Progress of implementation of the World Health Organization strategy for HIV drug resistance control in Latin America and the Caribbean

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ABSTRACT

By the end of 2010, Latin America and the Caribbean (LAC) achieved 63% antiretroviral treatment (ART) coverage. Measures to control HIV drug resistance (HIVDR) at the country level are recommended to maximize the efficacy and sustainability of ART programs. Since 2006, the Pan American Health Organization has supported implementation of the World Health Organization (WHO) strategy for HIVDR prevention and assessment through regional capacity-building activities and direct technical cooperation in 30 LAC countries. By 2010, 85 sites in 19 countries reported early warning indicators, providing information about the extent of potential drivers of drug resistance at the ART site. In 2009, 41.9% of sites did not achieve the WHO target of 100% appropriate first-line prescriptions; 6.3% still experienced high rates (> 20%) of loss to follow-up, and 16.2% had low retention of patients (< 70%) on first-line prescriptions in the first year of treatment. Stock-outs of antiretroviral drugs occurred at 22.7% of sites. Haiti, Guyana, and the Mesoamerican region are planning and implementing WHO HIVDR monitoring surveys or threshold surveys. New HIVDR surveillance tools for concentrated epidemics would promote further scale-up. Extending the WHO HIVDR lab network in Latin America is key to strengthening regional lab capacity to support quality assured HIVDR surveillance. The WHO HIVDR control strategy is feasible and can be rolled out in LAC. Integrating HIVDR activities in national HIV care and treatment plans is key to ensuring the sustainability of this strategy.

Key words

HIV; drug resistance; epidemiologic surveillance; world strategies; regional strategies; Latin America; Caribbean region.
each country’s HIV prevention, treatment, and care programs. WHO developed a global HIVDR prevention and assessment strategy (Table 1), with normative documents available on the Web (www.paho.org/HIVDR, www.who.int/hiv/topics/drugresistance/en/) (3).

The purpose of the WHO HIVDR strategy is to minimize the emergence of drug resistance, prolong first- and second-line ART effectiveness, and maximize the quality of life of people living with HIV by supporting optimal ART program functioning through evidence-based quality improvement strategies. As of mid 2011, up to 50 countries worldwide had implemented WHO-recommended HIVDR early warning indicators (EWIs), 13 countries had implemented HIVDR monitoring surveys, and 22 had implemented threshold surveys for surveillance of transmitted resistance (1). The objective of this report is to present the progress of implementation of the WHO HIVDR strategy in LAC with general recommendations for scale-up of sustainable HIVDR prevention and assessment activities in the region.

ROLLOUT OF HIVDR STRATEGY IN LAC

The WHO HIVDR strategy was introduced in LAC in 2006 through a number of regional and subregional capacity-building activities (Table 2) with the objective of raising awareness about the challenge of HIVDR control from a public health perspective, advocating for the implementation of national HIVDR control strategies, presenting the WHO HIVDR prevention and assessment package, and evaluating the feasibility of its implementation in LAC. All countries in the region participated in these training, consensus-building, and experience-sharing activities.

Between 2006 and 2011, direct technical cooperation and in-country training for the development and implementation of national plans for HIVDR prevention and assessment were provided to 30 countries: Anguilla, Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, 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.

TABLE 1. Elements of World Health Organization HIV drug resistance prevention and assessment strategy (3)

| a. | Formation of a national HIVDR working group and development of a 3- to 5-year work plan and budget |
| b. | Regular assessment of HIVDR early warning indicators from all ART sites (or a selection of representative ART sites) |
| c. | HIVDR monitoring surveys to monitor HIVDR prevention and associated factors at sentinel ART sites |
| 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 more |
| e. | Development of a national HIVDR database |
| f. | Designation of a national or regional WHO-accredited HIVDR genotyping laboratory |
| g. | Review of and support for HIVDR prevention activities |
| h. | Preparation of an annual HIVDR report and recommendations |


