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 zidovudine 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 de-
ophant 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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