When To Start Therapy for HIV Infection: A Swinging Pendulum in Search of Data

Among the fundamental questions that need to be addressed regarding the treatment of patients with HIV infection are the strategy questions of when to start therapy, what therapy to start, and when to change therapy. The current inability to eradicate HIV, which has led to a need for long-term therapeutic strategies, and the increased recognition of long-term drug toxicities have made these questions compelling. Unfortunately, the answers remain unclear.

Over the past 7 years, in the absence of definitive evidence, several professional societies and governmental entities have provided guidelines for the initiation of antiretroviral therapy (ART). These organizations have suggested guidelines that deal with a wide range of issues—from the treatment of all patients with viral loads greater than 10 000 copies/mL (1) to the more recent recommendation to definitely begin therapy only in patients with CD4+ T-cell counts less than 0.200 × 10^9 cells/L. Guidelines for the best approach to patients with CD4+ T-cell counts between 0.200 and 0.350 × 10^9 cells/L remain uncertain (2). As stated in the most recent edition of the guidelines from the U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation (3), “While randomized clinical trials provide strong evidence for treating patients with <200 CD4+ T cells/mm³, the optimal time to initiate antiretroviral therapy among asymptomatic patients with CD4+ T-cell counts > 200 cells/mm³ is not known.” Unfortunately, this swing in the pendulum of expert opinion from early, aggressive therapy to a more cautious approach was not concluded from data derived from randomized trials with clinical outcomes. It was due to the influence of data from observational studies, case reports, and short-term trials that showed unexpected toxicities associated with treatment and little evidence that earlier intervention had any impact on progression to AIDS (4–9).

The study by Palella and colleagues in this issue (10) attempts to swing the pendulum back toward earlier intervention. This analysis of data from 1994 to 2002 from the Centers for Disease Control and Prevention-sponsored HIV Outpatient Study (HOPS) observational cohort divided patients into groups based on CD4+ T-cell count (0.201 to 0.350 × 10^9 cells/L, 0.351 to 0.500 × 10^9 cells/L, and 0.501 to 0.750 × 10^9 cells/L). The investigators compared mortality rates of patients who began ART in their initial CD4+ T-cell group with those of patients who deferred therapy until their CD4+ T-cell count declined to a lower group. For patients with initial CD4+ T-cell counts between 0.201 and 0.350 × 10^9 cells/L, initiating therapy at this time rather than waiting until CD4+ T-cell counts declined to less than 0.201 × 10^9 cells/L was associated with reduced mortality (15.4 vs. 56.4 deaths/1000 person-years, respectively; P < 0.001).

The work of Palella and colleagues is unique compared with other recent reports on this topic (4–7) because the authors compared survival for participants who began ART in a specific CD4+ group with that of participants in the same group who deferred treatment until their CD4+ T-cell counts declined to a lower CD4+ group. In contrast, other studies typically classified participants by CD4+ T-cell count at the time of initiation of treatment and thus compared risk for AIDS or death on the basis of CD4+ group at the time of initiation of therapy. By “starting the clock” at the same time for those who initiated and those who deferred therapy, Palella and colleagues overcame one of the problems of using observational data to decide when to start ART. However, like the other reports, these comparisons may be subject to confounding. Although Palella and colleagues adjusted for many potentially confounding variables (age, sex, race, insurance status, viral load at time of first ART, receipt of highly active antiretroviral therapy [HAART], and CD4+ T-cell count at time of first observation within each subgroup), the decision to start treatment probably involved several additional factors related to prognosis.

As the authors point out, another important limitation relates to statistical power. Overall, a total of only 53 end points (deaths) occurred during the follow-up period. Even for the subgroup that formed the basis for their main conclusion, the 399 participants in the 0.201 to 0.350 × 10^9 cells/L subgroup, the distribution of the 33 end points, once adjusted for known confounding variables, did not achieve statistical significance (hazard ratio, 0.57; P = 0.16). To directly address the question of whether to defer therapy in patients with CD4+ T-cell counts greater than 0.200 × 10^9 cells/L would require a randomized trial of considerable size. For example, a study of treatment-naive patients with CD4+ T-cell counts greater than 0.250 × 10^9 cells/L, randomly assigned to immediate or deferred therapy, would require 650 events to show a 20% difference in mortality between groups with 80% power. At a rate of progression of 1% per year, 65 000 patient-years of follow-up or a study of 6500 patients for 10 years would be required. While studies of this size exist in other areas (11, 12), they are the exception in HIV research.

We applaud Palella and colleagues’ novel approach to observational data; however, because of potential confounding factors and limited power, their data are unlikely to change current recommendations about when to initiate therapy. These data do, however, generate new uncertainty in this area and may motivate the design and conduct of trials that will contribute to this important debate. As one
views the global epidemic of HIV infection and the vast numbers of untreated patients, one also sees opportunities to perform studies that involve large sample sizes and that require long-term follow-up. The questions regarding treatment strategy are equally pressing and important for developed and developing countries. In developing countries, these questions can be addressed in a way that is consistent with the ethical principles of clinical research (13, 14) and that helps to develop the infrastructure required for delivery of state-of-the-art care to patients with HIV infection. Our enthusiasm to test the newest class of drugs, such as entry or integrase inhibitors, must be balanced by a need to define better strategies for the use of existing drugs.

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