibility criteria:** (1) provide informed consent, (2) diagnosed with HIV and (3) starting or restarting first-line ART
- **Key variables to collect include:** (1) a unique patient identifier, (2) date of birth or age, (3) gender, (4) previous exposure to ARV drugs and (5) ART regimen started
- **Specimens:** plasma or dried blood spots. Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance[22,23]
- **Survey duration:** patients are enrolled over three to six months

How frequently should this survey be repeated?

WHO recommends implementing pretreatment HIV drug resistance surveillance every 3 years.

What is the cost of implementing this survey?

To estimate the cost of implementing a pretreatment HIV drug resistance survey, the following six main budget categories should be considered: protocol development and training, survey coordination, site support visits, laboratory (such as shipping specimens and the cost of genotyping), technical support (such as adapting the protocol and analysis), and producing, printing and distributing a report. Assuming a sample size of 460 specimens from 20 sites and genotyping costs of US$ 150 per specimen, the estimated budget is about US$ 240 000 (Annex 2, Table A7).

What tools and guidance are available to support countries to implement this survey?

- *Surveillance of HIV drug resistance in adults initiating antiretroviral therapy:* https://www.who.int/publications/i/item/9789241507196
- Implementation toolkit: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/pretreatment-hiv-drug-resistance-adult

4.3 Survey of pretreatment HIV drug resistance among treatment-naive infants newly diagnosed with HIV

What is the purpose of this survey?

The purpose of this survey is to assess the prevalence of HIV drug resistance among treatment-naive infants younger than18 months who have been newly diagnosed with HIV using early infant diagnosis over a 12-month period. This survey is especially relevant in settings in which many infants acquire HIV infection, providing critical information to support the optimal choice of first- and second-line ART regimens[25].

What are the survey outcomes?

- Prevalence of exposure to ARV drugs as part of preventing mother-to-child transmission
- Prevalence of HIV drug resistance in the following subgroups:
  - treatment-naive children younger than 18 months, regardless of exposure to regimens to prevent mother-to-child transmission;
  - treatment-naive children younger than 18 months with exposure to regimens to prevent mother-to-child transmission; and
  - treatment-naive children younger than 18 months with no or unknown exposure to regimens to prevent mother-to-child transmission.

What is the survey method?

Briefly, HIV drug resistance testing is conducted on a random sample of remnant dried blood spots collected for early HIV infant diagnosis from treatment-naive infants younger than 18 months newly diagnosed with HIV (25). The total number of specimens testing HIV positive for early HIV infant diagnosis during the previous 12 months and stored for genotyping is determined. Each participating laboratory will contribute case specimens to the survey. The sample is assigned proportional to the number of remnant specimens available for testing during the defined

survey period in that laboratory. Specimens are sampled for genotyping using systematic sampling. HIV drug resistance is predicted using the Stanford HIVdb algorithm[20,21].

- **Target population:** treatment-naive infants younger than 18 months newly diagnosed with HIV.
- **Participating sites:** all laboratories performing early infant diagnosis in the country.
- **Specimens:** remnant dried blood spots collected as part of routine early infant diagnosis programme. Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance[22,23].
- **Specimen eligibility criteria:** (1) specimen from a treatment-naive child younger than 18 months, (2) tested HIV-positive by PCR and (3) only the first specimen obtained from an individual in the survey period
- **Sample size:** the recommended sample size is 500. If this sample size exceeds the number of eligible case specimens in the country, the country should perform a census of all available case specimens.
- **Key variables to collect include:** demographic information and clinical data, including exposure to regimens for preventing mother-to-child transmission, should be abstracted from laboratory requisition forms, with no participant-level identifying information recorded.
- **Survey duration:** The method is a retrospective survey of stored remnant dried blood spots collected for early infant diagnosis of HIV during a 12-month period.

How frequently should this survey be repeated?

WHO recommends implementing this survey every three years.

What is the cost of implementing this survey?

Since the survey uses remnant specimens, most implementation costs are related to entering data, shipping and handling specimens, genotyping, technical support for analysis and producing and distributing a report. Assuming an average genotype testing cost of US$ 150, the generic estimated survey cost is about US$ 136 000 (Annex 2, Table A8).

