Implementing Early-Warning Indicators of HIV Drug Resistance in the Caribbean

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A key component of the World Health Organization’s (WHO’s) Global HIV Drug Resistance (HIVDR) prevention and assessment strategy is to monitor HIVDR early-warning indicators (EWIs), which provide strategic information for HIVDR containment. The Pan American Health Organization (PAHO)/WHO supported implementation of HIVDR EWI monitoring in 16 Caribbean countries. Results from 15 countries were analyzed by year of patient initiation of antiretroviral therapy for the period 2005–2009. This report demonstrates the need for capacity-building to standardize prescribing practices and to strengthen adherence strategies and antiretroviral drug procurement management systems.

The Pan American Health Organization (PAHO)/World Health Organization (WHO) Caribbean subregion comprises 32 countries and territories, including Belize in Central America and Guyana and Suriname in South America. This region has the second highest adult HIV prevalence outside of sub-Saharan Africa [1.0% (0.9%–1.1%)], with the estimated HIV prevalence ranging from 0.1% (Cuba) to 3.1% (Bahamas) [1]. At the end of 2009, there were an estimated 240 000 (220 000–270 000) people living with HIV, three-quarters of them residing on the island of Hispaniola in Haiti and the Dominican Republic. The HIV epidemic in this sub-region has remained stable, with new infections continuing to occur predominantly among vulnerable and most at-risk populations, with an estimated 17 000 (13 000–21 000) adults and children acquiring HIV in 2009.

Over the past 10 years, all countries have implemented antiretroviral treatment (ART) programs. By December 2009 the number of persons receiving ART in low- and middle-income Caribbean countries was estimated at 52 700, a coverage of 48.0% based on WHO 2010 HIV care and treatment guidelines [2]. Challenges for continued scale-up and sustainability of these programs include financing mechanisms in the era of a global financial crisis, continuing vertical models of ART delivery, limited human resources and infrastructure, and HIV drug resistance (HIVDR). HIVDR has the potential to increase the cost of ART programs due to the higher costs of second-line and salvage treatments.

In 2000, the WHO Global HIVDR Network (HIVResNet) was formed to address HIVDR worldwide. HIVResNet has developed a global HIVDR prevention and assessment strategy based on public health principles; the strategy includes monitoring of HIVDR early warning indicators (EWIs). The guidance document for these EWIs was updated in 2010 [3]; indicators recommended in the 2008 WHO EWI guidance were used in the Caribbean during the period of this review. EWI findings are utilized to make programmatic improvements in order to minimize the occurrence of situations known to be associated with resistance. The WHO HIVDR strategy, including EWI monitoring, is described elsewhere [3, 4].

METHODS

In 2006, PAHO/WHO introduced the WHO HIVDR strategy in the Caribbean to understand the impact of...
increasing ART availability on the development of resistance. Another strategy goal was to establish a Pan-Caribbean approach to guide public health actions that would limit HIVDR emergence and optimize use of available first- and second-line ART regimens. In collaboration with Caribbean stakeholders and partners, the first regional meeting was held in 2006 to build awareness, advocate for the adoption of the WHO HIVDR strategy, and agree on key activities and priorities for a Caribbean regional HIVDR strategy. This strategy included:

- Establishing a Caribbean HIVDR working group and a Regional Plan of Action.
- Establishing national HIVDR technical working groups and HIVDR plans.
- Identifying genotyping laboratories in the region to support the implementation of HIVDR surveys.
- Monitoring EWIs at ART clinics in all countries.
- Where feasible, implementing HIVDR surveys to assess transmitted HIVDR and acquired HIVDR.
- Implementing databases at regional and country levels for HIVDR survey data collection and analysis.
- Summarizing results in annual national and regional reports and highlighting the most common resistance patterns and public health actions required to minimize HIVDR emergence and transmission.

Sixteen countries were prioritized for technical support, representing more than three-quarters of the persons on ART in the Caribbean: Antigua and Barbuda, The Bahamas, Barbados, Belize, Dominica, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Montserrat, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Suriname, and Trinidad and Tobago. Each country developed a locally adapted national HIVDR strategy that, in all cases, prioritized EWI monitoring at ART clinics.

