Approaches to Interrupting HAART for the Treatment of HIV Infection

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From San Francisco AIDS Foundation

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Highly active antiretroviral therapy (HAART) has radically changed the face of HIV disease in economically developed countries. However, after the initial hope for a "cure," we are sobering to the realization that HAART, effective and important as it is, will not eradicate HIV. In addition, we have begun to see the significant toxicity and complexity of these regimens, making long-term, continuous therapy impractical for many HIV-infected individuals. In this regard, in community settings, the number of people with undetectable plasma HIV RNA (viral load) levels after one year of HAART can be as low as 20%. Finally, the cost of continuous HAART is prohibitive for many individuals and countries.

The changing demographics of HIV infection in developed countries, and the exploding epidemic in economically less developed countries, may make sustainable continuous HAART a remote possibility for many infected individuals. These facts have led to a reconsideration of the goals of HIV therapy. Rather than continuous HAART aiming at eradication of HIV, it might be better to achieve durable suppression of HIV replication and steady CD4 cell counts while minimizing cost and toxicity and enhancing adherence.

These new goals will require creative strategies to develop effective long-term therapy that could be used on a global scale. One approach to attaining these goals may be interrupting HAART to allow for prolonged periods off anti-HIV medications. While interrupting therapy has become increasingly popular, there is yet no uniformity of purpose or design to help direct people taking HAART and their physicians. It is the purpose of this article to outline some of the approaches and their theoretical justifications as well as to review the available information. It is too early to know the effects of therapeutic interruptions and to know if this strategy will be beneficial or harmful. It is strongly urged that persons interested in interrupting HAART and their physicians seek out one of the many available studies so that individuals may be carefully monitored.

STI Approaches

Structured therapeutic interruption (STI) means something different to almost everyone who writes or talks about it. In general there have been two approaches to STI: STI as salvage therapy and STI as immunotherapy. A third, slightly different strategy, is Structured Intermittent Therapy (SIT). [Ed. note: these new acronyms may be confusing in that STI in medical parlance is frequently used to refer to "sexually transmitted infections." For the purposes of this article, STI will refer to structured therapeutic interruption and SIT to structured intermittent therapy.] For more information on STI, see "Structured Treatment Interruption: Future Protocol or Wishful Thinking?" in *BETA*, Spring 2000.

STI as Salvage Therapy

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STI as salvage therapy has the goal of shifting a predominance of drug-resistant HIV to wild-type (drug-sensitive, i.e., no mutations) HIV in persons who have cycled through and failed treatment with the available antiretrovirals. The theory is that wild-type HIV is more "fit" and in the absence of selective pressure, i.e. drugs, the more fit drug-sensitive virus will outgrow the less fit drug-resistant virus. In this case, theory seems to match reality. In several studies of a single interruption of HAART, using phenotypic and/or genotypic drug susceptibility tests, by 8-12 weeks off medications, plasma virus that was predominantly drug-resistant becomes predominantly drug-sensitive in more than 90% of individuals. However, drug-resistant HIV seems to persist in cells. Thus, one would predict that with the reintroduction of selective pressure with HAART, the resistant HIV would return in time. Also, in all studies there is a significant increase in plasma virus and decrease in CD4 cell counts (often to life-threateningly low levels) indicating another aspect of more fit virus -- often it is more capable of causing disease. Therefore, it remains to be seen if STI as salvage therapy is a useful clinical strategy, although at this point it does not look promising. Extreme caution should be used with this approach in people with low CD4 cell counts.

STI as Immunotherapy

While STI as salvage therapy is geared to individuals who have few options with available HAART medications, STI as immunotherapy attempts to boost HIV-specific immune responses in people whose HAART has successfully controlled HIV replication. It is important to note that these strategies have only been studied in individuals who have achieved and maintained a viral load below 50 copies/mL for an extended period of time (generally greater than one year) and who have relatively high CD4 cell counts (generally more than 300 cells/mm^3). The theory proposed to support STI as immunotherapy is based on a series of observations regarding components of HIV-specific immune responses, the most studied being CD8 cell-mediated cytotoxic T-lymphocyte (CTL) responses. During the initial stages of primary infection there is a massive surge in HIV replication. Over the next several weeks to months, the level of HIV RNA in the plasma comes under some control, to a level that can persist for a long time without any therapy. This level is called the *viral set point*.

