CD4 Cell Count–Guided Treatment Interruption: Be Smart and Wait for More Evidence

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(See the article by Nuesch et al. on pages 728–34)

The striking improvement of HIV infection–related morbidity and mortality after the introduction of HAART in the mid 1990s [1] was followed by the daunting realization that eradication of HIV infection is not possible with current antiretrovirals and that prolonged HAART leads to substantial abnormalities in the metabolism of glucose and lipids, which may accelerate the progression of atherosclerosis. Indeed, several reports have linked the use of combination antiretroviral therapy to an increased risk of cardiovascular disease [2, 3]. In addition, changes in body appearance, such as lipoaccumulation and lipoatrophy, as a result of HAART may negatively impact quality of life and long-term adherence to anti-HIV therapy.

These findings have driven the exploration of 2 major strategies of structured treatment interruptions (STIs) for chronically HIV-infected individuals receiving prolonged suppressive HAART: (1) discontinuation of all antiretroviral drugs for a defined period of time, and (2) discontinuation of all antiretroviral drugs until the CD4 cell count drops below a pre-determined level. By decreasing the duration of exposure to antiretroviral drugs, these strategies seek to prevent long-term toxicities, to improve quality of life, and to reduce the cost associated with continuous HAART. Achievement of these goals depends on the length of time of the HAART interruption while the integrity of the immune system is preserved. Lower CD4 cell count nadir [4], greater CD4 cell count increase after HAART is commenced, and older age [5] have been associated with a more rapid decline in CD4 cell count after interruption of therapy. Patients with these characteristics might expect planned CD4 cell count–guided interruptions to be shorter.

Risks associated with the rebound in viremia after discontinuation of HAART include the progression of HIV disease as a result of an abrupt decline in the CD4 cell count, the emergence of antiretroviral drug resistance that may hinder future treatment options, the reseeding of viral reservoirs, the occurrence of acute retroviral syndrome, the increased transmission of HIV, and decreased quality of life. HIV-1 resistance mutations may be archived in the latent reservoirs of resistant viruses and reemerge after antiretroviral drugs are discontinued or may emerge under the selective pressure of repeated cycles of intermittent therapy. Simultaneous discontinuation of all components of a regimen containing antiretrovirals with different half-lives may select for resistant viruses during periods of exposure to “monotherapy” in patients without detectable plasma viremia. The non-nucleoside reverse-trancriptase inhibitors (NNRTIs) efavirenz and nevirapine and the nucleoside reverse-trancriptase inhibitor (NRTI) lamivudine have prolonged plasma and intracellular half-lives, respectively. In addition, these drugs have a low genetic barrier, since even a single mutation confers a high level of resistance to them. These properties might explain, in part, the emergence of resistance mutations that has been reported after repeated STIs in patients receiving these antiretrovirals [6, 7].

The article by Nuesch and colleagues [8] in this issue reports the risk of virologic failure and emergence of resistance mutations during CD4 cell count–guided STIs in chronically HIV-infected individuals after 3 years of continuous suppressive HAART. This study enrolled individuals at high risk for development of HIV with major resistance mutations. Participants had been previously treated with dual-NRTI therapy—either standard or half-dose zidovudine plus zalcitabine—and the majority had experienced virologic failure before commencing ritonavir-boosted, saquinavir-based HAART. Almost half of the individuals were receiving a lamivudine-containing HAART.
regimen, but no one was receiving an NNRTI-containing regimen. Data were analyzed from 20 individuals with well-preserved immune systems whose antiretroviral treatment was interrupted and then reinitiated when the CD4 cell count dropped to <350 cells/mm³ or to 30% of the preinterruption count. After 96 weeks, continuous HAART was commenced for all participants, and follow-up continued for 12 additional weeks.