EWI monitoring requires the abstraction of basic patient and clinic characteristics that are normally routinely recorded in ART clinics. Each country determined which EWIs to monitor based on availability of required data. Patient monitoring systems (PMSs), through which standardized HIV care and treatment information is routinely collected, varied from country to country and ranged from electronic systems to paper-based methods. The standardized methodology for abstracting EWIs is described elsewhere [5].

Data quality assurance for EWI monitoring was provided in some countries through direct technical support for PMS data analysis, including data cleaning and verification. In countries that did not share their databases, support was provided to generate appropriate data queries for EWI reports or through an in-depth validation process. EWI results included in national HIVDR reports for the period 2005 to 2009 have been aggregated to produce this regional report.

RESULTS

By the end of 2010, 14 countries reported on EWI data: The Bahamas, Barbados, Belize, Dominica, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Montserrat, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, and Suriname. Here we present Caribbean regional EWI data from ART clinics for patients initiating ART in the years 2005–2009 distributed by year. Data for 5 indicators were collected from most ART clinics and are presented in Table 1. Too few clinics participated to estimate trends; no significant differences are implied by the numbers provided.

Table 1. Percentage of Clinics Achieving World Health Organization-Suggested HIV Drug Resistance Early Warning Indicator Targets by Year

<table>
<thead>
<tr>
<th>HIVDR EWI</th>
<th>WHO-Suggested Target</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWI 1: First-line ART prescribing practices</td>
<td>100%</td>
<td>1/3</td>
<td>12/16</td>
<td>18/35</td>
<td>5/30</td>
<td>17/38</td>
</tr>
<tr>
<td></td>
<td>34.0%</td>
<td>75%</td>
<td>51.0%</td>
<td>17%</td>
<td>45.0%</td>
<td></td>
</tr>
<tr>
<td>EWI 2: Patients lost to follow-up during the first 12 months of ART</td>
<td>≤20%</td>
<td>5/5</td>
<td>20/20</td>
<td>32/35</td>
<td>5/5</td>
<td>12/12</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>EWI 3: Patient retention on first-line ART at 12 months</td>
<td>≥70%</td>
<td>3/5</td>
<td>8/8</td>
<td>25/36</td>
<td>17/23</td>
<td>30/36</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>100%</td>
<td>69%</td>
<td>74%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>EWI 4: On-time drug pick-up</td>
<td>≥90%</td>
<td>Nil</td>
<td>11/12</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>92%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWI 6a1: Drug supply continuity</td>
<td>0%</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>4/5</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>80%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>EWI 6b: Drug supply continuity</td>
<td>100%</td>
<td>Nil</td>
<td>4/11</td>
<td>13/27</td>
<td>1/2</td>
<td>16/17</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>48%</td>
<td>50%</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EWI, early warning indicator; HIVDR, HIV drug resistance; WHO, World Health Organization.
Monitoring EWI 1, First-Line ART Prescribing Practices, demonstrated poor prescribing practices. The best results were observed in 2006, with 75% of clinics achieving the WHO suggested target of 100%, falling to approximately 50% in 2007 and 2009 and to 17% in 2008. Definition of appropriate first-line was based on national guidelines that, in most instances, followed the 2006 WHO guidelines [6] or the Caribbean Guidelines for Care and Treatment of Persons with HIV Infection (2007) [7].

For EWI 2, Patients Lost to Follow-Up During the First 12 Months of ART, the WHO target of $\geq$20% was achieved by 96% of the 77 reporting clinics over the period and by 100% in 2005, 2006, 2007, and 2009, with a small drop to 91% in 2007.

EWI 3, Patient Retention on First-Line ART at 12 Months, was reported by 108 clinics. During the period, an increasing number of clinics met the WHO target of $\geq$70%, from 60% in 2005 to 83% in 2009.

EWI 4, On-Time ARV Drug Pick-Up, was reported by 12 clinics in 1 country in 2006; 11 of 12 clinics (91%) achieved the WHO target of $\geq$90%.

