

WORLD HEALTH ORGANIZATION GLOBAL STRATEGY FOR THE  
SURVEILLANCE AND MONITORING OF HIV DRUG RESISTANCE

2012





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# CONTENTS

<b>Acronyms and abbreviations</b> .....	<b>2</b>
<b>Introduction</b> .....	<b>3</b>
<b>Monitoring HIV drug resistance early warning indicators (EWI)</b> .....	<b>5</b>
<b>Surveillance of HIV drug resistance in populations prior to treatment initiation and among those receiving ART</b> .....	<b>7</b>
<b>Cross-sectional surveys of HIV drug resistance in adults prior to ART initiation at representative ART clinics</b> .....	<b>8</b>
<b>Cross-sectional surveys of acquired HIV drug resistance in adults and children on ART for more than 12 months at nationally representative ART clinics</b> .....	<b>10</b>
<b>Surveys of HIV drug resistance in children less than 18 months of age</b> .....	<b>12</b>
<b>Surveys of transmitted drug resistance (TDR) in recently infected populations</b> .....	<b>14</b>
<b>Implementation and funding HIV drug resistance surveillance activities within national ART programmes</b> .....	<b>16</b>
<b>References</b> .....	<b>17</b>

## ACRONYMS AND ABBREVIATIONS

<b>ANC</b>	Antenatal clinic
<b>ART</b>	Antiretroviral therapy
<b>ARV</b>	Antiretroviral
<b>CDC</b>	Centers for Disease Control and Prevention
<b>DBS</b>	Dried blood spots
<b>DRM</b>	Drug resistant mutation
<b>EID</b>	Early infant diagnosis
<b>EWI</b>	Early warning indicator
<b>HIVDR</b>	HIV drug resistance
<b>LMIC</b>	Low and middle income countries
<b>LPV/r</b>	Lopinavir/ritonavir
<b>NNRTI</b>	Non-nucleoside reverse transcriptase inhibitor
<b>NRTI</b>	Nucleoside/nucleotide reverse transcriptase inhibitor
<b>NVP</b>	Nevirapine
<b>PEPFAR</b>	President's Emergency Plan for AIDS Relief
<b>PI</b>	Protease inhibitor
<b>PMTCT</b>	Prevention of mother to child transmission
<b>TDR</b>	Transmitted drug resistance
<b>UNGASS</b>	United Nations General Assembly Special Session on HIV/AIDS
<b>VCT</b>	Voluntary counseling and testing

## INTRODUCTION

As of the end of 2011, more than 8 million people in low- and middle-income countries (LMIC) were receiving antiretroviral therapy (ART), up from 6.6 million in 2010 – representing an increase of about 20% (1). This figure reflects a remarkable scale-up in the provision of ART from 400,000 people receiving it in 2003 at the launch of the “3 by 5” initiative. This dramatic increase has been attributed to multiple factors, including the use of standardized and simplified regimens and guidelines for initiation and monitoring of ART. Low- and middle-income countries have benefited from international donors such as the President’s Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, TB, and Malaria. Recipient countries have committed to the expansion and strengthening of their health systems to provide universal access to ART.

Despite the obvious benefits that rapid scale-up has had on AIDS-related morbidity and mortality, the potential for widespread emergence and transmission of HIV drug resistance (HIVDR) to antiretrovirals (ARVs) has been a major ongoing concern of public health experts. In 2004, in response to this concern, the World Health Organization (WHO) created HIVResNet, a global network of over 50 institutions, laboratories, clinicians, epidemiologists, and other HIVDR experts to support development and implementation of a of global drug resistance surveillance strategy (2).

In 2004, WHO and the United States Centers for Disease Control and Prevention (CDC), in collaboration with HIVResNet, developed a global strategy for the assessment and prevention of HIVDR. Components of the strategy included: 1) Formation of national HIVDR working groups in countries scaling-up ART, 2) Monitoring the quality of care in ART programmes using “Early Warning Indicators” of HIVDR (EWI), 3) Surveillance of acquired HIVDR at sentinel ART clinics, 4) Surveillance of transmitted drug resistant HIV in recently infected populations, 5) Designation, by national HIVDR working groups, of one or more HIVDR testing (genotyping) laboratories for HIVDR surveillance, and 6) Formation and maintenance of a national HIVDR database. Additionally the strategy included the development of a network of HIVDR genotyping laboratories that support public health surveillance.

