Regional Challenges in the Prevention of Human Immunodeficiency Virus Drug Resistance

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In diverse global regions with significant human immunodeficiency virus (HIV) burden, programmatic, cultural, and provider-, patient-, and virus-related factors may result in HIV drug resistance, with global implications. This article reviews such common and unique challenges in Russia, Latin America and the Caribbean, China, and India, to suggest potential solutions.

Keywords. HIV drug resistance; Russia; China; Latin America; India.

Challenges with human immunodeficiency virus (HIV) epidemics in emerging and growing economies may lead to broad-reaching global consequences. Though similarities exist among locations, differences must be recognized. Factors that are programmatic (eg, models of care delivery, treatment monitoring, reagent and drug supply shortages, appropriate guidelines), cultural (eg, stigma), provider related (eg, expertise, nonpreferred regimens, traditional medications), and patient or virus related (eg, adherence, risk factors, subtype) may result in the development of extensive drug resistance (DR) and must be regionally addressed. Throughout resource-constrained settings, limited access to third-line regimens and resistance testing restricted to specialized centers, and not consistently used for regimen construction, must be balanced with emerging options for less toxic and more effective and “forgiving” integrase-based first-line regimens. This article identifies DR-associated common and unique challenges in Russia, Latin America and the Caribbean, China, and India, diverse settings with an important HIV burden.

RUSSIA

There are an estimated 1.5 million individuals with HIV in the Russian Federation; new infections are estimated at 10%–15% per year, >5 times the rate in Western Europe [1]. The HIV epidemic in Russia is concentrated among injection drug users and men who have sex with men (MSM), but recent phylogenetic evidence suggesting substantial mixing of these populations

is worrisome because it may portend a more generalized epidemic [2]. The government of Russia has issued a strategy for epidemic control that focuses on education, expanded access to testing to the general population, and surveillance and support of programs providing care to individuals with HIV. Although sexual minorities are identified in the strategy, there are no performance targets with respect to this population. The development and implementation of interagency HIV prevention programs for injecting drug users is a key performance indicator, but there are no specific strategies for retaining this population in care [3]. HIV treatment in Russia is initiated at a CD4 count <350 cells/ μ L [4] or at viral load (VL) >100 000 copies/mL, and test-and-treat strategies are under discussion [5] with an official “60-60-60 by 2020” strategy in which 60% of individuals with HIV know their status, 60% are on therapy, and 60% on therapy are suppressed [6]. First/second-line regimens per global guidelines are provided [7], but drug supply is subject to frequent interruptions, resulting in delays in antiretroviral therapy (ART) initiation and drug substitutions/omissions [6]. In 2016, 41 of 82 regional AIDS centers reported supply issues and suboptimal mono/dual ART. Drugs may be available outside the federal system, but individuals incur their costs if purchased privately, which may be high because of international generic licensing requirements: Russia is classified as a high-income country. In a review of the central Russian database, of estimated >1.3 million HIV-infected individuals in 2013, only 9% (127 754) achieved virological suppression, representing 81% of those on ART [8]. In 2016, according to the Ministry of Health, 30.6% of HIV-infected persons were on ART, 81%–82% suppressed [3]. Hence, the calculated overall viral suppression rate for the entire HIV-infected population is approximately 25.0% [3].

Laboratory monitoring includes CD4 cell count and VL, with standard definitions for virological failure. Frequent laboratory

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supply interruptions exist and monitoring schedules are not always followed [9]. Genotyping access is limited because of supply shortages, and its quality is difficult to assess because of lack of quality-control systems. There are significant HIV drug resistance (HIVDR) surveillance challenges. Drug resistance testing is typically not performed on ART-naïve individuals and is frequently unavailable upon ART failure; World Health Organization (WHO) DR population surveillance is not performed. Regional laboratories performed >15 000 DR tests, but these are unavailable for analysis, making DR prevalence/incidence estimates difficult. Clinical unpublished data available to the authors suggest transmitted DR of 6%–11%. HIVDR may thus be an emerging problem with difficult-to-identify geographic regions and populations that may have higher rates of resistance, a problem exacerbated by difficulties in keeping highly marginalized individuals in care.

