

Update on World Health Organization HIV Drug Resistance Prevention and Assessment Strategy: 2004–2011

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The HIV drug resistance (HIVDR) prevention and assessment strategy, developed by the World Health Organization (WHO) in partnership with HIVResNet, includes monitoring of HIVDR early warning indicators, surveys to assess acquired and transmitted HIVDR, and development of an accredited HIVDR genotyping laboratory network to support survey implementation in resource-limited settings. As of June 2011, 52 countries had implemented at least 1 element of the strategy, and 27 laboratories had been accredited. As access to antiretrovirals expands under the WHO/Joint United Nations Programme on HIV/AIDS Treatment 2.0 initiative, it is essential to strengthen HIVDR surveillance efforts in the face of increasing concern about HIVDR emergence and transmission.

In 2010, 6.6 million adults and children in low- and middle-income countries received antiretroviral therapy (ART), representing a 22-fold increase from 2001 [1]. Successful ART scale-up in resource-limited settings (RLSs) was realized using a public health approach, including the use of standard protocols and simplified patient monitoring. The Joint United Nations Programme on HIV/AIDS and the World Health Organization (WHO) launched the Treatment 2.0

initiative in 2010, which is aimed at sustaining universal access to treatment and maximizing the preventive benefits of ART [2]. The treatment of millions of human immunodeficiency virus (HIV)-infected patients will inevitably be accompanied by the emergence and transmission of HIV drug resistance (HIVDR); moreover, the use of antiretroviral (ARV) drugs for prevention has the potential to increase the prevalence of HIVDR.

In high-income countries, HIVDR testing of individual patients is used to tailor regimen selection and predict treatment response. However, in most, if not all RLSs, HIVDR testing is neither routinely available nor recommended for individual patient management. Even with recent technological advancements, it is unlikely that HIVDR testing for patient care will be routinely available for millions of patients in the

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near future. Furthermore, the limited availability of alternative regimens restricts treatment change based on test results [3]. HIVDR remains a threat to the long-term effectiveness of ARV treatment [4–8]. The absence of accessible HIVDR testing for individual patient care in RLSs necessitates that efforts be intensified to optimize population-based ARV treatment and to minimize HIVDR [9]. Unless carefully monitored and contained, HIVDR has the potential to reduce the efficacy of standard ART regimens in a high proportion of patients in RLSs.

WORLD HEALTH ORGANIZATION HIVDR STRATEGY

The WHO, in collaboration with HIVResNet, an advisory body of international experts from >50 institutions, has led global efforts for the prevention and assessment of HIVDR and has developed a standardized, minimum-resource, population-based strategy, which provides comparable data over time and across regions [10]. The strategy consists of 3 main assessment elements: HIVDR early warning indicators (EWIs) and surveys of acquired and transmitted HIVDR [10–12] for pediatric and adult populations. Additionally, the strategy includes the development of a network of HIVDR testing (genotyping) laboratories that support public health surveillance [13].

As of June 2011, 52 countries had implemented 1 or more elements of WHO's HIVDR prevention and assessment strategy, and 27 laboratories had become members of the WHO HIVDR laboratory network [14] (Figure 1). The purpose of this supplement is to update the reader on global, regional, and country-level results generated by the strategy, as well as resulting public health actions. Additionally, this supplement reports a new surveillance method to assess HIVDR in children aged <18 months [15] and provides an update on the WHO external quality assurance process for genotyping, as well as WHO-supported operational research on the use of dried blood spots as specimens for HIVDR testing [16, 17].

HIVDR EARLY WARNING INDICATORS

The foundation of the global HIVDR prevention and assessment strategy is the annual monitoring of HIVDR EWIs at all ART clinics or representative clinics [10]. HIVDR EWIs assess prescribing practices, rates of retention, losses to follow-up, population-level adherence to ART, drug supply continuity, and virological suppression, which have been shown to be major predictors of HIV disease progression, death, and HIVDR [18–26]. Each EWI is associated with a suggested clinic-level target. The WHO HIVDR EWIs and their associated targets are listed in Table 1 of Bennett et al

