STI Roundtable Discussion:

Moving the Agenda Forward

A meeting organized by

the Forum for Collaborative HIV Research

August 29, 2002 – Chicago

Prepared by Richard Jefferys

Held in Memory of Linda Grinberg, 1951 – 2002

On August 29, 2002, the Forum for Collaborative HIV Research (FCHR) sponsored a one-day roundtable discussion on structured treatment interruptions (STI) in HIV infection. The meeting was intended as a follow up to the Third International Workshop on STIs, which took place in Montreal, March 23-24, 2002. The purpose of the roundtable was to draw on the data presented in Montreal (see separate report at: http://www.hivforum.org/publications/STI%20III%20Montreal.pdf) and outline agendas for three different areas of STI research:

1. Analytic use of STIs in the development of immune-based treatments and/or strategies (including the concept of autovaccination)
2. STIs as drug sparing strategies
3. STIs in patients with multi-drug resistant virus

For each of these areas, discussants were asked to focus on the following questions:

- What research gaps exist and which questions need answering?
- What collaborations, new initiatives or other activities are necessary for this agenda to move forward?
- What funding mechanisms need to be put into place for the agenda to move forward?

Introduction

The meeting was chaired by FCHR's Executive Director, Dr. Veronica Miller. Miller opened the proceedings by asking Gregg Gonsalves to briefly summarize key points from the Montreal workshop. Gonsalves started with the topic of STIs as an autovaccination strategy, highlighting the divergence between results obtained in acute and chronic HIV infection. He pled the case for a renewed commitment to the development of immune-based therapies, citing IL-7 and IL-18 as examples. Offering a patient perspective on STIs as a drug-sparing strategy, Gonsalves raised the question – based on data presented by Joel Gallant in Montreal – of how long interruptions might safely be extended, particularly in individuals who began therapy with high CD4 T cell counts: could it possibly be years rather than just months? On the one hand, such approaches promise benefit in terms of reducing toxicity and costs while preserving treatment options, but Gonsalves also acknowledged the importance of knowing whether their might be a public health downside due to the potentially increased risk of transmission during prolonged STIs. Addressing the final topic of treatment interruptions in the setting of salvage therapy, Gonsalves expressed concern that this strategy posed both the most clearly delineated risk (in terms of documented examples of CD4 T cell loss and symptomatic disease) and the least certain benefits. He noted that outcomes have varied from study to study, and that there is a need to try and better understand the reasons for these differing results.

<u>Topic 1</u>: Analytic use of STIs in the development of immune-based treatments and/or strategies (including the concept of autovaccination)

Summary

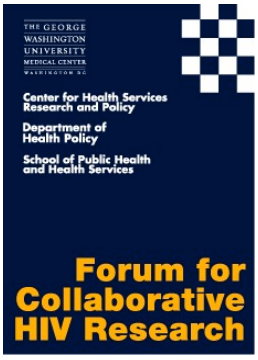
What research gaps exist and which questions need answering?

The majority (but not all) of the round table discussants questioned the need for further enrollment of chronically infected patients in STI trials for the purpose of autovaccination in the absence of additional immunomodulatory agents. Future STI studies should be carried out in the context of immune modulating approaches. However, some of the questions listed below should asked in the currently ongoing or completed studies in chronically infected patients.

- What are the ideal endpoints for these studies? E.g. Delta viral load (viral load setpoint compared to pre-HAART baseline), CD4 T cell counts, time to next indication for HAART based on treatment guidelines.
- Why do some individuals appear to respond to autovaccination approaches in chronic infection?
- How does the incidence of drug resistance during STIs compare to continuous therapy?
- Can STI protocols be improved? (E.g. are there optimal durations for both STIs and on-treatment periods?)
- Which assays (if any) best reflect functional HIV-specific immunity? Do new assays need to be developed/utilized? To what extent can these assays be standardized to facilitate cross-study comparisons?
- Can simpler assays to measure immune responses against autologous virus be developed?
- The potential role of “immunosuppressive” drugs (e.g. cyclosporine, mycophenolic acid (MPA), hydroxyurea) needs clarification.

What collaborations, new initiatives or other activities are necessary for this agenda to move forward?

- A list of desirable reagents and their availability.
- The possibility of a meta-analysis of STI trials in chronic HIV infection should be explored.
- A database of STI trials (both national and international).
- Sharing of stored samples from STI trials should be encouraged.
- Meetings/working groups to work on specific areas, e.g. therapeutic vaccines, cytokines, immunosuppressive drugs, the basic immunology of STIs.



- Discussions with the FDA regarding trial endpoints.

