Technical Guidance Note for Round 11 Global Fund HIV Proposals

UNAIDS I World Health Organization I 2011

HIV drug resistance (HIVDR)

Rationale for including HIVDR prevention and assessment in the proposal

- As access to antiretroviral treatment services expands, maintaining optimal outcomes remains a challenge for antiretroviral treatment programmes throughout the world. The emergence of some human immunodeficiency virus (HIV) drug resistance (HIVDR) is inevitable, given HIV's high replication and mutation rates and the necessity for lifelong antiretroviral treatment.
- Activities to monitor HIV drug resistance and associated factors are crucial for successful programme management and for generating evidence that can be used to:
  - maintain the effectiveness of first- and second-line therapy;
  - reduce unnecessary switches to more costly and less well-tolerated regimens;
  - improve patient retention and treatment adherence;
  - predict population-level efficacy of current and future first- and second-line therapy and pre- and post-exposure prophylaxis;
  - generate hypotheses for operational research and inform targeted interventions for the optimization of patient care and minimization of HIVDR.
- Since 2002, the Global Fund Board (GF/B4/2) has strongly recommended to recipients that they implement mechanisms to monitor and minimize HIVDR according to the World Health Organization (WHO) and other existing international guidelines. The principal recipient's obligation to ensure that drug resistance monitoring and containment are carried out is part of the Fund's Standard Grant Agreement with recipient countries[1] and is 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.'[2]

Situation analysis

- Progress in implementing the eight WHO recommended HIVDR strategy elements:[3]
  - Description of country's strategy and plan to prevent and assess emergence and transmission of HIVDR, if any.
  - Description of any activities undertaken or planned to assess treatment programme elements that can be associated with emergence of HIVDR (e.g. monitoring of programmatic HIVDR early warning indicators) or to estimate the extent of drug resistance in treated or recently infected populations (e.g. surveys of acquired HIVDR in treated populations, or surveillance of transmitted resistance in recently infected populations).[4]
  - Description of HIVDR database, if any.
  - Results of any implemented HIVDR prevention and assessment activities and public health actions taken to address results.
  - Challenges encountered in the implementation of the HIVDR strategy.

1 Article 19 states that 'The principal recipient shall implement mechanisms to ... monitor and contain drug resistance.'

2 *Guide to the Global Fund's policies on procurement and supply management*. Geneva, Global Fund to Fight AIDS, Tuberculosis and Malaria, 2009, page 25.

3 These strategy elements are described in detail at http://www.who.int/hiv/drugresistance/.

4 Article 19 states that 'The principal recipient shall implement mechanisms to ... monitor and contain drug resistance.'

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 multidisciplinary national HIVDR working group;
  - to adapt, develop or support the implementation of a national strategy for HIVDR prevention and assessment;
  - to use HIVDR early warning indicators in periodic monitoring of pilot or nationally representative antiretroviral treatment sites;
  - to implement surveys in pilot antiretroviral treatment sites or representative antiretroviral treatment sites to monitor acquired HIVDR in populations on antiretroviral treatment;
  - to implement a survey of transmitted resistance among individuals recently infected and naive to antiretroviral treatment in a specific geographical area.

Focus populations

- Adults and children starting antiretroviral treatment.
- Adults and children currently on antiretroviral treatment (continued treatment).
- Adults and children recently infected with HIV and naive to antiretroviral treatment, including pregnant women diagnosed at antenatal clinics.

In concentrated epidemics with well-identified key affected populations, such as men who have sex with men, sex workers and people who inject drugs, HIVDR prevention and assessment activities could be planned to target specific populations.

Suggested actions

HIVDR prevention and assessment should be integrated into every national treatment programme, with or without the financial support of the Global Fund. The Global Fund proposal can be used to facilitate establishment of a national HIVDR programme, to maintain or expand existing programme activities, or to add new programme activities.

Development of a national HIVDR working group, 5-year plan and budget

Ministries of health in coordination with national AIDS councils should form national HIVDR working groups, made up of antiretroviral treatment programme planners, clinicians, epidemiologists, laboratory scientists, pharmacists, monitoring and evaluation specialists, community members and partner organizations, to develop the strategy.

Routine assessment of HIVDR early warning indicators from all antiretroviral treatment sites or representative sites

HIVDR early warning indicators are quality-assurance indicators of antiretroviral treatment sites that assess the extent to which antiretroviral treatment sites are functioning optimally to minimize HIVDR. Information to enable their assessment should be available in well-run treatment sites as part of routine patient and site records. Early warning indicators evaluate factors known to be associated with the emergence of HIVDR, such as prescribing practices, losses to follow-up during the first year of antiretroviral treatment, the extent to which patients collect their antiretroviral drugs and attend their clinical appointments on time, and antiretroviral drug shortages at the

site level. Monitoring HIVDR early warning indicators annually at all sites, or at a large number of representative sites, supports standardized record-keeping and forms the foundation for interpretation of laboratory-based surveillance (surveys to monitor acquired and transmitted HIVDR). Guidance and standardized data abstraction/analysis tools on WHO early warning indicators are available at http://www.who.int/hiv/topics/drugresistance/hiv_dr_early_warning_indicators.pdf and http://www.who.int/hiv/topics/drugresistance/hiv_dr_tool_en.xls.

