Monitoring Early Warning Indicators for HIV Drug Resistance in South Africa: Challenges and Opportunities

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The sociopolitical impact and consequent scale and scope of the human immunodeficiency virus (HIV) treatment program are unprecedented in the history of infectious diseases. Internationally coordinated efforts, such as the "3 by 5" initiative, as well as the updated global target of providing antiretroviral therapy (ART) to 15 million people by the end of 2015, resulted in ART becoming accessible, not only in unparalleled volumes, but also in previously inconceivable locations. Globally, the number of people receiving ART has tripled over the last 5 years and, of the estimated 10.6 million people on treatment at the end on 2012, 9.7 million were in low- and middle-income countries (LMICs). This number is expected to increase sharply, given that a total of 26 million people in LMICs are now eligible for ART under the 2013 World Health Organization (WHO) Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. The exponential expansion of treatment programs has averted an estimated 6.6 million AIDS-related deaths between 1995 and 2012, including 5.5 million deaths in LMICs [1].

Despite the undisputed benefits of ART in terms of reduced HIV-related morbidity and mortality, the long-term success of the treatment program is threatened by the emergence and spread of drug-resistant HIV. The development of HIV drug resistance (HIVDR) has significant public health implications, such as limiting the response to ART, restricting future treatment options, increasing treatment costs, and creating a reservoir for transmission of resistant virus to newly infected individuals [2]. National health systems in many LMICs are plagued by unique treatment and program deficiencies that may facilitate the development of HIVDR, such as the use of low-cost, less-tolerable (eg, stavudine), and substandard regimens (eg, single-dose nevirapine for prevention of mother-to-child HIV transmission); limited access to HIV RNA monitoring; drug stockouts; suboptimal systems to support long-term adherence; and frequent drug-drug interactions due to the unavailability of newer medications (eg, unavailability of rifabutin necessitates the use of rifampicin together with nevirapine or lopinavir in patients coinfected with tuberculosis) [3–7]. Given the limited number of ART regimens available in resource-constrained settings, the emergence of high-level HIVDR can devastate the goal of long-term treatment success.

Acknowledging and responding to the threat of HIVDR, the WHO and the US Centers for Disease Control and Prevention (CDC), in collaboration with HIVResNet, an advisory body of international laboratories, clinicians, epidemiologists, and other HIVDR experts from >50 institutions, developed a global drug resistance surveillance strategy. As individual HIVDR testing is neither recommended nor feasible in most LMICs, this is a public health strategy, based on standardized, minimum-resource, routine population-level laboratory-based surveillance of HIVDR and assessments of ART program and clinic function. The strategy consists of 3 main assessment elements: (1) early warning indicators (EWI) of HIVDR; (2) surveys of acquired and transmitted HIVDR; and (3) surveys of HIVDR in children <18 months of age. EWIs are quality-of-care indicators that specifically assess factors at individual ART clinics known to create conditions that favor the emergence of HIVDR and provide the necessary programmatic context to interpret results of the latter 2 assessment elements [8].

The 3 elements are to be implemented as a complete package, with the ultimate aim of being integrated into routine country surveillance. As such, the HIVDR prevention strategy is envisaged to provide countries with a comprehensive picture of HIVDR and ART program functioning over time, which can guide adjustments to optimize patient care on both the clinic and program levels [9]. Implementation challenges related to cost, human resource capacity, and infrastructure neces-

sitated by the enrollment of a relatively large number of patients in prospective cohorts at sites representative of national treatment programs have, however, precluded widespread implementation of the strategy. Even relatively well-resourced LMICs, such as South Africa, have failed to submit national reports. As of 2012, EWI reporting has mostly been limited to pilot experiences, whereas acquired and transmitted HIVDR surveys have been performed in only 13 and 22 countries, respectively (for a full discussion, see [10]). Lack of reporting on a national scale has led to descriptions of HIVDR that are in all likelihood not representative of the true picture of HIVDR in populations failing ART [9].