What funding mechanisms need to be put into place for the agenda to move forward?

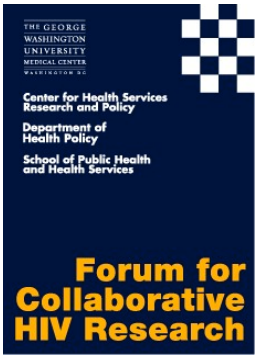
- Investigate whether NIH accelerated grant program for new immunological endpoints can be amended to include HIV research.
- Can the Office of AIDS Research (OAR) human immunology grants be used to fund STI studies?
- Is it possible to supplement a current NIH grant in order to fund a meta-analysis?
- Can NIH be persuaded to issue a program announcement for the development of assays that measure immune responses to autologous virus?

Discussion

Moderator: Alan Landay

Alan Landay opened with some of the key questions relating to this topic. He echoed Gregg Gonsalves's point about the contrast between the promise of STIs as an autovaccination strategy in acute infection – as reported primarily by Bruce Walker and colleagues at the Massachusetts General Hospital – and the lack of similar success in chronic infection. Landay asked meeting participants whether they thought autovaccination remains a possibility in the setting of chronic infection. He also posed the question of whether STIs will be useful analytical tools for assessing the impact of immune-based therapies on HIV-specific immunity. Adding one subject not covered in Montreal, Landay raised pediatric STIs as an area as yet largely uncharted by researchers. Finally, he challenged the group to think about the ideal endpoints for autovaccination or STI plus immune-based therapy studies.

Kicking off the discussion, Steve Deeks agreed that STIs alone have not worked well as an autovaccination strategy in chronic infection, but stressed the many unknowns that need to be addressed by future research. Deeks highlighted the knowledge gap regarding factors that determine viral load setpoint in untreated HIV infection, and pointed out that uncovering the immunologic mechanisms involved could provide a much clearer idea of which aspects of HIV-specific immunity need to be improved. In terms of study endpoints, Deeks suggested that the difference between the pre-treatment viral load and the viral load setpoint after STI – known as the Delta viral load – is likely to be the best choice. He also noted that the optimal timing, duration and schedule of STIs is far from clear, and asked "what is the best way to deliver autologous virus?" In Deeks' studies, a "slow and low" rebound in HIV viral load as a result of



partial treatment failure has been associated with enhanced HIV-specific T cell responses. Although this is not likely to be a widely applicable strategy, Deeks felt it illustrates the potentially delicate balance between levels of HIV replication that might stimulate and expand HIV-specific T cell immunity versus levels of HIV that are likely to delete or compromise the function of HIV-specific T cells.

Alan Landay then cut to the chase, posing the question: Is there still a rationale for pursuing STIs as an autovaccination strategy in chronic HIV infection?

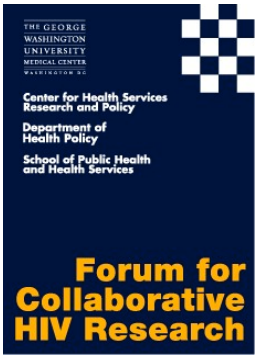
Steve Deeks responded with a qualified yes, as long as care is taken to maximize the safety of study participants and avoid risks such as the development of drug resistance. He believes that these studies are generating new insights into HIV pathogenesis that have "relevance far beyond STI."

Jeff Harris asked whether these studies may already be seen as pursuing a failed approach. He reported that the Institutional Review Board (IRB) at the University of California, San Francisco has stopped further enrollment in an STI trial involving chronically infected participants due to safety and ethical concerns. Harris suggested that samples from completed trials should be stored to allow retrospective analyses and avoid repetition.

Martin Delaney brought up the different perspectives that come into play when assessing the success or failure of trials to date. Enhancing immunologic control of HIV replication in only one-third of study participants may be seen as a failure if STIs are judged by the same criteria as most drugs, but Delaney argued that since the goal is weaning people off antiretrovirals for extended periods, these results should be viewed positively. The key goal, he believes, is to work out if it is possible to increase the response rate by refining STI strategies and/or adding additional immune-based therapies.

Cal Cohen expressed alarm that an IRB had already concluded that staying on therapy was better than stopping. He also pointed out that definitions of a successful outcome for STIs in chronic infection have at times been based on arbitrary viral load setpoint thresholds, and that additional criteria may need to be considered. Cohen cited the CPCRA SMART study, which will focus on immunologic thresholds with the goal of reducing time on therapy rather than stimulating HIV-specific immunity. This study should help clarify the risks and benefits of intermittent vs. continuous HAART, since as Cohen noted, "both have their perils."