As the viral load is decreasing, we begin to detect immune responses to HIV, particularly CTL. The temporal association of the emergence of CTL with the initial decline in plasma HIV levels and the resolution of symptoms in the earliest stages of infection have led to the widespread belief that CTL is important in controlling HIV replication. A relatively stable CTL response is seen in many individuals during the time the viral load remains relatively stable. This level of immune response is often referred to as the *immune set point*. It is thought that the immune set point plays an important role in maintaining the viral set point.

With the initiation of HAART, CTL responses decrease significantly, often to levels below the limits of assay detection (i.e., undetectable). This is an expected result of effective therapy: as virus replication decreases, the stimulus and need for a significant immune response also decreases. However, this waning immunity may explain the rapid and vigorous rebound of plasma HIV RNA in most people when HAART is initially interrupted. Since there is such a low level of HIV-specific immune response available to suppress the virus, when therapy is first stopped, HIV can replicate quickly without immune-mediated inhibition. (For more information on immunotherapy, see "Restoring Immunity in HIV Disease.")

It has been proposed that if plasma HIV RNA is allowed to resurface in a structured, sequential manner, it might be possible to augment HIV-specific immune responses. The thought is that with each cycle off drugs there will be a stepwise increase in the immune response as the host is again exposed to a certain amount of plasma HIV RNA and that the immune response will not be diminished with the resumption of HAART since the on-drug period is relatively short. This is called *autovaccination*, which means using one's own virus to boost immune responses. The hope is that one can achieve a new (higher) immunologic set point that will create a new, lower virologic set point when anti-HIV therapy is withdrawn indefinitely. The available evidence suggests that CTL responses are in fact increased as the viral load increases following HAART interruption. However, it is unclear if this will maintain itself when therapy is resumed, or if this will be sufficient to affect plasma HIV levels with subsequent interruptions. One might predict that the new immune set point must be qualitatively or quantitatively superior to the initial immune set point in order to achieve a new viral set point. Unfortunately, since most people begin STI studies with low-level plasma HIV and therefore low-level HIV immune responses, it may be difficult to evaluate this.

Bernard Hirschel, MD, from Switzerland, provided an update on the largest study to evaluate STI as immunotherapy at the XIII International AIDS Conference held in Durban, South Africa, this past July. One hundred twenty-two individuals with a viral load below 50 copies/mL and a CD4 cell count above 300 cells/mm^3 were assigned to undergo four cycles of two weeks off HAART followed by eight weeks on HAART. At the end of these four cycles (40 weeks), participants went off HAART until their viral load was above 5,000 copies/mL. At the time of presentation, 56 individuals had completed four cycles, and 13 were off drugs their final time. There was no difference in the mean rebound viral load during the first four cycles off drugs. Of the 13 persons who completed the study, 11 had resumed HAART within six weeks of their final interruption, all with viral loads above 10,000 copies/mL. This may suggest that clinically significant autovaccination may be unlikely to occur in many individuals even if there is a decrease in total viral load from cycle to cycle on/off HAART in some people. In addition, it should be noted that not all participants were able to return to a viral load of fewer than 50 copies/mL after the eight weeks of HAART, but all had fewer than 200 copies/mL.

In addition, one subject had evidence of drug-resistant HIV. Dr. Hirschel also reported that there was no clear evidence of enhanced CTL responses with the interruption cycles they used. The final results from this study should indicate whether STI as immunotherapy is clinically useful for persons treated with HAART after the initial stages of HIV infection.

