Structured Treatment Interruptions Workshop Summary

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Report and Recommendations from the STI Workshop

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STRUCTURED TREATMENT INTERRUPTIONS WORKSHOP

Workshop Summary

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This report was compiled and written by Mark Harrington. It was edited by Ben Cheng and Martin Delaney. The author and editors thank members of the STI Workshop Steering Committee for their input on the report and, more importantly, their commitment to the Workshop and the research that was its focus.

STRUCTURED TREATMENT INTERRUPTIONS WORKSHOP

EXECUTIVE SUMMARY

From 30 July to 1 August 1999, a diverse, international group of biomedical researchers, statisticians, clinicians, research administrators and community treatment advocates met to discuss and develop plans for research on structured treatment interruptions (STIs) in the context of highly active antiretroviral therapy (HAART). Participants reviewed observations to date, currently available virologic, immunologic and clinical hypotheses, and reviewed studies now underway or in the planning stages. They evaluated STI research in the context of fully-virally suppressed patients with primary or chronic HIV infection, and multi-drug resistant (MDR) patients who are failing to achieve full viral suppression. In a series of intradisciplinary and interdisciplinary breakout-groups, participants identified gaps in current STI research and developed several proposals and mechanisms to address these gaps, and to coordinate and expedite the overall STI research effort. Among the conclusions and follow-up steps to emerge by consensus from the STI Workshop were the following:

1. The need to establish a prospective observational STI cohort study to pool observations regarding patients who elect to undergo an STI and to assess its safety, efficacy, and virologic, immunologic and clinical impact;
2. The need to establish an STI Laboratory Working Group to pool resources and improve the ability of researchers to take advantage of new virologic, immunologic and pathologic assays;
3. The need to develop and promulgate a carefully-worded and thought-out clinical practice guideline outlining the potential risks & benefits, and the knowns and (far more) the unknowns about undertaking an STI at various stages of HIV disease;
4. The need to address pharmacologic and quality-of-life considerations in STI research; and
5. The need to coordinate STI research, particularly vis-à-vis studies of STIs in heavily pre-treated patients with few treatment options and (possibly) low CD4 T cell counts, or those at risk for a CD4 T cell plunge or clinical progression during an STI.

Workshop participants discussed these and other objectives. The following report summarizes the workshop proceedings and the discussions that led to the workshop conclusions and follow-up recommendations. The STI Steering Committee will undertake to facilitate their implementation.

PRELIMINARY RESULTS: NEW COLLABORATIONS, NEW DATA

In late 1999 the STI Workshop steering committee solicited brief, one-paragraph summaries from workshop participants of new partnerships and research results which occurred as a result of the STI Workshop. The results are given below. Additional work has been submitted to the Seventh Conference on Retroviruses & Opportunistic Infections, and to peer-reviewed journals.

"We have recently completed a randomized study of structured treatment interruptions among patients experiencing long-term virologic failure with a protease inhibitor-based regimen. The objective of this clinical trial was to determine the effect of treatment interruption on the evolution of viral resistance and replication capacity ("fitness"), and to determine if changes in viral fitness predicted changes in viral replication and/or CD4 T cell turnover. Our primary hypothesis was that long-term CD4 T cell gains in the setting of virologic failure are associated with reduced viral fitness and prolonged CD4 T cell survival, and that discontinuation of therapy is associated with increased viral fitness, increased viral replication and reduced CD4 T cell production. Our secondary hypothesis was that drug discontinuation leads to loss detectable drug resistance and a durable response to subsequent salvage therapy. The primary outcomes of the study included: change in HIV RNA and CD4 T cell levels; change in viral resistance using both phenotypic and genotypic resistance assays, change in CD4 T cell turnover, change in spontaneous CD4 T cell apoptosis and change in viral fitness. Secondary outcomes included change in the quality of life.

This study had both a randomized and non-randomized component. To be eligible for the randomized part of this study, patients must have met the following criteria: (1) long-term therapy with a protease inhibitor based regimen (> 18 months), (2) documented evidence of virologic failure (HIV RNA > 5000 copies/mL) for the preceding 6 months, and (3) CD4 T cell count at least 100 cells/mm3 above pre-therapy nadir. Patients experiencing virologic failure but who had not had a sustained CD4 T cell count were entered into a single arm non-randomized observational study, and followed off therapy in an identical manner.

Sixteen subjects with a sustained CD4 increase were randomized in a 2:1 manner to discontinue all antiretroviral therapy or to continue their stable regimen; 8 subjects who had not had a sustained CD4 increase were enrolled in the non-randomized arm. All subjects were seen weekly for 12 weeks and then every 4 weeks. Using a deuterated glucose/mass spectrometry method, CD4 and CD8 T cell turnover was measured at baseline and at week 12 (sooner in subjects restarted therapy). Viral fitness was measured using recombinant HIV-1 vectors expressing patient derived protease and reverse transcriptase genes and containing a luciferase indicator gene (this assay is similar to the PhenoSense drug susceptibility assay except that read-out is normalized for viral inoculum, and no anti-retroviral drugs are used).

