

Technical guidance for Round 9 Global Fund HIV proposals

Broad Area

TREATMENT

Service Delivery Area

Prevention and assessment of HIV drug resistance (HIVDR)

This technical brief provides key information to guide development of proposals to ensure that they include key elements to assess and minimize the emergence and transmission of HIV drug resistance (HIVDR).

Rationale for including HIVDR prevention and assessment in the proposal

As access to ART services expands, maintaining optimal outcomes remains a challenge for ART programmes throughout the world. The emergence of some HIV drug resistance is inevitable, given HIV's high replication and mutation rates and the necessity for lifelong antiretroviral treatment (ART). Activities to monitor HIV drug resistance and associated factors are crucial for successful programme management and for generating evidence that can be used to improve patient retention and treatment adherence, and to maintain the effectiveness of treatment options.

Since 2002, The Global Fund Board (GF/B4/2) has strongly recommended to Recipients that they implement mechanisms to monitor and contain HIVDR according to WHO and existing international guidelines.¹ The Principal Recipient's obligation to ensure that drug resistance monitoring and containment is carried out is part of the Fund's Standard Grant Agreement with recipient countries,² and reiterated in the 2009 Guide to the Global Fund's Policies on Procurement and Supply Management, which states that "recipients must ensure that systems are in place to monitor and contain resistance".³

¹ Report of the 3rd Board Meeting, Global Fund; <http://www.theglobalfund.org/documents/board/04/GF%20B4%202002%20Report%20of%20the%20Third%20Board%20Meeting.pdf>

² Article 19q states that '*The Principal Recipient shall implement mechanisms to ... monitor and contain drug resistance*'.

³ Guide to the Global Fund's Policies on Procurement and Supply Management, November 2009, page 25.

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WHO has developed a global strategy for HIVDR prevention and assessment in consultation with WHO HIVResNet, a global network of international experts and institutions. Sixty countries have already adopted WHO's global strategy, which focuses on collecting and using crucial programme and clinical information to guide programmatic decisions. In particular, such information can guide clinic and programme decisions to:

- prolong and maximize the quality of life of people living with HIV,
- maintain the effectiveness of first line therapy, and
- reduce unnecessary switches to more costly regimens.

Implementation of HIVDR activities has assisted countries to assess barriers to continuity of care at ART sites (such as costs, transport, and clinic and pharmacy hours), to assess quality of medical and pharmacy records, and to support evidence-based recommendations for in-depth surveys, programmatic changes or requests for additional support at ART site and/or ART programme level.

Elements to be considered in the situation analysis

The situational analysis for the drug resistance element of this Service Delivery Area should include a review of HIVDR prevention activities. These are:

- National guidelines on ART eligibility and prescribing
- Methods and practices to support and monitor adherence
- Removal of barriers to continuous access to care, including patient charges and transport difficulties
- Methods and practices for follow-up of ART patients who miss clinic appointments
- Ongoing quality assurance for ARV drugs
- Continuity of ARV drug supplies; monitoring of shortages
- Minimum standard ART data recording
- Prevention programs to reduce HIV transmission from persons in treatment

In addition, the following information can be included:

- Number and percentage of adults and children on second line ART.

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- Progress in implementing the 8 WHO recommended HIVDR strategy elements⁴:
 - Description of country's strategy and plan to prevent and assess emergence and transmission of HIV drug resistance, if any.
 - Description of any activities undertaken or planned to assess treatment programme elements that can be associated to HIVDR emergence (for example, monitoring of programmatic HIVDR Early Warning Indicators - EWIs), or to estimate the extent of drug resistance in treated or recently infected populations (for example, monitoring surveys in treated populations, or surveillance of transmitted resistance).²
 - Description of HIVDR data base, if any.
 - Results of any implemented HIVDR prevention and assessment activities, and public health actions taken to address results.
 - The challenges encountered in the implementation of the HIVDR strategy.

Examples of programme objectives

- To develop and implement a national strategy for HIVDR prevention and assessment
- To implement a specific element of a national HIVDR strategy, for example:
 - To form a multi-disciplinary national HIVDR Working Group,
 - To adapt or develop a national strategy for HIVDR prevention and assessment;
 - To implement a monitoring system for HIVDR early warning indicators in pilot or nationally representative ART sites;
 - To implement survey in pilot ART sites or representative ART sites to monitor HIVDR prevention among populations on ART;
 - To implement a survey of transmitted resistance among individuals recently infected and ART naive in a specific geographic area.

⁴ These strategy elements are described in detail on the WHO HIVDR web page: <http://www.who.int/hiv/drugresistance/>

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Target populations

Target population for the HIVDR prevention and assessment strategy include:

- Adults and children starting ART
- Adults and children currently on ART (continued treatment)
- Adults and children recently infected with HIV and naive to ART, including pregnant women diagnosed at Antenatal Clinics (ANC).

In concentrated epidemics with well identified 'most at risk populations' (MARPS) - such as men who have sex with men (MSM), sex workers (SWs), or intravenous drug users (IDUs) - HIVDR prevention and assessment activities could be planned to target specific populations.

