



# Feasibility of the World Health Organization's HIV Drug Resistance Assessment Strategy for Resource-Limited Countries Scaling Up Antiretroviral Treatment

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### Background

- The emergence of HIV drug resistance (HIVDR) is inevitable, given HIV's high mutation and high replication rates and the necessity for lifelong antiretroviral treatment (ART).
- In resource-limited countries where there are one first-line regimen and one alternate, + one second-line regimen, successful treatment with a first-line regimen should be maintained for as long as possible.
- WHO recommends that countries develop a public-health strategy
  - To minimize the emergence and transmission of HIVDR
  - To assess ART program and HIV prevention practices related to HIVDR prevention
  - To assess HIVDR emergence and transmission

### Goals:

Within the context of the national HIV prevention and treatment plan, to support ART program practices and national planning

1. to minimize the preventable emergence of HIV drug resistance
2. to restrict the extent to which resistance jeopardizes the effectiveness of the available ART regimens

### The WHO HIV Drug Resistance Prevention and Assessment Strategy

- Development of a national HIVDR Strategy Working Group, five year plan and budget
- Regular assessment of HIVDR "early warning" indicators from all ART sites (or representative sites)
- Surveys to monitor HIV Drug resistance prevention and associated factors in sentinel ART sites
- HIVDR transmission threshold surveys in geographic areas where ART has been widespread for > 3 years
- HIVDR database development
- Designation of one or more in-country or regional WHO-accredited HIVDR genotyping laboratories for surveillance
- Review of and support for HIVDR prevention activities
- Preparation of annual HIVDR report and recommendations; use of data for ART and HIVDR prevention planning

### Methodology

The National HIV Drug Resistance Working Group should consist of clinicians, epidemiologists, pharmacists, laboratory staff, ART monitoring staff, HIV surveillance staff, community representatives, and representatives of groups involved in ART scale-up, HIV surveillance, ART monitoring, and HIVDR research. A five-year plan and budget should be developed.

**HIV Drug Resistance Early Warning Indicators**  
Early Warning Indicators should be monitored at all ART sites, or a representative sample of sites. Indicators are monitored only if information can be abstracted from routinely used medical or pharmacy records. Pediatric and adult EWIS should be monitored separately.

- 1. Prescribing practices** *Target: 100%*
  - % of patients initiating ART who are initially prescribed an appropriate first-line regimen
- % lost to follow-up during the first 12 months of ART** *Target: <20%*
- 2. Patient retention on first-line ART** *Target: >70%*
  - % of patients initiating ART who are on an appropriate first-line ART regimen 12 months later
- 3. On-time ART Drug pick-up** *Target: > 80%*
  - % of ART patients picking up prescribed ART drugs on time (before previous drugs run out)
- 4. ART appointment-keeping** *Target: > 80%*
  - % of ART patients attending all clinic appointments on-time
- 5. Drug Supply Continuity** *Target: 0%*
  - ART stops, substitutions, and switches due to ART shortages during a specified time period
- % of months during a year with no ART drug stock outsages** *Target: 100%*

### Two optional indicators:

6. **Pill count/adherence** (target to be set depending on measurement)
7. **Viral load suppression** at 12 months (target > 70%)  
(Only countries where pill counts/standardized adherence measures and/or viral loads are performed and recorded routinely for all patients should consider monitoring these)

Site	Year	Number with no ART drug stock outsages	% of months with no ART drug stock outsages	Number of ART patients with HIVDR	% of ART patients with HIVDR	% of ART patients with HIVDR who are on 1 <sup>st</sup> line ART
1	12	100 (100%)	100 (100%)	0 (0%)	0 (0%)	0 (0%)
2	12	91 (91%)	91 (91%)	10 (10%)	10 (10%)	10 (10%)
3	8	80 (80%)	80 (80%)	10 (10%)	10 (10%)	10 (10%)
4	12	100 (100%)	100 (100%)	0 (0%)	0 (0%)	0 (0%)
5	12	110 (110%)	110 (110%)	0 (0%)	0 (0%)	0 (0%)
6	11	90 (90%)	90 (90%)	10 (10%)	10 (10%)	10 (10%)
7	12	90 (90%)	90 (90%)	10 (10%)	10 (10%)	10 (10%)
8	12	200 (200%)	200 (200%)	10 (10%)	10 (10%)	10 (10%)
9	12	100 (100%)	100 (100%)	10 (10%)	10 (10%)	10 (10%)
10	12	90 (90%)	90 (90%)	10 (10%)	10 (10%)	10 (10%)
11	12	200 (200%)	200 (200%)	10 (10%)	10 (10%)	10 (10%)
12	12	100 (100%)	100 (100%)	10 (10%)	10 (10%)	10 (10%)
13	12	100 (100%)	100 (100%)	10 (10%)	10 (10%)	10 (10%)
14	12	100 (100%)	100 (100%)	10 (10%)	10 (10%)	10 (10%)