This study is now fully enrolled (24 adults; all male; 3 African Americans; 3 Latino). Results from drug susceptibility, viral fitness and T cell turnover assays are expected first quarter 2000.

We have developed a large specimen bank (PBMCs, virus stock and plasma) and would be willing to collaborate with other participants from the STI workshop."

— **Steven Deeks**
San Francisco General Hospital

There's been plenty of attention focused on STIs at DAIDS. Immediately following the STI Workshop last August, we held the Therapeutic Vaccines meeting, in which STIs were discussed both as a vaccination strategy, either alone or in combination with a vaccine, and also as a means of testing the efficacy of a vaccine or other immune-based therapy, by interrupting antiretroviral therapy at the end of the clinical trial and seeing if the immune-based therapy enhanced the host's immunologic containment of the virus. These issues will be addressed again in May, at the 2000 Immune Reconstitution and Surrogate Markers in HIV/AIDS Meeting, which we've been developing through the sponsorship of the Institute of Human Virology. I've continued to talk with colleagues at the FDA, who will probably be convening an advisory panel meeting in June, to address endpoints in clinical trials and will doubtless include a discussion of how to regard surrogate marker changes that may arise as a result of STI. I've assisted Bob Redfield in designing a therapeutic tat vaccine study that employs an STI at the conclusion. We are now in the process of designing a concept to bring to the ACTG for further development of tat vaccines, and the final protocol design is likely to employ an STI, once safety, immunogenicity, and biological activity have been demonstrated. Three ACTG protocols are in the final stages of development, that employ STI in subjects with chronic HIV disease, good viral suppression on HAART and CD4 counts >500. ACTG 5063 will look at the effects of cycles of STI in such a population, ACTG 5068 will look at a therapeutic vaccine plus cycles of STI, and ACTG 5024 will explore the effects of therapeutic vaccine or IL-2 or both, using an STI at the conclusion. I am the medical officer for those three protocols. A protocol is under development in the ACTG looking at the effect of STI for patients in need of salvage antiviral therapy. The CPCRA protocol for STI+salvage therapy that was discussed both at the STI workshop and at the Immune Restoration Think Tank is in the final stage of development. The final modifications that are being worked on in the CPCRA protocol are safety checks to make sure the trial is halted if we see the pattern of CD4 fall following STI without return to baseline when therapy is resumed, that was seen in the Frankfort study presented at the summer workshop. A trial is planned by the intramural division of the NIAID, comparing continuous HAART to cycles of HAART and STI, looking at whether the two strategies might simply be equivalent in terms of disease progression. Thanks for the opportunity to participate in the very valuable workshop.

— **Larry Fox**
Division of AIDS, NIAID, NIH

STIs in already responding patients are a strategy to boost the immune system. In our hands, after two cycles of interruption, four out of nine patients developed a spontaneous drop of plasma viral load coincidentally with the recovery of proliferative and cytotoxic activity against HIV antigens. For the moment, this should be considered exclusively a research activity not applicable for routine clinical practice. Moreover, STIs in already responding patients should be clearly differentiated from drug holidays in failing patients.

— **José M. Gatell**
Universidad de Barcelona

The STI Workshop reinforced the enthusiasm of the ACTG [Adult AIDS Clinical Trials Group] A5063 protocol team (chair: Ian Frank, MD/University of Pennsylvania; co-chairs, Joe Eron, MD/University of North Carolina; and Trip Gulick, MD, Cornell University). A5063 is a study of STIs in a group of chronically HIV-infected subjects taking antiretrovirals with maximal virologic suppression. Subjects will undergo four repeated cycles of treatment interruption and reinitiation. In addition, enthusiasm was generated for development of the ACTG A5086 study (chair: Connie Benson, MD/University of Colorado; co-chairs: John Mellors, MD/Pittsburgh; and Diane Havlir, MD/University of California at San Diego). A5086 is a study of STIs in a group of HIV-infected subjects experiencing virologic breakthrough. Subjects will be randomized to initiate a "salvage" regimen based on resistance testing either immediately or after an eight-week STI. The primary endpoint will be virologic suppression at 24 weeks after starting treatment.

— **Roy "Trip" Gulick**
Cornell University Medical Center

The meeting was successful in bringing investigators from around the world and from multiple disciplines to the same table, to discuss a wide range of issues related to structured treatment interruption. Although considerable and growing excitement surrounds this concept, very little has been published to date about the immunologic, virologic, and clinical effects (not to mention the risks) of such a maneuver. The discussion thus seemed to fill a void, to focus attention on multiple layers of interrelated issues and—perhaps most importantly—to highlight areas of potential collaboration. Given the complexity of the problem and the urgency with which it needs to be addressed, I can think of no more efficient way to move forward.

