Monitoring HIV Drug Resistance Using Early Warning Indicators in China: Results From a Pilot Survey Conducted in 2008

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Robust programmatic monitoring of factors associated with the emergence of human immunodeficiency virus (HIV) drug resistance is an essential component of antiretroviral therapy (ART) program evaluation and treatment optimization. China piloted World Health Organization HIV drug resistance early warning indicators to assess the feasibility and usefulness of results. Overall, early warning indicator monitoring showed high levels of appropriate ART prescribing, low rates of loss to follow-up 12 months after ART initiation, and high rates of retention of first-line ART at 12 months. On-time drug pick-up, which may signal treatment interruptions, was identified as a challenge. HIV drug resistance early warning indicator monitoring provides a valuable assessment of ART service delivery, and its application will be scaled up throughout China.

Monitoring of human immunodeficiency virus (HIV) clinic and antiretroviral therapy (ART) program performance with use of HIV drug resistance (HIVDR) early warning indicators (EWIs) is a key component of the World Health Organization (WHO)–recommended HIVDR prevention strategy [1]. HIVDR EWIs provide actionable information to ART clinics and program planners about potential factors that may contribute to the emergence of HIVDR. Routine monitoring of EWIs, coupled with appropriate clinic- or program-level adjustments, can help minimize HIVDR, thus preserving population-level efficacy of currently available treatment regimens [1].

China began providing ART free of charge in 2002, starting with 100 patients in a single county. By the end of 2009, >80 000 adults and children had initiated ART at >2000 hospitals and clinics across 31 provinces, representing an estimated 46.8% of those in need [2]. In 2008, China’s national ART guidelines recommended that the CD4 lymphocyte cell count threshold for ART initiation be increased from ≤200 cells/μL to ≥350 cells/μL, thus broadening access to ART [3]. As more patients initiate ART, more will inevitably develop HIVDR, necessitating a switch to more expensive and often less well-tolerated second-line regimens. In China, ART is provided at different levels of the health-care system, ranging from highly specialized provincial infectious disease hospitals to township and village clinics [4]. This pilot assessed WHO HIVDR EWI monitoring at 6 ART sites to assess the feasibility and usefulness of EWI monitoring as an ART program evaluation tool in China.

METHODS

In 2008, 6 hospitals from 3 provinces were selected as pilot sites. Two sites were chosen from each level (provincial-level infectious diseases hospitals, district-level hospitals, and township-level hospitals). Sites were
not randomly chosen and were not intended to be representative of different levels of care. Hospitals 1 and 2 were provincial specialized infectious diseases hospitals situated in the capital city of their respective provinces. Hospitals 3 and 4 were district-level general hospitals, and hospitals 5 and 6 were township hospitals.

At sites with ≤100 adult patients receiving ART, all patients aged >15 years who were registered during the period from July 2006 through June 2007 were included in the sample. At sites with >100 adult patients receiving ART, those registered from January through June 2007 were included in the sample.

We assessed the following WHO HIVDR EWIs according to the 2007 WHO EWI guidance: (1) proportion of patients initiating ART who were prescribed an appropriate first-line ART regimen (EWI1), (2) proportion of patients initiating ART who did not return to the clinic >90 days after the last missed appointment or drug pick-up during the 12 months after ART initiation (EWI2), (3) proportion of patients initiating ART who were taking an appropriate first-line ART regimen 12 months later (EWI3), and (4) proportion of patients initiating ART who picked up all prescribed antiretroviral drugs on time during their first 12 months of ART (EWI4). For EWI1 and EWI3, appropriate first-line ART was defined as a regimen combining the following antiretroviral drugs: zidovudine or stavudine, lamivudine, and efavirenz or nevirapine [3]. For EWI4, on time was defined as picking up pills on or before the date that the prescription would have run out if taken according to schedule.

China’s National Center for AIDS/STD Prevention and Control established a central electronic ART database in 2004 (National Free ART Database) that contains an assortment of baseline and follow-up data from patients enrolled in the National Free Antiretroviral Treatment Program [5]. However, in the planning of this pilot, it was recognized that the database did not provide patient information on antiretroviral drug pick-up (EWI4) and that the definition of loss to follow-up (EWI2) differed from the recommended EWI definition. Therefore, to operationalize EWI monitoring according to WHO guidance, raw data were abstracted by trained staff using original patient medical and pharmacy records, and analyses were performed in accordance with WHO guidance.

RESULTS

Of the 6 ART sites initially selected for the pilot, the 2 township hospitals were found to be using record-keeping systems that did not capture the necessary raw data and were therefore excluded. Data from the remaining 4 sites were successfully abstracted.