Suggested activities

Countries that have not yet developed a national HIVDR prevention and assessment programme are strongly encouraged to do so, with or without the support of Global Fund. The Global Fund proposal can be used to facilitate establishment of a national HIVDR programme, to expand existing programme activities outlined by the National HIV Drug Resistance working group, or to add new programme activities. Detailed information on WHO's global HIV Drug Resistance Prevention and Assessment Strategy is available at the following link: <http://www.who.int/hiv/drugresistance>.

HIV Drug Resistance Prevention and Assessment National Strategy

The WHO-recommended strategy includes the following elements:

- A. Development of a national HIVDR Working Group, five year plan and budget
 - *Ministries of Health in coordination with National AIDS Councils should form national HIV drug resistance working groups, made up of ART program planners, clinicians, epidemiologists, laboratorians, monitoring and evaluation specialists, community members, and partner organizations, to develop the strategy.*
- B. Regular assessment of HIVDR Early Warning Indicators from all ART sites or representative sites
 - *HIVDR EWI are ART site quality assurance tools to assess the extent to which ART sites are functioning optimally to minimize HIVDR. EWIs evaluate factors known to be associated with the emergence of HIVDR at the ART site level (including prescribing practices, losses to follow-up during the first year of ART, the extent to which patients pick up their ARV drugs*

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or attend their clinical appointment on time, and ARV drug shortages at the site level) without the expense of HIVDR genotyping. EWI are abstracted retroactively so that results are available more quickly than in prospective surveys and can be used to support rapid optimization of both ART site and national ART program functioning.

C. Surveys to monitor HIV drug resistance prevention and associated factors in ART sites

- *Surveys to monitor HIVDR prevention and emergence in sentinel ART sites are designed to be implemented in ≥ 3 sites annually in a rolling-three year cycle. Approximately 150 patients starting ART are monitored at baseline and at 12-15 months by genotyping, and factors associated with the emergence or prevention of HIVDR are evaluated.*

D. HIVDR transmission threshold surveys where ART has been widespread for ≥ 3 years

- *Surveys to evaluate transmitted HIV drug resistance using the threshold survey method are performed in geographic areas within a country where ART has been widespread for at least three years, because HIVDR transmission is likely to be detected first in those areas.*

E. HIVDR database development

- *Adoption of the WHO database to hold HIVDR data is recommended.*

F. Designation of an in-country or regional WHO-accredited HIVDR genotyping laboratory

- *National HIVDR working groups coordinating WHO-recommended surveys involving genotyping should designate either a national or regional WHO-accredited genotyping laboratory to provide quality-assured results for the surveys. WHO HIVResNet can provide you a list of accredited labs.*

G. Review of and support for HIVDR prevention activities

- *Review of HIVDR prevention activity data will provide the context necessary for HIVDR working group to make recommendations to national programmes and the Ministry of Health on how best to optimize ART programme practice and public health policy initiatives.*

H. Preparation of annual HIVDR report and recommendations for ART and prevention planning

- *National HIVDR working groups should report on all aspects of the strategy annually, and disseminate the reports. The reports should include recommendations for action to prevent HIVDR emergence and transmission.*

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Approach to costing these activities

The following list of activity components is provided to facilitate country costing of HIVDR activities. Proposed activities should be costed using the Global Fund format of cost per unit, based on country circumstances.

	Components	Notes
Coordination	<ul style="list-style-type: none"> HIV Drug Resistance Coordinator HIV Drug Resistance Working Group Meetings Training of Working Group 	
HIVDR Early Warning Indicators	<ul style="list-style-type: none"> Site assessments (~3 hours per site); include travel and per diem costs Training of abstractors Abstractor travel costs (to sites) and per diem Supervision costs (travel to sites, materials) Data entry Data analysis Report writing and dissemination 	<p>Abstraction costs depend on the number and location of sites, the size of the patient population, whether records are paper or electronic, and whether abstraction is integrated with other monitoring activities. Abstraction usually requires ~2 days per site. The average cost of a country EWI exercise is approximately \$20,000.</p>
HIVDR Monitoring	<ul style="list-style-type: none"> Any staff or meeting costs related to protocol adaptation. Site assessments (~3 hours per site); include travel and per diem costs Training of participating staff Supervision costs (travel to sites, materials) Laboratory supplies Genotyping, sample transport and international shipment costs (180 samples) Viral load testing (approx. 100 samples) Data entry Data analysis Report writing and dissemination 	<p>Survey costs depend on the number and location of sites. WHO recommends completing surveys at 3-10 representative sites per year. Costs should be consistent across sites. An average cost per site is approximately \$100,000.</p> <ul style="list-style-type: none"> Genotyping costs \$80 - \$200/sample, depending on methodology.
HIVDR transmission survey in 1 area	<ul style="list-style-type: none"> Any staff or meeting costs related to protocol adaptation. Site assessments (~3 hours per site); include travel and per diem costs Training of participating staff Supervision costs (travel to sites, materials) Laboratory supplies Genotyping, sample transport and international shipment costs (60 samples) Data entry Data analysis Report writing and dissemination 	<p>An average cost per site is approximately \$60,000.</p> <ul style="list-style-type: none"> Genotyping costs \$80 - \$200/sample, depending on methodology.
HIVDR Database	<ul style="list-style-type: none"> Set-up costs Maintenance costs 	
Annual report	<ul style="list-style-type: none"> Data analysis Meetings and/or workshops to interpret data Report writing and dissemination 	
Genotyping laboratory development	<ul style="list-style-type: none"> Staff training Accreditation process Maintenance of accreditation (participation in assessments) 	<p>Only recommended for countries that have an experienced genotyping laboratory already in place. Countries are advised to prioritize capacity for clinical lab tests for HIV care including LFTs, CD4 counts and viral loads before developing capacity for genotyping, which is for surveillance purposes and not clinical care.</p>

