

PAHO HIV REPORT

Progress of Implementation of the World Health Organization

Drug Resistance Strategy

in Latin America and the Caribbean: 2006–2009

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PAHO HIV Drug Resistance Status Report

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the Caribbean: 2006–2009**



1. INTRODUCTION

The emergence and transmission of HIV drug resistance (HIVDR) in Latin America and the Caribbean (LAC) is a serious concern considering the rapid scale-up of antiretroviral treatment (ART) in recent years.^{1,2} Strategies designed to prevent and assess HIVDR at the national level should be integrated within each country's HIV prevention, treatment, and care programs.

The World Health Organization (WHO) has developed a global strategy for HIVDR prevention and assessment³ (Table 1) that is based on the following public health principles:

- ongoing evaluation and support of ART program factors and practices potentially associated with HIVDR prevention
- use of standard methodology for ongoing population-based surveys to assess HIVDR emergence and transmission`
- evidence-based actions to minimize preventable HIVDR and maintain the efficacy and durability of ART

The purpose of the WHO HIVDR strategy is to minimize the emergence of drug resistance, as well as to prolong first- and second-line ART efficacy and maximize the quality of life of people living with HIV, by supporting optimal ART program functioning through evidence-based quality improvement strategies.

Table 1: Elements of the WHO-recommended HIVDR prevention and assessment strategy

- A. Formation of a national HIVDR working group and development of a 3–5-year work plan and budget
- B. Regular assessment of HIVDR early warning indicators (EWIs) from all ART sites (or a selection of representative ART sites)⁴
- C. HIVDR monitoring surveys to monitor HIVDR prevention and associated factors at sentinel ART sites⁵
- D. Threshold surveys for surveillance of transmitted HIVDR among recently infected individuals and in geographic areas where ART has been widespread for 3 years or more⁶
- E. Development of a national HIVDR database
- F. Designation of a national or regional WHO-accredited HIVDR genotyping laboratory⁷
- G. Review of and support for HIVDR prevention activities
- H. Preparation of an annual HIVDR report and recommendations

2. HIVDR STRATEGY IMPLEMENTATION PROGRESS

As of February 2009, the WHO-recommended HIVDR prevention and assessment strategy was being implemented worldwide in more than 30 countries (see Figure 1), as recently reported by WHO, UNICEF, and UNAIDS.¹

The WHO strategy had been introduced in parts of the LAC region as early as 2006 through a number of subregional workshops and capacity-building activities (Table 2). The objectives of these activities were to raise awareness about the challenge of HIVDR, advocate for the implementation of national HIVDR prevention and assessment strategies, present the WHO-recommended HIVDR package, and evaluate the feasibility of the package and its potential application in the region. Representatives from national HIV/AIDS programs, epidemiologists, and HIV and lab specialists from almost all of the countries in the LAC region participated in these training and consensus-building activities.

