Structured Treatment Interruption for patients with HIV taking Non-nucleoside reverse transcriptase inhibitors-based antiretroviral therapy

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A. Study Purpose and Rationale

As the treatment of HIV infection with anti-retroviral (ARV) therapy has become increasingly effective, the question of how best to use these regimens has become increasingly unclear. Recommendations for the use of ARVs have evolved over the past several years with current recommendations strongly supporting initiation of ARVs for patients with CD4 cell counts of 200/mcL or less but not for those with CD4 cell counts above 350/mcL. Thus, patients who began receiving care before the current recommendations may have been initiated on therapy too early in the course of their disease. The duration of HIV disease highlights the challenges facing patients in terms of need for long term adherence. In addition, the recent appreciation of the occurrence of metabolic and other complications with long term use of ARV has also highlighted the need for new strategies for use of these agents. Allowing for "drug holidays" or structured treatment interruptions is being increasingly studied and offered as an option or patients with HIV on HAART.

Several studies have been performed since the mid 1990's to investigate the possibility of interrupting HIV antiretroviral treatment in patients with acute HIV, multi-drug resistant (MDR) HIV in need of salvage therapy, and in patients with chronic HIV well controlled on antiretrovirals. At this time, the use of treatment interruption in patients with MDR HIV is not recommended since it has been shown that STI is associated with worse clinical outcomes. Clinical trials involving patients with acute HIV are ongoing but unlikely to be wide-reaching since the numbers of acute HIV diagnoses are few. The most promising and practical realm for STIs is in patients who have well controlled virus on HAART. There have been two approaches to the concept of structured treatment interruptions in these patients with chronic HIV disease who have stable CD4 counts and/or undetectable viral loads: cycled-intermittent treatment interruption and pulse therapy. The first strategy involves interrupting therapy for a predetermined amount of time, usually days to weeks, then resuming the patients on the same therapy for a set amount of time and then repeating the cycle multiple times until eventual cessation of therapy while measuring immunologic and virologic changes during the process. Pulse therapy involves the interruption of treatment for patients guided by CD4 and/or viral load criteria, then following the patients closely for changes in these measurements, restarting therapy once the CD4 cell count or viral load approaches pre determined levels, then continuing the stopping and starting of therapy based on the same criteria.

These two strategies arose in response to small observational trials that showed that most patients, when taken off ARV, returned to their pre-therapy CD4 counts and viral load levels (Hatano 2000, Neumann 1999). In the largest cycled-intermittent treatment interruption trial to date, the Swiss-Spanish Intermittent Treatment Trial (SSITT) followed 133 patients with CD4 counts above 300/μL and undetectable viral loads for 6 months through cycled treatment interruptions (2 weeks off/ 8 weeks on therapy for 4 successive cycles), then stopped ARV, measuring viral load, T-cell responses, and various host immune responses. At week 52, 64% of the original 133 patients remained without therapy, and 41% remained free of therapy at week 96. Two studies have been conducted by Dybul et al , evaluating both short-cycle and long-cycle intermittent cycling of ARV in patients with chronic HIV and good viremic control. The first, published in 2001, followed 10 patients with stable, undetectable viral loads and $CD4^+$ cell counts above 300/μL who underwent repeated cycles of 7 days with and 7 days without medication. Patients maintained viral suppression for 32 to 68 weeks without a change in $CD4^+$ cell

counts and without development of resistance or significant increase in HIV-specific $CD4^+$ or $CD8^+$ T-cell immune responses. Patients' lipid levels improved over the course of the study (Dybul 2001). The second study published in 2003 was a randomized controlled trial which evaluated the effect of long-cycle structured intermittent therapy (4 weeks off, 8 weeks on therapy) versus continuous antiretroviral therapy. The study was designed to enroll 90 patients, but was prematurely terminated to new enrollment after 52 patients because of the emergence of genetic mutations associated with resistance to antiretroviral drugs in 5 patients (Dybul 2003).