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Additional guidance can be found at <http://www.who.int/hiv/drugresistance/en/>

Suggested key indicators

1. HIVDR Early Warning Indicators:

The following indicators are included in the set of Early Warning Indicators for HIVDR, developed as site-specific indicators that can be used for programmatic action. Additional detail on the indicators and how to collect them is available at <http://www.who.int/hiv/drugresistance/en/>.

- Percentage of adult patients initiating ART who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen (EWI 1a).
- Percentage of patients initiating ART who are lost to follow-up during the 12 months after starting ART (EWI 2).
- Percentage of adult patients initiating ART who are taking an appropriate first-line ART regimen 12 months later (EWI 3a).
- Percentage of adult patients initiating ART whose initial ART regimen was switched during the first 12 months of ART to another regimen involving a different drug class (EWI 3b).
- Percentage of patients picking up all prescribed antiretroviral (ARV) drugs on time (EWI 4a).
- Percentage of patients initiating ART who picked up all prescribed ARV drugs on time during their first 12 months of ART (EWI 4b).
- Percentage of ART patients attending all clinical consultations on time (EWI 5a).
- Percentage of patients initiating ART who attended all clinical consultations on time during the first 12 months of ART (EWI 5b).
- Percentage of patients on first-line ART whose regimen was stopped, modified, or incompletely dispensed at the pharmacy due to ARV stock-outs or shortages during a designated year (EWI 6a1).

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- Percentage of patients initiating ART whose regimen was stopped, modified, or incompletely dispensed at the pharmacy during the first 12 months of ART due to ARV stock-outs or shortages (EWI 6.a2).
- Percentage of months in a designated year in which there were no ARV drug stock-outs (EWI 6b).
- Percentage of patients who demonstrate >90% adherence by pill count or standardized adherence measure (EWI 7a).
- Percentage of patients initiating ART whose viral load is <1000 copies/ml after 12 months of first-line ART (EWI 8).
- Number of HIVDR Early Warning Indicators, of the six recommended by WHO, monitored in the country (summary)
- Number of ART sites in which HIVDR Early Warning Indicators abstracted (summary)
- Percentage of ART sites meeting EWI targets (summary, for each EWI)

2. Monitoring survey to evaluate HIVDR emergence in treated populations

- Number of HIVDR Monitoring Surveys implemented
- Number of HIVDR Monitoring Surveys in which HIVDR prevention was ≥ 70 at month 12

3. Surveillance of transmitted HIVDR

- Number of HIVDR Transmission Surveys implemented
- Number of HIVDR Transmission Surveys in which transmitted resistance was <5%, 5-15%, and >15%

In addition, two HIVDR-related programmatic output indicators are included in the Global Fund's M&E Guidelines:

- T3 - Percentage of health facilities dispensing antiretroviral therapy that have experienced a stock-out of at least one required antiretroviral drug in the last 12 months
- T5 - Number and percentage of people starting antiretroviral therapy who picked up all prescribed antiretroviral drugs on time

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Key implementing partners to be considered

- Providers of ART services, including public sector, NGO/FBO and private sector
- National health programme
- National drug supply chain management system
- PMTCT programme
- PEPFAR implementers, (e.g. CDC, ICAP, EGPAF ,FHI , Basics)
- Other development partners (PharmAccess, TreatAsia, etc)
- UN partners (WHO, UNICEF, UNAIDS)

Type and sources of technical assistance that might be required during implementation

Support for:

- Developing national HIVDR prevention and assessment implementation plans
- Developing programme activities to support HIVDR prevention and assessment
- Developing and implementing training, supervision and mentoring
- Developing recommendations to promote public health actions, based on results of HIVDR assessment activities
- Developing technical briefings for government leadership, CCMs and senior Ministry of Health officials on the WHO HIVDR strategy
- Technical assistance is available to countries from the WHO HIV Drug Resistance Team and from other specialists in the network. WHO also provides protocols and tools on request. Please see <http://www.who.int/hiv/drugresistance/>

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