| b. | Port of Spain, Trinidad and Tobago, 23–26 January 2007: Caribbean HIV Drug Resistance (HIVDR) Monitoring and Surveillance Training Workshop |
| d. | Port of Spain, Trinidad and Tobago, 18–21 November 2008: Regional Meeting Toward the Implementation of HIV Drug Resistance Strategies in the Caribbean |
| e. | Port of Spain, Trinidad and Tobago, 20–22 October 2009: Prevention of HIV Drug Resistance (HIVDR) in the Caribbean: Adherence Strategies, HIVDR Early Warning Indicators, and Use of Patient Monitoring Tools |
| f. | Port of Spain, Trinidad and Tobago, 21–23 June 2010: Simplifying ART reporting including early warning indicators in the Caribbean |
| g. | San Salvador, El Salvador, 5–7 July 2010: HIV drug resistance and patient monitoring system meeting of Central America and Mexico |
| h. | Bogotá, Colombia, 11–12 November 2010: Workshop on HIV resistance to antiretrovirals |

NATIONAL WORKING GROUPS

WHO recommends that the HIV/AIDS national program, based at the ministry of health, support the creation of a national HIVDR working group to develop and coordinate a national HIVDR control strategy. HIVDR working groups usually include ART program officers from different technical areas (treatment and care, surveillance, monitoring and evaluation), epidemiologists, HIV clinicians and researchers, lab specialists, civil society, and national and international partner organizations.

PAHO facilitated and directly supported the formation and ongoing technical meetings of HIVDR working groups in LAC for planning and implementing national HIVDR control strategies. National HIVDR working groups are fully functioning in up to 14 countries, and in some cases ad hoc working groups have been formed to coordinate implementation of EWIs.

Countries that maintained active and technically strong working groups, with formal recognition by national authorities, have demonstrated greater capacity for development and timely implementation of their HIVDR control strategies. In addition, active involvement of national and international partners in HIVDR working groups contributed to timely planning and implementation of activities by sharing start-up costs and facilitating technical collaboration.

EARLY WARNING INDICATORS

EWIs are ART site-based tools for HIVDR prevention and quality assurance to assess the extent to which sites are optimally functioning to prevent resistance (4). EWIs evaluate programmatic factors known to be associated with the emergence of resistance to antiretroviral (ARV) drugs at the ART site level. These factors include ARV drug-prescribing practices, loss to follow-up and retention of patients on first-line ART during the first year of ART, on-time ARV drug pickup and appointment keeping, drug supply continuity, adherence to treatment, and suppression of viral load. EWI monitoring generates strategic information to optimize ART site and national ART program functioning through evidence-based recommendations.

As of December 2010, 21 countries implemented EWI monitoring in a repre-
sentative selection of ART sites or ad hoc pilot HIV clinics (Argentina, Bahamas, Barbados, Belize, Colombia, Dominica, Dominican Republic, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Vincent and the Grenadines, St. Lucia, Suriname, and Venezuela) and 19 countries reported EWI results from a total of 85 ART sites (Table 3).

Preliminary EWI results, presented in Table 3, highlight important gaps in ART and HIV care delivery which could contribute to the development of drug resistance. Low levels of compliance with national guidelines in ART prescribing practices was observed throughout the reporting period (cohorts of patients initiating ART in 2007, 2008, and 2009), with fewer than 50% of sites achieving the WHO target of 100% first-line prescriptions in line with national or international guidelines. The extent of loss to follow-up of patients during the first year of treatment varied greatly among countries and over time, with 63% of sites assessed in 2009 still experiencing high default rates (> 20%) during the first year of treatment. Retention of first-line ART at 12 months of treatment seemed to improve over time in the subsets of ART sites selected for EWI monitoring in the reporting period, but 16.2% of sites in 2009 still reported retention below the WHO target (70%). EWI 6 results for drug supply continuity showed that stock-outs of ARV drugs persist in LAC (EWI 6b), even though the impact of drug shortages on ARV prescribing and dispensing practices may be minimal (EWI 6a); very few sites selected this version of the indicator.