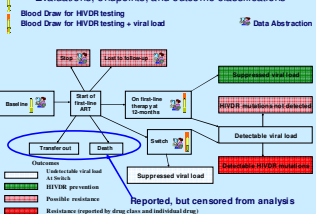
### ART Site Surveys to monitor HIVDR prevention

- Cohorts of approximately 100-150 patients starting ART followed for ≥ 12 months at representative sentinel ART sites.
- Baseline assessment of HIVDR/potential HIVDR
  - Genotyping ARV history
- 12-month assessment of HIVDR
  - Status (lost to follow-up, stop, switch, still on first-line ART)
  - Still on first-line ART + genotyping at 12 months if still on first-line ART, or at regimen switch if earlier
- HIVDR baseline measures:
  - Resistance to ≥ 1 first-line regimen drugs
  - "Possible resistance" - Report prevalence of ≥ 1 ARV drugs associated with cross-resistance to ≥ 1 first line ART
- Pilot in 1-3 sites, then move to rolling 3-year cycle of 5-15 sites

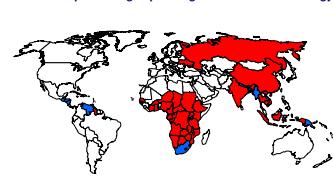
*Resistance at both baseline and endpoint defined as live, intermediate or high resistance to specific drug classes and drugs as defined by the Stanford HIVDR. (Note: WHO mandated for surveillance of transmitted resistance is not used to determine baseline resistance)*

Pediatric Surveys include additional information: Mother's ARV history during pregnancy and breastfeeding, weight at each clinic visit

### Evaluations, endpoints, and outcome classifications



### Countries implementing or planning a national HIVDR strategy



### Outcome measures

- Undetectable viral load at switch before 12 months
- HIVDR prevention (defined as viral load < 1000 copies)
- "Possible resistance" - Lost to follow-up, ART stop, Viral load > 1000 copies with no resistance mark detected
- Resistance to specific first or second-line drugs

### Associations: HIVDR prevention/HIVDR patterns + Factors:

- Previous ARV exposure (PMCT, HIV mono or dual therapy, partner's ARVs, informal sector ARVs) before first-line ART
  - Baseline sequence (resistance mutations, subtype)
  - Timeliness of ARV drug pick-ups/baseline -> endpoint
  - Adherence (30-day Visual Analogue Scale)
  - Timeliness of clinic attendance baseline -> endpoint
  - Regimen(s): initial, substitutions
  - WHO stage at baseline, endpoint
  - Initial and subsequent CD4 counts
  - HIV-1 subtype
- Multiple analyses will be required for sufficient power to assess associations.*

### Surveys to evaluate HIVDR transmission

**The HIVDR threshold survey (HIVDR-TS) assesses transmitted HIVDR, focusing on geographic areas in the country where resistance is most likely to emerge first**

- Focus on informative geographic areas where ART has been widely available for ≥ 3 years
- Small number of specimens from each area: separate prevalence categorization in each area
- Categorize prevalence of transmitted resistance to each drug and each drug class
- Incorporate surveys into routine public health activities
  - Use of remnant diagnostic specimens and information already being collected
- The HIV Drug Resistance Threshold Survey Method supports classification of the prevalence of transmitted HIV drug resistance in a specific geographic area as ≥ 2 or < two thresholds, 5% and 15%

*Similar methods using small numbers of specimens are used here because it is difficult to categorize rates other than conditions in small areas within countries*

### Target group: Individuals infected with HIV within the past 3 years who remain ART-drug naive

- It is not possible to identify individuals infected in the past 3 years or to validate reports of ART-drug naivety, so target site and individual criteria are used to minimize the risk of
  - including individuals who report themselves as drug-naive but who have previously taken ART drugs
- Participant criteria:
  - Documented positive HIV test result, aged < 25 years and no previous pregnancy
  - If numbers are sufficient, < 22 years of age
  - Or laboratory evidence of seroconversion
  - No previous positive HIV test
  - No known exposure to antiretroviral drugs
  - No known AIDS-defining illness
  - Not eligible to start ART
  - CD4 count > 500 (where available)
  - First risk-defining event within the past 3 years, if known

### Results

Twelve countries reported results from surveys implemented in previous years; five of those countries implemented new surveys in 2008-2009 and are currently analyzing data. Ten additional countries implemented surveys in 2008; eight additional countries are planning surveys for 2009.

