Challenges in the Study of Patients with HIV Type 1 Seroconversion

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(See the article by Madec et al. on pages 1350–4)

In this issue of Clinical Infectious Diseases, Madec et al. [1] report that spontaneous and sustained clearance of HIV type 1 (henceforth, HIV) viremia (defined as repeated HIV RNA levels in plasma of $<500$ copies/mL) is not uncommon in persons recently infected with HIV. Undetectable viremia occurred in 4% and 6% of 426 individuals in the French SEROCO cohort within 1 and 2 years after infection, respectively, and was observed in $\sim7\%$ of these persons at 5 years after infection. Low-level viremia is recognized to be correlated with long-term nonprogressive HIV infection [2]. Thus, it is an important clinical end point for studies of interventions during acute-phase and early-phase HIV infection. Nevertheless, use of low-level viremia to interpret the impact of treatments in nonrandomized studies of patients with HIV seroconversion (i.e., HIV seroconverters) is problematic.

Discrepancies in reported frequencies of undetectable viremia among HIV seroconverters highlight the difficulty of using such studies to interpret the results of treatment trials. Among an Amsterdam cohort of 123 HIV seroconverters, plasma HIV RNA level was $<1000$ copies/mL in 14% of untreated HIV seroconverters 1 year after seroconversion, but only 2% had virus loads $<1000$ copies/mL 5 years after seroconversion [3]. These data suggest a substantially higher incidence of baseline low-level viremia among HIV seroconverters than that reported by Madec et al. [1] but a lower incidence of sustained low-level viremia 5 years after seroconversion. Long-term rates of undetectable viremia have also varied in studies of HAART-treated HIV seroconverters. Of 14 HIV seroconverters who were selected on the basis of intact HIV-specific lymphoproliferative responses after having received HAART, 4 (29%) had episodes of viremia of $<500$ copies/mL during $\geq 1$ structured treatment interruption (STI), and 1 (7%) had sustained plasma HIV RNA concentrations below that level a median of 5.3 years after infection [4], which is similar to the results reported by Madec et al. On the other hand, in 2 other small studies of HAART-treated HIV seroconverters who had received early antiretroviral therapy and, in some cases, HIV vaccination, sustained viremia of $<500$ copies/mL within the first 1.5 years of discontinuation of antiretroviral treatment did not occur [5, 6].

Discrepant prevalences of undetectable viremia during follow-up are likely to be, at least in part, due to differences in the study participants’ characteristics. Although as many as 90% of HIV seroconverters experience some sort of clinical illness associated with primary HIV infection [7], most individuals are unaware that their symptoms could indicate HIV infection, and many do not seek medical treatment. Of those individuals who seek medical care for symptoms of primary infection, the correct diagnosis is often overlooked during medical evaluation [7–9]. Severe and prolonged symptoms [10–12], as well as a history of having sought medical attention for symptoms of primary infection [13], have been correlated with higher virus loads and more-rapid progression of disease. Thus, studies that rely heavily on the identification of HIV seroconverters by clinical symptoms are likely to be biased toward individuals with aggressive disease. Such bias is substantially less likely in studies in which HIV seroconverters were identified retrospectively from archived serial specimens obtained from men who have sex with men, such as in the Multicenter AIDS Cohort Study (MACS) [14] or the Amsterdam cohort study [3]. Nevertheless, even these studies contain inherent sources of bias. The study by Madec et al. [1], as well as previous studies [15], have shown that women, compared with men, have significantly lower plasma HIV RNA concentrations up to 5 years after seroconversion, suggesting that the MACS
and the Amsterdam cohort study overestimated virus loads in mixed populations of men and women. Individuals who are experiencing symptoms of seroconversion may not appear for required cohort-study visits, which may lead to discontinued participation in the study. Indeed, those rare individuals who develop opportunistic infections at the time of seroconversion and those who die from AIDS within the first year of seroconversion also would be less likely to be included in these cohorts, suggesting additional bias toward subjects with slower disease progression. Although behavioral correlates of disease progression have not yet been identified, it is not implausible that behavior that may predispose patients to rapid disease progression, such as multiple sex partners leading to superinfection [16], could be correlated with diminished participation in research studies.