Figure 1: Status of WHO HIVDR strategy implementation as of February 2009¹

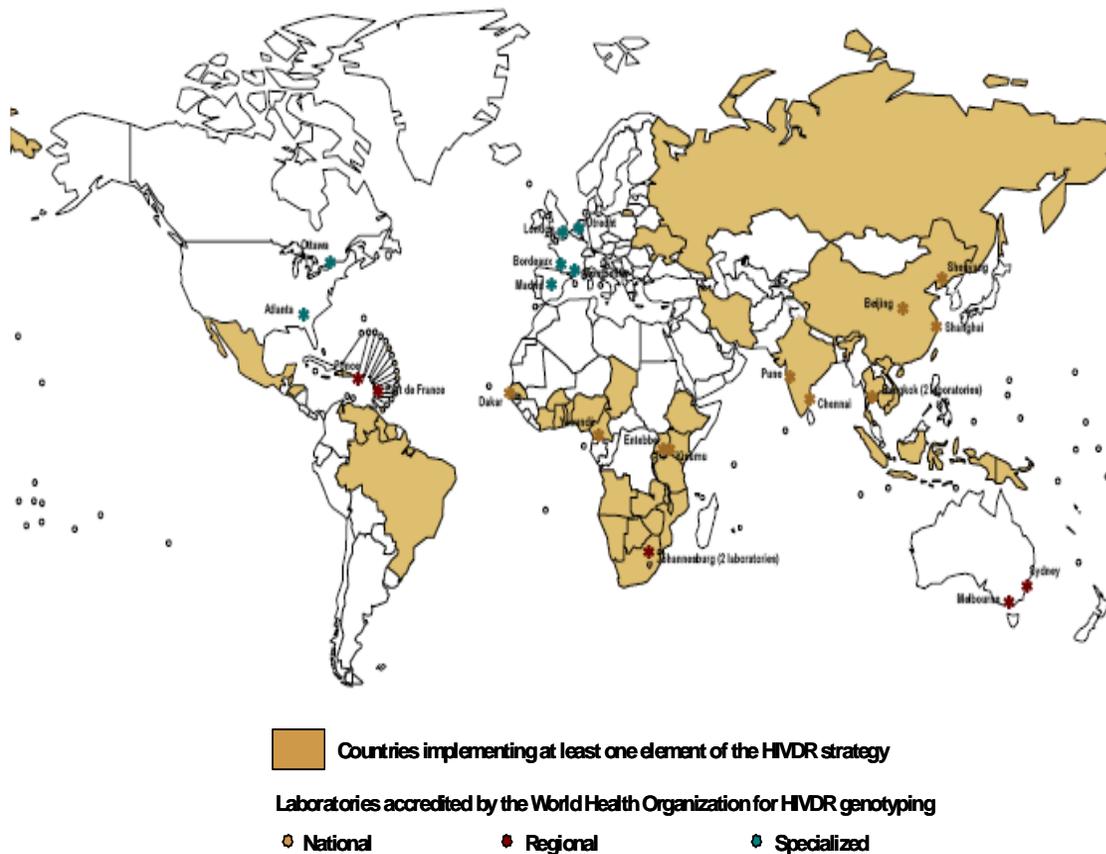


Table 2: Workshops and capacity-building activities in Latin America and the Caribbean focusing on the WHO HIVDR strategy

- **Fort de France, Martinique, May 10–12, 2006:** *First Workshop on the Development of a Caribbean Strategy for the Prevention, Surveillance and Monitoring of HIV Drug Resistance*
- **Port-of-Spain, Trinidad and Tobago, January 23–26, 2007:** *Caribbean HIV Drug Resistance (HIVDR) Monitoring and Surveillance Training Workshop*
- **Rio de Janeiro, Brazil, November 26–28, 2007:** *Latin American Workshop on HIV Drug Resistance Prevention, Surveillance, and Monitoring*
- **Port-of-Spain, Trinidad and Tobago, November 18–21, 2008:** *Regional Meeting towards the Implementation of HIV Drug Resistance Strategies in the Caribbean*
- **Port-of-Spain, Trinidad and Tobago, October 20–22, 2009:** *Prevention of HIV Drug Resistance (HIVDR) in the Caribbean: Adherence Strategies, HIVDR Early Warning Indicators and Use of Patient Monitoring Tools*

The WHO and PAHO websites provide guidance on the development of national HIVDR working groups, planning and implementation of surveillance and monitoring surveys, EWI monitoring, and production of annual HIVDR reports; generic protocols and other tools are also available. Both WHO and PAHO HIVDR web pages, as well as most relevant technical documents on the WHO HIVDR strategy, are now available in English and Spanish.

Between 2006 and 2009, direct technical cooperation to support the development and implementation of HIVDR prevention and assessment national plans was provided to 26 countries in the LAC region: Anguilla, Antigua and Barbuda, Bahamas, Barbados, Belize, Bolivia, Brazil, Colombia, Dominica, Dominican Republic, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, and Venezuela.

3. NATIONAL HIVDR WORKING GROUP

The first step of the WHO-recommended strategy is the formation of a national HIVDR working group. HIV/AIDS programs at the Ministry of Health level, in coordination with national AIDS councils where applicable, should form national HIV drug resistance working groups to develop and coordinate the implementation of a country's HIVDR strategy. These working groups are usually made up of ART program planners, clinicians, epidemiologists, lab specialists, monitoring and evaluation specialists, civil society representatives, and national and international partner organizations.

WHO-recommended national HIVDR working groups have been formed and are currently operating in the following 16 countries in the LAC region: Bahamas, Bolivia, Brazil, Colombia, Dominica, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Nicaragua, Suriname, Trinidad and Tobago, and Venezuela.

Lessons Learned

The key element in successful planning and implementation of a national HIVDR prevention and assessment strategy is the formation of an interdisciplinary national working group under the leadership of the Ministry of Health's HIV/AIDS program. In most cases, HIVDR prevention and assessment activities have been undertaken by preexisting national antiretroviral (ARV) drug resistance or ART technical committees, with the integration of additional members from relevant institutions. Countries that have strong technical working groups, with formal recognition by national authorities and regular meetings, have demonstrated greater capacity for protocol development and timely implementation. Furthermore, building of national expertise on HIVDR prevention and assessment and retention of capacity have been much more effective in countries with solid and active working groups.