There are no completed trials investigating pulse therapy or CD4- guided treatment interruption, however there are preliminary results from a multi-centre, observational, retrospective study involving 140 patients from several treatment centers in Italy, Sweden and the UK. To be included in the analysis, a patient must have taken highly active antiretroviral therapy (HAART) for at least twelve months, have a nadir CD4 cell count above 250 cells/mm^3, a pre-treatment interruption CD4 cell count of at least 500 cells/mm^3, and to have taken a break from HIV therapy for at least four weeks. HAART was restarted if a patient's CD4 cell count fell below 350 cells/mm^3 or if they expressed a wish to recommence treatment. Median CD4 cell count when the study patients initially started HAART was 410 cells/mm^3, and median viral load was 26,000 copies/ml. The study participants had been infected with HIV for an average of three and a half years. At the point of treatment interruption, median CD4 cell count was 804 cells/mm^3 and median viral load was 50 copies/ml. At 104 weeks, 53% of patients were still off-therapy, 24.3% had experienced a drop in their CD4 cell count to below 350 cells/mm^3 and 22% had restarted HAART. The median duration of the treatment interruption at this point was 104 weeks (Maggiolo 2003). There is also evidence from other retrospective studies that patients who are well-controlled on ARV and then experience treatment interruptions often return to CD4 and viral loads unchanged from their pre-interruption levels, indicating that this strategy might be a safe and effective way of minimizing treatment exposure and resultant toxicity and costs. The Swiss HIV Cohort Study showed that of 1299 patients experiencing treatment interruption of less than 3 months at least once (mainly for social factors), there was no significant increase in risk of HIV-associated morbidity and mortality, except in those patients with CDC stage C HIV disease, after their first treatment interruption (Taffe 2002). A retrospective analysis of an observational database at a university HIV clinic of 75 patients treated after 1996 on ARV for more than 90 days, who then experienced a treatment interruption for more than 30 days before resuming ARV again showed no significant deleterious effects of declining CD4 or rising viral loads due to the treatment interruption (Chen 2002). A small retrospective cohort study done at the NIH followed 14 patients who achieved an undetectable viral load in a median of 28 days, maintaining a viral load for a median of 2 years and had a treatment interruption for a median of 6 weeks. The majority of patients had rebound in VL approximating pre HAART levels, even after significant lapse of time reaching 5 years (Hatano 2000). A retrospective chart review of 135 patients with an undetectable viral load who underwent treatment interruption from HAART showed that the majority of patients returned to undetectable viral loads once therapy with the same combination of drugs was reinitiated (Yozviak 2002).

The most concerning risk of treatment interruption is the development of treatment failure or drug resistance. Although the above mentioned trials reveal the overall safety of STI in patients with well controlled HIV on HAART, it has been shown that patients who are on a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen experience much higher rates of treatment failure when HAART is stopped because the NNRTI has a long half life, leading to the maintenance of drug levels in the blood for a week after the other drugs have been discontinued. Women who received NNRTI for one to two days to prevent transmission of HIV to their children experience increased rates of NNRTI resistance. A review of 45 patients who recommenced HAART after a treatment interruption found that those who had been taking an NNRTI-containing regimen prior to treatment interruption were significantly more likely to show evidence of drug resistance during the treatment interruption and experience treatment failure when they resumed their NNRTI-based regimen. Of the 34 patients who restarted HAART with an NNRTI, only 44% (15 of 34 individuals), achieved a viral load of below 50 copies/ml three months after reinitiating treatment. This was significantly inferior to the response of patients taking protease inhibitors ($p < 0.001$). (Barriero 2004).

Because patients on NNRTI-based regimens are at risk for developing treatment failure when they undergo STIs due to the long half life of the drug and effective 1 week period of NNRTI monotherapy that the patient experiences, HIV specialists are currently using two strategies for these patients: 1. stopping the NNRTI one to two weeks before the other meds and 2. stopping the NNRTI but replacing it with a protease inhibitor for about two weeks so that there is decreased chance of the patient being exposed to less than 3 effective ARVs at once. There is no evidence to suggest that one strategy is more effective than the other but theoretically it would seem safer to add an additional drug during the vulnerable period. Such a comparison is proposed for this study.

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Hatano H, et al. Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy in patients with sustained viral suppression. AIDS. 2000; 14: 1357-1363

Maggiolo F et al. Individualized structured treatment interruptions: results of a randomised controlled study (BASTA). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, abstract H-448, 2003.

Neumann AU, et al. HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated treatment. Comet Study Group. AIDS. 1999; 13(6): 677-683

Taffe, et al. Impact of occasional short interruptions of HAART on the progression of HIV infection: results from a cohort study. AIDS. 2002; 16(5): 747-55

Yozviak, et al. Resupression of virus load after interruption in treatment with nevirapine and 2 nucleoside reverse-transcriptase inhibitors. Clin Infect Dis. 2002; 34(4): 547-50.