After 1–3 cycles of treatment interruption, a major resistance mutation was detected in only 1 of 17 amplifiable plasma samples. The identified reverse-transcriptase mutation—T215Y—was not present before the patient commenced the current zidovudine- and lamivudine-containing HAART regimen. Except for 1 patient with virologic failure attributed to nonadherence to antiretroviral therapy, all participants achieved complete viral suppression 12 weeks after the same antiretroviral regimen was resumed continuously. Of note, the M184V mutation was not detected in any of the 7 plasma samples from patients receiving a lamivudine-containing regimen. As the authors indicate, a limitation of this study relates to the performance of genotypic resistance testing 28–64 days after antiretroviral therapy was discontinued, which may have allowed either a shift of resistant viruses to wild type or the outgrowth of the wild-type virus, resulting in the low frequency of other major resistance mutations [9]. Low-frequency drug-resistant variants present in <25% of the HIV population may have not been reliably detected by the genotypic testing method used. Indeed, the emergence of minor populations of HIV-1 harboring the M184V and L90M mutations was detected in individuals undergoing repeated cycles of STI, after a very high sensitive quantitative real-time PCR assay and allele-specific oligonucleotides were used for detection of these mutant sequences [10].

Nuesch and colleagues [8] detected clinically significant resistance mutations in 4 of 11 plasma samples obtained from the participants before HAART was commenced, but these mutations were not detected in samples from the same patients obtained after treatment was stopped. The loss of resistance mutations may not represent a true genetic reversion of the resistant virus after therapy was discontinued, but rather the outgrowth or reemergence of wild-type virus probably archived in the latent reservoir in resting memory CD4 cells. In addition, these mutations may be present as low-frequency variants. These archived resistance mutations may reemerge after HAART is reinitiated.

As Nuesch and colleagues [8] indicate, other limitations of this study are the small sample size and the low number of treatment interruptions experienced by the individuals during the follow-up period. Indeed, for the 20 patients analyzed, only 11 plasma samples were available before HAART was commenced and 17 plasma samples were available during CD4 cell count–guided STIs. A unique aspect of this study is that it provides information on antiretroviral drug resistance for patients who have previously received dual-NRTI therapy and experienced virologic failure who initiate CD4 cell count–guided STI.

The time-defined interruption strategy was initially reported to be safe and to decrease total serum cholesterol and triglyceride levels, when the time of exposure to antiretroviral drugs was halved, in a small pilot study of 10 chronically HIV-infected individuals [11]. Repeated short cycles of 1 week of HAART followed by 1 week without HAART did not promote the emergence of resistance mutations, despite the fact that most of the patients in the study received extensive suboptimal antiretroviral therapy before commencing HAART [11]. However, when the same group of investigators evaluated repeated, long-cycle, STI with 4 weeks without HAART followed by 8 weeks of HAART, the study was prematurely terminated because of the emergence of new resistance mutations [12]. Nuesch and colleagues [8] had to terminate early the study arm receiving 1 week of HAART followed by 1 week without HAART because of the unacceptable high frequency of emergence of antiretroviral drug resistance. Results from the Swiss-Spanish Intermittent Treatment Trial also suggest that repeated treatment interruptions for 2 weeks followed by 8 weeks of continuous therapy with the same regimen may select for resistance to antiretroviral drugs with a low genetic barrier [13].

Recent data from observational cohorts identified the CD4 cell count as a strong predictor of progression to AIDS or death in individuals receiving HAART [14, 15]. The risk of disease progression markedly increases as CD4 cell count drops to <200 cells/mm³. These data suggest that a strategy of discontinuation of HAART until the CD4 cell count drops to 250 cells/mm³ may have merit. Although the study by Nuesch and colleagues [8] suggests that a CD4 cell count–guided STI strategy may be safe among patients previously treated with dual-NRTI therapy, the benefits and risks of strategic treatment interruptions for chronically HIV-infected individuals like those studied and others who initiate HAART can best be determined by a large, long-term, randomized, clinical end point trial that is adequately powered not only to evaluate risk of resistance for CD4 cell count–guided STI and continuous treatment strategies but also to compare clinical outcomes, including AIDS, major toxicities, and survival. The SMART Study (a large trial comparing 2 strategies for management of antiretroviral therapy) plans to randomize 6000 HIV-infected subjects with a CD4 cell count >350 cell/mm³ to receive 1 of 2 different strategies: (1) “drug conservation,” aimed at minimizing patients’ exposure to antiretroviral drugs by use of episodic antiretroviral treatment to maintain a CD4 cell count between 250 and 350 cell/mm³; or (2) “viral suppression,” aimed at maintaining the viral burden as low a level as possible by use of continuous antiretroviral treatment. Given the established benefits of continuous HAART, we need much more defin-
itive data on CD4 cell count–guided strategies before they should be recommended in clinical practice.

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