In the context of a financial crisis and limited resources, building partnerships at the national and international levels and sharing "start-up" costs with partners have been other key factors facilitating implementation. Financial integration of HIVDR prevention and assessment activities within national budgets should be targeted for long-term sustainability. Inclusion of HIVDR prevention, monitoring, and surveillance in Global Fund proposals is strongly recommended to guarantee continuity of implementation.

4. HIVDR EARLY WARNING INDICATORS

HIVDR early warning indicators are ART site-based quality assurance tools designed to assess the extent to which sites are functioning optimally to prevent HIVDR. EWIs evaluate specific programmatic factors known to be associated with the emergence or prevention of resistance to ARV drugs at the ART site level.⁴ These factors include ARV drug prescribing practices, loss to follow-up of patients during the first year of ART, on-time ARV drug pick-up and appointment keeping, retention of patients on first-line ART, adherence to treatment, and ARV drug supply continuity. EWI results can be used to optimize both ART site and national ART program functioning through evidence-based recommendations.

Between 2007 and 2009, PAHO provided direct technical assistance and training in 26 countries in the LAC region for the development and implementation of national EWI monitoring plans.

As of December 2009, 17 countries were collecting EWIs from a representative selection of ART sites or ad hoc pilot HIV clinics: Bahamas, Barbados, Belize, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Vincent and the Grenadines, Suriname, and Venezuela. Fifteen countries have completed data collection and reported preliminary results to PAHO.

Lesson Learned

The implementation of EWI monitoring in 17 countries in the region, mainly pilot experiences at national reference ART clinics, has highlighted a number of issues related to the quality of medical and pharmacy record systems. Problems such as incomplete information, lack of compliance with international consensus on patient monitoring guidelines,⁸ and fragmented and non standardized information systems, as well as deficiencies in the quality of data recording for manual systems and data entry for electronic systems, were encountered in the majority of countries during the planning and pilot phase. Collection of data on EWIs created opportunities for medical and pharmacy data record systems to be revised, updated, improved, and implemented in a standardized manner at the country level. Although such operations may have delayed the generation of results, they have been of substantial importance with respect to improving national capacity for ART program monitoring and evaluation. In fact, elaboration of data quality assurance strategies must be a complementary part of any monitoring and evaluation plan, and it has been crucial to generating reliable results

that will support evidence-based recommendations.

Preliminary EWI results, mainly from Caribbean countries, have highlighted important gaps in ART and HIV care delivery potentially related to the development of drug resistance. Low levels of compliance with national guidelines among ART prescribing practices, unacceptably high loss to follow-up of patients during the first year of treatment, below-expected rates of retention of patients on first-line ART at 12 months of treatment, and high frequencies of ARV drug stock-outs are warning signs of the potential emergence and transmission of resistance. Appropriate and evidence-based actions at the ART site level, aiming at improving service delivery and quality of care, will have a direct impact on prevention of resistance and will be documented by positive trends in EWI results over time.

Appropriate interpretation of EWI results and subsequent use of this information for public health interventions remains an important gap across the region. Ongoing technical assistance is required focusing on data validation, analysis, and interpretation to generate relevant evidence-based recommendations for quality improvement of HIV care and HIVDR prevention.

5. HIVDR THRESHOLD SURVEYS

HIVDR threshold surveys are population-based studies designed to assess transmitted drug resistance among recently infected individuals and estimate the current prevalence of resistant infections among such individuals.⁶ These surveys should be limited initially to geographic areas where transmitted HIVDR is likely to be seen first (i.e., cities or health planning areas where ART has been widely available for more than 3 years). WHO recommends genotyping remnant specimens collected from individuals less than 25 years of age (and, among females, without previous pregnancies) consecutively diagnosed with HIV in antenatal clinic–based serosurveys or at diagnostic sites within each area. Separate surveys may be performed in different subgroups of interest in each area.

Myatt and Bennett developed a binomial sequential sampling method to categorize transmitted resistance to relevant drugs and drug classes as low (<5%), moderate (5%–15%), or high (>15%) on the basis of a small number of specimens (47) collected from eligible individuals consecutively diagnosed with HIV.⁹ Site selection criteria and participant eligibility criteria are designed to minimize the likelihood that participants have been infected more than 3 years previously and that are not drug naive.

