Recent HIV-1 Infection: To Treat or Not to Treat, That Is the Question

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(See the article by Hogan et al, on pages 87–96.)

The first description of acute human immunodeficiency virus (HIV) infection as a mononucleosis-like syndrome was published in 1985 [1]. Since that time, it has become clear that recent viral infection may be accompanied by a variety of symptoms, at least partly related to the mode of acquisition [2], and may often be asymptomatic [3]. Despite this apparent lack of specificity of clinical presentation, it still remains possible to identify individuals who have acute/early HIV infection by educating healthcare providers and patients alike to consider this diagnosis in the context of a significant systemic illness in an individual with a recent risk exposure. Alternatively, a strategy of repeated testing for infection (using fourth-generation tests to detect the virus as well as the antibody response) in some groups may be employed. The main reason to develop such a strategy would be the availability of an intervention to change the natural history of the disease.

An early controlled trial of a 6-month course of zidovudine monotherapy in primary HIV infection showed a clinical effect on minor opportunistic infections over a 15-month period, as well as significant increases in CD4+ cell counts [4]. Interestingly, study recruitment was ended prematurely, at least in part because practitioners of the day believed that the correct course of action was to initiate treatment and were unwilling to randomize their patients to observation. In an accompanying editorial, Ho reasoned that the observed benefit related to a marked effect on viral dynamics at a time when viral turnover was at its peak [5]. He further proposed that when more effective treatment modalities were available, the benefit would be even greater. Over time, an immunologic benefit of intervention (the preservation of HIV-specific T-helper cells) was demonstrated to support the rationale for intervention [6]. Since then, enthusiasm for the systematic use of highly active antiviral therapy in this setting has waned, with the benefit of interrupted therapy expected to be modest and without long-term benefit [7].

The current Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents states that “The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time” [8].

It is in this nebulous context that the important work of Hogan and colleagues is published in this issue of the *Journal of Infectious Diseases* [9]. The Setpoint Study (ACTG A5217) was a randomized clinical trial in which patients who had been infected with HIV in the previous 6 months were assigned to receive a 36-week course of antiretroviral therapy (with tenofovir-emtricitabine administered along with lopinavir-ritonavir) or observation. The principal end point was a lowering of the virologic set point at week 72 (thus comparing 36 weeks of therapy followed by 36 weeks of observation with 72 weeks of observation). The secondary end point was the time required to meet eligibility for therapy based on clinical, virologic, and/or immunologic criteria. As with the original trial of zidovudine monotherapy in this setting, the study was discontinued prematurely. The Data Safety Monitoring Board (DSMB) determined that study subjects who did not receive immediate treatment were progressing to require such treatment on clinical grounds at such a rate that an actual comparison of virologic set points between the 2 study groups would not be possible.

Of the planned 150 participants, 130 had been enrolled before the closure of...
the study. The key finding of interest to the DSMB was that 7 of 66 (11%) of subjects initially assigned to treatment required treatment during study follow-up, compared with 23 of 64 (36%) who were initially assigned to be observed. Clinical disease progression (Centers for Disease Control and Prevention category B or C events) was noted in 5 cases, 4 in patients who were simply observed. The median until antiretroviral therapy was required was 70 weeks in those not initially randomized to receive it.

Hogan and her team are to be commended for their dedication in designing and recruiting this protocol and publishing its results. This is to be compared with the SPARTAC trial of patients with early infection for which updated results have recently been presented [10]. A total of 371 individuals were enrolled and randomized to observation or 12 or 48 weeks of therapy. The 48-week course of therapy is associated with a 32% reduction in the risk of reaching a CD4+ count of <350 cells/mm3 during a median follow-up period of 4.2 years. This difference is statistically significant ($P = .03$) and is associated with a persistent virologic benefit of $0.44 \log_{10}$ copies/mL that persisted for 60 weeks. It is not, however, associated with a demonstrable clinical benefit, but it should be noted that fully 46% of study participants (172 of 371) required initiation or reinitiation of antiviral therapy during the conduct of the study. Another large North American study of patients with acute or early HIV infection, CTN 214, enrolled 117 subjects, and outcomes of that study are expected to be presented within the next year.

So what are we to make of these results? The fact that any individual benefit can be demonstrated is, perhaps, remarkable. Immune preservation and reduction in the latent pool of HIV-1–carrying CD4+ T cells seems to require intervention at the earliest possible time of acute infection [11]. It is difficult enough to identify and engage patients within months of exposure, let alone days or weeks. If this were the standard, it would limit us to offering intervention to the privileged few. It is, therefore, heartening that even in those who have become infected as remotely as 6 months before their first presentation, a measurable advantage of immediate treatment can be demonstrated. This seems to be achieved at little or no cost to the patient, in terms of either drug-related toxicity or emergence of drug resistance. In the SPARTAC trial report, particular note is made of the identical virologic response rates in subjects in whom therapy was reinitiated after interruption, compared with those in whom it was initiated for the first time [10]. Furthermore, an important finding of ACTG A5217 is that an initial 36-week course of treatment at presentation may delay the need to restart treatment for longer than those 36 weeks. Thus, over the lifetime of the patient, there will be less cumulative drug exposure. This could be personally beneficial, in addition to the obvious savings in healthcare expenditures that could result. As an extremely positive benefit, a short course of treatment may allow hosts to control viral replication on their own without further intervention, making them, effectively, into long-term nonprogressors. The ACTG A5217 study adds to the considerable body of evidence showing that this particular outcome is unusual, and the desire to achieve it should not be used to justify intervening in the setting of early HIV infection.

In light of recent reports from the HPTN 052 study [12] showing the benefits of early initiation of antiretroviral therapy in reducing sexual transmission rates for HIV infection, the case could be made for antiretroviral therapy as a public health intervention in persons with early HIV infection. Circulating viral load is typically quite high, often several million copies per milliliter of plasma. The risk of transmission increases 2–3-fold for every 10-fold increase in viral load [13], so the benefit of rapid viral load reduction with antiviral therapy could be quite great with respect to transmission.

One of the main findings of ACTG A5217 is the documentation of the rate of disease progression after recent HIV infection. In those assigned to the non-treatment arm of the protocol, more than half required treatment on medical grounds within 18 months, paralleling the findings of the SPARTAC trial. For those whose HIV infection are newly diagnosed and who consider that antiviral therapy may be many years away, this helps put things into better perspective. It is often not possible or medically indicated to start taking medications at first presentation. However, the discussion can now be framed in an evidence-informed manner. Immediate treatment may be associated with a better prognosis, decreased risk of disease transmission, and, possibly, less lifetime exposure to antiretroviral therapy. However, if treatment is delayed, it is likely to be needed within the next 18 months, so the approach should be to actively plan for it as part of the care plan from the very beginning.

It is often said that knowledge is power. This important study certainly empowers us, as well as the men and women living with HIV infection, to optimize disease management from the moment these patients enter our care, regardless of when their infection may have been acquired.

**Notes**

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**References**