LATIN AMERICA AND THE CARIBBEAN

Latin American and Caribbean countries provide HIV care through free, public, and universal treatment programs, some providing ART since the 1990s—representing a significant commitment to provide ART to all people living with HIV. In 2015, the region reached 55% ART coverage [10]. In 2016, all countries formally approved a new regional Plan of Action for HIV including the 90-90-90 targets by 2020 developed through a highly participative process in consultation with governments, providers, civil society, and people living with HIV [11]. DR emergence and subsequent transmission are of great concern for this region, as they may undermine progress toward epidemic control. Monitoring WHO DR early warning indicators began in 2006, and by 2010 there were data from 85 sites in 19 countries. Early data suggested specific areas for concern, including nonstandard first-line regimens in nearly half the sites surveyed, drug supply interruptions, and suboptimal virological suppression [12]. In 2011, 53% of reporting countries (14/26) had ≥ 1 drug supply interruption (54%); there were 92 interruptions averaging 40 days in 12 countries [13]. In 2013, 41% of reporting countries (9/22) suffered ≥ 1 interruption in 1 treatment site. Most frequent causes were bidding (29%) or procurement (13%) delays, distribution problems (10%), or drug production complications (9%) [14]. Recent efforts have been aimed at optimizing first-/second-line regimens, strengthening supply-chain management to avoid drug supply interruptions, and expanding access to cheaper prequalified generic drugs [15], with significant improvement in the use of standardized first-/second-line regimens [16].

Across the region, access to VL requires strengthening, particularly of the laboratory supply chain. Although regional average VL coverage is 91%, driven by Brazil's very high coverage, the median is 66%, with marked intercountry differences (range, 15%–100%). Leasing contracts with local suppliers including equipment maintenance are a challenge, likely improved by

moving from local to pooled procurement or price negotiation. Regional average VL suppression rates are high (86% of treated individuals with available VLs), with significant intercountry differences (median, 66% [range, 22%–90%]). Improving adherence support strategies and quality of care remains critical [17].

Until 2015, specific DR data came from local research initiatives with some methodological limitations such as lack of representativeness, small sample sizes with convenience sampling, heterogeneous DR definitions for surveillance purpose, and limited genotyping quality assurance. Although country-specific DR data are still limited, a recent meta-analysis suggested moderate (7.7%) rates of pretreatment DR throughout the region, significantly driven by an increase of nonnucleoside reverse transcriptase inhibitor (NNRTI) mutations [18]. Since 2015, nationally representative surveys based on a WHO-recommended approach and supported by WHO-designated laboratories have been scaled up in the region. The first surveys, implemented in Argentina and Mexico, confirmed trends of moderate DR with even higher NNRTI mutation prevalence in naïve individuals (>10%) [18, 19]. In Brazil, where sufficient regional data exist, high levels of DR were observed in macro-urban centers of Rio de Janeiro and São Paulo. This level of detail is unavailable in other countries, but a convenience survey of pretreatment HIVDR in Managua, Nicaragua, suggested high resistance rates (19.4%) with increasing NNRTI resistance [20]. Taken together, data suggest that specific populations and regions may have higher DR rates.

CHINA

An estimated 850 000 HIV-infected persons live in China [21], 653 865 reported to the Chinese Center for Disease Control and Prevention, with 60% ART coverage [22]. The epidemic is concentrated in the southern/western provinces and areas affected by plasma donor outbreaks in the 1990s. The Myanmar-bordering Yunnan province, positioned along drug trafficking routes, accounted for 21% of infections in 2010 [23]. ART, provided by government programs since 2003, is available to all infected individuals since June 2016. VL testing began in 2008, and at the end of 2014, 90% of treated individuals had ≥ 1 VL test, but coverage varies among provinces, with anecdotal reports of significant delays in receiving results. A pilot survey monitoring early warning indicators was conducted in 2008 in 4 hospitals in Beijing and Yunnan provinces [24]. Drug supply adequacy has not been an issue in China; low loss to follow-up rates were reported, but on-time pill pickup (a surrogate adherence marker) ranged from 40% to 60% [24]. From 2010, HIVDR testing is recommended in virologic failure. A cross-sectional survey of acquired DR performed in 2014 on 765 patients treated for 9–18 months showed virological failure in 8.5%, half with DR [25]. Risk factors for DR included incomplete adherence and lower education levels. A meta-analysis in 2014 yielded a low pooled prevalence rate of 3.6% transmitted