Table 3 presents only the four indicators with the higher reporting rate during the selected period (2007–2009); very few ART sites were able to collect data and report EWI 4 (percentage of on-time drug pickup), EWI 5 (percentage of on-time appointment keeping), EWI 7 (percentage of patients with 100% adherence), and EWI 8 (percentage with viral load suppression at 12 months). Lack of documentation, low coverage of viral load monitoring, and inadequate records of drug pickups and appointment keeping made it difficult to collect these proxy indicators of adherence. In addition, a vast majority of ART sites in the region do not usually perform direct standardized adherence measurements.

Through the experience of EWI monitoring in LAC a number of issues related to the quality of medical and pharmacy record systems were identified. Incomplete patient information, fragmented information systems, and poor quality of data recording and data entry in electronic systems were encountered in most 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 as recommended by international consensus guidelines on patient monitoring (5). Such operations may have initially delayed the generation of results, but they have been of substantial importance to strengthen national capacity for ART program monitoring and evaluation and data quality assurance to generate reliable results.

**THRESHOLD SURVEYS FOR TRANSMITTED HIVDR**

In the past decade, transmitted resistance surveys have been conducted in many countries in Latin America, and evidence of low (< 5%) to moderate (5%–15%) prevalence of resistance among newly diagnosed and ARV-naïve individuals has been documented (6–16). Nevertheless, transmitted resistance surveillance in LAC has been performed with different methodologies—targeting different populations, generally over long periods of time (> 12 months), and using different selection criteria and definitions for 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, highlighting the need to adopt standardized methodologies.

WHO-recommended HIVDR threshold surveys are population-based surveys designed to classify the prevalence of transmitted drug resistance among recently infected individuals at three levels: low (< 5%), moderate (5%–15%), and high (> 15%). The WHO-recommended threshold survey methodology and the truncated sequential sampling method to categorize transmitted resistance are described elsewhere (17, 18).

This methodology was used for the first time in Latin America in Mexico in 2004, when a threshold survey was performed at voluntary counseling and testing sites (results not published), and the dried blood spot methodology for HIV genotyping was tested (19). In Brazil, a national HIVDR surveillance study was performed in 2007–2008, which included five threshold surveys conducted in large state capitals (São Paulo, Rio

### TABLE 3. Summary of four HIV drug resistance early warning indicator results in Latin America and the Caribbean, 2007–2009

<table>
<thead>
<tr>
<th>HIVDR early warning indicatorb</th>
<th>WHO target, %</th>
<th>Sites meeting WHO target, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWI 1a: Percentage of patients initiating ART during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen</td>
<td>≥ 70</td>
<td>29.3 (20/69)</td>
</tr>
<tr>
<td>EWI 2: Percentage of patients initiating ART in a selected time period who are lost to follow-up during the 12 months after starting ART</td>
<td>≤ 20</td>
<td>93.7 (33/35)</td>
</tr>
<tr>
<td>EWI 3a: Percentage of patients initiating ART during a selected time period who are taking an appropriate first-line ART regimen 12 months later</td>
<td>≥ 70</td>
<td>83.8 (30/36)</td>
</tr>
<tr>
<td>EWI 6b: Percentage of months in a designated year in which there were no ARV drug stock-outs</td>
<td>100</td>
<td>77.3 (18/23)</td>
</tr>
<tr>
<td>EWI 6a: 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</td>
<td>0</td>
<td>100.0 (4/4)</td>
</tr>
</tbody>
</table>


