EDITORIAL COMMENTARY

Running with Scissors: Using Antiretroviral Therapy without Monitoring Viral Load

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(See the article by Marconi et al. on pages 1589–97)

"As viral loads are not normally available in resource-limited settings it is recommended that programmes primarily use clinical, and, where possible, CD4 count criteria, in order to define treatment failure," the World Health Organization stated in 2004 [1]. As antiretroviral therapy is rolled out to resource-limited settings, will clinicians remember what has been learned?

In the beginning of the HIV/AIDS pandemic, clinicians and researchers were behind the curve. Unabated, AIDS ravaged communities, families, and individuals until clinicians, researchers, and HIV-infected volunteers were mobilized. Seven years after the first published reports of the disease that the world would come to know as AIDS, monotherapy with azidothymidine showed promise [2], but within 2 years, HIV drug resistance was found [3]. With dual-drug therapy, the development of drug resistance was delayed, and clinical benefits were somewhat enhanced [4, 5], but not until at least 3 antiretroviral medications from at least 2 different classes were combined did HAART emerge, providing greater virologic suppression, a broader barrier to the development of drug resistance, and longer-term clinical benefits [6, 7]. Researchers found that preventing viral evolution of drug resistance required suppressing viral RNA replication to undetectable levels in the peripheral blood using sensitive molecular techniques [8, 9].

Giving prescriptions to a patient does not guarantee that the patients will achieve an undetectable viral load. Incomplete medication adherence [10], insufficient drug levels [11], drug and food interactions [12], and acquisition of drug-resistant virus are among the many factors that can contribute to treatment failure [13–15]; therefore, HAART is not a "start-it-and-forget-it" treatment. It requires monitoring for optimal outcomes. Currently, the standard of HIV care in resource-wealthy settings relies on laboratory monitoring of the immune system using CD4 cell counts, of viral suppression using viral loads, and of the development of drug resistance using genotypic or phenotypic testing [16]. These approaches to monitoring therapy emerged in the context of clinical trials, and a delay in the clinical use of each technique occurred, because clinicians and scientists argued that patients did well clinically without these "expensive" studies. Eventually, each monitoring method was found to improve patient outcomes and to be cost-effective [17–22]. As the challenges of vaccine development became increasingly apparent, researchers found that HAART coupled with behavioral strategies was perhaps the only real tool to stem the tide of the epidemic for a long time [23–26]. Therefore, understanding and preventing drug resistance wherever HAART is used is essential to maintaining the value of HAART in the future.

In this issue of *Clinical Infectious Diseases*, Marconi et al. [27] add to the understanding [28–31] that, whether the setting is rich or poor in resources and whether HIV is subtype B or C, HAART failure and HIV drug resistance can still occur. Similar to other reports [32], Marconi et al. [27] demonstrate that subtype C virus can develop mutations that decrease susceptibility to HAART; however, the genetic changes that develop in subtype C virus are not always the same as those that develop in subtype B virus. Because of its prevalence in the developed world, subtype B is the best characterized of all HIV subtypes [33–36]; thus, most of what is known about the development of drug resistance is based on subtype B HIV [37]. However, subtype B virus accounts for only 10% of the burden of HIV infection worldwide, and subtype C is the most common subtype worldwide [38]. Because subtype C virus may differ from subtype B virus with regard to the devel-

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opment of drug resistance [39–42], researchers will need to be diligent in documenting the genetic determinants of drug resistance among circulating HIV genetic backgrounds (subtypes and recombinant forms) for the surveillance of transmitted drug resistance and to guide the clinical selection of HAART regimens.

Optimal clinical outcomes require maximal suppression of viral replication with combination therapy, and current World Health Organization recommendations to assess adherence, clinical findings, and changes in CD4 cell count cannot predict virologic HAART failure [43, 44]. In addition, drug-resistant HIV infection represents a real public health threat, because the transmission of such infection limits the usefulness of certain HAART regimens. Therefore, clinicians' thinking must shift from HAART being an emergency intervention in resource-limited settings (used until a vaccine is developed) to HAART being an intervention that must be sustained. Failing to use laboratory tools that monitor treatment success is like running with scissors; it is all quick and easy until someone falls down. Over a decade ago, researchers discussed whether to incorporate viral load monitoring in clinical care in resource-wealthy settings, because patients who were not monitored were less likely to achieve viral suppression and contributed to the substantial amount of drug-resistant viruses being transmitted in these locations. This experience should not be repeated. If a choice must be made between monitoring viral load or CD4 cell count during HAART, we believe that it would be more useful to monitor viral load than CD4 cell count. Monitoring CD4 cell count is important for determining when to start prophylaxis for opportunistic infection and HAART [45, 46], but HAART has a direct effect on viral replication, not on CD4 cell count.