Surveys to monitor acquired HIVDR and associated factors in sentinel antiretroviral treatment sites

Surveys to monitor acquired HIVDR and related factors in sentinel antiretroviral treatment sites are designed to be implemented in three or more sites annually in a rolling 3-year cycle. Approximately 150 patients starting antiretroviral treatment are monitored at baseline and at 12–15 months by genotyping, and factors associated with the emergence or prevention of HIVDR are evaluated. Surveys of acquired HIVDR build on HIVDR early warning indicators and provide descriptions of HIVDR in populations before the start of therapy and after 12 months of therapy. In multisite analyses, surveys of acquired HIVDR permit assessment of the relationship between site and programme factors and HIVDR. See http://www.who.int/hiv/drugresistance/HIVDR_prev_survey_article.pdf.

Surveys of transmitted HIVDR in geographical regions where antiretroviral treatment has been widespread for more than 3 years

Surveys of transmitted HIVDR use truncated sequential sampling to classify transmitted HIVDR as low (below 5%), moderate (5–15%) and high (over 15%) in specific geographical regions and within sentinel populations. Surveys are performed in geographical areas within a country where antiretroviral treatment has been widespread for at least 3 years, because HIVDR transmission is likely to be detected first in those areas. Survey results inform the selection of current prevention of mother-to-child transmission regimens, pre- and post-exposure prophylaxis, and future first-line therapy. Additionally, results inform indirectly on the success of prevention programmes in HIV-infected populations receiving antiretroviral treatment. See http://www.who.int/hiv/drugresistance/WHO_HIVDR_transmission_survey.pdf.

HIVDR database development

Adoption of the WHO database to store and analyse HIVDR data is recommended. WHO has developed a database tool that supports data capture and analyses for countries implementing surveys of transmitted and acquired HIVDR. See http://www.who.int/hiv/topics/drugresistance/en/index.html.

Selection of a WHO-accredited laboratory to analyse survey samples

WHO has developed an accreditation process for national, regional and specialized laboratories performing HIV genotyping for the purpose of public health surveillance. The quality-assurance process supports quality-assured results and capacity-building. Nationally accredited laboratories perform testing for national surveillance. Regionally accredited laboratories perform genotyping for countries in their region and support technology transfer to countries developing HIVDR testing capacity. Specialized laboratories perform genotyping for countries without accredited laboratories, support capacity-building and implement key operational research related to HIVDR testing. WHO recommends the use of a WHO-accredited laboratory for HIVDR so that the results are internationally comparable and of assured quality. See http://www.who.int/hiv/topics/drugresistance/laboratory/en/index1.html for a list of currently accredited laboratories.

Review of and support for HIVDR prevention activities

Annual review by country HIVDR working groups of HIVDR prevention and assessment activity data and other relevant national programmatic and HIVDR data will provide the context necessary for HIVDR working groups

to make recommendations to national programmes and ministries of health on how best to optimize antiretroviral treatment programme practice and public health policy initiatives.

Suggested key indicators

HIVDR early warning indicators

The following indicators are used as early warning indicators for HIVDR. They are site-specific indicators with specific targets that should be used to improve site management and prevent the emergence of HIVDR:

- Percentage of adult patients initiating antiretroviral treatment who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line antiretroviral treatment regimen (early warning indicator 1).
- Percentage of patients initiating antiretroviral treatment who are lost to follow-up during the 12 months after starting antiretroviral treatment (early warning indicator 2).
- Percentage of adult patients initiating antiretroviral treatment who are taking an appropriate first-line antiretroviral treatment regimen 12 months later (early warning indicator 3a).
- Percentage of adult patients initiating antiretroviral treatment whose initial antiretroviral treatment regimen was switched during the first 12 months of antiretroviral treatment to another regimen involving ¡ferent drug class (early warning indicator 3b).
- Percentage of patients picking up all prescribed antiretroviral drugs on time (early warning indicator 4a).
- Percentage of patients initiating antiretroviral treatment who picked up all prescribed antiretroviral drugs on time during their first 12 months of antiretroviral treatment (early warning indicator 4b).
- Percentage of patients on antiretroviral treatment attending all clinical consultations on time (early warning indicator 5a).
- Percentage of patients initiating antiretroviral treatment who attended all clinical consultations on time during the first 12 months of antiretroviral treatment (early warning indicator 5b).
- Percentage of months in a designated year in which there were no antiretroviral drug stock-outs (early warning indicator 6a).
- Percentage of patients on first-line antiretroviral treatment whose regimen was stopped, modified or incompletely dispensed at the pharmacy due to antiretroviral stock-outs or shortages during a designated year (early warning indicator 6c1).
- Percentage of patients initiating antiretroviral treatment whose regimen was stopped, modified or incompletely dispensed at the pharmacy during the first 12 months of antiretroviral treatment due to antiretroviral stock-outs or shortages (early warning indicator 6c2).
- Percentage of patients who demonstrate 100% adherence by pill count (early warning indicator 7a).
- Percentage of patients who demonstrate 100% adherence by another standardized adherence measure (early warning indicator 7b).
- Percentage of patients initiating antiretroviral treatment whose viral load is below 1000 copies/ml after ¡onths of first-line antiretroviral treatment (early warning indicator 8).

