HIV JournalView


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Table of Contents

When to Start Antiretroviral Therapy?

Faye A, Le Chenadec J, Dollfus C, et al. *Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1*. ***Clin Infect Dis. December 1, 2004;39(11):1692-1698.***

Holmberg SD, Palella FJ Jr, Lichtenstein KA, Havlir DV. *The case for earlier treatment of HIV infection*. ***Clin Infect Dis. December 1, 2004;39(11):1699-1704.***

Cohen CJ, Boyle BA. Editorial commentary: antiretroviral therapy: the "when to start" debates. Clin Infect Dis. December 1, 2004;39(11):1705-1708.

Few topics in HIV medicine evoke as much heated debate as the subject of when to start antiretroviral therapy. The December 1, 2004 issue of Clinical Infectious Diseases provides a relevant research paper and excellent viewpoint articles.

In the first research article, Albert Faye and his team examined the effects of early versus delayed antiretroviral therapy in 83 HIV-infected infants in the French Perinatal cohort. Given the potential for life-long use of combination HIV treatment for HIV-infected infants and children, this group of patients amplifies the concerns about long-term drug toxicities and the interest in strategies that might decrease the total time of drug exposure. Additionally, about one fifth of infected children go on to develop a more severe form of HIV disease (including HIV encephalopathy) and an understanding of prognostic factors for children at risk are lacking.

In this study, early drug therapy was defined as initiation of treatment before the infants turned 6 months. Baseline characteristics of the 2 study groups were similar. Forty of the infants received early multi-drug therapy: 74% of the infants received a regimen of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), 10% of the infants received a regimen of 3 NRTIs and 3% received 2 NRTIs with an non-nucleoside reverse transcriptase inhibitor (NNRTI). Forty-three infants received delayed therapy -- 18 initiated treatment between ages 6 and 24 months and 14 started dual-drug treatment before age 24 months and 11 patients did not receive treatment before 24 months of age.

Among the early treatment group, there were *no* AIDS-defining events during the study. By

contrast, in the delayed group, there were 7 AIDS-defining events, including 3 cases of encephalopathy. All AIDS-defining events occurred *before* the initiation of highly active antiretroviral therapy (HAART). Indeed, no other demographic or laboratory characteristic (such as CD4+ cell count, CD8+ cell count or HIV viral load) was predictive of having an AIDS-defining event. The authors conclude that only receipt of multi-drug therapy *before* age 6 months was protective against having the severe form of childhood HIV disease.

In my view, because of the high proportion of patients that develop early AIDS manifestations, this population of infant patients provides a temporally compressed view of adult HIV disease. The suggestion that treatment of the entire population of infants protects 20% from developing severe disease, therefore, is not surprising, but rather reinforces the concept that HAART results in immune reconstitution. Lacking from the analysis of this small cohort (and potentially interesting long-term follow-up) is a description of the *negative* consequences of the treatment, if any. It is this intersection of benefit and risk that forms the core of the debate concerning when is the optimal time for the initiation of antiretroviral therapy.

There are two accompanying articles also in this journal on this topic that are well worth the read. The first, authored by Scott Holmberg and other prominent clinical investigators (including some who have collaborated with me on research), summarized recent information about the timing of starting HAART. While there was initially some controversy regarding the authors' incomplete disclosure of potential conflict (which once again raised awareness of how important it is for writers to disclose pharmaceutical honoraria since it clearly has the potential to bias), I believe that the points raised by this viewpoint article nevertheless deserve attention.

Indeed, many of the endpoints used to evaluate the merits of early or late initiation of treatment are measures of advanced AIDS; potential benefits of HAART could result in the prevention of non-AIDS, HIV complications. Revelations by Lichtenstein[1-2] reveal the relationship between nadir CD4 + cell count and the development of lipodystrophy and peripheral neuropathy -- two complications that were once believed only to be the result of drug exposure.

HAART, once burdened by high pill burden and side effects, is clearly easier to adhere to now than in the mid 1990s; drug resistance risk also appears to be improved with the newer treatment combinations, particularly those regimens that include a boosted PI. Lastly, the notion that HAART, once started, can never be discontinued is also being challenged by strategic clinical trials. Hence, a contemporary view of the risks and benefits of HIV treatment also must include a revisit of the risks and benefits of HIV-related adverse events.

In the second editorial, Boyle and Cohen (both contributors to TheBodyPro.com) provide a concise review of arguments, both pro and con for early and late initiation of treatments. The article also reviews advances in treatment and the understanding of HIV complications. Boyle and Cohen point out that while newer regimens are both easier to take and less toxic, there are remaining disadvantages, including toxicity and drug resistance. In an era of increasingly evidence-based decision-making for HIV, we must hope and wait that the optimal study that addresses these issues will be conducted. Until that time, the debates will continue.

When to Stop Antiretroviral Therapy?