STI for People Who Begin HAART During Primary Infection

There may be a difference in the impact of STI as immunotherapy based on when a person initiates effective HAART, i.e., during the earliest stages of disease (primary infection) or during later stages (chronic infection). HIV-specific CD4 cells may be important to mount and maintain an effective CD8 cell response. Unfortunately, except in a minority of individuals, HIV-specific CD4 cells do not seem to be

functional after primary infection. But if HAART is initiated prior to seroconversion (i.e., a positive HIV antibody test), CD4 cell responses to HIV seem to be preserved. Therefore, people who begin HAART in the earliest stages of infection may have more potent boosting of CTL with STI.

In a study recently published in the September 28 issue of *Nature*, Eric Rosenberg, MD, and Marcus Altfeld, MD, and colleagues from Harvard University, present their work on STI as immunotherapy in persons treated with HAART during the earliest stages of HIV infection. Seven of the eight subjects discussed were treated while they had symptoms (severe flu-like symptoms) from acute infection; they had HIV RNA in their plasma, but they were not yet HIV positive by standard antibody-testing techniques. All of these individuals were treated with HAART for approximately one year, and had a viral load below 50 copies/mL. After the first interruption of therapy, all had a rebound viral load between 20,000 and 180,000 but three had a spontaneous decrease to less than 5,000 which did not require further therapy. However, five patients went back on treatment. Four months after a second interruption all subjects had plasma HIV RNA below 5,000 copies/mL. Three of these individuals remain off therapy with viral loads less than 5,000 between five and nine months after the interruption. So five of eight patients continue off HAART. Therefore, it would appear that STI as immunotherapy may have different results depending on when HAART was initiated.

Unfortunately, however, it is not common to diagnose and treat HIV infection during the very early period of infection, as was done by Dr. Altfeld and his colleagues. Therefore, this approach is not likely to be clinically useful for many HIV-infected individuals.

Structured Intermittent Therapy (SIT): Research at the National Institutes of Health (NIH)

Another philosophically different approach is Structured Intermittent Therapy (SIT), defined as regularly scheduled periods off HAART regardless of blood test results. This strategy is not particularly aimed at autovaccination nor does it depend on autovaccination for its success. The purpose of SIT is to spare persons taking HAART as much drug as possible while maintaining clinical efficacy. The cost of medications would be reduced in proportion to the reduced need for them. In addition, it is hoped that substantial drug-free periods may slow, prevent, or reverse some of the toxicity associated with HAART and increase adherence, possibly extending the usefulness of HAART for individuals.

At the XIII International AIDS conference in Durban this past July, we [at the Laboratory of Immunoregulation at the NIH] presented preliminary data from two SIT studies that are ongoing here at the NIH. One study is a randomized, controlled trial designed to last for 22 months. In this study, persons receiving continuous HAART are compared with those receiving long-cycle intermittent HAART, i.e., one month off drugs followed by two months on drugs. With this design individuals receiving intermittent HAART take 30% less drug than individuals receiving continuous HAART. At the time of presentation, nine participants had completed two to three cycles on and off HAART. All subjects had viral loads below 50 copies/mL by the end of each of the eight weeks back on HAART. While CD4 cell counts decreased during the off drug cycle, within four weeks of resuming HAART they were back to their baseline.

With more people enrolling (the study is designed for 70 participants) we expect that, as in Dr. Hirschel's study, some participants will not return to a viral load of fewer than 50 copies/mL by the end of all of the treatment periods. However, some individuals receiving continuous HAART have times when their viral load is above 50 copies/mL as well. At the end of the 22-month study period, we will be able to determine if the group of persons receiving intermittent HAART has the same percentage of people with a viral load below 50 copies/mL, and if the mean CD4 cell counts are the same as for individuals receiving continuous HAART.