What tools and guidance are available to support countries to implement this survey?

- *Surveillance of HIV drug resistance in children newly diagnosed with HIV by early infant diagnosis:* https://www.who.int/publications/i/item/9789241512541
- Implementation toolkit: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/pretreatment-hiv-drug-resistance-infants-newly-diagnosed

4.4 Survey of HIV drug resistance among PrEP users diagnosed with HIV infection

What is the purpose of this survey?

WHO recommends PrEP as an additional prevention option for HIV-negative individuals at substantial risk of HIV infection as part of combination prevention approaches[26,27]. HIV drug resistance was rarely reported among people using PrEP and diagnosed with HIV in randomized controlled trials or open-label studies[28,29]. However, PrEP-selected HIV drug resistance could potentially negatively affect the effectiveness of ART options among PrEP users who acquire HIV, since there is a potential for overlapping resistance profiles between ARV drugs used for both PrEP and first-line ART. WHO recommends that PrEP scale-up be accompanied by surveillance of HIV drug resistance[14,26,30]. The survey of HIV drug resistance among PrEP users diagnosed with HIV is especially relevant in countries scaling up PrEP programmes to inform the selection of maximally effective first-line ART combination for PrEP users who acquire HIV.

What is the survey outcome?

Estimates of the prevalence of resistance among PrEP users diagnosed with HIV during the survey period who have taken tenofovir-containing PrEP at any time in the three months before the HIV diagnosis. As new PrEP regimens become available, the outcome will be expanded to include them.

What is the survey method?

WHO developed methods to assess the prevalence of HIV drug resistance among individuals who have taken PrEP at any time during the previous three months and diagnosed with HIV over a 12-month period[30].

A census of all individuals diagnosed with HIV despite using PrEP during a defined survey period of 12 months will be enrolled in the survey. The specimens collected are genotyped and HIV drug resistance is predicted using the Stanford HIVdb algorithm[20,21].

- **Target population:** PrEP users diagnosed with HIV. HIV infection is expected to be infrequent among PrEP users, because PrEP substantially reduces the risk of acquiring HIV (especially among those who adhere to their regimen)[29]. Therefore, a cross-sectional survey intends that a census of all eligible individuals will contribute information during a defined survey period.
- **Participating sites:** all sites providing PrEP services in a country
- **Participant eligibility criteria:** (1) provide informed consent, (2) newly diagnosed with HIV and (3) have taken PrEP at any time during the three months before HIV diagnosis
- **Key variables to collect include:** (1) a unique patient identifier, (2) date of birth or age, (3) gender, (4) PrEP delivery mode, regimen and dosing strategy and (5) date of HIV diagnosis
- **Specimens:** plasma or dried blood spots. Specimens should be collected, processed, handled and shipped following WHO HIV drug resistance laboratory guidance[22,23].
- **Survey duration:** 12 months

How frequently should this survey be repeated?

Annually if the country is performing HIV drug resistance testing routinely for clinical management. In countries where individual HIV drug resistance testing is not routinely performed for individual clinical management, the survey should be repeated periodically, generally every 3–5 years.

What is the cost of implementing this survey?

In countries performing HIV drug resistance testing for individual patient management of all people currently or recently taking PrEP at the time of HIV diagnosis, the generic estimated survey cost is about US$ 61 000 (Annex 2, Table A9). In countries where individual HIV drug resistance testing is not routinely performed for individual clinical management, the generic estimated survey cost is about US$ 115 000 (Annex 2, Table A10).

What tools and guidance are available to support countries to implement this survey?

- *HIV drug resistance surveillance in countries scaling PrEP:* https://www.who.int/publications/i/item/9789240009813
- Implementation toolkit: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/hiv-drug-resistance-among-prep-users-diagnosed-with-hiv

5. HIV DRUG RESISTANCE LABORATORY NETWORK

HIV drug resistance testing of specimens collected for WHO surveys must be performed by a laboratory designated by WHO for this purpose. These laboratories are members of the WHO HIVResNet and function under the WHO HIV drug resistance laboratory operational framework[22]. The WHO HIVResNet laboratory network supports national, regional and global HIV drug resistance surveillance by providing timely and accurate genotyping results.