B. Study Design and Statistical Analysis

- Randomized placebo-controlled double-blind prospective trial
- Power analysis using chi squared test with expected rate of NNRTI-based ARV STI without PI treatment failure at one year = 15% vs. with PI 10% for n=450 in each group (based on generalized treatment failure rate annually about 5-10%, NNRTI-based treatment failure rate 10-20%)

C. Study Procedure

- Enrolled patients will stop taking the NNRTI at time zero, with the control group taking a placebo and continuing their other HAART for the following two weeks and the treatment group taking the PI + other HAART for two weeks. Then all patients will stop all HAART at 2 weeks.
- Women of child bearing age will be tested for pregnancy
- Blood will be drawn at 2 weeks, 1 month, 2 months, 3 months, 6 months, and 9 months.
- Patients will be monitored for adverse drug reactions, flu-like sx associated with viral rebound, laboratory irregularities including CD4.
- Patients will visit their clinicians every month during the STI and bimonthly afterward. Patients will meet with a study nurse on days of their blood draws for monitoring. MD visits and blood draws will be coordinated.
- Study length = 9 months
- Patients may the treatment interruption at any time to continue their HAART treatment.

D. Study Drugs

- Patients will continue with their current HAART when discontinuing the NNRTI. Treatment patients will take a FDA-approved PI.
- PI side effects include GI distress, rash.

E. Questionnaire

- To be completed by a study assistant/nurse
- Includes: CD4 nadir, most recent CD4, VL, history of HAART, time on HAART, history of OIs.

F. Study Subjects

- Inclusion criteria: NNRTI-based ARVs, participating MD, CD4≥350, nadir≥200, VL<50, on HAART>1 year, age≥18, woman of child bearing age should be taking adequate methods of birth control.
- Exclusion criteria: non-NNRTI based ARVs, CD4<350, nadir<200, VL>50, on HAART<1 year, age < 18, pregnant, known major contraindication to PI, patients with acute illness.

G. Recruitment of Subjects

- Patients will be recruited through HIV clinics in NYC.
- Based on each clinic protocol, either flyers will be placed in public clinic space or physicians will be reminded through flyers, emails of the study.
- Patients will approach or be approached by their physicians for the possibility of enrolling in the trial if they are appropriate.

H. Confidentiality of Study Data

- Study participants will be coded by number
- All data will be maintained in a study locker, locked and available only to investigators.

I. Potential conflict of interest

- Not applicable

J. Location of the Study

- CPMC and potentially other HIV clinics in NYC

K. Potential Risks

- Patients will be made aware that they will be receiving either placebo or a PI for two weeks prior to stopping all HAART. It is not known if one strategy is more efficacious than the other in terms of preventing treatment failure. There may be some increased risk of adverse effects such as GI distress with the PI regimen.
- There is the potential risk with all STI of causing treatment failure, drug resistance, decrease in CD4, and flu like symptoms associated with rebound of HIV.

L. Potential Benefit

- Patients will be made aware that they may not benefit personally from participation in the study but that the data accumulated will be of benefit to people with HIV in general in terms of how safest to conduct a STI.

M. Alternative therapies

- Patients can alternatively decide to stay on treatment and not interrupt treatment. The standard of care is to continue treatment. Benefits of interrupting treatment are quality of life in terms of not having to take medications every day, decreased side effects of HAART including potentially improving the lipid profile, lypodystropy, glucose intolerance. Disadvantages of interrupting therapy are worrying about treatment failure, potential for treatment failure, potential increased transmissibility of HIV, flu-like symptoms, decreasing CD4 with increased risk of HIV associated infections.

N. Compensation to Subjects

- Patients will be compensated for their travel costs by way of pre-paid metrocard. They will also receive a meal voucher for each visit.

O. Costs to Subject

- Patients should not incur any costs

HIV Treatment Interruption Trial

Recruiting Subjects

- Patients with HIV on treatment with HAART including Nevirapine or Efavirenz for over one year with CD4 over 350 and undetectable viral load.

- Patients willing to stop treatment, take a "drug holiday" for three months, then to resume their HAART regimen.

- Ask your doctors for more information if you are interested.