— **J. Michael McCune**
The Gladstone Institute, UCSF

It is a tribute to the organizers, the speed and the effective manner in which they have captured the emergence of a field of study in AIDS therapy. The discussion the workshop facilitated will have great impact on how all attendees will design and execute studies in this area by addressing consensus views on goals, safety and quality of life issues that otherwise may have been undefined (or highly varied among prospective studies). In summary, the workshop did great service to researchers and people infected with HIV-1 by facilitating a coordinated and "peer-reviewed" approach to what may be the hopeful approach to AIDS therapy to date.

We have completed the analysis of a detailed observational study in five chronic infected/suppressed persons who interrupted therapy as compared to five untreated controls. Although data continue to be gathered, analysis to date supports that CD4 and CD8 T cell HIV-1 specific responses can be boosted in this subset of patients in association with viral rebound. Planned studies are centered on applying the results from the observational data into a prospective clinical trial to test safety and the immune and viral outcomes of HIV-1 therapy interruption following sequential STIs of varying duration. A single center, randomized, non-blinded study is planned as a collaborative team effort by Drs. L.J. Montaner (Wistar Institute), R. Gross (University of Pennsylvania), J. Kostman (Jonathan Lax Treatment Center), D. Nixon (Aaron Diamond AIDS Research Center), M. McCune and R. Grant (both from UCSF's Gladstone Institute).

— **Luis Montaner**
The Wistar Institute

The main new area concerning use of STIs that I've been working on since June is on the re-design of the Quest study. This is a Glaxo-Wellcome study of primary infection patients that was originally designed to try to document viral eradication. All patients are given all 4 GW drugs. They were originally going to be randomized to drop amprenavir or not at 18 months. Then at 2 years anyone with no evidence of active infection would stop therapy to assess if there is viral rebound. We now have assays of course which mean we always know there is replication competent virus around. The adapted design will drop the 4 vs 3 comparison and instead randomize to adding a vaccine or not. The endpoint will be assessed by looking at the time to viral rebound above some cut-off (perhaps 1000 copies). The idea is to see whether use of vaccines in PHI-treated patients can affect the viral "set-point".

On a separate note, I have discussed with Mike Youle doing a study of patients virologically failing on a regimen. Resistance testing is done then they are taken off all drugs and then restarted on the same regimen, to see whether re-suppression with the same regimen is ever possible... He's done this for a few patients, one of whom who has just restarted. I guess the overall impression from the July meeting was to make us slightly more wary about stopping, especially in those with low CD4 nadir.

I was also involved in a discussion with MRC and know that they are now planning jointly with the Canadian HIV Trials network a comparison of STI vs. no STI before starting salvage regimen, along the lines I was suggesting in Boston. This is a 2x2 factorial, also comparing "mega" and "mini" HAART.

— **Andrew Phillips**
Royal Free Hospital

STRUCTURED TREATMENT INTERRUPTIONS WORKSHOP

WORKSHOP SUMMARY

I. INTRODUCTORY PRESENTATIONS

The Structured Treatment Interruptions (STI) Workshop was held on July 30–August 1, 1999 at the Boston Marriott Newton Hotel. This workshop was co-sponsored by the Foundation for AIDS & Immune Research (FAIR), Project Inform and Treatment Action Group (TAG).

Introductory presentations focused on:

- Preliminary observations which stimulated interest in STI research
  - Primary HIV infection (PHI), suppressed
  - Chronic HIV infection (CHI), suppressed
  - Chronic HIV infection (CHI), unsuppressed (viral load detectable)
- Virologic issues which STI research could address
- Immunologic issues which STI research could address

Subsequent discussions focused on:

- Different study designs which could address the safety and efficacy of STIs from virologic, immunologic and clinical perspectives across the spectrum of HIV disease
- Necessary laboratory and clinical baseline data, study data points, switchpoints and endpoints for various STI study designs.

Finally, the workshop identified four working groups to carry out five specific tasks which emerged:

- Prospective STI Observational Database (ODB) Working Group
- STI Laboratory Working Group
- Clinical Practice Guideline Working Group
  - Including pharmacology and quality-of-life issues
- STI Salvage/Safety Working Group

A. Preliminary Observations

- Some individuals who discontinue highly active antiretroviral therapy (HAART) continue to maintain viral suppression during an STI.
- In some cases, prolonged suppression of plasma viral load to beneath 500 copies/ml in the absence of drug therapy has been observed. Is this related to start/stop therapy?
- There are observational indications that the time to rebound of viral load increases in some people with each subsequent start/stop STI cycle, suggesting that the viral setpoints may decrease with repeated interruptions.

Researchers from the Aaron Diamond AIDS Research Center (ADARC) have shown that slower decay rates in the latently infected cell compartment (L cell) occur in people who have intermittent episodes of plasma viremia (>50 but <500 copies/ml) while on HAART. Those with more than two episodes of intermittent viremia per year had non-decaying L cell slopes.

