World Health Organization

TECHNICAL UPDATE

HIV DRUG RESISTANCE

HIV DRUG RESISTANCE SURVEILLANCE – 2015 UPDATE

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INTRODUCTION

HIV Drug Resistance emerges when HIV replicates in the presence of antiretroviral drugs. If HIV drug resistance becomes widespread, drugs currently used to treat HIV infection may become ineffective. To date, though levels of HIV drug resistance in countries scaling up antiretroviral therapy (ART) remain manageable, they are slowly increasing. For example, in East Africa, resistance rates above 10% to non-nucleoside drugs (such as nevirapine and efavirenz) have been recently reported.

To maximize the long-term effectiveness of first-line ART regimens and ensure that people are taking the most effective regimen, it is essential to minimize the further spread of HIV drug resistance. The World Health Organization (WHO) recommends that HIV treatment scale-up should always be accompanied by measures to monitor and improve quality at the site and programme levels, and surveillance of the emergence of drug resistance. This includes the following key priority activities:

1. monitoring of early warning indicators of HIV drug resistance;
2. surveillance of pre-treatment HIV drug resistance in populations initiating ART (pre-treatment HIV drug resistance, or PDR);
3. surveillance of acquired HIV drug resistance in populations of adults and children receiving ART (acquired HIV drug resistance, or ADR);

This technical briefing provides an overview of the essential elements programme managers should include in programme planning to prevent and monitor the emergence of HIV drug resistance.[1]

1 Due to its greater operational complexity, WHO no longer recommends the implementation of surveys of transmitted HIV drug resistance among recently infected populations.

MAIN COMPONENTS

1. Early warning indicators (EWI) of HIV drug resistance

The first and most important step is to assess whether ART programmes deliver their services with the quality required to minimize the emergence of HIV drug resistance. This assessment is achieved through the use of a set of indicators known as *"early warning indicators of HIV drug resistance"*. These indicators should be integrated into the routine monitoring and evaluation systems of ART programmes and the results should be used to improve ART clinic and programme performance.

Standardized definitions and performance targets have been developed for each indicator along with a colour-based scorecard system in which "red" signals situations which require corrective actions and "green" signifies satisfactory performance.

It is recommended to monitor EWI annually at all treatment sites. If this is not feasible, EWI may be monitored in a nationally representative sample of treatment sites, with the goal of progressively adding more sites until all of them are reached. This approach will generate a reliable overview of the performance of a national programme.

EWI should be integrated as much as possible into routine monitoring and evaluation systems to minimize costs and strengthen existing data collection and reporting processes. If EWI data are not routinely available, the following costs should be taken into account when planning for their abstraction:

1. sensitization of staff at treatment sites to the relevance of measuring performance against a series of standardized indicators, and on how these can be used to improve service delivery
2. organization of data abstraction and entry (training and salaries for data abstraction and data entry to ensure that high-quality data are obtained)
3. supervisory costs related to data quality assurance (e.g., travel to sites, per diem costs, etc.);
4. data analysis (e.g., data manager, statistician, etc);
5. report writing and dissemination

Responsibility for data abstraction can be assigned to existing staff or new staff may be recruited for a limited time for this specific task. Abstraction costs depend on the number and location of sites, the size of the patient population, whether records are paper- or electronic-based and ultimately on whether abstraction is integrated with other monitoring activities.

Past experience with the monitoring of EWI suggests that data abstraction in sites working exclusively with paper records may take between two to three days per site at an average cost of US$ 500 per clinic.

Additional information to support country planning of early warning indicator monitoring, including a more comprehensive description of indicators and associated targets, can be found at http://www.who.int/hiv/topics/drugresistance/en/index.html[1].

2. Surveillance of HIV drug resistance

WHO recommends that countries use the methods listed in Tables 1 and 2 for the surveillance of HIV drug resistance.