DR, with apparent differences in major urban centers [26]. Several small studies have reported on DR in specific populations: 7.8% in 536 ART-naïve MSM in Beijing [27]; 5% in 320 newly diagnosed, ART-naïve individuals in the western district of Yunnan province [23]; and 65% “any” resistance in patients switching to second-line in Henan province in 2010–2011 [28]. Taken together, data suggest that although DR rates appear low, there may be significant heterogeneity not captured by current methodologies, and better national and regional estimates of resistance with adequate quality control are needed.

INDIA

On World AIDS Day 2016, India, the world’s second most populated country and third largest HIV epidemic with 2.1 million infections, announced the millionth free ART initiation [17]. This important accomplishment is added to the demonstrated decline in annual AIDS-related deaths by 54% and new infections by 32% between 2007 and 2015. Despite these optimistic achievements, significant challenges remain, including risk of HIVDR development/transmission and its consequences. Emerging in-country data, currently not nationally representative, demonstrate 3%–7% transmitted DR [29–31], 59%–96% first-line failure DR [32–35], and up to 50% second-line failure DR [36, 37].

The Indian epidemic is heterogeneous, geographically concentrated, and in high-risk groups (eg, people injecting drugs, female sex workers, MSM, transgender individuals, bridge populations [38–41]). HIVDR challenges are an amalgamation of “conventional” global and India-specific issues. Continued potential for HIV transmission due to late detection, low testing, limited linkage between counseling/testing and treatment centers, and low testing of partners of HIV-infected people can increase transmitted DR risk. Limited openness to key populations increases their invisibility, linkage challenges, and unsuccessful treatment, further supporting DR development. Limited laboratory access, particularly no routine VL testing, mostly limited by financial and infrastructural constraints, can lead to late failure detection and DR [42]. Limited adherence tracking mechanisms, retention and loss to follow-up, and high disease burden further raise this risk [43]. A weak drug supply chain management, limited stocks, and long drug procurement procedures have led to drug supply interruptions, even in India, which manufactures drugs globally [44]. Regimen exposure not per guidelines, without clear disclosure, further predisposes to the development of DR. Moreover, family and culture-related problems, including HIV-associated inequality, stigma, and discrimination, especially among key populations [45, 46], prevent disclosure leading to lack of support, further compromising adherence and enabling DR. Last, in a highly pluralistic health sector like India, with multiple medicine systems in diverse institutional settings and a privatized healthcare system, differences in outcomes associated with care settings, including DR development, must be recognized [47]. Such challenges, in the setting of overloaded ART centers and

overwhelmed staff, further compromise quality of care, setting the stage for DR development [48, 49].

Despite challenges, achievements in battling HIV in India are recognized, and are significantly enhanced by recent governmental commitments to implement test and treat, routine VL monitoring, and third-line ART [50].

CONCLUSIONS

Some critical challenges to prevent DR are common across regions. Uninterrupted access to drug and laboratory supplies and routine and timely virological monitoring are critical elements of successful programs. Ministries of health should strengthen the efficiency of supply chain processes and the laboratory capacity to address these priorities and ensure long-term effectiveness and sustainability of their treatment programs. More unique regional challenges must also be recognized and targeted. Beyond the implementation of WHO-recommended DR surveillance tools [51], more sophisticated, efficient, feasible, and accessible surveillance technologies and strategies, discussed in this supplement, should be developed and implemented to derive reliable data. The research community has an important role to play in this regard. Taking advantage of the momentum and global political commitment to address antimicrobial resistance more broadly, governments should include in their antimicrobial resistance strategies specific actions to tackle HIV DR [52] by strengthening surveillance, health service, laboratory and supply-chain systems and networks, and improving the quality of care to minimize DR emergence, accumulation, and transmission.

Notes

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