Country	Year	% Undetectable	% Subtype	ART Regimen	HIVDR
Bhutan	2008	100%	C	1 <sup>st</sup> line	0 (0%)
India	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Kenya	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Malawi	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Senegal	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Tanzania	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Thailand	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Uganda	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Vietnam	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Zambia	2008	100%	C	1 <sup>st</sup> line	0 (0%)
Zimbabwe	2008	100%	C	1 <sup>st</sup> line	0 (0%)

### HIVDR Prevention Review and Support

- HIVDR working groups collect information on, and support activities that will minimize HIVDR.
- Standard guidelines and training for prescribing ART
- Support for and monitoring of adherence
- Removal of barriers to continuous access to care
- Resources and personnel for follow-up of ART patients
- Ongoing quality assurance for drugs (not only initial QA)
- Adequate and continuous drug supplies; monitoring at site and regional levels of drug supply shortages
- Standard ART patient records or minimum standard data recording to facilitate ART patient and cohort monitoring
- Prevention programs to reduce HIV transmission from persons in treatment
- Collection of strategic information to support HIVDR prevention

### Global and Regional Activities

The WHO Strategy for HIV Drug Resistance Prevention and Assessment has been developed and implemented by the individuals and institutions that make up the HIVResNet Laboratory Network (see poster 139) and the HIVResNet Surveillance and Monitoring Network.

The Surveillance and Monitoring Network includes all countries within national HIVDR Working Groups where the WHO strategy is being implemented, and individuals and institutions supporting implementation in those countries or at the global or regional level, including six WHO regional HIV focal points.

The network, with three WHO subregional focal points in Africa, one in the Western Pacific, one in Southeast Asia, one in the Caribbean, and one in Latin America, has conducted numerous training workshops for HIVDR working group country members since 2005. In 2009, the network has so far conducted four training workshops in Africa with 38 countries in attendance and one workshop in Asia for 11 countries.

The network includes a Working Group on monitors for use in surveys of transmitted drug-resistant HIV, which has recently published a 2009 update, and a mathematical modeling working group, currently addressing the HIV drug resistance implications of:
 

- Pre-exposure prophylaxis (PrEP) scenarios,
- Increasing the "when to start ART" CD4 count level to 350 to reduce limited countries,
- Use of various strategies to determine when to switch from first- to second-line ART, and
- Universal testing with starting with ART diagnosis

### Future plans

In 2009, the HIVResNet Surveillance and Monitoring Network will develop methodology for additional surveys and studies to be implemented in countries already implementing the basic strategy. Research under discussion includes adherence evaluations, assessments to provide additional information to support sites in meeting EWI targets, cross-sectional studies of mutation patterns at ART failure, and TB/HIV resistance evaluations. Further workshops are planned in Latin America, Asia, and Africa.

### Summary and Conclusions

Forty-one countries have formed national HIVDR working groups, and have developed HIVDR Prevention and Assessment strategies, based on WHO's recommendations but with country-specific additions. Results are being used in several countries to target public health support to ART sites to improve record-keeping, increase timeliness of ART pick-ups, address barriers to care, and support continuity of ARV drug supplies. To date, results have not indicated that first-line regimens should be changed because of transmitted drug resistance.

Regional workshops in Africa, Asia, Eastern Europe, the Caribbean, and Latin America have provided opportunities for countries to exchange information on field implementation, and to share ideas with WHO on improvements in methodology, additional EWIS, and other research proposals.

Data from countries implementing EWI and sentinel ART site surveys to monitor HIVDR prevention will be available this year. These assessments will add substantially to global data on factors associated with the prevention or emergence of HIVDR.

Countries have found the emphasis on HIVDR prevention, rather than genotyping for clinical management, to be useful. New strategies have been proposed to address sample size limitations in smaller countries. Implementation of the WHO strategy is feasible in resource-limited countries and is producing useful data to support public health action to limit HIVDR.