Debate over the optimal time to initiate antiretroviral therapy for HIV infection is as old as the availability of effective anti-HIV treatment. As I've noted in several past editorials, there were cogent arguments on both sides,

HIV treatment guidelines issued by the US Department of Health and Human Services, in line with those of the International AIDS Society, recommend that most asymptomatic HIV-positive persons delay antiretroviral therapy until their CD4+ cell counts fall below 350/µL. Last year, I reported on a computer simulation of data from the Veterans Aging Cohort Study, which arrived at a very different conclusion. It involved 5742 HIV-infected patients and 11,484 matched, uninfected controls seen from 1997 through 2004. The HIV-positive cohort was selected for an initial low risk of HIV-related death on the basis of a threshold T-cell count of 500/µL. Their simulation showed that earlier therapy, starting at CD4+ cell counts around 500/µL, improved life expectancy in many of the scenarios evaluated, despite the fact that it hastened accumulation of resistance mutations and reduced future drug options.

This modeling study has now been confirmed in the real world: an analysis of the International Epidemiologic Databases to Evaluate AIDS (IEDEA), a global network of HIV clinics. In this analysis, 8374 asymptomatic HIV-positive persons participating in 22 US and Canadian treatment trials from 1996 to 2006 with CD4+ cell counts between 351/µL and 500/µL at study entry were examined. There were 2473 patients who began antiretroviral treatment immediately and the remaining 5901 opted to delay therapy. The relative hazard for death, with the immediate-treatment group as a reference, was 1.7 (range, 1.4 to 2.1). This result was highly significant (P < .001) and was unaffected when controlling for injection drug use or concurrent hepatitis C virus infection.

Dr Mari Kitahata, lead author of the study, noted, “This does impact on and differ from current guidelines and recommends treatment earlier in disease. All patients with a CD4 count 500 and below should receive antiretroviral treatment.”

Dr Daniel Kuritzkes, head of an AIDS treatment program at Harvard, who was not involved in the study, concurred. He felt that the data were “strong enough to change practice.” Given that the gold standard of evidence-based medicine, ie, a large, randomized controlled trial, is unlikely to yield comparable data for many years, I would agree. But not without several reservations.

Health issues beyond survival, including medication adherence and drug-related adverse effects, quality of life, drug resistance, and the effect of age, were not analyzed in the IEDEA study; these are far from trivial omissions. Returning to the Veterans Aging Cohort Study simulation, the use of antiretroviral therapy was associated with a 3.8-fold (range, 3.1- to 4.6-fold) increased hazard of non-HIV-related mortality. Non-AIDS cancer provided the highest comorbid condition, with a 2.4-fold risk, followed by congestive heart failure, with a 2.2-fold risk.

Risk of non-HIV-related mortality also varied greatly by age in the Veterans study. It was 2.3-fold higher for those aged 40 to 49 years but more than double that (5.4-fold) for those 60 years and older. For 30-year-olds, earlier initiation of antiretroviral therapy was always favored, regardless of the viral load (HIV RNA levels of 10,000 to 300,000 copies/mL or higher). For 50-year-olds, deleterious effects of an early initiation outweighed benefits until the CD4+ cell count fell below 200/µL, and the same was true for a cell count below 350/µL when the HIV RNA level was 300,000 copies/mL or above.