In a smaller pilot study we used two shorter cycles of intermittent HAART, seven days off drugs followed by seven days on drugs or five days off drugs followed by two days on drugs, to determine if by using shorter cycles we could prevent rebound of plasma HIV RNA. Five persons enrolled in the group receiving HAART for seven of 14 days. At the time of presentation of the data, while there were infrequent "blips" of several hundred copies or less, all four participants still on the study for 6-14 weeks had viral loads below 50 copies/mL. All determinations were made after the off-drug periods.

Given these encouraging preliminary results, we are enrolling more people to receive HAART for seven days followed by seven days off drugs. One participant came off study after he went on vacation for a few weeks without his medication. When he returned his viral load was 20,000 copies/mL, suggesting that there is unlikely to be a component of autovaccination with this approach.

Three subjects received HAART for two of seven days with less promising results. Two of the three were off study by ten weeks of participation with viral loads of approximately 1,000 copies/mL. Both subjects quickly returned to a viral load below 50 copies/mL with the resumption of continuous HAART. However, we are no longer enrolling people in this latter study. [Ed. note: again, although this was a pilot study with only a very small number of people, the benefits did not appear to outweigh the risks, so enrollment in the study was halted.] Of interest, there was no change in CD4 cell counts with either group.

It is important to emphasize that these are preliminary results in a small number of individuals and there are serious risks as discussed below. It is not recommended that any of these approaches be attempted outside of a clinical study. For more information on the studies we are conducting, please contact Christian Yoder at 800-772-5464, ext. 57745.

Serious Potential Risks of STI

We have discussed the possible benefits of interrupting HAART therapy, but there are some real and potential risks with any of these approaches. It is clear that interrupting HAART results in a substantial decrease in CD4 cell counts and a rapid and vigorous rebound of plasma HIV levels, at least during the first cycle off therapy. This is true even in studies of HAART as salvage therapy in which the viral load is already high and participants have clear resistance to the medications they are taking. While the CD4 cell counts usually return to their preinterruption levels when HAART is restarted, great caution should be

used in persons with low CD4 cell counts. Moreover, it may take several months until they return to normal.

Furthermore, there is evidence that prolonged effective HAART reduces levels of HIV in important reservoir sites and improves overall immune responsiveness. There is little doubt that rebound plasma HIV will increase the amount of virus in reservoir sites. However, if eradication is no longer the goal, the importance of this replenishment of reservoirs is questionable. We do not yet know if there will be immune damage from repeated episodes of rebound plasma HIV RNA. Finally, because with each cycle of stopping and starting medications there are two periods of subtherapeutic drug levels, there is a risk of pushing an individual with no evidence of drug resistance who is effectively suppressing HIV replication to drug resistance and an inability to suppress viral load even when the same HAART regimen is restarted. This may be particularly true if the drugs in the regimen are cleared at different rates. It may be advisable to stop drugs with a longer clearance time, e.g., efavirenz (Sustiva) or didanosine (Videx), before stopping other medications in a regimen. It is also theoretically possible that interrupting therapy will slow or prevent the induction of resistance since with each cycle wild-type virus could outgrow smoldering resistant virus. However, given the substantial risks involved and the highly theoretical (some may say heretical) nature of these strategies, it is important for individuals interested in interrupting HAART to participate in one of the many available clinical trials.

Summary

It is clear that we are unlikely to eradicate HIV with the medications currently available. We now face the challenge to develop long-range therapeutic strategies that will suppress HIV replication and maintain CD4 cell counts while minimizing cost and toxicity and enhancing adherence. Interrupting HAART in a well-defined, well-conceived manner offers some hope of helping achieve these new goals. However, it is too early to know which, if any, of these approaches will be beneficial. While we measure many things in the laboratory to help direct strategies, we are greatly limited by what we do not know, and the many things we have not begun to understand about the immune response to this unusual retrovirus. Many factors, including changes in the virus itself and in the activation of the cells, may be important in determining the success of interrupting HAART as a therapeutic option. The ultimate proof will be the effects of multiple interruptions of HAART on viral load, CD4 cell counts, and disease progression.

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