

New Perspectives in HIV Treatment Interruption: The SMART Study

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Based on a presentation at PRN by Wafaa El-Sadr, MD, MPH

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"THE ADVENT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN THE MID 1990s resulted in a dramatic increase in survival of HIV patients, especially among those with advanced disease," Dr. Wafaa El-Sadr said in beginning her February 2006 PRN lecture. Follow-up studies, she explained, demonstrated the durability of this effect, with decreasing HIV-associated morbidity and mortality during the late 1990s and early 2000s. She also acknowledged, however, that while combination antiretroviral treatment has changed the face of the HIV epidemic and enabled physicians to provide truly effective therapy, several issues and limitations of these regimens have emerged.

The most significant limitation has been the necessity and challenge of continued daily adherence to the medications. "Taking these medications day in, day out is difficult for patients," she said. The frequently cited multicenter study of antiretroviral adherence, conducted by Dr. Sharon Mannheimer and her colleagues, demonstrated rapid waning of adherence with only 60% of patients reporting 100% adherence eight months after initiation of therapy (Mannheimer, 2002). Extrapolating these data implies worsening of adherence over years of therapy, resulting in drug resistance and resultant loss of treatment options.

Metabolic effects are another concern with HIV treatment. More alarming is evidence of increased myocardial infarction rates among patients on antiretroviral therapy. An important study on this subject is the DAD study (Data Collection on Adverse Events of Anti-HIV Drugs), which found an increased risk of coronary artery disease in people on all types of antiretroviral therapy (Law, 2003). Additional metabolic and general side effects of antiretroviral therapy include cardiovascular complications, lipodystrophy, peripheral neuropathy, and accelerated liver disease (Julg, 2006).

The occurrence of severe therapy-related adverse events has gained prominence in the era of combination antiretroviral therapy. In a cross-protocol study, rates of grade 4 adverse events associated with antiretroviral treatment were shown to be higher than those of AIDS events or deaths (Reisler, 2003). "While we see a dramatic decrease in the development of AIDS as well as associated deaths, there has been an increase in the development of adverse events of a variety of organ systems," noted Dr. El-Sadr.

The high cost of medications also continues to be an issue. Although programs exist in New York State and New York City for financial support for treatment, many parts of the United States and most other parts of the world do not have such programs established. The continued inability to eradicate or cure HIV gives the prospect of lifelong drug treatment enormous monetary implications.

Rationale and Strategies for Treatment Interruption

"THERE IS A NEED FOR STRATEGIES THAT CAN OPTIMIZE THE USE OF available antiretroviral drugs in order to maximize the benefits while minimizing the risks," Dr. El-Sadr explained. Treatment interruption is a potential way to optimize antiretroviral therapy. However, its safety and efficacy have yet to be established.

Two main strategies for treatment interruption have been studied: time-defined and CD4+ cell-guided. Time-defined strategies involve pre-determined treatment interruption, such as medication breaks on weekends and one-month-on/one-month-off scheduling, in an effort to improve quality of life, promote adherence, decrease antiretroviral exposure, and minimize the development of resistance. The CD4+ cell-guided strategy, used in the National Institutes of Health's Strategies for Management of Antiretroviral Therapy (SMART) study, utilizes CD4+ cell counts to determine the starting and stopping point of intermittent therapy (IT). In other words, antiretroviral treatment is started when the CD4+ cell count falls below a certain threshold, stopped when it increases above a certain level, restarted when the CD4+ cell count again falls below the threshold, and so on.

The potential risks and benefits of continuous therapy (CT) are familiar to most practitioners. Potential benefits include maximal suppression of HIV-RNA, consistent CD4+ cell count gains, and a decreased risk of HIV transmission. The potential risks of CT include higher rates of drug side effects, more difficult adherence, and potentially more drug resistance resulting in fewer drug options secondary to higher antiretroviral therapy exposure.

Conversely, the potential benefits of IT include fewer side effects, better adherence, and improved quality of life. The risks include possible increase in the development of resistance, lasting damage to the immune system, and an increase in the risk of HIV transmission due to non-suppression of viral load.

Studies Assessing Treatment Interruption

SEVERAL STUDIES, REPORTED AROUND THE TIME OF SMART, HAVE INVESTIGATED both CD4+ cell- and time-guided IT strategies. The Staccato trial randomized 430 patients to CT or IT (Ananworanich, 2006). Patients in the IT group only used therapy when their CD4+ counts dropped below 350 cells/mm³. Interestingly, this small study showed 5.8% of the IT patients experienced acute retroviral syndrome. Minor manifestations of HIV infection, such as candidiasis and thrombocytopenia, were more common in the IT group, while adverse events, including diarrhea and neuropathy, were more common in the CT group. Ten patients (2.3%) had resistance mutations; there were no differences between groups. There was a 62% savings in antiretroviral therapy costs (Julg, 2006). However, this study was not powered to determine clinical efficacy.

The Window-ANRS 106 trial randomly assigned 403 patients with undetectable viral loads and CD4+ counts greater than or equal to 450 cells/mm³ while on antiretroviral therapy to receive either CT or IT in eight-week off/on cycles (Marchou, 2006). The primary endpoint of CD4+ counts less than 300 cells/mm³ was reached by 3.6% in the IT group, compared with 1.5% in the CT group. At week 96, the proportion of patients with CD4+ counts greater than 450 cells/mm³ and viral loads of 400 copies/mL or less was 75% vs. 92% and 81% vs. 90%, IT or CT, respectively. The IT arm, the investigators concluded, appeared safe and without excess resistance, while reducing antiretroviral exposure by 48.5%.