Treatment interruptions have been studied in several settings:

- Primary HIV infection — Lori *et al.*; Ortiz *et al.*
- Chronic HIV infection with full suppression:
  - Comet (quick rebound, but retreatment successful, no resistance),
  - NoHRT (Rich Davey/NIAID; 22 treated; HAART ± IL-2, STIs, different patterns),
  - Gatell/Garcia (Barcelona, one or two STIs. All patients had fewer than 20 HIV RNA copies/ml. When the viral load rose to 200 copies, patients were rechallenged, then interrupted a second time after going below the detection limit. There was evidence of HIV-specific immune activity some patients and some interesting viral load rebound curves, potentially indicating immune system containment of viral load.
  - Phillips (10 people with AIDS – five in each group – comparing the viral rebound on STIs; those with lower CD4 T cell counts low CD4 T cell had higher rebound kinetics than those with higher counts.)
  - Several additional reports have been made since the STI workshop.
- Late salvage/MDR patients
  - Frankfurt HIV Cohort (Miller *et al.)*
  - Royal Free Hospital, London (Youle *et al.)*

These patients were later challenged with mega-HAART regimens. Patients who had experienced an STI seemed to have an independently elevated chance of going beneath the limit of quantitation when resuming therapy.

There were important differences in the Frankfurt patients between those whose virus shifted to wild-type (WT) and those whose virus did not shift.

CD4 T cell Count Changes in Frankfurt HIV Cohort Treatment Interruption Patients

	BASELINE	CHANGE
WT shifters	180	-122
Low Viral load	190	-129
Non-shifters	60	- 29
Low Viral load	210	- 88

Those who experienced a treatment interruption and had a viral shift back towards wild-type had a five-fold greater chance of having their viral load go beneath the limit of quantitation (500 copies / ml) than those who did not revert to wild-type during the interruption.

However, there is a major unresolved risk / benefit equation in the disconnect between rising viral load and persistently elevated CD4 T cell counts in patients experiencing partial suppression. The immunologic benefit may persist, but at the cost of the further evolution of multi-drug resistance. The disconnect between viral load and CD4 T cells in partial suppression – disconnect vs. further evolution of MDR. How far will those viruses evolve?

B. Virologic Issues

Why is viral replication contained in some individuals during an STI?

Several observational studies have observed temporary containment of HIV replication during treatment interruptions. The HIV-specific CD4 T cell response seen in Franco Lori's Berlin patient increased despite a lack of significant viral outgrowth.

Why is viral load contained (for variable periods) in some individuals who interrupt treatment?

- It could be stochastic (due to random variation).
- The individuals could actually be long-term non-progressors [LTNPs].
- It could be due to immunologically mediated suppression, change in virologic type, both, or other causes.
- It could reflect direct HIV-specific immune responses or other immune responses.
- There may be other unexplained factors.
- Primary HIV infection
  - What are the kinetics of viral rebound?
  - What are the dynamics of free virus?
  - What are the dynamics of viral compartments?
  - Is there evidence of viral evolution?
  - Does an STI post-HAART reset the viral set point?
  - What is the virologic response after re-initiation of treatment?

We know that in most PHI patients there is a quick rebound in virus levels, but in some individuals there is a delayed rebound. Usually the subsequent response to therapy has been good with no evidence of drug resistance.

- Chronic HIV infection (CHI), suppressed viral load.
  - What are the kinetics of viral rebound?
  - What are the dynamics of free virus?
  - What are the dynamics of viral compartments
  - Is there evidence of viral evolution?
  - Does an STI post-HAART reset the viral set point?
  - What is the virologic response after re-initiation of HAART?

The results have been similar to the PHI patients.

- Chronic HIV infection, non-suppressed / unresponsive to therapy.
  - What are the kinetics of viral rebound?
  - Is there evidence of viral evolution?
  - What treatments were left to select from?
  - Are there changes in drug resistance patterns?
  - Are there changes in fitness of the virus?
  - Are there changes in co-receptor usage?
  - Are the compartments reseeded with wild-type virus or drug-resistant virus?
  - Is there a new viral set point?
  - What are the kinetics of viral load rebound?
  - Is there any immune response?
  - What will the virus do to the CD4 T cells?
  - If damage occurs, is it reversible?
  - How much risk is the patient being exposed to?

Before treatment, the HIV/CD4 T cell interaction typically leads to advanced disease (AIDS).

When intervening with HAART, suppressing HIV replication reduces the HIV/CD4 interaction and reverses disease. When measurable plasma viremia returns, disease progression eventually resumes (although possibly in different forms).

So the question of stopping therapy immediately raises the danger that the patient will experience an immediate recurrence of the HIV/CD4 interaction that could once again lead to progression. It is unclear whether the timing and pace of progression, however, follow the same patterns as seen in natural history data.

C. Immunologic Issues

- Will viral replication after STI stimulate an antiviral immune response that can keep viral replication in check?
- How can the immune response be broadened assuming that broader equals better?
- In chronically-infected patients who are suppressed, can re-exposure to the virus after an STI lead to a stronger immune response to HIV?
- In salvage patients who are not suppressed, can an STI convert the drug-resistant virus into a drug-sensitive one?
- What causes the rapid declines in CD4 T cells observed in some people during an STI? Is it T cell destruction or redistribution? How functional are those cells? Why is this drop apparently seen less often in people with very low baseline CD4 counts?
- Do individuals, particularly those in late-stage disease, lack the residual capacity to mount an immune response against HIV, possibly due to insufficient CD4 or CD8 T cells, antigen presenting cells (APC) defects, defective microenvironments, etc. What can be done to help?