Skiest DJ, Morrow P, Allen B, et al. *It is safe to stop antiretroviral therapy in patients with preantiretroviral CD4 cell counts >250 cells/µL*. ***JAIDS. November 1, 2004;37(3):1351-1357.***

Antiretroviral therapy has been shown to successfully result in immune reconstitution in a wide variety of patients, including those who have a low CD4+ cell count. With all the recent attention to the question of *when* to start antiretroviral therapy, an offsetting question looms: Is it ever safe to stop therapy? These discussions began years ago when the pill burden and scheduling of treatment was much more complex and patients pushed for treatment interruptions -- structured or unstructured. The focus of structured treatment interruptions (STIs) has always been on minimizing the physical and financial (and, lest we forget, emotional) costs of antiretroviral therapy.

This discussion is particularly relevant to many of today's patients, who were started on treatment with a CD4+ cell count typically higher than current treatment initiation recommendations.[3] It would be clinically important to find out if these patients can safely discontinue therapy.

The current study, from clinical investigators Daniel Skiest et al in Texas, attempts to answer this question. The researchers describe the experiences of 107 HIV-infected patients who underwent a

treatment interruption. For analytical purposes, study end points were a Centers for Disease Control and Prevention category B or C adverse event, or time to reaching a CD4+ cell count $\leq$250 cells/mm^3. The patients' median pre-antiretroviral therapy CD4+ cell count and viral load were 463 cells/mm^3 and 4.35 $\log_{10}$, respectively.

Patients lost an average of 65 CD4+ cells each month for the first 2 months following discontinuation of therapy, with a slower rate of decline thereafter. Two patients experienced a retroviral syndrome following treatment interruption. The median time it took for patients to reach a study endpoint was approximately 9 months. Importantly, having a pre-antiretroviral therapy CD4+ cell count greater than 250 was highly protective from reaching an endpoint (odds ratio = 0.156, P = .03).

This study corroborates previous analyses from Baltimore[4] and Europe.[5] In aggregate, these studies show that HIV treatments can be safely discontinued without significant clinical events. The studies all correlate patients' ability to remain off antiretroviral therapy to their nadir CD4+ cell count. Thus, for people who initiated treatment with a CD4+ cell count greater than 350 (which, as mentioned earlier, is higher than current treatment guidelines recommend), discontinuation can be a reasonably safe treatment strategy. Of concern for such patients is the risk of the emergence of drug resistance, particularly among those who are receiving antiretroviral medications with very different half lives, such as NNRTIs, which have long half lives, and the much shorter-lived NRTIs. The optimal management of the discontinuing of such regimens remains to be elucidated. No matter what, the available research data is limited to retrospective, observational cohorts. The ideal prospective study remains to be fully presented, but the ongoing behemoth Strategies for Management of Anti-Retroviral Therapy (SMART) study[6] should hopefully answer some of these concerns.

Effectiveness of Antiretroviral Therapy in Older Patients

Grabar S, Kousignian I, Sobel A, et al. *Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age*. ***Results from the French Hospital Database on HIV. AIDS. October 21, 2004;18(15):2029-2038.***

Although the success of combination antiretroviral therapy in suppressing HIV replication and facilitating immune recovery has been well documented, the majority of these studies have focused on young, mostly gay men, since they have been the patient group that has formed the epicenter of the AIDS epidemic in the United States and Europe. As the faces of the AIDS epidemic begin to change in the developed world, attention has begun to focus on special populations of persons -- groups of patients who differ by racial, ethnic or other demographic parameters. Of particular interest for many physicians as our patient population ages, is the effectiveness of antiretroviral treatments in older patients.

This article details the French Hospital Database analysis of an approximately 3,000-person cohort of HIV-infected patients initiating HAART. (The French Database[7] is one of the largest prospective databases, containing patients from all over France. More than 89,000 patients have been included since 1989.) Of the 3,015 study subjects, 401 were older than 50. The study compared the effectiveness of treatment of those who were younger than 50 years of age to those who were over 50. The median time of follow-up was 31.5 months.

In this cohort, older patients tended to have a lower CD4+ cell count than younger patients (median 193 versus 252 cells/mm^3) and a higher plasma viral load. In addition, nearly one third of the older patients had already developed AIDS at study enrollment, compared with 20.2% of the younger patients. There was no significant difference in the year of HAART initiation or the type of medications prescribed.

Younger patients were found to have statistically a significantly greater CD4+ cell rise while on HAART than the older patients. The absolute difference in CD4+ cell change was modest, only 3 and 6 cells/mm^3 per month for patients with baseline viral load <100,000 and >100,000 copies/mL, respectively.

On the positive side, virologic responses showed that older patients achieved undetectable viral loads more rapidly than younger patients. After 6 months, 77% of the older patients had undetectable viral loads compared with 71% of the younger patients. Curiously, older patients were 23% more likely to ever achieve an undetectable viral load -- hazards ratio (HR) = 1.23 (95% CI, 1.11-1.38).

On the negative side, older patients were found to be significantly more likely to have an AIDS-defining event; the hazards ratio of clinical progression for the older group was 1.52 (95% CI, 1.15-2.00). In particular, the incidence of cytomegalovirus disease (HR = 5.1), HIV encephalopathy (HR = 2.8) and Kaposi's sarcoma (HR = 2.3) was significantly higher in the older group than in the younger group.