Table 1. Recommended high-priority activities for the surveillance of HIV drug resistance

Type of survey	Population of interest	Outcome measure	Programmatic relevance	Recommended periodicity
Pre-treatment drug resistance (PDR)[2]	Individuals initiating ART	Nationally representative estimate of HIV drug resistance among individuals about to start ART	Results inform the choice of drugs to be included in first-line treatment, as well as pre- and post- exposure prophylaxis. Presence of resistance prior to ART initiation can compromise both the therapeutic as well as the prevention benefits of first-line ART.	Priority element. To be repeated every 3 years
Acquired drug resistance (ADR)	Individuals receiving ART (a) for 12 (±3) months and (b) for at least 48 months	Nationally representative estimates of viral load suppression and levels/ patterns of HIV drug resistance in individuals who have been on ART for 12 (±3) months and/ or ≥ 48 months	Viral load suppression is a strong indicator of regimen and programme performance. Acquired drug resistance may compromise the effectiveness of second- and third-line ART as well as of Pre- and Post-Exposure Prophylaxis. Adult and paediatric acquired drug resistance surveys should be conducted separately.	Priority element. To be repeated every 3 years

1 EWI guidance is under revision and will be made available on the WHO HIVDR website. http://www.who.int/hiv/topics/drugresistance/en/.

2 Due to its greater operational complexity, WHO no longer recommends the implementation of surveys of transmitted HIV drug resistance among recently-infected populations.

Table 2. Activities which should be considered in specific circumstances

Type of survey	Population of interest	Outcome measure	Programmatic relevance	Recommended periodicity
HIV drug resistance among children less than 18 months old	HIV-positive children < 18 months old newly diagnosed with HIV and treatment-naive	Nationally representative estimate of HIV drug resistance among children newly diagnosed with HIV using early infant diagnosis	Results inform the choice of first- and second-line paediatric ART regimens.	Implementation recommended prior to the update of paediatric ART guidelines at the national level

Some countries provide, as a matter of national policy, routine viral load and HIV drug resistance testing to individuals on ART. WHO is currently in the process of developing guidance for such countries on how to use such routinely collected data to inform public health decision-making.

Due to its greater operational complexity, WHO no longer recommends the implementation of surveys of transmitted HIV drug resistance among recently infected populations.

2.1. Surveillance of pre-treatment drug resistance in populations initiating antiretroviral therapy

In 2014, WHO and partners developed and published new methods to assess pre-treatment HIV drug resistance. The PDR survey is designed to generate a nationally representative prevalence estimate of HIV drug resistance among populations initiating ART. Its main objective is to inform the selection of optimal regimens for first-line treatment and for post-exposure prophylaxis (and, when used, pre-exposure prophylaxis). Conducting this survey requires the following:

- identification of a representative sample of 15–40 clinics from a list of all clinics initiating ART in the country.
- HIV drug resistance genotypes from patients initiating ART on or after a pre-defined survey start date.

The number of patients to be included will vary according to a number of factors, such as the number of sites included in the survey, but typically falls within the range of 300 to 500. It is recommended that the duration of patient enrolment be limited to six months to ensure that the results are available in a timely fashion.

Operationally, individuals initiating ART at the selected clinics will be enrolled in the survey regardless of their prior exposure to antiretroviral drugs. However, information on prior antiretroviral drug exposure must be obtained upon enrolment and will be used at the data analysis stage to distinguish prevalence of HIV drug resistance among initiators with and without prior exposure to ARVs. WHO recommends the implementation of PDR surveillance every three years.

To estimate the cost of implementing a PDR survey, the following six main budget categories should be considered:

- protocol development and training;
- survey coordination;
- site support visits;
- laboratory (e.g., cost of genotyping and shipment of specimens);
- technical support (e.g., protocol adaptation and analysis);
- report production, printing and distribution.

Assuming a sample size of 460 specimens from 20 sites, and assuming genotyping costs of US$ 150 per specimen, the estimated budget is approximately US$ 240,000 (see **Table 3** in the Annex). All figures should be adapted to reflect the local context and costs. Several laboratories in the HIVResNet network offer genotyping at no or considerably reduced cost. Countries which can use these laboratories can significantly reduce survey costs.

A generic concept note for the surveillance of pre-treatment drug resistance has been developed and is available for country adaptation (http://www.who.int/hiv/pub/drugresistance/pretreatment_drugresistance/en/). In addition to a technical description of the survey method, the concept note addresses various issues related to survey implementation.

2.2. Surveillance of acquired drug resistance in populations receiving antiretrovial therapy

The ADR survey methodology is designed to yield nationally representative point prevalence estimates of (1) programme-level viral load suppression and (2) the prevalence of HIV drug resistance in populations receiving ART for 12 (±3) months and for at least 48 months.

The level of viral load suppression in a population, measured in a representative sample of treatment sites, is a strong indicator of regimen and programme performance. The description of resistance patterns in patients failing treatment informs the selection of second-line and potentially third-line regimens.