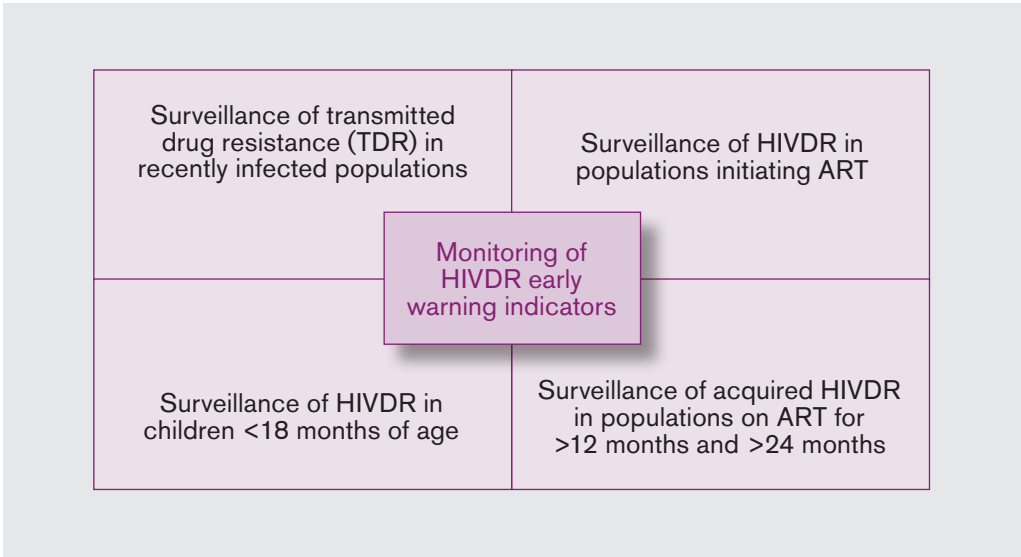
As seen in the recently released WHO Global Report on HIV Drug Resistance (3) (July 2012) and in a recently published supplement in *Clinical Infectious Disease* (4) (May 2012), surveys using WHO surveillance methods have yielded valuable information about transmitted and acquired HIVDR in the setting of the rapid scale-up of ART. However, lessons learned from implementation of the WHO strategy and the realities of ongoing expansion of ART programmes suggested that parts of the strategy require updating. Therefore, WHO in consultation with HIVResNet updated its guidance on monitoring the quality of care in ART programmes related to HIVDR prevention using EWIs. Updates to guidance on surveillance of acquired HIVDR and surveillance of transmitted drug resistant HIV in recently infected populations were initiated. Additionally, new guidance on surveillance of HIVDR in children

less than 18 months of age and surveillance of HIVDR in populations initiating ART has been developed.

This document provides an overview of the different strategy elements, so as to inform its implementation in resource-limited settings. The guidance on the development and ongoing activity of national HIVDR working groups and the designation of WHO-recommended genotyping laboratories for drug resistance testing, as described previously remains unchanged (5).

The updated 2012 global HIVDR surveillance and monitoring strategy (Figure 1) presented in this document summarizes a comprehensive package of HIVDR surveys that should be implemented in all countries scaling-up and maintaining populations on ART.

**Figure 1.** WHO 2012 HIV drug resistance surveillance and monitoring strategy





## MONITORING HIV DRUG RESISTANCE EARLY WARNING INDICATORS (EWI)

EWI assess factors at individual clinics that are associated with the emergence of HIVDR. Monitoring EWIs of HIVDR alert clinics and ART programmes to situations favouring emergence of HIVDR and provide an opportunity for corrective action to be taken.

Following a review of their performance in 2011, the number of HIVDR EWIs was reduced from 8 to 5. In the revision process, indicators which were both practical and most strongly associated with HIVDR were prioritized; updated guidance was published in 2012 (6). The definitions of the 5 selected indicators were simplified and where possible were harmonized with indicator definitions used for reporting to UNGASS/PEPFAR. Finally, an updated data abstraction tool reflecting the revised EWIs was developed (see “data abstraction tool” available at [http://www.who.int/hiv/pub/meetingreports/ewi\\_meeting\\_report/en/index.html](http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/index.html)).

A scorecard system was proposed for the return of results with three classifications: red (poor performance, below the desired level), amber (fair performance, not yet at desired level), and green (excellent performance, achieving desired level). Score-carding also allows for a “grey” classification if clinics do not monitor a specific EWI and a “white” classification if an indicator is not reported in a specific year following predetermined national convention<sup>1</sup>.