National level indicators for the functionality of HIVDR early warning indicators monitoring include:

- number of HIVDR early warning indicators monitored in the country (summary);
- number of antiretroviral treatment sites in which HIVDR early warning indicators are abstracted (summary);
- percentage of antiretroviral treatment sites meeting early warning indicator targets (summary, for each early warning indicator).

Additional details on the indicators and their selection and use are available at http://www.who.int/hiv/drugresistance/en.

Of note is that two HIVDR-related programmatic output indicators are included in the Global Fund's monitoring and evaluation guidelines:

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

Survey of acquired HIVDR in treated populations

- Number of HIVDR monitoring surveys implemented.
- Number of HIVDR monitoring surveys in which HIVDR prevention was at least 70% at month 12.

Guidance is available at http://www.who.int/hiv/drugresistance/HIVDR_prev_survey_article.pdf.

Surveillance of transmitted HIVDR

- Number of HIVDR transmission surveys implemented.
- Number of HIVDR transmission surveys in which transmitted resistance was below 5%, 5–15% and over 15%.

Guidance is available at http://www.who.int/hiv/drugresistance/WHO_HIVDR_transmission_survey.pdf.

Linkages with other interventions

- WHO HIVDR prevention and assessment guidance is designed to be integrated into routine national monitoring and evaluation processes, including pharmacovigilance.

Approach to costing

The following table is provided to facilitate country costing of HIVDR activities. Please refer to the WHO Global Fund Costing Tool for Round 11 (http://www.who.int/hiv/topics/ppm/costing/en/index.html).

	Components	Notes
Coordination	◆ HIVDR coordinator ◆ HIVDR working group meetings ◆ Training of working group	
HIVDR early warning indicators	◆ Site assessments (about 3 hours per site); include travel and per diem costs ◆ Training of abstractors ◆ Abstractor travel (to sites) and per diem costs ◆ Supervision costs (travel to sites, materials) ◆ Data entry ◆ Data analysis ◆ Report writing and dissemination	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 about 2 days per site. The average cost of data abstraction is US$ 500–1000 per site, although costs can be minimized by integration into routine monitoring and evaluation activities

	Components	Notes
Surveys of acquired HIVDR	◆ Any staff or meeting costs related to protocol adaptation ◆ Site assessments (about 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 (about 100 samples) ◆ Data entry ◆ Data analysis ◆ Report writing and dissemination	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. The average cost per site is US$ 100 000. Genotyping costs US$ 80–200 per sample, depending on the method and laboratory
HIVDR transmission survey in one area	◆ Any staff or meeting costs related to protocol adaptation ◆ Site assessments (about 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	The average cost per site is approximately US$ 60 000; this is the cost of one survey conducted in one geographical region in a specific sentinel population. Genotyping costs US$ 80–200 per sample, depending on the methodology
HIVDR database	◆ Set-up costs ◆ Maintenance costs	The WHO HIVDR database is available free of charge from WHO and supports data abstraction and analysis for survey of acquired and transmitted HIVDR
Annual report	◆ Data analysis ◆ Meetings and workshops to interpret data ◆ Report writing and dissemination	
Accreditation of genotyping laboratory	◆ Staff training ◆ Accreditation process ◆ Maintenance of accreditation (participation in assessments)	Recommended only for countries that already have an experienced genotyping laboratory in place. Countries are advised to prioritize capacity for clinical laboratory tests for HIV care, including liver function tests, CD4 counts and viral loads, before developing capacity for genotyping, which is for surveillance purposes and not clinical care

Technical assistance that may be required during implementation

Potential types of support

- 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, country coordinating mechanisms and senior ministry of health officials on the WHO HIVDR strategy.

Key implementing partners to consider

- Providers of antiretroviral treatment and antenatal care services in the public and private (nongovernmental organizations, profit-making organizations) sectors.
- United States President's Emergency Plan for AIDS Relief (PEPFAR) implementers, e.g. Centers for Disease Control and Prevention, International Center for AIDS Care and Treatment Programs, Elizabeth Glazer Pediatric AIDS Foundation, Family Health International, and Basics.
- Other development partners, e.g. PharmAccess, TreatAsia and Agence Nationale de Recherches sur le Sida.
- National reference laboratory and WHO accredited genotyping laboratory.
- Company experienced in the shipping of biological samples on dry ice or in liquid nitrogen.

Key reference materials

Additional information on the WHO global HIV drug resistance prevention and assessment strategy is available at http://www.who.int/hiv/drugresistance.

20 Avenue Appia
CH-1211 Geneva 27
Switzerland

+41 22 791 3666

unaids.org