Concurrent with the release of the IEDEA study results, a group from South Africa reported that infants 6 to 12 weeks of age who began antiretroviral therapy at the time of HIV diagnosis were 76%
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less likely to die, and 75% less likely to otherwise progress clinically, than those who did not receive treatment until their CD4 counts declined or symptoms developed. In the same study, HIV-positive infants with CD4 percentages of 25% or higher were randomly assigned to 2 groups: a deferred-treatment group of 125 infants who received zidovudine, lamivudine, and ritonavir-boosted lopinavir when the CD4 percentage decreased to less than 20% or to less than 25% if the child was younger than 12 months or certain clinical criteria were met. The immediate-treatment group, with 252 infants, received the same antiretroviral regimen at the time of HIV diagnosis. Twenty infants (16%) in the deferred group died versus 10 (4%) in the immediate group (P < .001). Furthermore, HIV disease progressed in 32 infants (26%) in the deferred group versus 16 (6%) in the immediate group (P < .001). In the deferred group, this included 4 instances of Pneumocystis jiroveci pneumonia, 8 of HIV encephalopathy, 3 of cytomegalovirus (CMV) pneumonia or disseminated CMV infection, and 1 of esophageal candidiasis. Grade 3 or 4 adverse events, including anemia, neutropenia, and hypernatremia, were more common in the immediate-treatment group. The lead author of the South African study, Dr Avy Violari of the Perinatal HIV Research Unit in Johannesburg, was “alarmed” at how fast the disease progressed in these infants, noting that the findings “reinforce the view that there are no reliable predictors” for disease progression in such very young children. But the expense in drug costs, manpower, and adverse medication effects did not go unnoticed by Violari and colleagues. And among adults, whether in resource-rich or resource-poor countries, early identification of those who need therapy has been poor, and medication adherence remains an issue. The reported 95% or higher adherence level demanded by initial PI-based regimens may no longer be a prerequisite for an excellent treatment response with newer PI-boosted or NNRTI-based regimens; yet, a study of medical records from the HIV/AIDS Drug Treatment Program in British Columbia indicated that the risk of hospitalization was 1.9-fold higher in those with suboptimal adherence to regimens containing newer antiretroviral agents.

In a recent review of the 2008 reauthorization of the President’s Emergency Plan for AIDS Relief (PEPFAR), in which funds were increased from the current level of $15 billion to $48 billion over 5 years, public health and legal expert Dr Larry Gostin reiterated what many of us have known since the discovery of antiretroviral therapy: “Treatment is, at best, a stop-gap measure that requires enormous resources because of the life-long need of millions of persons. . . . The cost, moreover, could increase considerably with the increase in drug-resistant forms of HIV.” The recognition that earlier treatment of HIV-infected infants and adults may block HIV progression and save more lives will not make this any less costly. In the absence of any palpable evidence for a breakthrough in AIDS vaccine research, other prevention strategies remain our best hope. Finally, this is a fitting point in the history of HIV/AIDS treatment to announce my retirement as editor in chief of The AIDS Reader. I was founding editor 18 years ago and wrote in my inaugural editorial that “AIDS is a catastrophe,” but quickly modified that statement appreciating the hope offered by novel agents “that act against HIV at various stages in its life cycle.” I could not have foreseen how great a promise that was. Five years later, we had the first truly effective antiretroviral combination therapies. And now, near the close of my tenure, I had the opportunity to organize and moderate a think tank at MIT, sponsored by The Foundation for AIDS Research (amfAR), on the possibility of curing AIDS, exploring the first proof-of-concept that this indeed had been accomplished. This involved the case of an HIV-positive man in whom acute leukemia developed and, following 2 allogeneic stem cell transplants using a single donor homozygous for the Δ32 CCR5 HIV coreceptor mutation, is free of leukemia and HIV. Both active RNA and latent proviral DNA forms of the virus are no longer detectable, and he has been off all anti-HIV therapy for almost 2 years. According to the first press report in the Wall Street Journal:

“The case was presented to scientists earlier this year at the Conference on Retroviruses and Opportunistic Infections. In September, the nonprofit American Foundation for AIDS Research, or AmFAR [sic], convened a small scientific meeting on the case. . . . The scientists agreed that the patient is ‘functionally cured.’”

As suggested by Dr David Baltimore, its significance surpassed this unusual patient, providing “a virtual 'proof of principle' for gene-therapy approaches” to curing AIDS. Given this, I can only imagine the exciting reports that the next editorial team will have for you. I wish them the best of luck on this intriguing journey.

References:
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References


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