Implementation of an ADR survey requires the following:

- identification of a representative sample of 17–40 clinics from a list of all clinics dispensing ART in the country.
- enrolment of consecutive eligible patients receiving ART for a defined time period (e.g. 12 months and/or for at least 48 months) on or after a pre-determined survey start date.

Specimens are obtained from the sampled patients and viral load is assessed. Specimens from individuals with viral loads > 1000 copies/ml are subsequently genotyped.

The number of patients to be included in the survey will vary according to a number of factors, but should typically fall in the range between of 400 to 600. It is recommended that the duration of patient enrolment be limited to six months to ensure that the results are available in a timely fashion. WHO recommends implementing acquired drug resistance surveillance every three years.

Separate surveys should be conducted among adult and paediatric populations, as different ART regimens are used in each group.

To estimate the cost of an acquired HIV drug resistance survey, the same budget categories described for the pre-treatment drug resistance survey should be considered. For the early time point (12 ±3 months), assuming a sample size of 460 specimens collected from 20 sites, and viral load and genotyping costs, respectively, of US$ 60 and US$ 150 per specimen, the generic estimated budget is approximately US$ 205 000 (see **Table 4** in the Annex).

For the late time point (≥ 48 months), assuming a sample size of 560 specimens from 20 sites, and similar genotyping and viral load costs, the generic estimated budget is around US$ 230 000 (see **Table 5** in the Annex).

Due to the overlap of certain survey implementation costs (e.g., training, protocol development, on-site supervision), countries are encouraged to include both time points when designing and implementing ADR surveys. This combined approach maximizes the amount of data collected while optimizing the use of resources and capacity. The combined implementation of both time points, assuming similar sample sizes obtained from 35 sites, is estimated to cost approximately US$ 335 000 (see **Table 6** in the Annex). All figures should be adapted to reflect the local context and costs. Several labs in the HIVResNet network offer genotyping at no or considerably reduced cost. Countries which can use these labs can significantly reduce survey costs.

A generic concept note for the surveillance of acquired HIV drug resistance has been developed and is available for country adaptation (http://www.who.int/hiv/pub/drugresistance/acquired_drugresistance/en/). Similarly to the pre-treatment drug resistance concept note, it provides a technical description of the survey method and addresses various issues related to survey implementation.

3. HIV drug resistance surveillance activities which should be considered in specific circumstances

3.1. Surveillance of HIV drug resistance among treatment-naive children less than 18 months of age

The purpose of this survey is to assess the prevalence of HIV drug resistance among treatment-naive children younger than 18 months of age and newly diagnosed with HIV using early infant diagnosis (EID). It is particularly relevant in settings where many infants are exposed to or acquire HIV infection.

The survey method requires the genotyping of a sample of remnant dried blood spots (DBS) collected for paediatric polymerase chain reaction (PCR)-based HIV diagnosis stored at EID laboratories. When possible, all laboratories where EID is performed in the country should participate in the survey and, thus, contribute to the overall sampling. The average sample size is estimated to be approximately 500.

Since the survey will use remnant specimens, most implementation costs are related to data entry, specimen shipping and handling, genotyping, technical support for analysis and report production and distribution. Assuming an average genotype testing cost of US$ 150, the generic estimated survey cost is approximately US$ 135 000 (see **Table 7** in the Annex).

IMPLEMENTATION CONSIDERATIONS

High-quality treatment programmes are critical to minimize the emergence of HIV drug resistance. To assess programme performance, WHO recommends that countries monitor early warning indicators annually at all treatment sites, and use results to inform quality improvement efforts. HIV drug resistance surveillance data are also critical to support national decision-making. It is therefore suggested that pre-treatment and acquired drug resistance surveys be repeated every three years. When planning the survey implementation cycle, prioritization may be given to surveys of pre-treatment drug resistance in the year immediately preceding the revision of national ART guidelines. In countries where domestic resources are limited, programme managers should consider requesting donor support for HIV drug resistance prevention and surveillance.

ANNEX – GENERIC BUDGETS

The annexes below provide generic estimated budgets for implementing the different surveys of HIV drug resistance described in this document. All figures should be adapted to reflect the local context and costs.