In response to these challenges, HIV-ResNet developed a simpler survey methodology in 2012. Accordingly, the number of EWIs has been reduced from 8 to 5, with only those shown to be major predictors of HIV disease progression, HIVDR, and death retained. EWI definitions have also been simplified and harmonized with other routinely abstracted and reported data, such as those collected for the United Nations General Assembly Special Sessions and the President's Emergency Plan for AIDS Relief. In addition, surveys of acquired HIVDR now follow a cross-sectional design, with a maximum specimen collection period of 3 months. It is expected that LMICs will find it more feasible to implement these revised surveys in large numbers of sentinel ART clinics [11].

In this issue of Clinical Infectious Diseases, Dube and colleagues present the first EWI results from South Africa. They conducted a pilot study in 2 public sector clinics, following implementation of the new WHO EWI methodology. Even though they affirmed the feasibility of implementing this strategy in South Africa, their findings are a cause for concern. Clinic A satisfied the international target for only 2 of the 5 EWIs— prescribing practices and retention in care—whereas clinic B only reached 1 target (prescribing practices), and 1 indicator, pharmacy stockouts, could not be assessed at that site.

The reasons why clinic A outperformed clinic B are speculative, but the authors propose that factors related to differences in infrastructure and interventions to optimize patient care might be responsible. Clinic A, even though it had a worse staff-to-patient ratio, had follow-up procedures and internal adherence support services in place, as well as access to an electronic patient information system. Patients visiting clinic A generally traveled shorter distances and waited shorter times than in clinic B, factors that might have contributed to the higher rate of treatment interruptions seen in the latter clinic. This is worrisome, because treatment interruptions and inadequate adherence are major drivers of the development of HIVDR [12, 13]. The findings at clinic B are similar to those reported from many LMICs where the rate of patients lost to follow-up, rate of patient retention on first-line ART at 12 months, and on-time pill pickup often fall below suggested targets, warranting further investigation [10].

Significantly, 62% of HIV RNA results were missing in clinic B. The authors reason that this could be ascribed to the unavailability of funds to employ a data entry clerk. High rates of missing viral load results have also been reported in other sites in South Africa [14].Measuring HIV RNA enables early detection of treatment failure and is critical to minimize HIVDR. However, the high cost and lack of laboratory capacity and skills preclude its widespread implementation in LMIC. It is worrisome that clinics in South Africa do not harness the full benefit that could be realized from this valuable monitoring tool, effectively wasting this costly resource. EWI monitoring in several countries has also reported similar weaknesses in patient information systems, such as incomplete records and missing data, that have subverted the usefulness of measuring specific EWIs [10].

Dube and colleagues highlight drug stockouts as being another enormous challenge. The main hospital pharmacy, supplying clinic A, experienced ART stockouts for 11 of the 24 months observed. Even though this did not directly affect dispensing practices at the ART site, the occurrence of stockouts in a treatment program is alarming. South Africa has the largest HIV treatment program in the world, with an estimated 2.15 million people on ART in 2012 [1]. It is of concern that a national electronic database that can track ART forecasting, procurement, and distribution is not in place. The uniform implementation of electronic systems for managing patient information and ART stock levels is germane to the successful management of such an ambitious treatment program and is indispensable if HIVDR is to be averted.

With the South African government poised to introduce EWI monitoring at public sector ART treatment sites, the results of this pilot study are timely and provide valuable information regarding logistical considerations and weaknesses in the current system that should be addressed before EWI monitoring is implemented on a wider scale. It is unfortunate that the researchers could not present data from sentinel clinics representing the different models of care found in the country, which may have revealed a more accurate and comprehensive picture of HIVDR in the population. This study is also interpreted in isolation without the advantage of complementary surveys of acquired and transmitted HIVDR, which could have framed interpretation of the results. Nevertheless, the findings from this study will alert regional and na-

tional health authorities to deficiencies in current monitoring systems. Ultimately, this information could provide the necessary impetus for South Africa to implement improved systems to facilitate monitoring of HIVDR in South Africa.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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