Once HIV seroconverters are identified, there are additional potential sources of selection bias related to their enrollment in studies. Individuals who present with opportunistic infections or encephalitis during seroconversion and, consequently, have a poor prognosis may be excluded from participation in clinical trials because of those symptoms. Assessment of the potential effect of these issues on study findings requires that investigators report the reasons for exclusion of subjects or for discontinuation of participation, as well as provide a comparison of included and excluded subjects. Retention of subjects in a research study and the regularity of follow-up for study visits also could be affected by the rapidity and severity of disease progression. Decreases in CD4+ T cell counts and increases in virus loads may precipitate treatments that result in removal of subjects from a study, thereby creating a bias in the data set toward subjects with less-aggressive disease. Indeed, it was reported previously that 41% of HIV seroconverters enrolled in the SEROCO cohort between February 1996 had received antiretroviral therapy before they developed AIDS [17]. In the study by Madec et al. [1], 13 individuals in the SEROCO cohort were observed to have undetectable viremia at year 5, and individuals who received antiretroviral therapy were excluded from the analysis. Consideration of this observation in combination with the reported rate of undetectable viremia of 6.7% at year 5 suggests that less than half of the initial 426 subjects remained eligible. Thus, in this study, the reported rate of undetectable virus load at year 5 may have overestimated the true rate among HIV seroconverters.

The interval between study visits also may introduce bias into results such as the identification of subjects who spontaneously achieve and maintain undetectable viremia. Virus load measurements taken closer together have more correlation than those taken farther apart [18]. Therefore, subjects with 1 undetectable virus load are more likely to demonstrate undetectable viremia if the follow-up virus load measurement is taken sooner rather than later. Subjects with only 2 measurements also have a reduced chance of success, compared with subjects with multiple measurements [19]. Average time between visits, follow-up time, and recruitment year should be considered as potential confounders in logistic regression analyses. Long intervals between study visits can lead to an overestimation of the duration of undetectable viremia [20]. Between visits, patients may have detectable virus loads that are either missed or not identified until the following visit. Statistical methods that fail to compensate for intervals in data collection can lead to misleading results [21, 22].

The multiple potential sources of bias involved in recruitment and retention of HIV seroconverters in studies indicate that it is perilous to use historical data as a control in the interpretation of clinical outcomes among HIV seroconverters. Unfortunately, data from an uncontrolled study of 8 HIV seroconverters [23] were widely interpreted to show that early treatment of HIV infection with HAART followed by STI led to a lower virus set point, implying significant clinical benefit. This interpretation fostered a widespread perception that withholding therapy from HIV seroconverters, particularly those with acute HIV infection, was unethical. As a consequence, few randomized clinical trials of treatment of HIV seroconverters have been performed [24]. The results of longer follow-up now suggest that the clinical benefits initially observed were not sustained over the long term in HIV seroconverters with acute-phase infection who received early treatment followed by STI [4]—although, again, these studies were not controlled. The lack of randomized controlled clinical trials of interventions among patients with acute and recent HIV infection has been a great disservice to HIV-infected patients and has left clinicians caring for such patients without clear treatment guidelines. It is imperative that clinicians and researchers realize the importance of randomized controlled studies in validating or refuting anecdotal and uncontrolled observations of the treatment received by HIV seroconverters. Although studies of HIV seroconverters pose multiple logistical, statistical, and clinical challenges, the proper design and performance of these studies are critical to gain better insight into HIV immunopathogenesis and optimal treatment strategies.

Acknowledgments

Financial support. This work was funded by the National Institutes of Health through the following grants: Immunopathogenesis of HIV-1 Infection (grant P30 AI 054907) and Colorado AIDS Clinical Trials Unit (grant U01 AI32770).

Potential conflicts of interest. All authors: no conflicts.

References


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