Table 3. Estimated budget for pre-treatment resistance surveillance among ART initiators

Number of sites 20
Sample size 460

Protocol Development & Training					
	Number of staff per site	Transportation costs	Per diem cost	Number of nights	Total
Training of site staff (1 day training)	2	$200.00	$150.00	1	$14,000.00
Production of protocol and training materials					$15,000.00
				Sub-total	$29,000.00

Survey coordination					
	Number of staff	cost per staff/ month	Number of months	Number of sites	Total
Site coordination	1	$300.00	8	20	$48,000.00
Nurse incentive	2	$50.00	8	20	$16,000.00
National coordination	1	$1,000.00	8	1	$8,000.00
Data manager	1	$800.00	6	1	$4,800.00
				Sub-total	$76,800.00

Site support visits			
			Total
Study coordinator + driver	*Note: 2 days per visit, USD 50 per diem, 2 visits*		$8,000.00
Fuel (for six months)	*Note: for six months*		$2,000.00
Air tickets to remote sites	*Note: 5 flights, USD 200 each*		$1,000.00
Local transportation			$1,000.00
		Sub-total	$12,000.00

Laboratory			
		per unit	Total
Blood collection		$3.00	$1,380.00
DBS preparation & storage		$5.00	$2,300.00
Genotyping		$150.00	$69,000.00
Laboratory labor cost for genotyping			$2,500.00
Shipment of specimens	*Note: USD 100 per site for national shipping, USD 250 for intl*		$2,250.00
		Sub-total	$77,430.00

Technical support		
		Total
Consultant (USD 500 daily fee, USD 200 per diem, 14 days) and flight		$12,800.00
Statistical Suppport for analysis and interpretation		$10,000.00
	Sub-total	$22,800.00

Report production, printing and distribution		
		Total
Report production & distribution		$10,000.00
Workshop to dicuss policy implication and actions required (15 outside participants, 15 local)		$10,500.00
	Sub-total	$20,500.00
	TOTAL	$238,530.00

Table 4. Generic budget for acquired drug resistance surveillance (12-month time point)

Number of sites	20
Sample size (12 months)	460
Estimated % with VL>1000 (12 months)	15%

12(±3) months

Protocol Development & Training					
	Number of staff per site	Transportation costs	Per diem cost	Number of nights	Total
Training of site staff (1 day training)	2	$200.00	$150.00	1	$14,000.00
Production of protocol and training materials					$15,000.00
Survey coordination					
	Number of staff	cost per staff/ month	Number of months	Number of sites	Total
Site coordination	1	$300.00	8	20	$48,000.00
Nurse incentive	2	$50.00	8	20	$16,000.00
National coordination	1	$1,000.00	8	1	$8,000.00
Data manager	1	$800.00	4	1	$3,200.00
Site support visits					
					Total
Study coordinator + driver	*Note: 2 days per visit, USD 50 per diem, 2 visits*				$8,000.00
Fuel (for six months)	*Note: for six months*				$2,000.00
Air tickets to remote sites	*Note: 5 flights, USD 200 each*				$1,000.00
Local transportation					$1,000.00
Laboratory					
				per unit	Total
Blood collection				$3.00	$1,380.00
DBS preparation & storage				$5.00	$2,300.00
Viral load				$60.00	$27,600.00
Genotyping				$150.00	$10,350.00
Laboratory labor cost for genotyping & VL					$2,500.00
Shipment of specimens	*Note: USD 100 per site for national shipping, USD 250 for intl*				$2,250.00
Technical support					
					Total
Consultant (USD 500 daily fee, USD 200 per diem, 14 days) and flight					$12,800.00
Statistical Suppport for analysis and interpretation					$10,000.00
Report production, printing and distribution					
					Total
Report production & distribution					$10,000.00
Workshop to dicuss policy implication and actions required (15 outside participants, 15 local)					$10,500.00
				TOTAL	$205,880.00

Table 5. Generic budget for acquired drug resistance surveillance (48+ month time point)

Number of sites 20
Sample size (48+ months) 560
Estimated % with VL>1000 (48+ months) 30%

