Interplay Between Transmitted and Acquired HIV Type 1 Drug Resistance: Reasons for a Disconnect

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(See the major article by Yang et al on pages 28–38.)

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Despite the impressive achievements of antiretroviral treatment (ART), human immunodeficiency virus type 1 (HIV-1) drug resistance remains a relevant obstacle to effective control of HIV-1 replication at both the individual and population levels. Suboptimal treatments and medication nonadherence are the major causes for selection of acquired drug resistance (ADR) in treated patients. Consequent to the development of ADR, drug-resistant HIV-1 can be transmitted to ART-naive individuals (transmitted drug resistance [TDR]), both from treated patients and from other untreated subjects carrying TDR mutations (so-called onward transmission).

After an initial increase in the rate of HIV-1 drug resistance, more-recent population studies from resource-rich settings have documented a decreasing prevalence of ADR mutations in patients with virological failure while receiving ART (ie, those who do not achieve or maintain undetectable plasma HIV-1 RNA levels). This phenomenon is observed for all the 3 historical drug classes (nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTI], and protease inhibitors [PIs]) in several European cohorts [1, 2]. Despite this decrease in the prevalence of ADR mutations, which represents the initial source of circulating HIV-1 drug resistance, the prevalence of TDR mutations has remained stable, at around 8%–10%, in these countries over the years [3]. As a possible explanation for this apparent paradox, TDR can be significantly fed by onward transmission of drug-resistant strains among clusters of untreated individuals [4, 5]. Moreover, resistant mutants have shown multiple rounds of onward transmission, sometimes occurring over several years [6]. In addition, different resistant variants are transmitted with different efficiency. Indeed, the reverse transcriptase mutation M184V is highly prevalent in patients who are not responding to treatment but rarely observed in untreated patients [7], because of its marked reduction in viral fitness and transmission efficacy [8]. Understanding the dynamics and interplay between ADR and TDR at a population level is necessary to optimize the effectiveness of ART-based interventions and appropriately target critical issues.

In this issue of *The Journal of Infectious Diseases,* Yang et al, from the Swiss HIV cohort Study (SHCS), present their work trying to explain the apparent paradox between the decreasing prevalence of ADR mutations and stable or fluctuating prevalence of TDR mutations in their country [9]. The SHCS is highly representative of the whole country's epidemic, and the authors performed a number of retrospective resistance tests on stored samples, allowing them to obtain an accurate picture of the prevalence of TDR mutations even in calendar years when testing was not yet routinely performed. It is sometimes difficult to obtain correct estimates of the prevalence of TDR mutations, owing to the waning of drug-resistant variants over time, but Yang et al tested a large number of recently infected patients, more accurately reflecting true estimates of the prevalence TDR mutations, another strong point of their study. The authors examined 2421 recently infected, treatment-naive patients and 5399 nonresponding patients. They correlated the prevalence of TDR mutations with that of ADR mutations observed during the previous calendar year. Their major observations were that ADR mutation prevalences, after peaking at 85% in 1998, dropped continuously

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since then, reaching a plateau at approximately 38% in 2009. Meanwhile, the overall prevalence of TDR mutations in the recently infected population was 9.1% and tended to increase over calendar years, but there were marked fluctuations over time between 2% and 15%, with temporary reductions coincident with the introduction of new drug classes in the treated population (boosted PIs and integrase inhibitors) and new increases in periods when new drug options were not available. They found that the prevalence of TDR mutations showed a negative association with the population viral load in the nonresponding patients in the previous year. Moreover, when repeating the correlation using individual-mutation analysis for the most prevalent drug-resistance mutation for each drug class, they showed that the viral load of the NRTI resistance mutation M184V was correlated with its increased transmission, while this did not happen for K103N (NNRTI resistance) and L90M (first-generation PI resistance). On the contrary, the rate of transmitted L90M decreased with increasing population viral load among nonresponding patients carrying L90M from the previous year. These data indicate persistence of L90M within transmission clusters over several years despite the end of the use of first-generation PIs that have driven its selection in the treated population in the early ART era. The different ratio of the prevalence of ADR to TDR with specific mutations may be explained by the different fitness cost of the individual mutants, with lower fitness mutations surviving the transmission bottleneck only with high infectious dose, which may also be indicative of regained fitness through compensatory mutations.

Based on their longitudinal analysis of ADR and TDR in the intensively monitored context of Switzerland, Yang et al concluded that the prevalence of TDR mutations is influenced by the introduction of new drug classes and significantly driven by onward transmission within clusters of treatment-naive patients, with mechanisms that may be independent from their prevalence in nonresponding populations. Although the study was well conceived and performed, the authors acknowledge as a possible hidden confounder the immigration of patients with TDR patterns and rates reflecting ART scenarios from low-middle income countries. Indeed, they found a lower prevalence of TDR mutations in patients carrying non-B HIV-1, possibly a consequence of limited ART coverage in the country of origin. In addition, the inverse correlation between the overall population viral load of nonresponding patients and TDR mutation prevalences could also be explained by a lower probability of ADR at higher viral loads, owing to lack of adherence or undisclosed treatment interruption. Two European studies [10, 11] showed a reduced probability of detecting ADR with an HIV-1 RNA load of >100 000 copies/mL, when individuals are much more infectious.

Switzerland represents the optimal example of a resource-rich setting with universal access to ART and extensive use of HIV-1 drug resistance and viral load testing. Nevertheless, this study delivers the negative message that even under the optimized clinical and public health circumstances taking place in Switzerland, it does not seem possible to decrease the prevalence of TDR mutations. As a consequence, the challenge to contain the HIV-1 epidemic and, especially, transmission of drug-resistant HIV-1 in resource-limited countries may be much more difficult than anticipated. In resource-limited settings, ART scale up is now reaching a large proportion of HIV-1–infected persons [12]. However, only 2 treatment regimens are generally available. Initial therapy is based on an NNRTI with 2 NRTIs, and the second regimen is based on a boosted PI with 2 NRTIs, including 1 new NRTI [13]. Evidence shows that nonresponse to first-line therapy is associated with extensive NNRTI drug resistance, frequent selection of M184V, and increasing prevalence of other NRTI resistance mutations, depending on the timing of drug resistance testing [14]. The activity of second-line regimens based on a boosted PI is often preserved, although patients accumulating NRTI resistance may by necessity end up being treated with functional PI monotherapy, which eventually leads to an increased risk of treatment failure [15, 16]. Because of these limitations, the prevalence of TDR mutations is increasing in these settings [17], and its impact on future mortality may be significant [18]. Based on the Swiss data presented in the article by Yang et al, the limitation of the drug options in resource-limited countries could lead to increasing TDR mutation rates over time in this setting. However, a recent modeling study suggests that viral load monitoring in ART-treated populations may represent the most cost-effective measure to limit TDR mutations in several low-to-medium-income countries [19]. Evidence from Yang et al's SHCS work suggests that early detection and treatment of drug-naive patients, apart from limiting the spread of HIV per se, may also play a primary role in limiting the spread of TDR.

Despite undoubted progress in ART, HIV drug resistance will continue to be a major obstacle in our efforts to control the epidemic. To more accurately direct global resources, which are strongly based on the use of an effective ART, multicomponent approaches are needed, aimed at limiting ADR by appropriate monitoring and treatment, as well as by detecting and treating new infections, including those with TDR mutations.

Notes

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