(in this supplement [27]). EWI results provide clinic and program managers with data about how their clinics perform compared with international targets aimed at preventing emergence of HIVDR [10]. To date, EWIs have been monitored in 50 countries, assessing >2000 clinics [27]. This supplement contains the first global EWI report with data obtained from 50 countries in 5 regions: Africa, Latin America and the Caribbean, Southeast Asia, the Western Pacific, and Eastern Europe. One regional report comes from Latin America and the Caribbean. A report comes from PharmAccess, which has implemented EWIs in 6 countries; additionally, 4 country reports come from China, Papua New Guinea, Vietnam, and Zimbabwe [27–33]. Although these data represent early experiences, common themes have emerged. The rate of patients lost to follow-up, rate of patient retention on first-line ART at 12 months, and patient adherence as measured by on-time pill pickup often fall below suggested targets and merit concern and investigation. Additionally, EWI monitoring in several countries has highlighted weaknesses in patient information systems that have resulted in the inability to monitor specific EWIs. Reported weaknesses in current data systems include incomplete records, missing data, use of nonstandardized records, and intraclinic and interclinic variability in data recording. As a result of EWI monitoring, several countries have taken steps to strengthen their information systems [27–31, 34, 35].

SURVEYS OF ACQUIRED HIVDR

WHO prospective surveys of acquired HIVDR are performed at sentinel ART clinics and supplement EWI data by estimating the prevalence and patterns of HIVDR in adult and pediatric populations experiencing ART failure [11]. At each sentinel survey clinic, a cohort is formed of patients initiating first-line ART. HIVDR genotyping is performed on patients initiating ART, and HIV RNA quantification is performed at the time that treatment is switched to second-line or 12 months after ART initiation for patients remaining on first-line treatment. In patients with detectable virus (>1000 copies/mL), genotyping is performed to characterize drug resistance mutations. Other survey endpoints include loss to follow-up, death, ART stop, or transfer to another ART clinic.

As of June 2011, 51 surveys of acquired HIVDR had been performed in 13 countries. The results from 12 surveys performed in 4 countries are published in this supplement [36–40]. The overall prevalence of HIVDR prior to the initiation of ART remains relatively low, and the predicted level of susceptibility observed among patients with HIVDR at 12 months suggests that the nucleoside reverse transcriptase inhibitor component of currently recommended second-line