b Summary results from 85 ART sites in 19 countries in Latin America and the Caribbean (Bahamas, Barbados, Belize, Colombia, Dominica, Dominican Republic, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Montserrat, Nicaragua, St. Kitts and Nevis, St. Vincent and the Grenadines, St. Lucia, Suriname) that reported EWI as of December 2010.
de Janeiro, Porto Alegre, Salvador, and Brasilia and Belém) using an adapted version of the WHO method in recently diagnosed HIV patients at ART sites (20). Low transmitted resistance (< 5%) was estimated in Porto Alegre and Salvador, while intermediate resistance (5%-15%) was detected in the other three urban areas. While the WHO threshold survey protocol has been widely implemented in the context of generalized epidemics, mostly in the African region, very few countries in Latin America have suitable epidemiological conditions. In 2010, a threshold survey for transmitted resistance was started in Panama in the general population recently infected with HIV according to WHO criteria. In addition, the threshold survey methodology was integrated in a multicountry project for transmitted drug resistance surveillance (Mesoamerican project), which is ongoing in Mexico and selected Central American countries.

HIVDR MONITORING SURVEYS

HIVDR monitoring surveys are designed to be implemented at representative sentinel ART sites using cohorts of consecutively enrolled patients initiating treatment. Cohorts of 100–150 patients have baseline specimens genotyped to evaluate baseline resistance and a second specimen drawn at 12 months (or at switch from first-line treatment in case of treatment failure) for viral load and genotype, if the viral load is detectable (> 1 000 copies/mL). HIVDR monitoring surveys are described elsewhere (21). In most LAC countries, ART services have been decentralized, and the difficulty of reaching the required survey sample size (100–150) in the expected time (maximum 12 months) and in the expected number of sites in each country (3–10 per year during 3 years) makes it challenging to implement WHO HIVDR monitoring surveys in this region. Only two countries with generalized epidemics (Haiti and Guyana) developed national HIVDR monitoring protocols adapted from the one recommended by WHO. HIVDR monitoring surveys are currently being implemented in Georgetown, Guyana, and Port-au-Prince, Haiti.

HIVDR LABORATORY NETWORK

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 most lower-middle-income countries in the region. The WHO HIVDR strategy includes a global HIVDR laboratory network established to provide quality assured genotyping to countries implementing HIVDR monitoring and threshold surveys (22).

As of August 2011, 27 laboratories have been accredited, 5 of them in the region of the Americas (23): the Virology and Immunology Service of the Hospital and University Centre in Fort-de-France, Martinique; the AIDS Research Program–Immunology Reference Laboratory in Ponce, Puerto Rico; the National Laboratory for HIV Genetics of the Public Health Agency of Canada in Ottawa; the International Laboratory Branch of the Global AIDS Program of the Centers for Disease Control and Prevention in Atlanta, United States of America; and the AIDS and Molecular Immunology Laboratory of the Oswaldo Cruz Institute/Fiocruz in Rio de Janeiro, Brazil. To support the implementation of future HIVDR threshold surveys in Brazil and the Mesoamerican region, three additional laboratories (two in Brazil and one in Mexico) applied for accreditation in 2010 and are being evaluated. The procedures and criteria for the assessing laboratories applying for accreditation to the WHO drug resistance network were published in 2008 and are available on the WHO and PAHO websites.

CONCLUSIONS

LAC countries have advanced in the past few 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 implementation of HIVDR prevention, surveillance, and monitoring activities; promoting quality of care at the ART site level as a way to minimize drug resistance; and positioning HIVDR in the public health and research agenda of national HIV/AIDS programs and academic institutions. Challenges remain with respect to long-term sustainability and effective implementation of national strategies for HIVDR prevention and assessment in the years to come. From the experience gained in the past few years in LAC countries, the following recommendations are proposed as guidance for future planning and implementation of HIVDR strategies:

- National HIVDR working groups, characterized by interdisciplinary and intersectoral membership, should be formally recognized by ministries of health as advisory committees for national HIV/AIDS programs with regard to drug resistance control strategies.
- Coordination among national HIV/AIDS programs, HIVDR working groups, and national and international partners should be promoted to guarantee efficiency of resources and harmonized methodology. Timely implementation of HIVDR strategies has been possible through country-based and international partnerships that provide the required technical and financial start-up support; gradual integration of activities within national work plans and budgets is necessary for long-term sustainability.
- Medical and pharmacy information systems should be revised, updated, and standardized at the national level, if necessary, and maintained with data quality assurance strategies. Such systems will provide reliable information for EWI monitoring as well as for any ART program monitoring and evaluation activity.
- Countries should regularly monitor EWIs at all treatment sites, or at representative sites, and integrate these indicators within national monitoring and evaluation strategic plans; EWI reports should be used for continued quality improvement.
- Survey methodology for HIVDR monitoring and surveillance of transmitted resistance should be harmonized to enable appropriate comparisons among countries and over time. The development of regional HIVDR surveillance networks using standardized methodology should be supported. In LAC, threshold surveys were implemented exclusively in pregnant women and the general population, while transmitted HIVDR in most at-risk populations remains unevaluated. To improve the applicability of WHO threshold surveys in the context of concentrated epidemics, a revised methodology is required for transmitted resistance surveillance in most at-risk populations.
Future progress in the implementation of the WHO HIVDR strategy in LAC should aim at strengthening national working groups and creating new ones, expanding EWI monitoring to new countries or beyond the initial pilot phase, reviewing EWI data quality, presenting results at national and international forums and in peer-reviewed journals, implementing HIVDR monitoring and threshold surveys in selected countries, and expanding the WHO HIVDR laboratory network in LAC. Assessment and prevention of resistance is key to long-term effectiveness and sustainability of universal access to ART, and strategies for prevention, monitoring, and surveillance of resistance should be part of the national comprehensive response to the HIV epidemic.

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REFERENCES


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RESUMEN

Progreso en la aplicación de la estrategia de la Organización Mundial de la Salud para el control de la farmacorresistencia del VIH en América Latina y el Caribe

Hacia fines del 2010, América Latina y el Caribe lograron una cobertura de tratamiento antirretroviral de 63%. Se recomienda la ejecución de medidas para controlar la farmacorresistencia del VIH a nivel de país para potenciar al máximo la eficacia y la sostenibilidad de los programas de tratamiento antirretroviral. Desde el 2006, la Organización Panamericana de la Salud ha apoyado la aplicación de la estrategia de la Organización Mundial de la Salud (OMS) para la prevención y la evaluación de la farmacorresistencia del VIH mediante actividades regionales de formación de capacidad y de cooperación técnica directa en 30 países de América Latina y el Caribe. En 2010, 85 centros en 19 países notificaron indicadores de alerta temprana y suministraron información acerca del alcance de los posibles impulsores de la farmacorresistencia en los centros de tratamiento antirretroviral. En el 2009, 41,9% de los centros no lograron la meta de la OMS de 100% de prescripción de medicamentos de primera línea apropiados; 6,3% todavía tenían tasas elevadas (> 20%) de pérdida de seguimiento y 16,2% tenían una baja retención de pacientes (< 70%) en tratamiento con antirretrovirales de primera línea en el primer año de tratamiento. Se registraron desabastecimientos de medicamentos antirretrovirales en 22,7% de los centros. Haití, Guyana y la zona mesoamericana están planificando y ejecutando estudios de vigilancia de la farmacorresistencia del VIH o estudios del umbral de la OMS. Las nuevas herramientas para la vigilancia de la farmacorresistencia del VIH en las epidemias concentradas permitirán una mejor vigilancia. La ampliación de la red de laboratorios de farmacorresistencia del VIH acreditados por la OMS en América Latina es fundamental para el fortalecimiento de la capacidad de los laboratorios regionales, a fin de de efectuar una vigilancia de la farmacorresistencia del VIH de calidad garantizada. La estrategia para el control de la farmacorresistencia del VIH de la OMS es factible y puede implantarse en América Latina y el Caribe. La integración de las actividades de vigilancia de la farmacorresistencia del VIH con los planes nacionales de atención y tratamiento del VIH es fundamental para garantizar la sostenibilidad de esta estrategia.

Palabras clave VIH; resistencia a medicamentos; vigilancia epidemiológica; estrategias mundiales; estrategias regionales; América Latina; región del Caribe.