What is the effect of suppressive HAART on HIV-specific immune responses?

- HAART impacts HIV-antigen-specific and non-specific B cell responses.
- In the absence of HAART, vigorous HIV-specific CD4 T cell responses are associated with control of viremia.
- Evolution of cytotoxic T lymphocytes (CTLs) to HIV occurs in patients treated with HAART during primary HIV infection (PHI).
- Reductions are seen in frequency of HIV-specific CTL precursors post-HAART in children.
- People on effective HAART tend to see a gradual decrease in HIV-specific CTL cells.

Parameters affecting the immune response to HIV:

- *CD4 T cell nadir* – a reflection of the peripheral T cell functional reserve. Prediction: the lower the nadir, the less likely a response (though exceptions are often noted).
- *Age / thymic function.* Prediction: The older the individual, the less likely s/he will be to generate a diverse T cell receptor (TCR) repertoire.
- *Duration of viral suppression before STI.* Low viral loads might be associated with decreasing numbers of HIV-specific T cells, particularly after longer suppression. However, durable suppression might also be associated with improved immunologic function.
- *Magnitude/duration of antigenic stimulation during STI.* How long do you keep people off therapy? How high do you let HIV levels go? Prediction: the concentration of presented antigen may affect the size, diversity and specificity of the anti-HIV immune response.
- *The type of HIV which predominates* in vivo. Co-receptor utilization/tropism; pathogenic variants; fitness of strain (if on treatment) may all play a role.
- *Composition of antiretroviral regimen*. Protease inhibitors may affect antigen presentation.
- Original viral set point after acute infection?

What is the effect of drug discontinuation on viral load and HIV-specific immune responses?

- Rapid rebound of at least some plasma virus in a majority of patients. Insufficient data to know whether this results in return to baseline levels or peaks followed by a lower set point.
- Boosting of HIV-specific immune responses, at least in some.

II. STI RESEARCH NEEDS

As a result of intradisciplinary working groups focusing on virology, immunology and clinical issues and interdisciplinary working groups focusing on primary and chronic HIV infection (viral load suppressed) and chronic infection (viral load unsuppressed), several different study designs were proposed, involving different entry criteria, baseline variables, laboratory markers and endpoints.

- Observational studies – to gather information regarding the incidence, safety, virologic, immunologic and clinical impact of STIs occurring due to decisions of people with HIV and/or their clinicians;
- Safety trials – open to all comers, regardless of the duration of suppression;
- Studies in PHI and CHI, suppressed virologically – entry criteria limited to those with at least one year of maximal viral suppression.
- Studies in MDR/salvage patients – comparing various strategies to encourage the virus to revert to wild-type before undertaking a mega-HAART or salvage regimen;
- Quality-of-life studies in people experiencing poor quality of life as a result of ART or disease progression.

Several practical study design considerations were raised:

1. Randomization – Will patients be willing to be randomized to such studies?
2. In patients who stopped treatment, would they be willing to go back on treatment?
3. Care has to be taken in terms of risk of progression to ensure that study participants resume OI prophylaxis (before or during the study) and OI maintenance, when indicated.
4. The historical and current CD4 T cell nadir should be considered in the study design, both as an entry criteria in some studies and as a threshold for re-initiation of OI therapy or mega-HAART.
5. Durability – Short term responses will not give us adequate answers; we need long-term follow-up.
6. Access to medications. When a patient has discontinued antiretroviral therapy or OI prophylaxis, regaining access to the medications could be a problem in some states and with some third-party payment plans.
7. It's hard to plan trials today with the development of new, easier-to-use drugs and regimens and immune-based therapies.

Baseline data to be gathered:

- Baseline viral load, CD4 T cell count
- Highest viral load, CD4 T cell nadir
- Treatment history
- Baseline duration of suppression

Longitudinal data to be gathered:

1. Symptoms of treatment or disease
2. Psychological well-being – the anxiety of taking drugs, treatment fatigue (vs. the anxiety of plummeting T cells or increasing viral load during an STI).
3. Functional status
4. Tolerance to drugs over time.