The WHO HIV drug resistance laboratory operational framework was updated in 2020 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[22].

WHO encourages countries to identify a national laboratory with HIV drug resistance testing capacity (including the use of dried blood spots and HIV drug resistance testing of the integrase coding region) and to submit an application for membership in the WHO HIVResNet Laboratory Network[14,22]. If a suitable laboratory does not exist, WHO will support the country with developing capacity, and testing in a WHO-designated regional or specialized laboratory can be considered.

What tools and guidance are available to support HIV drug resistance testing for surveillance purposes?

- *WHO HIVResNet HIV drug resistance laboratory operational framework:* https://www.who.int/publications/i/item/978-92-4-000987-5
- *WHO manual for HIV drug resistance testing using dried blood spot specimens:* https://www.who.int/publications/i/item/9789240009424
- List of WHO-designated HIV drug resistance laboratories: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/laboratory-network

6. 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[15,31]. Representatives from health ministries are encouraged to use the WHO HIV drug resistance database for managing data from HIV drug resistance surveys. Data are entered and stored in the WHO HIV drug resistance database for 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.

Surveillance data belong to the countries generating the data and the access is restricted to countries´ designated personnel. The WHO HIV drug resistance database is a platform stored in a secure United Nations server. Information security at WHO is based on the ISO 27001 standard. WHO has a formal and comprehensive policy for securely managing all databases and information sources it hosts[32]. The policies cover information security, access to information and systems, cloud computing, application security, information classification and related security standards and confidentiality arrangements.

Representatives from health ministries can request the log-in credentials from WHO to grant access to the database. Requests should be sent to: hiv-aids@who.int. The WHO HIV drug resistance database is accessible through https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance.

7. DISSEMINATING HIV DRUG RESISTANCE INFORMATION AND USING DATA TO INFORM POLICIES

WHO promotes the dissemination and sharing of health data, including surveillance and epidemiological data. The primary purpose of data sharing is to advance public health by permitting analysis that enables the fullest possible understanding of health challenges, to help develop new solutions and to ensure that decisions are based on the best available evidence[32].

WHO regularly produces a global report on HIV drug resistance prevalence and trends based on the information shared by countries[3,33–36]. The global report on HIV drug resistance 2019[3] showed substantial progress in implementing HIV drug resistance surveillance. Between 2004 and 2020, 57 low- and middle-income countries implemented 214 surveys of HIV drug resistance using the WHO-recommended standard methods. The most recent HIV drug resistance data and maps are available at https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/data-and-maps.

The results of HIV drug resistance surveys have been used to inform national and global policies on optimal first- and second-line ART[2] and have guided the fast-track transition to dolutegravir-based ART.

Therefore, HIV drug resistance working groups are encouraged:

- to ensure that the quality of the survey data is optimal; this can be assessed by submitting the survey data to the WHO HIV drug resistance database, which checks the quality of epidemiological and sequence data and supports correct interpretation of resistance data;
- to promptly disseminate HIV drug resistance survey findings with national and international stakeholders; and
- to use the results (1) to provide evidence-informed advocacy tools for action on HIV drug resistance prevention and response, (2) to inform national policies on ARV drugs and (3) to improve ART service delivery and programme functioning[14].

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ANNEX 1. SUMMARY OF THE RECOMMENDED ACTIVITIES AT THE COUNTRY LEVEL FOR ASSESSING AND PREVENTING HIV DRUG RESISTANCE

