HIV Treatment Decisions and Transmitted Drug Resistance

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(See the article by de Mendoza et al. on pages 227–32)

The first observation of the transmission of zidovudine-resistant HIV was reported by Erice et al. in 1993 [1]. Since then, investigators from North America and Europe have reported highly variable estimated prevalences of transmitted drug resistance [2–6]. These estimates range from ~5% to ~25%, and such studies are almost uniformly limited by their relatively small sample sizes, nonuniform resistance testing methodologies, and differences in study populations with respect to HIV-associated risk behaviors and geographic differences, which influence HIV subtype prevalence. None of these studies represents a true surveillance system that measures HIV drug resistance among individuals with primary HIV infection, but, rather, they represent convenience samples of high-risk people within the geographic region of interest, which ultimately limits the generalizability of the observations.

In this issue of Clinical Infectious Diseases, de Mendoza et al. [7] report an inverse correlation between the proportion of individuals with chronic HIV infection and undetectable plasma virus load (i.e., nontransmitters) and the proportion of newly infected individuals identified with drug-resistant virus. Specifically, they note that the proportion of newly infected patients with drug-resistant virus was greatest during the years when the smallest proportion of chronically infected patients had detectable plasma virus loads. The authors identify several limitations of their study, including variation in sample sizes of newly infected patients from year to year and the use of individuals with undetectable plasma virus load as a surrogate marker for both the effectiveness of potent antiretroviral therapy and, conversely, the proportion of “potential transmitters” within the population each year. The authors also note that the population of potential transmitters was quite heterogeneous and included an unknown proportion of treatment-naive patients for whom the presence of drug resistance should be negligible. Perhaps more important is the fact that the newly infected patient population represents a relatively small proportion of patients in this study (0.4%–3.5% of the total). One must be cautious about conclusions drawn from such a small convenience sample. Several annual sampling intervals represented <10 patients with recent HIV infection and only 1 or 2 individuals with transmitted drug resistance. Despite these limitations, the proportion of patients identified by de Mendoza et al. [7] as having primary drug-resistance mutations does decrease from ~30% to 10% from 1997 to 2003. This stable or decreasing prevalence of transmitted drug resistance is supported by other reports from North America [3] and Europe [6] during a similar time period.

There are multiple possible explanations for these observations. First, patients with chronic HIV infection (whose antiretroviral treatment experience is largely composed of suboptimal, nonpotent antiretroviral therapy, such as sequential monotherapy, during the earliest years of HIV treatment) are more likely to harbor multiple drug-resistance mutations as a direct result of suboptimal treatment. This may be evident in the de Mendoza et al. [7] study population as well, because 14 of the 20 individuals identified with transmitted drug resistance harbored zidovudine resistance–associated mutations in reverse transcriptase at positions 215 and 41. As salvage treatment options diminish for these patients, they are less likely to survive and will be less likely over time to transmit drug-resistant virus. Second, although the use of effective antiretroviral therapy in a greater proportion of the chronically infected patients is one potential hypothesis to explain the decrease in transmitted drug resistance, another, equally plausible explanation is a gradual trend toward delayed initiation of potent antiretroviral therapy among patients with chronic, drug-susceptible HIV infection between 1997 and 2003 [8, 9] and the more frequent interruption of therapy as a result of the toxicity of available antiretroviral medications [10, 11]. Third, individuals treated with antiretrovirals who
have undetectable virus loads in the blood may continue to have virus in their genital secretions that harbors drug resistance and that can be transmitted to others [12, 13].

Consensus guidelines changed significantly between 1996 and 2004 [8, 9] and generally reflect an increasingly delayed approach to the institution of antiretroviral therapy. Although a recent study clearly demonstrated a direct correlation between HIV transmission risk and plasma virus load [14], it has not yet been demonstrated on a population level that antiretroviral treatment reduces the risk of HIV transmission. In fact, 3 separate studies suggest that this may not be the case. These studies compared the mean plasma virus load between antiretroviral-naive and treated patients and showed no significant difference between the groups [15–18]. These data suggest that the mean virus loads among many different treated populations (i.e., those treated with aggressive or conservative regimens) and untreated populations are comparable. This dampens the optimism that antiretroviral treatment with available therapy could reduce the pool of potential transmitters in a population and, therefore, be an effective prevention strategy, as has been suggested elsewhere [19].

The prevalence of resistance to HIV drugs in treated populations is high [16, 20]. In the United States, >60% of HIV-infected individuals who were receiving medical care during the period of 1996–1998 had virus loads of >500 copies/mL [16]. Of these individuals, 76% were infected with HIV that was resistant to ≥1 class of antiretroviral medications. Estimates of the frequency of transmission of drug-resistant virus, compared with drug-sensitive virus, suggest that drug-resistant virus is transmitted only ~20% as frequently as expected [17] and that some drug-resistant strains may be more efficiently transmitted than others [21]. However, once transmitted, drug-resistant virus persists for months to years without reversion to wild-type [22–26] and limits both the treatment options and virological responses of the newly infected individual [2, 27]. Because of this risk, current treatment guidelines recommend the performance of resistance testing before antiretroviral therapy is started for newly infected individuals [28]. Although the prevalence of transmitted drug resistance does not appear to be increasing in countries that have had the greatest historic access to antiretroviral therapy, it is difficult to determine a single simple explanation for this observation. The rate of transmitted drug resistance is influenced by a complex interaction of multiple variables, including changing rates of high-risk behavior, changing use and efficacy of antiretroviral therapy, and the relative transmission fitness of different viral variants. In this issue, de Mendoza et al. [7] offer a provocative hypothesis to explain how treatment efficacy may influence the transmission of drug resistance; however, it is premature to alter current treatment practices solely on the basis of the desire to limit the transmission of drug-resistant HIV.

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References

23. Barbour JD, Hecht FM, Wrin T, et al. Persis-