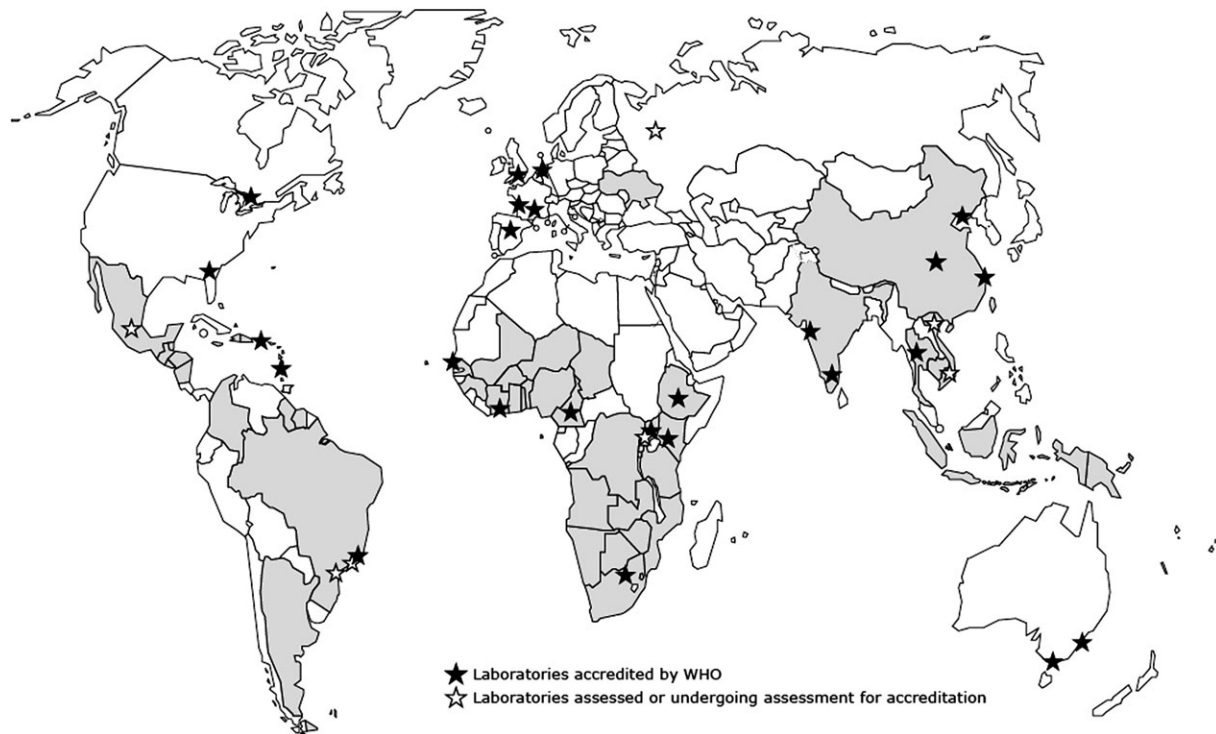


Figure 1. Countries implementing 1 or more elements of the World Health Organization human immunodeficiency virus drug resistance prevention and assessment strategy, June 2011. This map is an approximation of actual country borders. Abbreviation: WHO, World Health Organization.

regimens, in combination with a boosted protease inhibitor, is likely to be effective for the majority surveyed [14]. Notably, in surveys published in this supplement, patient resistance to nonnucleoside reverse transcriptase inhibitors at the time of first-line ART initiation and treatment interruption are factors shown to predict virological failure at 12 months [36–39]. Additionally, surveys have concluded that improved adherence, especially among young adults, and improved defaulter tracing mechanisms may lead to improved rates of virological suppression and HIVDR prevention [36–39].

SURVEYS OF TRANSMITTED HIVDR

WHO TDR surveys use truncated sequential sampling and small sample sizes of ≤ 47 to classify TDR as low (<5%), high (>15%), or moderate (5%–15%) in populations likely to have been recently infected [12, 41]. Where possible, these surveys use remnant specimens and data from regularly performed serosurveys that estimate HIV prevalence, which are already in place in many RLSs. Results contribute to ART policy decisions, including guidelines on ART regimens and HIV prophylaxis.

As of June 2011, 53 TDR surveys have been performed in 22 countries [27]. Rates of TDR remain low in most areas and

populations assessed using WHO-recommended methods [14]. However, as ART rollout continues, increased rates of TDR may occur. Recent publications, including reports published in this supplement, document moderate (5%–15%) levels of TDR in specific geographical regions [42–47]. These reports merit attention, warrant concern, and underscore the importance of routine TDR surveillance as well as addressing and preventing HIVDR at both national program and clinic levels.

NEW DIRECTIONS

Although monitoring of HIVDR EWIs are very important, their uptake has generally been limited to pilot experiences. Therefore, in 2011, WHO partnered with the Centers for Disease Control and Prevention (CDC) and the US President’s Emergency Plan for AIDS Relief (PEPFAR) to initiate a process that would update and simplify EWI guidance in order to facilitate monitoring at larger numbers of ART clinics. Simplifications of definitions and abstraction procedures are currently being considered that should facilitate integration into existing program monitoring and evaluation processes.

Additionally, in 2011, a less resource-intensive, cross-sectional survey using lot quality assurance sampling was developed to estimate acquired HIVDR. This cross-sectional

survey should enable rapid generation of HIVDR data from large numbers of ART clinics using significantly smaller sample sizes than the current prospective method. Furthermore, this method will provide more comprehensive datasets describing HIVDR in adult and pediatric patients experiencing ART failure at both 12 and >24 months after treatment initiation. WHO and CDC/PEPFAR will pilot this new method in several countries in 2012, and the results of the pilot experience will be used to inform future global surveillance guidance.

As prevention of mother-to-child transmission is scaled up, fewer children are expected to become infected with HIV, but for those who do, a substantial proportion will be expected to harbor drug-resistant virus. Assessments of HIVDR in children <18 months of age are performed to guide population-level, first-line treatment in children. WHO and the CDC have developed a new surveillance protocol that uses remnant specimens from early infant diagnosis to make nationally representative statements about HIVDR in this population. This generic protocol is described in this supplement, and it will be piloted in Sub-Saharan Africa in 2012 by WHO and CDC/PEPFAR [15].

In conclusion, under the Treatment 2.0 initiative [2], millions of infected people will initiate or be maintained on ART. Additionally, many may be exposed to prevention strategies using ARVs. Now more than ever, greater funding, infrastructure and political will are urgently required to sustain and expand global HIVDR surveillance efforts. Without the benefit of cumulative standardized HIVDR surveillance data and a commitment on the part of international organizations, national governments, ART programs, funders, and implementing partners to identify and address programmatic challenges associated with HIVDR, we risk suboptimal population-level responses to current and future ART regimens over the next decade.

Notes

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