Activity	Population of interest	Programmatic relevance	Priority	Recommended periodicity for implementation or update
National action plan on HIV drug resistance	National authorities	Provides a national framework for action to prevent, monitor and control HIV drug resistance	Very high	Every five years
Quality-of-care indicators (early warning indicators of HIV drug resistance)	People living with HIV receiving ART	Facilitates an at-a-glance understanding of clinic and ART programme performance on key factors correlated with treatment optimization and minimization of emergence of drug-resistant HIV. It also facilitates resource allocation to clinics and identifies the gaps in service delivery that require the most attention.	Very high	Annually
Surveillance of acquired HIV drug resistance	Adults and children receiving ART	Viral load suppression is a strong indicator of regimen and programme performance. Acquired HIV drug resistance may compromise the effectiveness of second- and third-line ART as well as PrEP and post-exposure prophylaxis.	Very high	Every three years
Surveillance of pretreatment HIV drug resistance among treatment-naive infants newly diagnosed with HIV	Treatment-naive infants <18 months of age newly diagnosed with HIV with and without previous ARV drug exposure	Results inform the choice of first- and second-line ART regimens for children	High	Every three years
Surveillance of pretreatment HIV drug resistance among adults initiating first-line ART	Adults initiating first-line ART with and without previous ARV drug exposure	Presence of resistance before initiating ART can compromise both the therapeutic and prevention benefits of first-line ART. The results inform the choice of drugs to be included in first-line treatment as well as PrEP and post-exposure prophylaxis	Low (very high in countries using efavirenz/ nevirapine in first-line ART)	Every three years
Surveillance of HIV drug resistance among PrEP users diagnosed with HIV	Individuals who have taken PrEP at any time during the previous three months diagnosed with HIV	The results inform the selection of maximally effective first-line ART combinations for PrEP users who acquire HIV	Low	Every 3–5 years (Annually if the country is performing HIV drug resistance testing routinely for clinical management)

ANNEX 2. GENERIC BUDGETS

The tables in this annex provide generic estimated budgets for implementing the various surveys of HIV drug resistance described in this document. All figures should be adapted to reflect the local context and costs. The cost of HIV drug resistance testing can vary from laboratory to laboratory (ranging from US$ 150 to US$ 350 per test). To develop a more realistic budget, countries are therefore encouraged to contact the laboratory they are willing to work with to obtain a quotation and adjust the budget accordingly in the planning phase. All costs are given in US dollars.

Table A1. Generic budget to develop the national action plan on HIV drug resistance[a]

Technical support		
		Total
Consultant (US$ 500 daily fee, US$ 200 per diem, 10 days) and flight		10 000
	Subtotal	**10 000**
Plan production, printing, and distribution		
		Total
Workshop to develop the national action plan on HIV drug resistance (15 outside participants, 15 local)		10 500
Printing and distribution		3 000
	Subtotal	**13 500**
	Total	**23 500**

a The budget does not include the cost of implementing the various strategies in the national action plan to prevent and monitor HIV drug resistance and to monitor, evaluate and review the proposed national action plan targets. The choice and extent of implementation of the different proposed strategies in the Global Action Plan are likely to vary between countries. Some of the activities may also already be part of other initiatives with their own budgets.

Table A2. Generic budget to monitor the early warning indicators of HIV drug resistance (in countries where data on early warning indicators are not routinely collected as part of the national monitoring and evaluation system)[a]

Example	Number of sites monitoring early warning indicators: 40

Training					
	Number of staff per site	Transport costs	Per diem cost	Number of nights	Total
Training of site staff (one-day training)	1	200	150	1	14 000
				Subtotal	**14 000**

Data abstraction		
	Cost per site	Total
Data abstraction and data entry (time required: 2–3 days per site)	500	20 000
	Subtotal	**20 000**

Technical support	
	Total
Consultant (US$ 500 daily fee, US$ 200 per diem, 10 days) and flight	10 000
Subtotal	**10 000**

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Subtotal	**10 000**
Total	**54 000**

a The budget does not include the cost of implementing the corrective actions that may be taken at the ART clinic or programme level to optimize overall programme performance based on the findings from monitoring early warning indicators. The clinics most in need of support and the resources needed to address the most pressing gaps in service delivery should be included in the quality improvement plans.