At all clinics, 100% of patients were initially prescribed an appropriate first-line ART regimen (EWI1) (Table 1). The proportion of patients lost to follow-up 12 months after ART initiation (EWI2) ranged from 1.4% to 5.6%. At hospitals 1, 2, and 3, >70% of patients were taking an appropriate first-line regimen 12 months after ART initiation (EWI3). However, at hospital 4, only 66% of patients were retained on an appropriate first-line regimen, despite the fact that only 1 patient had been changed to an inappropriate regimen at 12 months. The proportion of patients who picked up all ART on time during their first 12 months (EWI4) was low, ranging from 40.3% to 58.3% (Table 1). Of note, the mean delay in drug pick-up was 5.5 days (interquartile range [IQR], 2.0–19.3 days), and no statistically significant difference was observed across clinics for EWI4.

DISCUSSION

China has scaled up its National Free ART Program from 1 site in 2002 to >2600 sites in all 31 provinces by 2010. Overall, mortality among patients has decreased to 4–5 deaths per 100 person-years after 6 months of treatment [6]. However, studies have shown that patients receiving ART at different levels of care in China have different virologic outcomes [7]; this makes programmatic assessment with HIVDR EWIs appealing because results may be used to optimize clinic-level and overall program functioning. The results of this pilot demonstrate that HIVDR EWI data abstraction was feasible in 4 (66.6%) of 6 selected ART sites and that results are useful for public health planning and clinic- and program-level action.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Newly Registered Patients (Data-Reporting Period)</th>
<th>EWI 1</th>
<th>EWI 2</th>
<th>EWI 3</th>
<th>EWI 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1 (provincial level)</td>
<td>24(07/2006–06/2007)</td>
<td>24/24 (100%)</td>
<td>1/24 (4.2%)</td>
<td>21/24 (87.5%)</td>
<td>14/24 (58.3%)</td>
</tr>
<tr>
<td>Hospital 2 (provincial level)</td>
<td>89(01/2007–06/2007)</td>
<td>89/89 (100%)</td>
<td>5/89 (5.6%)</td>
<td>71/84 (84.5%)</td>
<td>39/89 (42.7%)</td>
</tr>
<tr>
<td>Hospital 3 (district level)</td>
<td>72(07/2006–06/2007)</td>
<td>72/72 (100%)</td>
<td>1/72 (1.4%)</td>
<td>63/71 (88.7%)</td>
<td>29/72 (40.3%)</td>
</tr>
<tr>
<td>Hospital 4 (district level)</td>
<td>73(01/2007–06/2007)</td>
<td>73/73 (100%)</td>
<td>4/73 (5.5%)</td>
<td>36/54 (66.7%)</td>
<td>40/73 (54.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: EWI1, proportion of patients initiating antiretroviral therapy (ART) who were prescribed an appropriate first-line ART (ART target: 100%); EWI2, proportion of patients initiating ART who were lost to follow-up 12 months after ART initiation (target: ≥20%); EWI3, proportion of patients receiving an appropriate first-line ART regimen 12 months after initiation (target: ≥80%); EWI4, proportion of patients initiating ART who picked up all prescribed drugs on time during the first 12 months after initiation (target: ≥90%).
All sites exceeded WHO targets for EW1 and EW2. For EW3, 3 of 4 sites achieved the WHO target. On-time drug pick-up emerged as an important challenge in this patient population and may signal treatment interruptions. Buffer supplies of 1–2 days of ART are commonly provided in China, but patient buffer stock could not be quantified in this analysis. However, the mean delay in drug pick-up was 5.5 days (IQR, 2.0–19.3 days), suggesting that our finding may indeed represent possible treatment interruptions or suboptimal population-level adherence. On-time drug pick-up will continue to be used in China as a measure of population-level ART adherence because it is easier to measure than pill count or other adherence assessment methods [8]. In the future, pharmacy records may be adapted to allow for the calculation of medication possession ratio, which will take into account patient buffer supply and, therefore, would be anticipated to provide a more accurate estimate of adherence. These pilot results suggest that further investigation into reasons for the delay in drug pick-up and operational research leading to adherence support is warranted.

Although an annual free viral load testing was theoretically available to all patients beginning in 2007, laboratory capacity was limited during the period of this survey, and a large proportion of eligible patients did not benefit from viral load monitoring. Thus, we were unable to assess clinic-level viral load suppression, one of the WHO-recommended EWIs. However, with recent emphasis on viral load testing scale-up throughout all regions, monitoring of population-level viral load suppression will become a priority EWI in China. Results of this pilot demonstrate that WHO HIVDR EWI monitoring can be used to assess the strengths and weaknesses of ART programs and guide managers and implementers on strategies to resolve and strengthen identified areas of weakness. With >2000 ART sites in China, nationwide scale-up of HIVDR EWI monitoring using data abstracted manually from paper-based medical records would not be feasible. Therefore, China has upgraded its Internet-based patient database to include collection of all relevant raw data and has written appropriate query programs to facilitate the calculation of selected EWIs, which will permit routine EWI monitoring at all ART clinics in the near future.

Notes

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