The ANRS 1269 Trivican trial randomized 326 patients on antiretroviral therapy who achieved a CD4+ counts greater than 350 cells/mm³ and undetectable viral loads to CT or one of two IT strategies: CD4+ cell-count-guided (stopping at 350 cell/mm³ and restarting at 250 cells/mm³) or time-guided (two-months-off, four-months-on) (Danel, 2006). At an interim point, the CD4+ cell-guided arm was terminated prematurely due to safety concerns. The results demonstrated a two-fold higher serious morbidity rate in the CD4+ cell-guided group, compared with the CT group, with recommendations for future studies to utilize higher CD4 count thresholds.

The ISS PART trial randomized 273 subjects to one of five different time-guided IT schedules (one to three months off therapy, followed by three months on treatment) or CT, with the primary endpoint being the proportion of patients with CD4+ counts greater than 500 cells/mm³ after 24 months (Palmisano, 2006). Significantly more patients in the CT group reached the primary endpoint (86.5% vs. 69.1%; $P=0.0075$), with similar rates of virological failure.

The SMART study is the largest IT trial to date. The study was a two-armed treatment comparison of CT to CD4+ cell-guided IT. The goal of the CT arm was to use antiretroviral therapy, irrespective of the CD4+ cell count, to achieve and maintain undetectable viral loads. The goal of the IT arm was to defer therapy until the CD4+ count was below 250 cells/mm³, continue treatment until the CD4+ count increased above 350 cells/mm³, with subsequent stops and restarts using these CD4+ cell count cutoffs. The study was powered to determine clinical efficacy.

Patients entering the study were required to have a current CD4 count of greater than 350 cells/mm³ (CD4+ count nadir was permitted to be lower). They were randomized 1:1, in an open-label fashion, to either CT or IT. The SMART investigators aimed to enroll 6,000 patients and to accumulate approximately eight years of follow-up data. The primary endpoints were progression to AIDS or death from any cause. Other important endpoints included: death, serious complications (e.g., cardiovascular, renal, and hepatic), serious disease progression events (e.g., disseminated MAC, toxoplasmosis, cryptococcosis, Kaposi's sarcoma), and grade 4 events. Additional comparisons involved adherence, side effects, metabolic complications, quality of life, drug resistance, and cost.

Enrollment in the study was halted on January 11, 2006, due to safety concerns. At that time, 5,472 patients were enrolled and included in an intent-to-treat analysis. In an effort to obtain a comprehensive understanding of the primary outcome, several substudies were conducted to assess various outcome measures, including quality of life, risk behavior, body composition and metabolic parameters, neurological complications, and anal dysplasia.

The study represents a true international effort with participants from 33 countries and 318 sites. The majority of the participants were from North America and the United States with additional participation through sites in Europe, Africa, Asia, and South America.

Baseline characteristics of the study participants include a median age of 46 years: 27% were women and 30% were black. The median follow-up time was 14 months, with 2% lost to follow up. The median CD4+ count at entry was approximately 598 cells/mm³, with median nadirs of approximately 251 cells/mm³. Seventy-one percent had viral loads less than 400 copies/mL, 24% had prior clinical AIDS, and 4.7% were antiretroviral naive (El-Sadr, 2006).

Results of the SMART study demonstrated statistically significant differences in clinical disease progression including death between the two groups. There were 117 AIDS or death events in the IT group, compared with 47 events in the CT group. This translated into a hazard ratio of 2.5 comparing IT to CT groups ($P<.0001$). Kaplan-Meier curves demonstrated slow and consistent accumulation of events in both arms

over time, but with the IT group showing higher event rates starting four months after randomization (El-Sadr, 2006).

The component breakdown of the primary endpoint shows that the relative risk favors the CT group with respect to survival and disease progression. Surprisingly, despite greater exposure to antiretroviral therapy, severe cardiovascular, hepatic, and renal complications were unexpectedly lower in the CT group, with a cumulative hazard ratio of 1.5 for IT compared to CT. When the primary endpoint of HIV disease progression or death was further subdivided by race and sex, the CT group still maintained a clear advantage over the IT arm in most groups of participants (El-Sadr, 2006).

The investigators also examined the outcomes by baseline CD4+ cell counts and viral loads, and demonstrated the same advantage to the viral suppression (CT) arm. There were particular safety concerns regarding the group of patients with low CD4+ nadirs. However, the data demonstrated that these patients were no more likely to experience AIDS or death when compared with patients with higher CD4+ nadirs. In fact, all groups of CD4+ nadirs favored the CT group in a similar manner. With respect to viral loads at study entry, patients with viral loads of 400 copies/mL or less had many more events in the IT arm, while those with HIV-RNA >400 copies/mL had similar outcome in both arms (El-Sadr, 2006).

The results of the SMART study showed that IT compared with CT, was associated with increased risks of AIDS or death, serious AIDS-defining events, and severe complications "A very consistent finding," Dr. El-Sadr noted. "These results were consistent across gender, race, baseline CD4+ cell count, or nadir CD4+ cell count, all favoring the CT strategy.

"Episodic use of antiretroviral therapy based on CD4+ cell counts, as utilized in the SMART study design, is inferior to continuous antiretroviral therapy for the management of antiretroviral-experienced patients," Dr. El-Sadr said in her concluding remarks. She added that an insufficient number of antiretroviral-naive patients (5%) were included to make a conclusion about the use of IT in this patient population.

In contrast to many other IT studies that assessed viral load and CD4+ counts as primary outcomes, the SMART study is particularly powerful because a broad range of clinical endpoints were examined. It is therefore crucial to look at all-cause mortality, not just HIV-related deaths, since there might be excess death not obviously attributable to HIV in the modern-day treatment era. Although results of SMART were discouraging, Dr. El-Sadr stated, "We should continue to investigate strategies to get the most from the drugs for the longest period of time." 

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