Virologic data to be collected during the studies (some variation due to varying hypotheses):

Virologic Data of Interest in STI Clinical Trials

	SUPPRESSED PHI OR CHI	UNSUPPRESSED/SALVAGE/MDR
Viral load	Every 2 days, 1st week Every week, 1st month Until threshold/reinduction	Every 2 days, 1st week Every week, 1st month At least monthly until reinduction
GART	As soon as viral load rises over 1,000 to sample low-level replicating virus During rebound Before reinduction	Before STI At least twice during to assess sequential mutation loss
Clonal analysis PART	Whenever GART is done No, except in patients with drug-resistant HIV or history of partial suppression	Whenever GART is done (if possible) Yes, whenever GART is done.
Env/Co-receptors (by sequencing) [1]	Whenever GART is done	Whenever GART is done (or less often)
Sanctuaries	LT, CSF, GS	Tissue distribution of WTV vs. DRV
L cells	Before STI 3-6m after reinduction when viral load goes BLQ	No
Fitness	No	Yes (competitive outgrowth assay)
Threshold for restarting	Test several – e.g., 500; 5,000; 50,000	Test several within constraints of safety concerns

BLQ = below limit of quantitation; CHI = chronic HIV infection; CSF = cerebro-spinal fluid; DRV = drug-resistant virus; GART = genotypic antiretroviral resistance testing; GS = genital secretions; LT = lymphoid tissue; MDR = multi-drug resistant; PHI = primary HIV infection; WTV = wild-type virus.

A. Prospective Observational Database (ODB) and Safety Studies

A1. Prospective STI Observational Database (ODB)

- *Goal: Collect data on patient or physician-generated individual STIs to gain more information about safety and general outcomes.*
- Collect plasma and cell cultures
- Consider using existing ODBs and cohort studies
- Feasibility issues:
  - Overnight express adequate (for shipping cells)
  - Immunologists will need standardized Becton-Dickinson CYTO-FACS

[1] ADARC's John Moore explained the importance of measuring coreceptor expression patterns during STIs. When "a small burst of viremia is associated with a much greater decline in CD4 T cell count ... during the period of limited viremia, the population of circulating CD4+ CCR5+ activated T cells increases, and these are excellent targets for HIV-1 infection. A small blip in viremia could easily take out a disproportionately large fraction of the circulating T-cell pool under these conditions. Normally, CCR5+ cells are only a minor fraction of the total, and this fraction is diminished during active infection ... The differential susceptibility to ... infection and the different virus production capacity of different subsets needs to be taken into account." (John Moore, personal communication).

A2. Safety Study

- *Goal: Better characterize the general safety profile of STIs*
- Determine whom to prophylax/maintain for OIs
  - Based on CD4 nadir
  - If ever on prophylaxis/maintenance
  - If CD4 cells drop below 200 (PCP) or 50 (MAC) during STI
  - CMV PCR if CD4<100, offer enrollment in valganciclovir trial
- Measure antigen-specific cell-mediated immunity (CMI)
- Randomized (with open-label arm for patients who *have* to stop)
- Unresolved issues
  - Length of STI
  - Risk thresholds (HIV/CD4) for re-initiation

B. Studies for Primary HIV Infection / Fully Suppressed

What are the differences between primary HIV infection (PHI) and early disease? PHI patients have very high viral loads—often in the millions. They haven't established a viral setpoint yet, or even necessarily seroconverted. By contrast, "early" patients have seroconverted and have established a setpoint. To distinguish between the two, use the "detuned ELISA" from Busch (Irwin Memorial Blood Bank, San Francisco).

Whether differences exist between the two groups, and how significant they are, is unknown. We don't know, so both should be studied. Both groups, especially PHI, are difficult to identify and study. It might be helpful to quantitate the level of antigen exposure and give therapy (or restart therapy) only after people have seen "enough" antigen.

The trial design and endpoints were left unresolved. There was no consensus on whether the primary endpoint should be where the viral setpoint would land, or time to relapse, or preservation of CD4 T cell cells. But there was general consent on the need for a comparison group and a control group who are not treated during PHI. There should be multiple rounds of STIs over one to two years in a group treated during PHI, cycling on and off therapy, comparing the viral load setpoint in that group to a continually treated group and an untreated group. Both treated groups would come off therapy at a later timepoint and see where the setpoint lands, or compare time to relapse.

C. Studies in People Chronically Infected / Suppressed

There is a need for two studies, one for those with viral load below 50 copies/ml (profoundly suppressed) and those with 50–5,000 copies (partial suppression). In both populations, individuals would be randomized to continual vs. intermittent HAART, or HAART with one (or more) STIs. Therapy would be resumed in people in the STI group when the CD4 T cell count dropped below 300. The endpoints would be 1) the proportion of people who respond to HAART after re-initiation of therapy, or 2) both viral load declines and CD4 T cell rebounds post re-challenge. The studies should be stratified by pre-treatment and baseline viral load. The studies also need to incorporate an evaluation of the impact of hydroxyurea, which blunts CD4 T cell responses. There needs to be an evaluation of whether the studies are doing patients harm.

D. Studies for Chronically Infected / Unsuppressed (viral load detectable)

There are profound differences between people with unsuppressed viral load and high CD4 counts and those with similar viral load but falling CD4 counts, for whom the drugs may be providing no benefit at all. While return to wild type virus may increase the chances of future response to therapy, if it fails to result in renewed ability to suppress virus, it may do harm. Wild type is the pathogenic virus which originally led to immune depletion and the decision

to initiate therapy. It's quite possible that the drug-resistant, but possibly less fit, virus is less pathogenic and hence more desirable. Some researchers would prefer to understand pathogenesis better in this subgroup before generating new hypotheses.

