

Transmitted HIV-1 Drug Resistance: Are We Seeing Just the Tip of an Epidemiological Iceberg?

Joanne Stekler^{1,3} and Robert W. Coombs^{1,2,3}

Departments of ¹Medicine and ²Laboratory Medicine and ³Center for AIDS and STD, University of Washington, Seattle

(See the article by Smith et al., on pages 356–60.)

Because of increasing recognition of HIV-1 drug resistance among antiretroviral (ARV)-naive individuals, national guidelines now recommend HIV drug-susceptibility genotyping before the start of HIV treatment (a moderate-strength recommendation based on expert opinion) and consideration of genotyping at the time of HIV diagnosis (an optional-strength recommendation based on expert opinion) [1]. In this issue of the *Journal*, Smith et al. [2] present data that further support the persistence of ARV drug-resistant HIV in seminal plasma and provide evidence for the horizontal transmission of HIV drug resistance in the absence of ARV therapy. Captain Edward John Smith ignored several warnings about icebergs and went down with the RMS *Titanic*; are Davey M. Smith and colleagues giving us a warning about a metaphorical HIV drug-resistance iceberg that we should heed to avoid a similar fate?

The authors describe 5 recently infected subjects who had HIV with nonnucleoside reverse-transcriptase inhibitor (NNRTI) mutations that were detectable in both blood and seminal plasma by a population-based sequencing assay. In 1 subject, the NNRTI mutation persisted in seminal plasma for at least 1179 days after HIV infection. Although the study size is too small to draw definitive conclusions about differences in the persistence of resistance mutations between blood and seminal plasma, this analysis provides further evidence that, at least in some individuals, transmitted drug-resistant virus can persist for >2 years after HIV infection [3–6]. Additional longitudinal studies are needed to determine differences in the detection and persistence of HIV drug-resistance mutations in different compartments over time.

The impact of drug resistance on “transmission fitness” (i.e., the relative ability of viruses to infect susceptible hosts and to maintain a reproductive number >1, thus guaranteeing the continued transmission of drug-resistant virus) is another area in need of further study. In their study of partner pairs, Smith et al. found very similar drug-resistance patterns in the blood and seminal plasma of both the previously treated source and the ARV-naive recipient partner in transmission pair 1. This case is a counterexample to the supposition that different selection pressures

exist between the blood and genital tract of individuals who receive ARV therapy [7, 8] and that HIV drug-resistance mutations may confer low transmission fitness, compared with wild-type virus, in individuals infected with a mixture of mutant and wild-type viruses [9–11]. Further study of transmission pairs is essential to assess whether the transmission of resistant virus is dependent on the quantity of virus in the genital tract, whether transmission fitness is correlated with the replication capacity of virus in the blood or genital tract, and what other factors may be associated with a relative advantage for the transmission of a drug-resistant virus.

On the population level, it is unclear whether ARV-experienced individuals represent the primary source of transmitted HIV drug resistance or whether secondary transmission occurs primarily from ARV-naive individuals (as is described for transmission pair 2) and which source contributes most to the forward transmission of drug-resistant virus [12]. Transmission of drug resistance from ARV-naive sources has been previously documented after mother-to-child [13] and heterosexual [14] transmission. It is intriguing to consider whether individuals with primary HIV infection (PHI) are not only more likely to transmit HIV infection [15] but also may contribute disproportionately to the transmission of HIV drug resistance [12]. HIV RNA levels in seminal plasma

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Reprints or correspondence: Dr. Joanne Stekler, Box 359931, Harborview Medical Center, 325 Ninth Ave., Seattle, WA 98104 (jstekler@u.washington.edu).

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are highest during the first few months after HIV acquisition [16], and sexual transmission from source partners with PHI contributes to a significant proportion of overall HIV incident infections [15, 17–20]. If the risk of transmission of HIV drug resistance is associated with increasing HIV RNA levels in the genital tract, then perhaps this transmission risk provides an additional impetus for HIV prevention efforts to identify individuals with acute HIV infection using pooled nucleic acid testing algorithms [21, 22]. Unfortunately, because the risk of HIV transmission likely affects the rate of transmitted HIV drug resistance and, conversely, HIV drug resistance likely affects the risk of HIV transmission, complex mathematical modeling will be required to more fully understand the population dynamics of HIV drug resistance [23, 24].

ARV resistance is an emerging issue in both resource-poor countries with limited ARV experience and industrialized nations in which ARVs have been used for >2 decades [25]. In countries with limited ARV experience, ARV rollout programs ideally should be coupled with HIV drug-resistance surveillance programs [26]. In industrialized countries, incomplete public health surveillance has left uncertainty about whether secular trends exist in transmitted HIV drug resistance (as reviewed in [27]). It is clear, however, that the number of persons infected with multidrug-resistant (MDR) HIV is increasing [27], and cases of extremely drug-resistant (XDR) HIV have been described in New York City [28] and, recently, in Seattle, Washington [29]. It is very likely that many cases of XDR HIV remain undiagnosed because of limited use of drug-resistance genotyping and that some diagnosed cases remain unreported outside of epidemiological surveillance studies. Given that population-based genotyping can only identify HIV drug-resistance mutations that occur in >10%–50% of the viral subpopulation [30–35], it is also likely that the prevalence of HIV drug resistance, MDR HIV, and XDR HIV would

be significantly greater if more-sensitive assays were used for the detection of drug resistance [36, 37].

The clinical implication of transmitted HIV drug resistance detected by standard genotyping is not clear [27, 38–43]. However, the potential impact of primary drug resistance on disease progression and blunting of the response to initial ARV therapy suggest that hitherto-unseen hazards may be lurking below the therapeutic surface. If sensitive resistance assays become more widely available and are used without appropriate clinical validation, there could be some unanticipated consequences. For example, HIV care providers might avoid convenient first-line agents that require fewer pills and less-frequent dosing. This might lead to a decrease in adherence because of the greater complexity of initial ARV regimens. As a consequence, the best intentions could lead to a paradoxical increase in the prevalence of HIV drug resistance. Given the potential risks and lack of clear benefits, we should confirm that the use of highly sensitive resistance testing improves immunological and virological outcomes before a new standard of care is implemented. If there is in fact true equipoise about whether transmitted drug resistance affects clinical outcome, then it behooves investigators to design and support randomized clinical trials to validate the utility of highly sensitive resistance testing.

Ultimately, our therapeutic task is to stop HIV transmission as early as possible, to mitigate the transmission of drug-resistant HIV, and to avoid the epidemiological drug-resistance iceberg. Should we screen patients for high levels of genital HIV RNA and for viral resistance in genital secretions, to counsel patients about the potential risk for transmission of drug-resistant HIV? Should we be more diligent about prescribing ARVs with good penetration into genital fluids? Will the use of ARVs to prevent HIV transmission in serodiscordant couples decrease HIV transmission but eventually increase the risk of transmission of resistant virus? These and

many other important questions remain unanswered but warrant further discussion and study.

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