The 2012 WHO updated HIVDR EWIs and associated targets are presented in Figure 2.

**Figure 2.** WHO updated HIV drug resistance early warning indicators and targets – 2012

Early Warning Indicator	Target
1. On-time pill pick-up	Red: <80% Amber: 80–90% Green: >90%
2. Retention in care	Red: <75% retained after 12 months of ART Amber: 75–85% retained after 12 months of ART Green: >85% retained after 12 months of ART
3. Pharmacy stock-outs	Red: <100% of a 12-month period with no stock-outs Green: 100% of a 12-month period with no stock-outs
4. Dispensing practices	Red: >0% dispensing of mono- or dual therapy Green: 0% dispensing of mono- or dual therapy
5. Viral load suppression at 12 months*	Red: <70% viral load suppression after 12 months of ART Amber: 70–85% viral load suppression after 12 months of ART Green: >85% viral load suppression after 12 months of ART

\*Children < 2 years: red: <60%; amber: 60–70%; green: >70% viral load suppression after 12 months of ART.

<sup>1</sup> The new retention EWI is identical to the UNGASS and PEPFAR retention indicator which is only monitored and reported biannually. Therefore, in non UNGASS/PEPFAR reporting years, clinics monitoring EWIs report “not applicable” and receive a “white” score.

It is recommended that all clinics providing ART monitor EWI annually as a component of routine programme monitoring and evaluation. A detailed report describing sampling procedures and data analysis can be accessed from the WHO website (page 42 of the report available at: [http://www.who.int/hiv/pub/meetingreports/ewi\\_meeting\\_report/en/index.html](http://www.who.int/hiv/pub/meetingreports/ewi_meeting_report/en/index.html)).

At the national level, individual indicators should not be aggregated beyond the clinic; however, national results should include the proportion of clinics able to achieve each target.

## SURVEILLANCE OF HIV DRUG RESISTANCE IN POPULATIONS PRIOR TO TREATMENT INITIATION AND AMONG THOSE RECEIVING ART

In 2006, WHO developed a prospective survey method to assess clinic and programmatic factors associated with HIVDR in patients receiving ART. This survey was designed to 1) describe HIVDR at initiation of ART (baseline) and after 12 months of first-line therapy, 2) evaluate the percentage of the cohort achieving “HIVDR prevention” (defined as viral load suppression after 12 months of ART), and 3) be implemented at 10–15 ART clinics in each country following a 3-year cycle. Survey results would be used to optimize clinic and programmatic function in minimizing acquired HIVDR. As noted in the recent WHO report, 82 surveys have been initiated in 22 countries (3). Baseline data are available from 40 surveys in 12 countries with corresponding 12-month data available from 29 surveys. Implementation of the prospective survey, especially in settings with decentralized service-delivery models and in areas of concentrated or low prevalence epidemics, has been challenging. Therefore, WHO is developing guidance for two cross-sectional survey approaches: the first, surveillance of HIVDR among patients initiating first-line ART and the second, surveillance of acquired HIVDR in populations experiencing virological failure while on first-line ART. It is anticipated that countries will find widespread implementation of the new protocols more feasible.

# CROSS-SECTIONAL SURVEYS OF HIV DRUG RESISTANCE IN ADULTS PRIOR TO ART INITIATION AT REPRESENTATIVE ART CLINICS

The presence of HIVDR in persons initiating ART is associated with poor virological response (7); therefore, where resources allow, drug resistance testing is considered the standard of care in the management of HIV infected persons initiating ART. However, in most resource-limited settings, routine resistance testing of individuals for clinical management is not feasible. Knowledge of the prevalence and pattern of HIVDR at the population level can assist countries in identifying which first-line treatment regimen is likely to have the greatest benefit. Therefore, WHO is developing a method to estimate the national prevalence of drug resistance in population starting therapy with the objective to inform effectiveness of first-line therapy at the population level.

Because the WHO-recommended global HIVDR surveillance package includes a separate survey for HIVDR in children <18 months of age, this survey is limited to adults initiating ART.

## Methods

The primary (ART clinic selection) and secondary (within clinic patient selection) sampling procedures are being determined at the time of writing of this document.

### Survey population and patient selection criteria

Although details of the primary and secondary sampling procedures are being defined, the survey will be performed by consecutive sampling of adult patients initiating first-line ART. Each patient will undergo genotyping for the presence of drug resistance mutations (DRMs). Relevant DRMs will be defined as those conferring high-, intermediate-, or low-level resistance to ARVs, according to the Stanford HIV Drug Resistance Database (5) available at: <http://hivdb.stanford.edu>. DRMs will be also described using the WHO surveillance drug resistance mutation list.

