

Balancing Adherence Concerns with the Risks of HIV Disease Progression

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(See the brief report by Braithwaite et al. on pages 822–6)

The appropriate time to initiate antiretroviral therapy (ART) for HIV infection is an area of much debate and some scientific study. In the absence of opportunistic infection, HIV-related symptoms, pregnancy, or comorbidities that may trigger the use of ART (e.g., hepatitis B), treatment guidelines have focused primarily on the CD4⁺ lymphocyte count and plasma HIV RNA level and have suggested immunologic and virologic thresholds for the initiation of ART [1, 2]. These thresholds are an attempt to balance the benefits of therapy with the limitations of therapy, the major limitations being the development of drug resistance and/or drug toxicity. The rapid development of new antiretroviral agents and the results of recent clinical trials that support higher rates of efficacy and lower toxicity with contemporary treatment regimens have led to recent changes in treatment guidelines, including recommendations to initiate ART at somewhat higher CD4⁺ cell counts [1, 2]. Recent data also suggest that earlier initiation of ART may be beneficial in pre-

venting serious non-AIDS conditions, such as renal, hepatic, and cardiovascular diseases [3]. However, current treatment guidelines also emphasize the individualization of therapy, and one of the important assessments in determining individual patient readiness is whether the patient is likely to adhere to therapy. Adherence to ART is critical to long-term success, and many clinicians may defer therapy if nonadherence is a significant concern. Potential problems resulting from nonadherence include both patient-specific issues, such as the development of drug-resistant infection and the loss of future treatment options, and a public health issue regarding the potential for transmission of drug-resistant HIV.

In this issue of *Clinical Infectious Diseases*, the study by Braithwaite et al. [4] used a computer simulation of HIV disease progression to estimate the potential benefits of ART among patients who initiate treatment for HIV infection at different CD4⁺ cell count thresholds and with different levels of adherence to therapy. This model incorporates estimates regarding HIV disease progression, HIV-related mortality, the development of drug resistance, and the risk of drug toxicity. The current study cites previous work by the same group [5–8] that has validated this model, including an analysis that found that outcomes obtained using their model were comparable with published out-

comes from cohorts of HIV-infected patients. In the current study [4], the authors varied the CD4⁺ lymphocyte count at which ART was initiated, including thresholds of 500, 350, and 200 cells/ μ L. In their model, they also stratified patients by the level of adherence, ranging from 50% to 100% adherence to therapy. They then estimated patient benefit in terms of life expectancy and quality-adjusted life-years. Somewhat surprisingly, initiating ART at a CD4⁺ cell count of 500 cells/ μ L led to an increased life expectancy at all levels of adherence, including for patients who were only 50% adherent to therapy. Highly adherent patients received the greatest benefit. The study concluded that deferral of ART because of adherence concerns may actually lead to worse patient outcomes. In their model, the benefits of therapy were less apparent when medications were assumed to have higher toxicity.

The benefit of ART for patients with incomplete adherence in this model likely rests on the fact that CD4⁺ cell counts are still maintained above levels than would be seen in patients who are not receiving ART, even without complete viral suppression. These findings are similar to those of some of the earliest studies of antiretroviral monotherapy and 2-drug combinations that documented both immunologic and virologic benefit, as well as improved clinical outcomes, despite the

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lack of complete viral suppression and the development of drug resistance. Somewhat more surprising is the finding that nonadherent patients might still have good long-term outcomes. Implicit in recommendations to defer therapy for potentially nonadherent patients is the concern that the rapid accumulation of drug resistance will exhaust therapeutic options and lead to HIV disease progression. In this study, the benefits of initiating ART for patients with reduced adherence seemed to outweigh those concerns. Braithwaite et al. [4] freely discuss the limitations of their study, which include an insufficient precision to stratify results by different antiretroviral sequencing strategies and the inability to evaluate how increased transmission of drug-resistant virus might alter the outcomes of individuals with new HIV infection.

Should the results of this study alter our current approach to ART? There are several considerations when incorporating these findings into clinical practice. First, current assessments of adherence in the clinic vary, and providers are not always accurate in predicting who will adhere to therapy [9]. Second, the degree of adherence necessary for complete virologic suppression may vary on the basis of the particular antiretroviral regimen chosen [10]. Third, this study does not address short deferrals of ART and should not dissuade such deferrals for time-limited acute medical or psychological events, such as a mental health crisis or hospitalization for acute illness. Fourth, there are some patients whose adherence to therapy may be even worse than the worst-case scenario in this study. In other words, even with a greater threshold to accept the risks of nonadherence, certain patients at certain

times will still be poor candidates for therapy. Finally, antiretroviral management should still strongly emphasize the importance of adherence to therapy when initiating therapy and at each follow-up. The current study supports many other studies that clearly demonstrate that adherent patients experience better outcomes [1, 2].

Despite these considerations, this study [4] does suggest that the consequences of nonadherence may not be as bad as the consequences of delaying ART initiation. Clinicians will need to carefully balance adherence concerns with the risk of HIV disease progression, especially when therapy is deferred. Coupled with other recent studies that document better outcomes associated with earlier initiation of ART [3, 11], this study supports a more aggressive approach to ART, with the initiation of therapy earlier in the course of HIV infection and inclusion of patients for whom adherence to therapy is a concern. In the subset of patients who may be at risk for reduced adherence, attempts to monitor and improve adherence to ART are critical to achieve our current therapeutic goals of complete viral suppression, complete reconstitution of the immune system, and a normal life expectancy.

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References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and

Human Services. 3 November 2008. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 9 November 2008.

2. Hammer SM, Eron JJ, Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society–USA Panel. *JAMA* 2008;300:555–70.
3. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. Major clinical outcomes in antiretroviral therapy (ART)–naïve participants and in those not receiving ART at baseline in the SMART study. *J Infect Dis* 2008;197:1133–44.
4. Braithwaite RS, Roberts MS, Goetz MB, et al. Do benefits of earlier antiretroviral treatment initiation outweigh harms for individuals at risk for poor adherence? *Clin Infect Dis* 2009;48:822–6 (in this issue).
5. Braithwaite RS, Roberts MS, Chung CH, et al. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy: a decision model. *Ann Intern Med* 2008;148:178–85.
6. Braithwaite RS, Justice AC, Fusco JS, et al. Estimating the proportion of patients infected with human immunodeficiency virus who will die of co-morbid disease. *Am J Med* 2005;118:890–8.
7. Braithwaite RS, Shecter S, Roberts MS, et al. Explaining variability in the relationship between variability and HIV mutation accumulation. *J Antimicrob Chemother* 2006;58:1036–43.
8. Braithwaite RS, Chang CC, Shecter S, et al. Estimating the rate of accumulating drug mutations in the HIV genome. *Value in Health* 2007;10:204–13.
9. Chesney MA. The elusive gold standard. future perspectives for HIV adherence and intervention. *J Acquir Immune Defic Syndr* 2006;43(Suppl 1):S149–55.
10. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis* 2006;43:939–41.
11. Kitahata MM, Gange SJ, Moore RD. Initiating rather than deferring HAART at a CD4 count between 351–500 cells/mm³ is associated with improved survival [abstract H-896b]. In: Program and abstracts of the 48th annual Inter-science Conference on Antimicrobial Agents and Chemotherapy ((ICAAC)/Infectious Diseases Society of America (IDSA) 46th annual meeting. Washington, DC: ICAAC/IDSA, 2008.