The HIV epidemic in the LAC region is primarily concentrated in at-risk populations such as men who have sex with men (MSM), intravenous drug users, and sex workers and their clients. As a result, feasibility assessments for HIVDR threshold surveys (as nested studies within larger HIV serosurveys) have been conducted in the MSM population (in Venezuela and Ecuador), among pregnant women (in Brazil and the Dominican Republic), and among individuals visiting HIV diagnostic sites (in El Salvador).

To date, only Brazil has completed a national HIVDR surveillance study, the RENIC Study, which included five threshold surveys conducted in large state capitals (São Paulo, Rio de Janeiro, Porto Alegre, Salvador, and Brasilia/Belém) representing the country's five macro-regions.¹⁰ Surveys were performed among recently diagnosed HIV patients at ART sites. A low level of transmitted resistance (<5%) was estimated in Porto Alegre and Salvador, while evidence of an intermediate level of resistance (5%–15%) was detected in the other three urban areas. Adaptation of the WHO threshold survey protocol for implementation among recently infected pregnant women diagnosed at ANC sites in six large urban areas in the country is ongoing, and the initial stages of implementation are planned for 2010.

Outside of the LAC region, HIVDR threshold surveys have been implemented in eight countries, and results have been reported at international conferences or in peer-reviewed journals. Data obtained from HIVDR transmission surveys have provided useful information on the extent and patterns of drug resistance in newly acquired HIV infections. Thus far, recommendations to continue the use of current ART regimens have been made based on the surveys from 2007 and 2008, each of which reported low (<5%) transmitted resistance to all drugs and drug classes in geographic areas where ART had been widely available. The WHO mutations list for HIVDR transmission surveys was recently updated¹¹ and is also available on the Stanford University website.

Lessons Learned

Transmitted resistance studies have been conducted in many countries in Latin America, and evidence of variable levels of resistance among newly diagnosed and ARV-naive individuals has been widely documented. In contrast, transmitted resistance surveillance has been performed according to different study designs and methodologies; has targeted different populations, generally over long periods of time (more than 12 months); and has used different participant selection criteria and definitions of key concepts such as “recent infection” and “recent diagnosis.” Such substantial methodological differences make it difficult to compare transmitted resistance data among countries in the region and even within countries over time. Standardization of surveillance methodology and formation of multicountry subregional surveillance networks would improve the level of comparability among countries and, over time, enhance the quality and reliability of results and their potential use for public health actions.

6. HIVDR MONITORING SURVEYS

HIVDR monitoring surveys are designed to be implemented at representative sentinel ART sites among cohorts of consecutively enrolled patients initiating treatment. Where feasible, WHO recommends a 3-year rolling cycle of surveys at approximately 10–30 selected sentinel sites. Cohorts of 100–150 patients initiating ART would have baseline specimens genotyped to evaluate baseline HIVDR and another specimen drawn at 12 months (or at switch of first-line to second-line in case of treatment failure) for a viral load and an additional genotype if the viral load is detectable (>1,000 copies/ml). Patient and site factors potentially associated with the outcomes of HIVDR prevention (undetectable viral load at 12 months of first-line ART) or detection are evaluated.

Considering the low average annual uptake of patients on ART at each ART site in the majority of Latin American and Caribbean countries, implementation of WHO HIVDR monitoring surveys is challenging in this region. National HIVDR monitoring protocols adapted from the WHO generic protocol have been developed in Haiti and Guyana.

Lessons Learned

WHO is currently adapting its generic HIVDR monitoring protocol for implementation in the context of concentrated epidemics and decentralized access to antiretroviral treatment and care. Extending enrollment to survey site entities such as reference hospital and satellite clinics, or combining ART sites within the same health planning unit, may increase the likelihood of implementation of HIVDR monitoring surveys in the LAC region.

7. WHO GLOBAL HIV DRUG RESISTANCE LABORATORY NETWORK

The WHO HIVDR strategy includes the Global HIV Drug Resistance Laboratory Network, established to provide quality-assured HIV drug resistance survey results to countries implementing the strategy. As of February 2009, 21 laboratories had been accredited. Basic information on currently accredited labs in the Americas is reported in Table 3. The procedures, accreditation criteria, and checklists used in assessments of genotyping laboratories have been finalized and were published in *Antiviral Therapy* in May 2008⁵; they are also available on the WHO website.

Table 3: WHO-accredited HIVDR laboratories as of February 2009.