Table A3. Generic budget for laboratory-based acquired HIV drug resistance survey among adults receiving ART

Example	Number of participating laboratories: 4	Sample size: 539

Protocol development and training					
	Number of staff per laboratory	Transport costs	Per diem cost	Number of nights	Total
Training of site staff (one-day training)	2	200	150	2	4 000
Production of protocol and training materials					10 000
				Subtotal	14 000

Survey coordination				
	Number of staff	Cost per staff member per month	Number of months	Total
National coordinator	1	1000	6	6 000
Data manager	1	800	4	3 200
Viral load laboratory survey coordinator and viral load laboratory data manager (per laboratory)	2	800	4	6 400
			Subtotal	15 600

Laboratory		
	Cost per unit	Total
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[a]	80 850
Shipment of specimens to a WHO-designated laboratory (outside the country)		5 000
	Subtotal	85 850

Technical support	
	Total
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000	15 400
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)	6 600
Subtotal	22 000

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	10 000
Subtotal	20 000
Total	157 450

a The cost of HIV drug resistance testing should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test). This includes sequencing of HIV reverse transcriptase, protease and integrase regions.

Table A4. Generic budget for laboratory-based acquired HIV drug resistance survey among adults and children receiving ART

Example	Number of participating laboratories: 4	Sample size for adults: 539	Sample size for children: 368

					Shared survey costs	Survey among adults	Survey among children
Protocol development and training							
	Number of staff per laboratory	**Transport costs**	**Per diem cost**	**Number of nights**	**Total**		
Training of site staff (one-day training)	2	200	150	2	4 000		
Production of protocol and training materials					**10 000**		
				Subtotal	**14 000**		
Survey coordination							
		Number of staff	**Cost per staff member per month**	**Number of months**	**Total**		
National coordinator		1	1000	6	6 000		
Data manager		1	800	4	3 200		
Viral load laboratory survey coordinator and viral load laboratory data manager (per laboratory)		2	800	4	6 400		
				Subtotal	**15 600**		
Laboratory							
				Cost per unit	**Total**	**Total**	**Total**
Genotyping for reverse transcriptase, protease and integrase; costs including labour				150[a]		80 850	55 200
Shipment of specimens to a WHO-designated laboratory (outside the country)					5 000		
				Subtotal	**5 000**	**80 850**	**55 200**
Technical support							
					Total		
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000					15 400		
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)					6 600		
				Subtotal	**22 000**		
Report production, printing and distribution							
					Total		
Report production and distribution					10 000		
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)					10 000		
				Subtotal	**20 000**		
				Total		**212 650**	

a The cost of HIV drug resistance test should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).

Table A5. Generic budget for clinic-based acquired HIV drug resistance survey among adults receiving ART

Example	Total number of ART clinics in the country: 800	Total number of ART clinics sampled: 30	Total number of adults receiving ART: 700 000	Sample size: 900

Protocol development and training					
	Number of staff per site	Transport costs	Per diem cost	Number of nights	Total
Training of site staff (one-day training)	2	200	150	1	21 000
Production of protocol and training materials					15 000
				Subtotal	**36 000**

Survey coordination					
	Number of staff	Cost per staff member per month	Number of months	Number of sites	Total
Site coordination	1	300	5	30	45 000
Nurse incentive	2	50	4	30	12 000
National coordination	1	1 000	12		12 000
Data manager	1	800	8		6 400
				Subtotal	**75 400**

Site support visits	
	Total
Study coordinator and driver (2 days per visit, US$ 50 per diem, 2 visits)	12 000
Fuel (for six months)	2 000
Air tickets to remote sites (5 flights, US$ 200 each)	1 000
Local transport	1 000
Subtotal	**16 000**

Laboratory		
	Cost per unit	Total
Blood collection	3	2 700
Dried blood spot preparation and storage	5	4 500
Viral load testing	60	54 000
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[a]	33 750[b]
Local shipment of specimens (US$ 100 per site for national shipping)		3 000
Shipment of specimens to a WHO-designated laboratory (outside the country)		5 000
Subtotal		**102 950**

Technical support	
	Total
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000	15 400
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)	6 600
Subtotal	**22 000**

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	10 000
Subtotal	**20 000**
Total	**272 350**

a The cost of HIV drug resistance test should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).
b Assuming 25% of individuals enrolled with viral load ≥1000 copies/mL.