### Clinic selection

Clinic selection criteria to be defined by WHO through an expert consultative process.

### Sampling plan

Sampling plan criteria to be defined by WHO through an expert consultative process.

### Specimen collection

Plasma specimens will be used if all the participating clinics have the capacity to collect, store, and transport plasma specimens. Otherwise, dried blood spots (DBS) will be the specimen type collected and processed for these surveys. All specimens should be genotyped at WHO designated laboratories. If DBS are used, laboratories will require WHO designation for genotyping of DBS specimens.

## **Analysis of results**

A point prevalence estimate of HIVDR with confidence intervals will be determined for the entire sample and not by individual clinic. HIVDR will be defined as the presence of relevant DRMs, as defined above.

## **Public health implications/actions**

Trends in prevalence of HIVDR in ART-naïve adults initiating ART will inform policy-makers when/if they should consider: 1) changing first-line regimens from non-nucleoside reverse transcriptase (NNRTI)-based to protease inhibitor (PI)-based regimens at the population level, 2) introducing individual pretreatment genotyping to guide therapy (where feasible) or 3) intensifying viral load monitoring (e.g. during first 12 months following ART initiation) to detect early failures associated with pre-ART HIVDR.

## CROSS-SECTIONAL SURVEYS OF ACQUIRED HIV DRUG RESISTANCE IN ADULTS AND CHILDREN ON ART FOR MORE THAN 12 MONTHS AT NATIONALLY REPRESENTATIVE ART CLINICS

The objectives of this survey are:

- 1) To classify the proportion of adult (on ART for 12–15 months and >24 months) or paediatric (on ART for  $\geq 12$  months) patients failing first-line ART (defined as viral load  $\geq 1000$  copies/ml) at nationally representative ART clinics
- 2) To describe the pattern of DRMs in those survey patients with detectable viral load

This survey first identifies a representative sample of ART clinics (the “primary sample”) in a country, and then selects patients on ART at those clinics for assessment.

In each participating country, representative ART clinics should be selected.

At each selected clinic, the survey population will include:

- a) Consecutive adult patients on ART for 12–15 months attending a participating clinic for a routine visit, until the required sample size for each clinic is reached.
- b) Consecutive adult patients on ART for >24 months attending a participating clinic for a routine visit, until the required sample size for each clinic is reached.
- c) Consecutive paediatric patients on ART for 12–36 months.

Each patient will have viral load testing performed; specimens with HIV viral load  $\geq 1000$  copies/ml will undergo genotyping. Relevant DRMs will be defined as those conferring high-, intermediate-, or low-level resistance to ARVs, according to the Stanford HIV Drug Resistance Database (8). Plasma specimens will be used if all the clinics chosen in a given country (including the smaller, more rural clinics) have the capacity to collect, store, and transport them. However, because many clinics will not have the capacity to maintain the integrity of plasma specimens, it is anticipated that DBS will be the specimen type collected and processed for these surveys. All the specimens should be genotyped at WHO-designated HIVDR testing laboratories. If DBS are used, laboratories will require WHO designation for genotyping of DBS specimens. The list of WHO accredited laboratories can be accessed online at: <http://www.who.int/hiv/drugresistance/>.

Details on the determination of sample size for each of the three survey populations are being determined. However, each selected clinic should contribute to a target sample size of 300 to 500 participants in each of the patient groups.

Whether suboptimal levels of virological suppression (below a threshold of 85%) are observed at representative ART clinics, the data from this survey will be useful to initiate additional investigations leading to improved patient outcomes and prevention of acquired HIVDR.

Data describing the prevalence and patterns of DRMs in patients failing first-line ART will identify:

- 1) The proportion of patients failing first-line ART without DRMs that lead to reduced drug susceptibility, and who consequently would benefit from measures to improve adherence
- 2) The predicted efficacy of the empiric second-line ARV regimens and whether the country's national guidelines need to be revised
- 3) The association between patterns of DRMs and length of time on first-line ART
- 4) The associations between patterns/frequency of DRMs, regimen, and HIV subtype

The survey results would also inform decisions on whether national algorithms for the detection and management of suspected treatment failure require change, including targeted use of viral loads and intensification of adherence support.