D1. Partial Suppression vs. Immediate vs. Deferred Mega-HAART

- Goal: Compare three strategies in people with limited treatment options and extensive multi-drug resistance (MDR).
- An important control arm in the heavily pre-treated population with few treatment options might be people who are continued on partially-suppressive regimens. Data suggests that partial viral suppression still has an effects on prolonging health and life. Their results could be compared to those who change to a new, more aggressive mega-HAART regimen either with or without an intervening STI. Randomize to:
  - Continue on partially-suppressive regimen;
  - Initiate mega-HAART immediately; or
  - Take an STI, then mega-HAART

D2. "DEEP SALVAGE" Strategy Study

- *Goal: Determine use of STIs as a strategy in salvage therapy*
- Multi-drug resistant (MDR) patients stratified by stable vs. falling CD4 counts
- Randomize to:
  - STI
  - Partial suppression (stay on PI regimen or go on NRTI regimen with slow emergence of resistance—e.g., ddI/d4T $\pm$ HU?)
  - Mega-HAART based on P/GART
- Outcome measures (unresolved):
  - Maximal suppression (eventually, after rechallenge)
  - Durable partial suppression with preservation of CD4 count

D3. Salvage Therapy Study #3

- *Goal: Determine whether a new drug, regimen or strategy performs differently in the context of a prior STI*
- Randomize all salvage therapy candidates to receive an STI, then the new agent, or to receive the new agent immediately (this would provide information about whether the new agent was more effective after the STI than when used immediately).

D4. Salvage Therapy Study #4

- *Goal: Determine use of new drug with or without an STI in the context of salvage therapy.*
- A factorial design in which all salvage therapy candidates would be randomized once to receive the new agent or not, and once in a cross-cutting fashion to start immediately or take an STI first. This would provide information about both the relative efficacy of the new drug and that of the STI first strategy.

E. Additional Issues

- Pharmacokinetics—particularly with NNRTIs, but also with protease inhibitors
- Resensitize to PIs by restoring activity of p-glycoprotein/MDR pump?
- Randomize to stay on regimen vs. alternate PI vs. NNRTI regimen every 3 or 6 months (to alleviate lipodystrophy and metabolic disorders)
- How many STIs, and what is their optimal length?
  - As long as safe (CD4 T cell threshold)
  - As much WT virus as possible
- Develop predictors of WT shift and of successful response to rechallenge
- How to measure viral fitness?
- Quality-of-life measures

III. RECOMMENDATIONS

Observational Database

There needs to be an observational database to:

- Define a case definition for STIs;
- Look retrospectively at existing cohorts and pull out whatever is relevant;
- Develop a report form and uniform standardized protocol available to the field to:
  - Provide guidance to primary care doctors;
  - Use in prospective observational databases;
  - Use standard case report forms;
- Quality-of-life (QOL) surveys should be included in STI studies
  - Because of the laboratory intensity of some studies, this may be less important here than in the larger overall safety and long-term management studies
- Look at various viral load thresholds for re-challenge—e.g., 50, 500, or a low stable viral load below 5,000;
- Look at development and changes in body composition during and after STIs, using a standardized assessment tool;
- Capture the *reason* why patients elected to undergo an STI;
- Capture baseline data;
- Enroll patients *before* STI to ensure proper data collection prior to interrupting treatment;
- Test these hypotheses in primate/animal models

A. Workshop Outcome One:
Establishment of a Working Group to Develop a Concept Sheet for a Prospective Observational STI Cohort Study

Prospective Observational STI Cohort Study
Working Group Volunteers

Ben Cheng	Veronica Miller
Victor DeGruttola	Luis Montaner
Bopper Deyton	Jim Neaton
Bill Duncan	Andrew Phillips
Larry Fox	Albert Wu
Brenda Lein	Mike Youle

B. Workshop Outcome Two:
Establishment of a Working Group to Facilitate Laboratory Research on STIs

The laboratory tools involved in assessing STIs are complex and not universally accessible. A Laboratory Working Group was set up to help ensure that researchers have access to relevant technologies, including viral resistance assays, HIV reservoir samples, and immune activation markers.

STI Laboratory Working Group Volunteers

Giuseppe Biondi	Louis Picker
Alan Landay	Eric Rosenberg
Brenda Lein	Rafick-Pierre Sekaly
Veronica Miller	Bob Siliciano
Christos Petropoulous	Linda Grinberg

C. Workshop Outcome Three:
Establishment of a Working Group to
Promulgate a Clinical Practice Guideline on STIs

It is important to develop and promulgate a statement about what is known and issues to consider for researchers, clinicians and people with HIV when considering an STI. The Guideline would:

- Focus on clinicians and patients;
- State what is known and what is unknown;
- Incorporate pharmacologic concerns not discussed extensively at the workshop;
- Discuss the known and unknown potential risks and potential benefits of STIs in different patient populations

STI Clinical Practice Guideline Working Group

Ben Cheng	Mark Harrington
Martin Delaney	Martin Markowitz
Nikos Dedes	Mike McCune
Gregg Gonsalves	Veronica Miller
Linda Grinberg	Schlomo Staszewski

D. Workshop Outcome Four:
Pharmacologic Considerations

The issue of STIs for people taking drugs with long half-lives such as efavirenz and nevirapine is complicated by the fact that patients may have to stop their NNRTIs before stopping their nucleoside analogues and/or protease inhibitors.