Access to HAART must be expanded in the most sustainable fashion. Marconi et al. [27] provide compelling evidence for concrete recommendations to attain this goal. As HAART is introduced throughout the developing world, we recommend that (1) drug access plans should proceed rapidly and should not be delayed by the false perception that a successful vaccine will soon be available, (2) local laboratory and technical capacity to monitor HAART (including viral load and drug resistance testing) be developed, (3) the availability of second-, third-, and fourth-line HAART regimens be increased, (4) resources for the scientific discovery of cost-effective methods to deliver high-quality HIV care (such as monitoring for viral replication [47]) be developed, (5) surveillance for both acquired HIV drug resistance and transmitted drug resistance within treated populations be performed, and (6) the cost-effectiveness of all aspects of HIV care in resource-limited settings (including monitoring CD4 cell count, viral load, and drug resistance) over the short and longer term be determined to better inform the allocation of limited resources. While HAART is introduced to the developing world, researchers should follow the advice of Santayana [48] and remember history.

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References

1. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach, 2003 revision. **2004**. Available at: http://www.who.int/3by5/publications/en. Accessed 3 January 2008.
2. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. N Engl J Med **1987**; 317:185–91.
3. Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. Science **1989**; 243:1731–4.
4. Schooley RT, Ramirez-Ronda C, Lange JM, et al. Virologic and immunologic benefits of initial combination therapy with zidovudine and zalcitabine or didanosine compared with zidovudine monotherapy. J Infect Dis **1996**; 173: 1354–66.
5. Katlama C, Ingrand D, Loveday C, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients: a randomized controlled comparison with zidovudine monotherapy. JAMA **1996**; 276:118–25.
6. Gulick RM. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med **1997**; 337: 734–9.
7. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. JAMA **1998**; 279:930–7.
8. Gulick RM. 3-Year suppression of HIV viremia with indinavir, zidovudine and lamivudine. Ann Intern Med **2000**; 133:35–9.
9. Wong JK, Gunthard HF, Havlir DV, et al. Reduction of HIV-1 in blood and lymph nodes following potent antiretroviral therapy and the virologic correlates of treatment failure. Proc Natl Acad Sci USA **1997**; 94:12574–9.
10. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient compliance and drug failure in protease inhibitor monotherapy. JAMA **1996**; 276:1955–6.
11. Durant J. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt study. AIDS **2000**; 14:1333–9.
12. Robertson SM, Penzak SR, Pau A. Drug interactions in the management of HIV infection: an update. Expert Opin Pharmacother **2007**; 8:2947–63.
13. Paris D, Ledergerber B, Weber R, et al. Incidence and predictors of virologic failure of antiretroviral triple-drug therapy in a community-based cohort. AIDS Res Hum Retroviruses **1999**; 15:1631–8.
14. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med **1999**; 131:81–7.
15. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. N Engl J Med **2002**; 347: 385–94.
16. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA **2006**; 296:827–43.
17. Hornberger J, Holodniy M, Robertus K, Winnike M, Gibson E, Verhulst E. A systematic review of cost-utility analyses in HIV/AIDS: implications for public policy. Med Decis Making **2007**; 27:789–821.
18. Weinstein MC, Goldie SJ, Losina E, et al. Use