Table A6. Generic budget for clinic-based acquired HIV drug resistance survey among adults and children receiving ART

Example	Total number of ART clinics in the country: 800	Total number of ART clinics sampled: 30	Total number of adults receiving ART: 700 000	Adults sample size: 900
	Total number of ART clinics in the country for children: 600		Total number of children receiving ART: 45 000	Children sample size: 1200

						Shared survey costs	Survey among adults	Survey among children
Protocol development and training								
		Number of staff per site	**Transport costs**	**Per diem cost**	**Number of nights**	**Total**		
Training of site staff (one-day training)		2	200	150	1	21 000		
Production of protocol and training materials						**15 000**		
					Subtotal	**36 000**		
Survey coordination								
	Number of staff	**Cost per staff member per month**	**Number of months**	**Number of sites**		**Total**		
Site coordination	1	300	5	30		45 000		
Nurse incentive	2	50	4	30		12 000		
National coordination	1	1 000	12			12 000		
Data manager	1	800	8			6 400		
					Subtotal	**75 400**		
Site support visits								
						Total		
Study coordinator and driver (2 days per visit, US$ 50 per diem, 2 visits)						12 000		
Fuel (for six months)						2 000		
Air tickets to remote sites (5 flights, US$ 200 each)						1 000		
Local transport						1 000		
					Subtotal	**16 000**		
Laboratory								
				Cost per unit		**Total**		
Blood collection				3			2 700	3 600
Dried blood spot preparation and storage				5			4 500	6 000
Viral load testing				60			54 000	72 000
Genotyping for reverse transcriptase, protease and integrase; costs including labour				150[a]			33 750[b]	45 000[b]
Local shipment of specimens (US$ 100 per site for national shipping)						3 000		
Shipment of specimens to a WHO-designated laboratory (outside the country)						5 000		
					Subtotal	**8 000**	**94 950**	**126 600**
Technical support								
						Total		
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000						15 400		
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)						6 600		
					Subtotal	**22 000**		
Report production, printing and distribution								
						Total		
Report production and distribution						10 000		
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)						10 000		
					Subtotal	**20 000**		
					Total		**398 950**	

a The cost of HIV drug resistance test should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).
b Assuming 25% of individuals enrolled with viral load ≥1000 copies/mL.

Table A7. Generic budget for pretreatment HIV drug resistance survey among adults initiating first-line ART

Example | Number of sites: 20 | Sample size: 460

Protocol development and training

	Number of staff per site	Transport costs	Per diem cost	Number of nights	Total
Training of site staff (one-day training)	2	200	150	1	14 000
Production of protocol and training materials					15 000
				Subtotal	**29 000**

Survey coordination

	Number of staff	Cost per staff member per month	Number of months	Number of sites	Total
Site coordination	1	300	8	20	48 000
Nurse incentive	2	50	8	20	16 000
National coordination	1	1 000	8	1	8 000
Data manager	1	800	6	1	4 800
				Subtotal	**76 800**

Site support visits

	Total
Study coordinator and driver (2 days per visit, US$ 50 per diem, 2 visits)	8 000
Fuel (for six months)	2 000
Air tickets to remote sites (5 flights, US$ 200 each)	1 000
Local transport	1 000
Subtotal	**12 000**

Laboratory

	Cost per unit	Total
Blood collection	3	1 380
Dried blood spot preparation and storage	5	2 300
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[a]	69 000
Local shipment of specimens (US$ 100 per site for national shipping)		2 000
Shipment of specimens to a WHO-designated laboratory (outside the country)		5 000
Subtotal		**79 680**

Technical support

	Total
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000	15 400
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)	6 600
Subtotal	**22 000**

Report production, printing and distribution

	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	10 000
Subtotal	**20 000**
Total	**239 480**

a The cost of HIV drug resistance test should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).