# SURVEYS OF HIV DRUG RESISTANCE IN CHILDREN LESS THAN 18 MONTHS OF AGE

## Introduction

Studies have evaluated the prevalence of HIVDR among children who received different prevention of mother-to-child HIV transmission (PMTCT) regimens. In 2010, 48% of pregnant women living with HIV in low and middle income countries received PMTCT, excluding single dose nevirapine (9). The widespread use of NNRTIs in pregnant or breastfeeding women, whether for PMTCT or as part of an ART regimen, may result in HIV-infected children acquiring NNRTI-resistant HIV and/or nucleoside reverse transcriptase (NRTI)-resistant HIV, which will compromise their subsequent response to ART.

Despite the revised 2010 WHO recommendations advocating lopinavir/ritonavir (LPV/r)-based ART as the regimen for HIV-infected children with prior NNRTI exposure, in many countries those children are started on NNRTI-based regimens because of cost and feasibility. Even in countries where a LPV/r based regimen is available, children with previous NNRTI/NRTI exposure may go unrecognized because of poor documentation.

## Methods

The survey method is retrospective and uses remnant DBS from HIV-infected children diagnosed with HIV at age less than 18 months that has been stored at early infant diagnosis (EID) laboratories. Demographic and clinical information are abstracted from laboratory requisition forms accompanying DBS. As surveillance is conducted retrospectively using remnant DBS, specimens must have been stored and handled according to WHO recommendations available at: [http://www.who.int/hiv/pub/drugresistance/dried\\_blood\\_spots/en/index.html](http://www.who.int/hiv/pub/drugresistance/dried_blood_spots/en/index.html).

Participant inclusion/exclusion criteria are described in Table 1.

**Table 1.** Participant inclusion and exclusion criteria

Inclusion criteria
<ul style="list-style-type: none"><li>• DBS tested HIV-positive by EID PCR from a child &lt;18 months of age</li><li>• If DBS for PCR is collected from a child at different time points, these should be clearly labeled with a unique ID so that the child is not counted twice or more times. The most recent DBS specimen from the child is selected for genotyping</li><li>• At least one viable remnant spot is available (two-four DBS optimal)</li><li>• From time of specimen collection DBS have been stored no longer than 14 days at ambient temperature, then stored at -20°C or -80°C with no thawing before genotyping</li></ul>
Exclusion criteria
<ul style="list-style-type: none"><li>• DBS from children ≥18 months of age</li><li>• Child is on ART at time of specimen collection</li></ul>



In some LMIC settings, all EID DBS are tested by one national laboratory, while other countries have many EID laboratories. When possible, all laboratories performing HIV EID will participate in paediatric HIVDR surveillance and will contribute to the overall sample. If only a subset of laboratories participate, a simple random sample of laboratories will be chosen. Once a laboratory is selected, HIV-positive DBS will be sampled using simple random sampling without replacement. Remnant DBS specimens will be tested anonymously, and no personal identifiers will be abstracted; a “non-research” waiver will be requested from Institutional Ethics Review Boards.

A generic WHO protocol for surveillance of HIVDR in infants <18 months of age may be downloaded from: <http://www.who.int/hiv/topics/drugresistance/protocols/en/index.html>.

## **Analysis of results**

The prevalence of HIVDR mutations leading to a classification of high-, intermediate-, or low-levels of HIVDR as determined by the Stanford algorithm is determined (5).

HIVDR prevalence will be estimated with 95% confidence intervals based on exposure to PMTCT (Yes/None/Unknown). If sample sizes are sufficient and patient data are available, separate analyses will be performed evaluating the association of HIVDR with specific PMTCT regimens.

## **Public health implications**

Surveillance to assess HIVDR prevalence among HIV-infected children <18 months of age eligible for ART initiation will be critical for improving health outcomes and minimizing subsequent accumulation of DRMs among HIV-infected children. Results will support national, regional and global decision-making on optimal selection of children’s first-line ART. It will also provide additional information to assess the feasibility of novel treatment strategies for HIV-infected children (i.e., starting LPV/r based regimen and substituting LPV/r with NVP once virological suppression is achieved).

# SURVEYS OF TRANSMITTED DRUG RESISTANCE (TDR) IN RECENTLY INFECTED POPULATIONS

## Introduction

WHO recommends that countries assess transmitted HIVDR at sentinel sites (10). Populations sampled for the TDR survey should be differentiated from populations initiating ART (HIVDR among populations starting ART, as defined above). Results from surveys of transmitted HIVDR are more likely to reflect recent transmission activity and less likely to reflect potential exposure to ART after infection.