This important study characterizes the natural history and effectiveness of antiretroviral therapy in older patients with HIV. While observational cohort studies are inherently limited by the challenge of recruitment or subject retention, the large size and long-term follow-up of this study are its strengths.

The finding that older patients tend to have less of a CD4+ cell increase than younger patients (despite virologic suppression) corroborates other studies and is useful in providing counsel to patients. While the quantitative difference in rates of CD4+ cell rise is small, the clinical significance of this difference is demonstrated by the large differences in the risk of AIDS-defining events. Missing is an important analysis of this risk of AIDS-defining event that controls for baseline CD4+ cell count or viral load.

Nevertheless, these data have important immediate implications for the clinical management of older patients with HIV, since we now know that even among those with virologic suppression, there is the necessity to aggressively monitor and provide appropriate preventive medicine to avoid AIDS-defining events.

Even while we try to understand whether this increased risk is due to delayed diagnosis and entry into the study or an intrinsic difference in immune function in older patients, it is clear that there is a need to increase surveillance for HIV among both the community and healthcare provider, so that older people get tested and if positive don't wait too long to get treatment and HIV-infected older people are carefully monitored for AIDS-related opportunistic infections.

Effectiveness of Hepatitis A Vaccination

Wallace MR, Brandt CJ, Earhart KC, et al. *Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects*. ***Clin Infect Dis. October 15, 2004;39 (8):1207-1213.***

It's hard to believe that it's taken this long, but until now there has been no study that demonstrates the effectiveness and safety of hepatitis A vaccination to prevent this serious and common form of hepatitis among immunodeficient persons. While hepatitis A virus disease does not appear to be more severe among persons with HIV, hepatitis A viremia persists for a longer duration.[8]

This later point raises the potential public health implications of vaccination in this population of persons, since longer duration of viremia could mean that hepatitis A infected, HIV-infected persons could readily transmit the virus to others. Hepatitis A immunization with inactivated vaccine is recommended for persons with HIV infection, though data on the safety and effectiveness of such a strategy is untested.

In the current double-blinded study, 180 HIV-infected adults were randomized to receive inactivated hepatitis A vaccination (VAQTA, Merck) or placebo. Patients were stratified by baseline CD4+ cell counts of $\geq$300 cells/mm^3 or <300 cells/mm^3. These HIV-infected persons were compared in a non-blinded fashion to age- and weight-matched HIV-uninfected individuals. Vaccine was administered by usual clinical practice, at 0 and 24 weeks. Immunogenicity was measured by hepatitis A IgG.

The overall seroconversion rate among the HIV-infected subjects at week 28 of the study was high -- 94%. Among the group of subjects with CD4+ cell counts more than 300, the seroconversion rate was similar to the uninfected control group, with 100% of the subjects seropositive. Among the trial participants with CD4+ cell counts less than 300, the vaccine was still immunogenic, but fewer subjects seroconverted (87%).

Adverse events were common, but were generally minor in severity. One limitation of this conclusion is the relatively small sample size of this study -- small enough that rare adverse events might not be observed. There was no significant impact on CD4+ cell count or plasma HIV viral load during the study and no differences between those subjects who received vaccine or

placebo.

This study demonstrates the safety and effectiveness of hepatitis A vaccination among HIV-infected individuals. Not surprisingly, the immunogenicity of the vaccine was lower among persons with more advanced immunosuppression.

These results have immediate clinical implications. Firstly, the data provides clear evidence for recommending that hepatitis A vaccination be part of the routine preventive medicine of HIV-infected individuals. Additionally, since the relative effectiveness appears to wane with this vaccine (as it does with other neoantigens), vaccination strategies should target those individuals with a higher CD4+ cell count -- indeed, the very individuals who might defer initiation of antiretroviral treatments.

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Footnotes

1. Lichtenstein KA, Armon C, Baron A, Moorman AC, Wood KC, Holmberg SD, and the HIV Outpatient Study Investigators. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV Outpatient Study cohort. Clin Infect Dis. January 1, 2005;40(1):148-157.

2. Lichtenstein KA, Delaney KM, Armon C, et al, and the HIV Outpatient Study Investigators. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. JAIDS. January 1, 2003;32(1):48-56.

3. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. US Dept of Health and Human Services; October 29, 2004.

4. Tarwater PM, Parish M, Gallant JE. Prolonged treatment interruption after immunologic response to highly active antiretroviral therapy. Clin Infect Dis. December 1, 2003;37 (11):1541-1548.

5. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS. February 20, 2004;18(3):439-446.

6. Smart Trial. Available at: www.smart-trial.org.

7. The French Hospital Database on HIV. The Forum for Collaborative HIV Research Web site. Available at: www.hivforum.org/cohorts/The%20French%20Hospital%20Database.pdf.

8. Ida S, Tachikawa N, Nakajima A, et al. Influence of human immunodeficiency virus type 1 infection on acute hepatitis A virus infection. Clin Infect Dis. February 1, 2002;34(3):379-385.

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