EWI 6, ARV Drug Supply Continuity, was reported using 2 alternate definitions. EWI 6a1 measures the percentage of patients on first-line ART whose regimen was stopped, modified, or incompletely dispensed at the pharmacy due to ARV stock-out in a 12-month period. This EWI was monitored by only 21 clinics, with 100% of clinics achieving the WHO target of 0% between 2006 and 2009, with the exception of 80% in 2008. EWI 6b, which measures the percentage of months in a designated year in which there were no ARV drug stock-outs, was reported in 57 clinics, with an increasing number of clinics reporting the WHO target of 100%, from 36% in 2006 to 94% in 2009.

DISCUSSION

Monitoring of HIVDR EWIs at ART clinics in the Caribbean provides strategic information for evidence-based decision-making and planning to minimize emergence of HIVDR local and national levels. An important issue identified in this analysis was poor first-line ART prescribing practices. The rational use of ART with standardized options for first- and second-line regimens contributes to the prevention of resistance from the early stage of treatment initiation, protecting the future option of more costly second-line regimens. The poor performance in first-line ART prescribing has several possible explanations. In specific cases, prescribing may have been due to patient-centered prescribing whereby prescribers take into account individual patient preference, previous antiretroviral exposure, and anticipated toxicities or adverse events. In many cases, protease inhibitors (PI) were prescribed even when national guidelines recommend regimens based on nonnucleotide reverse transcriptase inhibitors. Although prescription of a PI-based regimen as first-line ART is not necessarily a risk factor for emergence of HIVDR, it does demonstrate suboptimal adherence of prescribers to national treatment guidelines.

ART is lifelong and its success depends on optimal adherence, which is often challenging [8]. Healthcare services that deliver ART should have supportive mechanisms in place to promote adequate adherence and should proactively trace clients who fail to return for scheduled visits. EWI 2 addresses the capacity of ART clinics to minimize patient loss to follow-up for the first 12 months. The WHO target of $\leq$20% was generally attained, suggesting that patient retention on first-line ART for the first 12 months remained satisfactory. With the exception of 2006, between 60% (2005) and 83% (2009) of the clinics that monitored EWI did not reach the target of $\geq$70% patients still on first-line ART at 12 months, suggesting that a premature switch to second-line therapy, patient adherence, or loss to follow-up could be problematic in some clinics. The tracking of these indicators beyond 12 months is important as part of ongoing strategies to prevent HIVDR and provide quality HIV care. Ongoing programmatic responses to promote adherence and trace defaulters will be essential as ART programs expand to reach the goals of universal access.

Interpretation of the data from EWI 4 is limited because data were reported by only 1 country in only 1 year; however, that country’s reporting demonstrates that monitoring is possible if appropriate information systems are in place. This indicator is an important measure of adherence, and studies have demonstrated a correlation between on-time drug pick-up with population-level viral load suppression [9]. In the future, countries are encouraged to develop the capacity to record expected drug pick-up dates and readily identify defaulters.

CONCLUSION

HIVDR EWI monitoring should be scaled up at the country level, performed annually, and integrated within national monitoring and evaluation strategic plans. EWI results should be used strategically to support evidence-based decision-making for public health actions to minimize HIVDR. In addition, medical, pharmacy, and laboratory information systems should be strengthened and data quality assurance strategies improved and maintained. Such systems will provide reliable information not only for EWI monitoring but for all ART program monitoring and evaluation activities.

Long-term sustainability of EWI monitoring, as well as other HIVDR prevention, surveillance, and monitoring activities, will be possible only through national and international partnerships that provide the required technical and financial support. Funding to support these activities between 2006 and 2010 came from multiple sources, including the Pan Caribbean Partnership against HIV and AIDS (PANCAP); a Global Fund...
grant (round 3), a cooperative agreement between the Centers for Disease Control and Prevention (CDC) and PAHO/WHO; and the WHO/The Bill & Melinda Gates Foundation HIVDR grant for Haiti, Guyana, and the Dominican Republic. At the country level, funding for HIVDR prevention, monitoring, and surveillance should be included in strategic plans and budgets of HIV programs at the Ministry of Health. Technical support must be provided to strengthen patient information systems, improve data quality, validate and interpret EWI results, and support the development of remedial action at both clinic and programmatic levels. Finally, the impact of programmatic adjustments to minimize HIVDR must be evaluated over time through routine EWI monitoring and time-trend analysis of indicators.

**Notes**

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