## Methods

The survey should use sentinel sites. These sites should have the capacity to use remnant specimens and information already being collected to implement the survey. Most TDR surveys use either Antenatal clinics (ANC) or Voluntary Counselling and Testing centres (VCT).

### Survey population and patient selection criteria

Patient selection criteria have been established to predict the likelihood of recent HIV infection. These criteria include:

- 1) Age <25; preferably <22 years, if feasible
- 2) No previous pregnancies (females)
- 3) First HIV-risk defining event within past three years, if available
- 4) CD4 >500 cells/ $\mu$ l, if available

### Sampling plan

Point prevalence (with confidence intervals) is used to estimate levels of TDR in a country. It is recommended that countries piggyback periodic surveillance of HIVDR to HIV sentinel ANC sero-surveillance in pregnant women, or to any surveillance that estimate national prevalence of HIV in the general population or in a most at risk population. Remnant specimens from those surveys are typically used for HIVDR testing.

Sample size: All specimens from eligible individuals collected in the context of the HIVDR surveys should be genotyped.

### Specimen collection

Plasma or serum specimens will be used if all the participating sites have the capacity to collect, store, and transport plasma/serum specimens. Otherwise, DBS will be the specimen type collected and processed for these surveys. All the specimens should be processed for genotyping at WHO-accredited laboratories. If DBS are used, laboratories will require WHO accreditation for genotyping of DBS specimens.

## Analysis of results

The survey will provide national estimates of point prevalence of TDR from sentinel sites. TDR is determined by the detection of mutations as defined by the WHO surveillance drug resistance mutations list (11).

## Public health implications/actions

Figure 3 summarizes recent updated recommendations for public health actions in response to TDR survey results.

**Figure 3.** WHO-recommended public health actions for surveys of transmitted HIV drug resistance by drug resistance classification

### Low level of HIVDR (<5%)

1. Repeat survey in 2–4 years
2. No changes in ARV guidelines (PMTCT, ART, PEP, PrEP) based on survey data

### Moderate level of HIVDR (5–15%)

1. Repeat survey in 2 years
2. Critically review possible sources of HIVDR transmission: (a) assess HIVDR EWI data and data from surveys of acquired HIVDR from clinics; (b) review performance of HIV prevention programs for individuals aware of their HIV infection in the area of the survey; (c) assess coverage of HIV testing services in the area of the survey to estimate the risk of unintended HIVDR transmission

### High level transmitted HIVDR (>15%)

1. Repeat survey in 2 years
2. Take all actions listed for “moderate level of HIVDR (5–15%)”
3. If not already being done, immediately conduct HIVDR surveillance in populations initiating ART, in order to inform decision making around: intensified viral load monitoring, individual drug resistance testing prior to ART initiation and first-line regimen selection (change from NNRTI to PI-based first-line ART)
4. Perform sub-analysis of HIVDR surveillance in populations initiating ART to estimate prevalence of resistance in HIV infected women between 15–49 years of age to inform decision around: switch to PI-based PMTCT or HIVDR testing of all HIV infected pregnant women
5. Use national cost effectiveness models to inform decision making around point (2) and (3)

ANC = antenatal care; VCT = voluntary counselling and testing; STI = sexually transmitted infection clinic; TDR = transmitted drug resistance; PMTCT = prevention of mother to child transmission; ART = antiretroviral therapy; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis.

## IMPLEMENTATION AND FUNDING HIV DRUG RESISTANCE SURVEILLANCE ACTIVITIES WITHIN NATIONAL ART PROGRAMMES

When implemented routinely over time and as a package, the global strategy provides countries with a comprehensive picture of HIVDR and ART programme functioning for the purposes of programme planning and decision making leading to treatment optimization. Because each element provides information addressing one important aspect of HIVDR within a country and not a comprehensive picture, and because all elements are designed to be implemented as a package, elements of the strategy cannot be prioritized at the global level. However, countries may not find it feasible or necessary to implement all five components of the strategy simultaneously and therefore countries would need to prioritize based on their own public health and programmatic needs.

Commitment of funding and effort towards incorporating HIVDR surveillance into routine ART programmes will help inform countries on the need for ART guideline changes and assist in the promotion of best practices in provision of ART services that lead to higher rates of viral suppression and prevention of both acquired and transmitted HIVDR.

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