					48+ months
Protocol Development & Training					
	Number of staff per site	Transportation costs	Per diem cost	Number of nights	Total
Training of site staff (1 day training)	2	$200.00	$150.00	1	$14,000.00
Production of protocol and training materials					$15,000.00
Survey coordination					
	Number of staff	cost per staff/ month	Number of months	Number of sites	Total
Site coordination	1	$300.00	8	20	$48,000.00
Nurse incentive	2	$50.00	8	20	$16,000.00
National coordination	1	$1,000.00	8	1	$8,000.00
Data manager	1	$800.00	4	1	$3,200.00
Site support visits					
					Total
Study coordinator + driver	*Note: 2 days per visit, USD 50 per diem, 2 visits*				$8,000.00
Fuel (for six months)	*Note: for six months*				$2,000.00
Air tickets to remote sites	*Note: 5 flights, USD 200 each*				$1,000.00
Local transportation					$1,000.00
Laboratory					
				per unit	Total
Blood collection				$3.00	$1,680.00
DBS preparation & storage				$5.00	$2,800.00
Viral load				$60.00	$33,600.00
Genotyping				$150.00	$25,200.00
Laboratory labor cost for genotyping & VL					$2,500.00
Shipment of specimens	*Note: USD 100 per site for national shipping, USD 250 for intl*				$2,250.00
Technical support					
					Total
Consultant (USD 500 daily fee, USD 200 per diem, 14 days) and flight					$12,800.00
Statistical Suppport for analysis and interpretation					$10,000.00
Report production, printing and distribution					
					Total
Report production & distribution					$10,000.00
Workshop to dicuss policy implication and actions required (15 outside participants, 15 local)					$10,500.00
				TOTAL	$227,530.00

Table 6. Generic budget for acquired drug resistance surveillance (both time points combined)

Number of sites	35
Sample size (12 months)	460
Sample size (48+ months)	560
Estimated % with VL>1000 (12 months)	15%
Estimated % with VL>1000 (48+ months)	30%

					Shared survey costs	12(±3) months	48+ months
Protocol Development & Training							
	Number of staff per site	Transportation costs	Per diem cost	Number of nights	Total		
Training of site staff (1 day training)	2	$200.00	$150.00	1	$24,500.00		
Production of protocol and training materials					$15,000.00		
Survey coordination							
	Number of staff	cost per staff/ month	Number of months	Number of sites	Total		
Site coordination	1	$300.00	8	35	$84,000.00		
Nurse incentive	2	$50.00	8	35	$28,000.00		
National coordination	1	$1,000.00	8	1	$8,000.00		
Data manager	1	$800.00	4	1	$3,200.00		
Site support visits							
					Total		
Study coordinator + driver	*Note: 2 days per visit, USD 50 per diem, 2 visits*				$14,000.00		
Fuel	*Note: for six months*				$2,000.00		
Air tickets to remote sites	*Note: 5 flights, USD 200 each*				$1,000.00		
Local transportation					$1,000.00		
Laboratory							
				per unit	Total		
Blood collection				$3.00		$1,380.00	$1,680.00
DBS preparation & storage				$5.00		$2,300.00	$2,800.00
Viral load				$60.00		$27,600.00	$33,600.00
Genotyping				$150.00		$10,350.00	$25,200.00
Laboratory labor cost for genotyping & VL					$4,000.00		
Shipment of specimens					$250.00	$1,500.00	$2,000.00
Technical support							
					Total		
Consultant (USD 500 daily fee, USD 200 per diem, 14 days) and flight					$12,800.00		
Statistical Suppport for analysis and interpretation					$10,000.00		
Report production, printing and distribution							
					Total		
Report production & distribution					$10,000.00		
Workshop to dicuss policy implication and actions required					$10,500.00		
				Sub-total	$228,250.00	$43,130.00	$65,280.00
						Grand Total	$336,660.00

Table 7. Generic budget for surveillance of HIV drug resistance among children less than 18 months of age

Number of participating labs 10
Sample size 500

Protocol Development & Training		
		Total
Production of protocol and training materials		$10,000.00
Training of site staff (1 day training)		$14,000.00
	Sub-total	$24,000.00
Laboratory		
	per unit	Total
Genotyping	$150.00	$75,000.00
Laboratory labor cost for genotyping	$250.00	$2,500.00
Shipment of specimens	$100.00	$1,250.00
	Sub-total	$78,750.00
Technical support		
		Total
Consultant (USD 500 daily fee, USD 200 per diem, 14 days) and flight		$12,800.00
Statistical support for data analysis and interpretation		$10,000.00
	Sub-total	$12,800.00
Report production, printing and distribution		
		Total
Report production & distribution		$10,000.00
Workshop to dicuss policy implication and actions required		$4,000.00
	Sub-total	$14,000.00
	TOTAL	$129,550.00

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