of genotypic resistance testing to guide HIV therapy: clinical impact and cost-effectiveness. Ann Intern Med **2001**; 134:440–50.
19. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med **1998**; 338:853–60.
20. Schackman BR, Gebo KA, Walensky RP, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care **2006**; 44:990–7.
21. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis **2006**; 194:11–9.
22. Kimmel AD, Goldie SJ, Walensky RP, et al. Optimal frequency of CD4 cell count and HIV RNA monitoring prior to initiation of antiretroviral therapy in HIV-infected patients. Antivir Ther **2005**; 10:41–52.
23. Freedberg KA, Kumarasamy N, Losina E, et al. Clinical impact and cost-effectiveness of antiretroviral therapy in India: starting criteria and second-line therapy. AIDS **2007**; 21(Suppl 4):S117–28.
24. Wolf LL, Ricketts P, Freedberg KA, et al. The cost-effectiveness of antiretroviral therapy for treating HIV disease in the Caribbean. J Acquir Immune Defic Syndr **2007**; 46:463–71.
25. Goldie SJ, Yazdanpanah Y, Losina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings–the case of Cote d'Ivoire. N Engl J Med **2006**; 355:1141–53.
26. STEP study: disappointing, but not a failure. Lancet **2007**; 370:1665.
27. Marconi VC, Sunpath H, Lu Z, et al. Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa. Clin Infect Dis **2008**; 46:1589–97 (in this issue)
28. Weidle PJ, Downing R, Sozi C, et al. Development of phenotypic and genotypic resistance to antiretroviral therapy in the UNAIDS HIV Drug Access Initiative—Uganda. AIDS **2003**; 17(Suppl 3):S39–48.
29. Spacek LA, Shihab HM, Kamya MR, et al. Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda. Clin Infect Dis **2006**; 42: 252–9.
30. Rodrigues R, Custodio RM, Bueno SM, et al. Prevalence of ARV resistance mutations and impact of genotyping test in HIV patients with advance disease in Sao Paulo, Brazil. J Clin Virol **2005**; 32:336–7.
31. Seyler C, Adje-Toure C, Messou E, et al. Impact of genotypic drug resistance mutations on clinical and immunological outcomes in HIV-infected adults on HAART in West Africa. AIDS **2007**; 21:1157–64.
32. Harrigan PR, Montaner JS, Wegner SA, et al. World-wide variation in HIV-1 phenotypic susceptibility in untreated individuals: biologically relevant values for resistance testing. AIDS **2001**; 15:1671–7.
33. Geretti AM. HIV-1 subtypes: epidemiology and significance for HIV management. Curr Opin Infect Dis **2006**; 19:1–7.
34. Shaw GM, Hahn BH, Arya SK, Groopman JE, Gallo RC, Wong-Staal F. Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome. Science **1984**; 226: 1165–71.
35. Wong JK, Hezareh M, Gunthard HF, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. Science **1997**; 278:1291–5.
36. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science **1997**; 278:1295–300.
37. Richman DD. HIV chemotherapy. Nature **2001**; 410:995–1001.
38. Hemelaar J, Gouws E, Ghys PD, Osmanov S. Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004. AIDS **2006**; 20:W13–23.
39. Wainberg MA. HIV-1 subtype distribution and the problem of drug resistance. AIDS **2004**; 18(Suppl 3):S63–8.
40. Pillay D, Walker AS, Gibb DM, et al. Impact of human immunodeficiency virus type 1 subtypes on virologic response and emergence of drug resistance among children in the Paediatric European Network for Treatment of AIDS (PENTA) 5 trial. J Infect Dis **2002**; 186: 617–25.
41. Gupta RK, Pillay D. HIV resistance and the developing world. Int J Antimicrob Agents **2007**; 29:510–7.
42. Kantor R, Katzenstein DA, Efron B, et al. Impact of HIV-1 subtype and antiretroviral therapy on protease and reverse transcriptase genotype: results of a global collaboration. PLoS Med **2005**; 2:e112.
43. Bagchi S, Kempf MC, Westfall AO, Maherya A, Willig J, Saag MS. Can routine clinical markers be used longitudinally to monitor antiretroviral therapy success in resource-limited settings? Clin Infect Dis **2007**; 44:135–8.
44. Garcia R, Badaro R, Netto EM, et al. Cross-sectional study to evaluate factors associated with adherence to antiretroviral therapy by Brazilian HIV-infected patients. AIDS Res Hum Retroviruses **2006**; 22:1248–52.
45. Freedberg KA, Scharfstein JA, Seage III GR, et al. The cost-effectiveness of preventing AIDS-related opportunistic infections. JAMA **1998**; 279:130–6.
46. Vijayaraghavan A, Efrusy MB, Mazonson PD, Ebrahim O, Sanne IM, Santas CC. Cost-effectiveness of alternative strategies for initiating and monitoring highly active antiretroviral therapy in the developing world. J Acquir Immune Defic Syndr **2007**; 46:91–100.
47. Fiscus SA, Cheng B, Crowe SM, et al. HIV-1 viral load assays for resource-limited settings. PLoS Med **2006**; 3:e417.
48. Santayana G. The life of reason; or, the phases of human progress. New York: C. Scribner's Sons, **1905**.