Based on these basic principles:

- Can stop all nucleosides and protease inhibitors together (within 24 hours all will be undetectable in plasma or near undetectable);
- Stop nevirapine and efavirenz two to three days prior to stopping the rest of the antiretroviral regimen. Because these drugs have extended half-lives, if they are stopped early in this manner, their but blood levels will be generally near zero when the other agents are stopped.

E. Workshop Outcome Five:
Establishment of a Salvage/MDR Working Group

Several researchers indicated an interest in coordinating work on patients who are heavily pre-treated, not fully suppressed, and have few treatment options. This will be particularly useful for sharing information relating to protection of patient safety.

Salvage / MDR Working Group Volunteers

Steven Deeks	Jim Neaton
Linda Grinberg	Andrew Phillips
Trip Gulick	Mike Youle

APPENDIX I — Current and Planned Studies - I

	SITES	ENTRY CRITERIA	N	DESIGN	ASSESS	STATUS
PHI / SUPPRESSED						
Rosenberg et al.	MGH	PHI, on HAART, BLQ >8m, BL genotype WT SI ≥ 10	12	STI Rechallenge if VL >50K or VL >5Kx3	CD4, Im resp., setpoint time to rebound	Underway
Workman et al.	Australia	PHI, on HAART, VL <400 x ≥6m	24	Change to d4T/3TC/ RTV/ABT-378 A. 6 HAART B. 6 STI or 6 pts., 3 cycles each: C. 3 wks off, 3 on, then STI D. 6 wks off, 6 on, then STI	VL rise to >5K, CTL response, LT, CSF, cultures	Planned
CHI / SUPPRESSED						
Davey et al.	NIH	≥3 drugs (w PI) ≥ 1 yr. VL <500 x 1 yr (<50 at BL), CD4>350	50 (12 on IL-2) IL-2)	STI until VL >500 or 2 log increase ->Restart	VL relapse Proviral DNA FACS, LPA Apheresis, LN, CSF	Underway All relapsed All responded to rechallenge
Hirschel et al.	Swiss	VL<50, CD4>300	120	2w STI, 8w tx (4 cycles, 40 weeks)	VL, CD4, CD8	Underway
Montaner et al.	Wistar Penn ADARC	CD4>250 A. VL <400 x ≥6m B. Untreated controls	10	STI, then rechallenge follow for 96 days after suppression	CD4, CTL responses, virologic response	Complete 54 pts./group
Miralles et al.	Duke	CHI, suppressed	16	A. 2 STIs, 4w off, on, then STI (N=10) B. Stay on tx. (N=6)	CTL responses	Underway

APPENDIX I — Current and Planned Studies - II

	SITES	ENTRY CRITERIA	N	DESIGN	ASSESS	STATUS
CHI/SUPPRESSED						
Youle et al.	UK	On HAART, VL<50, CD4>350 (any nadir), desire to stop rx.	?	A. Stay on regimen B. STI until CD4<300, restart, STI if CD4 rises over 400 again	Time to VL failure (VL>500 x 2 on rx except 1st 16w), AIDS, CD4<150x2	Planned
ACTG 5063	ACTG	≥3 drugs, VL BLD≥ 18m, VL<50x2 at BL Stratified by LP SI to gag	20	STI, restart if VL>5K or >1Kx4 in4w If VL<50, no resistance, STI at 12w - 4 cycles	Time to VL rebound HIV-specific CTLs LN, CSF, GS	Planned
CHI/UNSUPPRESSED						
Deeks et al.	UCSF	VL>5K, CD4>100 PI failure > 12m	14	A. 12w STI B. Continue rx.	WT reversion, VL CD4, LT, CSF	Underway
Lange et al.	NATEC/ Amsterdam	Prior rx w ≥4 NRTIs, 2 PIs, VL >5K, No prior ABC or EFZ	100	A. Start ABC, EFZ, IDV, RTV, HU B. 16w STI, then A	VL, CD4, resistance PK in 40 pts., QOL	Planned
Mayers et al.	CPCRA	MDR HIV (genotype) VL>10K, stratify by CD4 >/<50, on curr. rx >4w	360	A. New regimen based on GART B. 4m STI, then start new regimen	Disease progression, death, VL, CD4, QOL, safety	Planned
Youle et al.	U.K.	VL>5K, no 3-drug regimen available	?	A. Start salvage regimen B. STI, then salvage	Time to VL failure (VL>5K x2), new AIDS disease	Planned
ACTG PR 291	ACTG	>12m rx., MDR to >1 drug in each class VL >10K	200	A. Start >5 drug salvage based on GART B. STI x 8w, then A	% BLQ at w24 % VL ≥ 1 log down safety & tolerance	Planned

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