Table A8. Generic budget for pretreatment HIV drug resistance survey among treatment-naive infants newly diagnosed with HIV

Example	Number of participating laboratories: 10	Sample size: 500

Protocol development and training					
	Number of staff per laboratory	Transport costs	Per diem cost	Number of nights	Total
Training of site staff (one-day training)	2	200	150	2	10 000
Production of protocol and training materials					**10 000**
				Subtotal	**20 000**

Laboratory		
	Cost per unit	Total
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[a]	75 000
Shipment of specimens to a WHO-designated laboratory (outside the country)		5 000
	Subtotal	**80 000**

Technical support	
	Total
Consultant and protocol development, data analysis and report writing and flight (US$ 550 for 20 days and daily per diem US$ 200 for 7 days); international flight US$ 3000	15 400
Statistical consultant – support statistical analysis (US$ 550 per day for 12 days)	6 600
Subtotal	**22 000**

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	4 000
Subtotal	**14 000**
Total	**136 000**

a The cost of HIV drug resistance test should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).

Table A9. Generic budget for HIV drug resistance surveillance among PrEP users diagnosed with HIV in countries where resistance testing is routinely performed in this population[a]

Example	Number of geographical areas or regions[b]: 40	Expected number of PrEP users diagnosed with HIV: 100

Training					
	Number of staff per region	Transport costs	Per diem cost	Number of nights	Total
Training of regional personnel (one-day training)	2	200	150	2	14 000
Production of training and implementation materials					**5 000**
				Subtotal	**19 000**

Laboratory		
	Cost per unit	Total
Blood collection	3	300
Dried blood spot preparation and storage	5	500
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[a]	15 000
Shipment of specimens (US$ 100 per month for national shipping)		1 200
	Subtotal	**17 500**

Technical support	
	Total
Support for analysis and interpretation	5 000
Subtotal	**5 000**

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	10 000
Subtotal	**20 000**
Total	**61 000**

a Countries performing HIV drug resistance testing for clinical management of PrEP users diagnosed with HIV can analyse the HIV drug resistance genotypes annually at the national level and estimate the prevalence of HIV drug resistance.

b HIV infection is expected to be infrequent among PrEP users, because PrEP substantially reduces the risk of acquiring HIV (especially among those who adhere to their regimen)[29]. Therefore, instead of site-level support for survey implementation, regional-level support is recommended.

c The cost of HIV drug resistance testing should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).

Table A10. Generic budget for HIV drug resistance survey among PrEP users diagnosed with HIV (in countries where HIV drug resistance testing is not routinely performed in this population)[a]

Example	Number of geographical areas or regions[b]: 40	Expected number of PrEP users diagnosed with HIV: 100

Protocol development and training					
	Number of staff per laboratory	Transport costs	Per diem cost	Number of nights	Total
Training of regional personnel (one-day training)	1	200	150	1	14 000
Production of: (a) protocol and (b) training and implementation materials					**10 000**
				Subtotal	**24 000**

Survey coordination				
	Number of staff	Cost per staff member per month	Number of months	Total
Regional staff incentive	40	50	12	24 000
National coordination and data management	1	1 000	14	14 000
			Subtotal	**38 000**

Laboratory		
	Cost per unit	Total
Blood collection	3	300
Dried blood spot preparation and storage	5	500
Genotyping for reverse transcriptase, protease and integrase; costs including labour	150[c]	15 000
Shipment of specimens (US$ 100 per month for national shipping, US$ 250 for one international shipment)		1 450
	Subtotal	**17 250**

Technical support	
	Total
Consultant (US$ 500 daily fee, US$ 200 per diem, 10 days); international flight US$ 3000	10 000
Support for analysis and interpretation	5 000
Subtotal	**15 000**

Report production, printing and distribution	
	Total
Report production and distribution	10 000
Workshop to discuss policy implications and actions required (15 outside participants, 15 local)	10 000
Subtotal	**20 000**
Total	**114 250**

a In countries where individual HIV drug resistance testing is not routinely performed for individual clinical management.

b HIV infection is expected to be infrequent among PrEP users, because PrEP substantially reduces the risk of acquiring HIV (especially among those who adhere to their regimen)[29]. Therefore, instead of site-level support for survey implementation, regional-level support is recommended.

c The cost of HIV drug resistance testing should be adapted based on the laboratory quotation (ranging from US$ 50 to US$ 350 per test).

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