Type	City	Country	WHO region	Assay*	Specimen type
Regional	Fort de France	Martinique	AMRO/PAHO	TG	Plasma
Regional affiliated	Ponce	Puerto Rico	AMRO/PAHO	TG, IH	Plasma
Specialized	Ottawa	Canada	AMRO/PAHO	IH	Plasma
Specialized	Atlanta	United States	AMRO/PAHO	VS	Plasma

*TG: *TruGene*; IH: *in-house*; VS: *ViroSeq*.

Other laboratory-related activities within the WHO HIVDR network are as follows:

- **Laboratory training and capacity building.** Laboratory technicians are provided with training through the WHO team and their consultants during site visits or as part of regional workshops on HIV drug resistance. A twinning program, coordinated by WHO, links WHO-accredited laboratories with strong capacity in HIVDR genotyping to labs with less capacity and experience. This method has been a very useful means of increasing technology transfer and knowledge sharing.
- **External quality assurance.** External quality assurance of laboratory performance for genotyping from plasma is carried out using proficiency panel samples provided by the Viral Quality Assurance (VQA) Program of the National Institutes of Health (NIH). NIH has modified the VQA panel to accommodate WHO specifications.

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- **Dried blood spot (DBS) testing.** The network is currently reviewing evidence on the use of DBS for genotyping in treated populations with low viral loads and planning operational research on DBS-related issues.

Additional labs from the LAC region are expected to apply for WHO accreditation in 2010 to support the implementation of HIVDR threshold surveys in Brazil, and Central America.

Lessons Learned

The regional capacity to perform HIV genotyping for clinical care and surveillance remains concentrated in a few upper-middle-income countries, while access to resistance testing remains generally limited for the majority of lower-middle-income countries in the region. The development of a regional network of genotyping laboratories supporting the implementation of WHO HIVDR surveys will provide all countries in the region the opportunity to conduct national surveillance of transmitted resistance with quality-assured genotyping performed at national, regional, or specialized HIVDR labs within the WHO network.

8. CONCLUSION

Enormous progress has been made in the last two years with regard to raising the awareness of HIV/AIDS policymakers about the importance of integrating HIVDR prevention and assessment activities within national strategic plans; building local capacity for the implementation of HIVDR prevention, surveillance, and monitoring activities; promoting quality of care at the ART site level as a way of minimizing drug resistance; and positioning HIV drug resistance in the public health and research agenda of national HIV/AIDS programs and academic institutions in the LAC region.

Nevertheless, many challenges remain with respect to long-term sustainable and effective implementation of HIVDR prevention and assessment national strategies in the years to come. The following recommendations should guide national and regional efforts to support appropriate HIV drug resistance prevention, surveillance, and monitoring in Latin American and Caribbean countries:

- National HIV drug resistance working groups characterized by interdisciplinary and intersectorial membership should be formally recognized by Ministries of Health and should continue to play a fundamental advisory role for national HIV programs with regard to drug resistance prevention and assessment activities.
- Long-term sustainability of HIVDR prevention, surveillance, and monitoring activities will be possible only through national and international partnerships that provide the required technical and financial “start-up” support, followed by gradual integration of activities within national work plans and budgets.
- Medical and pharmacy information systems, as well as ART program monitoring and evaluation plans, should be revised, updated if necessary, standardized at the national level, and maintained with quality assurance strategies. Such systems will provide reliable information not only for EWI monitoring but for all ART program monitoring and evaluation activities.
- Countries should regularly collect data on EWIs and integrate this information within national monitoring and evaluation plans. Improvements in ART site performance and quality of care can be documented only by assessing trends in EWI results over time.
- EWI results should be used as strategic information to support informed decision making for public health actions. Appropriate data analysis, interpretation of results, and

elaboration of recommendations still requires ongoing technical assistance in many countries.

- Survey methodology for HIVDR monitoring and surveillance of transmitted resistance should be harmonized to enable appropriate comparisons among countries in the region and over time within the same country. The development of regional or subregional networks for multicountry HIVDR surveillance using standardized methodology should be supported.
- Coordination among national HIV/AIDS programs, HIVDR working groups, and national and international partners involved in HIV surveillance, strategic information, and HIVDR prevention and assessment activities should be promoted to guarantee efficiency of resources and harmonized methodology.

Further progress in the implementation of the WHO HIVDR strategy in the LAC region is expected in 2010 with strengthening of existing national working groups and formation of new ones, expansion of EWI monitoring plans to new countries in region and beyond the initial pilot experiences, EWI data quality reviews, presentation of results at national and international forums and in peer-reviewed journals, implementation of population-based HIVDR monitoring and threshold surveys in selected countries, and expansion of the WHO HIVDR Laboratory Network in Central and South America.

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