EDITORIAL

Antiretroviral Therapy in Early HIV Infection

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Antiretroviral therapy (ART) has transformed the course of human immunodeficiency virus (HIV) infection. More than two dozen HIV drugs are now available in resource-rich environments, and newer combination regimens have ever-increasing efficacy and decreasing toxicity. As a result, life expectancy and quality of life are close to normal for HIV-infected persons with access to these medications.[1]

As more is learned about the long-term adverse effects of persistent viremia and the benefits of ART, HIV treatment guidelines have recommended earlier and earlier initiation of therapy. In resource-rich environments, guidelines frequently recommend treatment for nearly all persons who receive a diagnosis of HIV infection.[2,3] Current World Health Organization guidelines for more resource-limited settings recommend treatment for anyone with less than 350 CD4+ T cells per cubic millimeter of blood, a higher level than in previous guidelines.[4] Despite growing acceptance of the early-therapy approach, there are no randomized clinical trials demonstrating a clear clinical benefit for immediate treatment in acute or early HIV infection.

In this issue of the *Journal*, two studies address the timing of ART in relation to primary HIV infection and provide compelling support for early treatment on the basis of CD4+ T-cell restoration in peripheral blood.[5,6] The two studies assess the effect of early treatment quite differently, and both rely on surrogate measures of disease progression rather than on clinical outcomes.

Le et al.[5] investigated the effect of continuous therapy from the time of acute or early HIV infection on CD4+ T-cell recovery at 48 months in a prospective, nonrandomized observational study of a cohort of mostly white men in the United States who were infected with clade B virus and treated with standard-of-care combination ART regimens over a period from 1996 to 2010. They found that there was a transient and partial restoration of CD4+ counts during the first 4 months after the estimated date of HIV infection in untreated controls and that treatment initiated during this early period enhanced CD4+ T-cell recovery. A total of 64% of those treated within 4 months after the start of infection reached the primary CD4+ end point of 900 or more cells per cubic millimeter in peripheral blood within 48 months, whereas only 34% of those whose initial treatment was delayed beyond 4 months recovered CD4+ cell numbers to a similar degree. The likelihood of reaching the primary end point was lower and the rate of recovery was slower in those who initiated treatment more than 4 months after the estimated date of infection.

The accompanying article by the Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) Trial Investigators[6] reports on the effect of short-course ART on CD4+ T-cell decline in men and women infected with either clade B or clade C virus. Enrollment of 366 participants occurred in eight countries between 2003 and 2007; they were randomly assigned to 12 or 48 weeks of highly active ART or to no treatment. The primary end point was a peripheral-blood CD4+ cell count of less than 350 per cubic millimeter or initiation of long-term ART; certain HIV-specific immune responses were also measured. With an average of 4.2 years of follow-up, only those treated for 48 weeks had a reduced hazard ratio for the primary end point, but this could not be linked to immune func-

tion. No clinical benefit was evident. A post hoc analysis was performed to determine whether timing of therapy in relation to acute infection had an effect, as was shown in the study by Le et al. There was a trend ($P=0.09$) toward greater delay to the primary end point among participants in the 48-week treatment group who were treated earlier. In this treatment-discontinuation study, a potential virologic benefit could also be examined. Thirty-six weeks after participants stopped therapy, plasma viral loads in the 48-week ART group were lower by 0.44 $\log_{10}$ copies per milliliter than were viral loads in the control group at 36 weeks after randomization. The reason for this effect was not clear but did not appear to be related to the aspects of HIV-specific T-cell immunity that were measured.

What are we to conclude from these studies? Both provide evidence that greater CD4+ cell recovery is achieved with earlier initiation of therapy during primary infection, but both fall short of defining a clear clinical benefit for such early treatment. Both articles support the current Department of Health and Human Services and International Antiviral Society–USA guidelines for resource-rich settings, which suggest ART for nearly everyone who is HIV-infected, regardless of the stage of infection. Those recommendations, however, remain based on expert opinion and circumstantial data rather than on randomized clinical trials, and although the data presented in these two articles support this overall conclusion, they do not provide ironclad proof of clinical benefit. When resources are severely constrained (e.g., in developing countries), the bar for proving benefit deserves to be higher, and treatment emphasis should still be on saving the maximum number of lives by treating a greater number of patients at later stages of disease.

In interpreting these studies, it is important to consider several additional points. In clinical practice, it is difficult to identify persons at early stages of HIV infection because of limitations in diagnostic technology.[7] Thus, the participants in the current studies probably initiated therapy well after peak viremia, and extensive damage may already have been done. Still earlier therapy might provide additional benefit — for example, by limiting damage to the immune system and reducing the extent of viral reservoirs[8]; persons who receive a diagnosis shortly after infection may also have a better chance of responding to "cure" strategies. These potential benefits will need to be carefully evaluated in future studies. Similarly, whether more prolonged therapy courses than were used in the current studies would provide additional benefit is unclear. One recent study (Virological and Immunological Studies in Controllers after Treatment Interruption), which has been presented in abstract form, suggested that patients who began ART within 10 weeks after the start of infection and continued for up to 3 years were more likely to control HIV replication without medications after subsequent treatment discontinuation than were historical controls[9]; although this finding is of anecdotal interest, it requires confirmation in controlled trials.

Early treatment of HIV infections also has potential public health implications, possibly justifying this approach in situations in which resources allow. Treatment of infected partners clearly decreases the risk of subsequent infection to others,[10] and the risk of HIV contagion to uninfected partners appears several times higher from acutely infected persons than from chronically infected persons, presumably because of higher viral loads during primary infection.[11] Thus, early treatment during acute infection may offer substantial benefits beyond those to the infected person. It will be critical to increase HIV testing of patients with symptoms suggestive of possible acute primary infection, as well as to screen asymptomatic persons at high risk for infection, using the most current techniques available for early detection, including plasma HIV RNA measurements and fourth-generation antibody assays.[7]

The question of when to initiate ART remains a difficult one, particularly in resource-limited settings,[12] but the studies in this issue of the *Journal* provide strong supportive evidence suggesting a benefit for early therapy. Future studies of treatment even earlier in the course of infection may show additional benefits, and a population of such patients will be an important study group for eventual studies aimed at "cure" of infection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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