Turning the conversation back to autovaccination in chronic infection, Alan Landay asked whether more small studies are really needed to pursue this

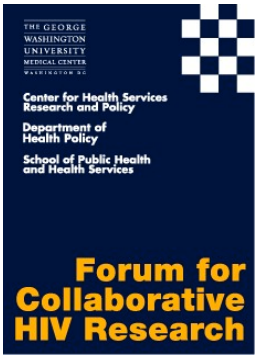


question further. He asked Lidia Ruiz, who has initiated a number of autovaccination studies in Spain, to review her main findings. Ruiz reported that in their studies, where autovaccination was the objective, approximately 1/3 of the patients were able to control viral load at the level of <5000 copies after 4 STIs. In some cases, the virological control was associated with an increased CTL response (quantitative rather than qualitative). Lidia Ruiz speculated that the humoral immune response may play a role, as others have suggested. Ruiz highlighted the fact that all participants in these trials underwent multiple interruptions, and stressed the need to compare these outcomes with a control group receiving continuous HAART followed by a single STI. She and her colleagues are currently conducting a larger study in which patients are randomized to continuous or interrupted HAART (first substudy will enroll 120 patients), with the main endpoints of time off therapy, reduction in drug toxicity, and quality of life. The preliminary results indicate that approximately 45% of patients can remain off therapy at week 48.

The issue of a continuous treatment comparison group was picked up on by Luis Montaner, who described the design of an ongoing study in Philadelphia that includes such a control arm. Forty-two participants will be randomized to receive either graduated STIs (of 2, 4 & 6 weeks duration) or continuous therapy, followed by an open ended treatment interruption. So far, Montaner is following around 10-12 participants in each arm and has not seen any adverse reactions, although one individual has failed to re-suppress viral load to less than 50 copies after 20 weeks of reinitiated treatment. One participant also showed evidence of drug resistance in viral samples taken during the first STI, but not subsequently, and no change in regimen was required to resuppress viral load. Montaner argued that as long as the approach can be studied safely, it would be a mistake to shut down autovaccination research in chronic infection. He believes that these studies offer a unique opportunity to learn more about correlates of immune control of HIV replication, and pointed out that while the results are not as impressive as those seen in acute infection, preliminary data from his trial shows a clear diminution in viral load rebound over successive STIs in some participants. Montaner also reported that assays such as those measuring HIV-specific lymphoproliferation do not seem to correlate with control of viral load, and stressed the need to find methodologies that better reflect functional virus-specific immunity.

Following up on this issue, Alan Landay pointed out the limportance of analyzing the immune response to each individual's autologous virus, currently a difficult and expensive endeavor.

Mark Dybul reported that these techniques are being employed at the NIH, so data will be forthcoming in the near future. He felt that it's unlikely that

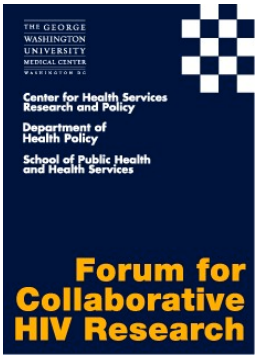


such tests will be commercially developed. Dybul also voiced reservations about further autovaccination studies in chronic infection. He cited the Swiss-Spanish Intermittent Treatment Trial (SSITT) as showing "zero effect except in a small number of patients," and cautioned that since resistance has been documented in STI trials "I wouldn't say we could say it's safe relative to continuous treatment." Gregg Gonsalves agreed that the ethics of STI trials need careful and continuing evaluation. Jeff Harris brought up a potential ethical issue that has not been widely discussed, noting that previous participation in an STI protocol is one of the exclusion criteria for Merck's therapeutic vaccine trials.

Julianna Lisziewicz concurred with Dybul's opinion on the prospects for autovaccination in chronic infection. In studies conducted at RIGHT, 3 week on/3 week off STI schemas have enhanced immune control of viral load in acute SIV infection, but failed to show similar benefit in chronic SIV or HIV infection. Her feeling is that other means of immunization beyond autologous virus will be required, and RIGHT is pursuing studies of a therapeutic vaccine construct known as Dermavir in collaboration with the AIDS Clinical Trials Group (ACTG). Lisziewicz echoed earlier comments about the need to better define acceptable criteria for success as STI/IBT trials move forward, posing the question: "what is a setpoint that would please everyone?" Another issue of concern for Lisziewicz is the limitation of sampling only peripheral blood when analyzing HIV-specific immune responses. She cited the example of four macaques in RIGHT's studies that are controlling SIV replication in the absence of detectable SIV-specific immune responses in the peripheral blood, and asked whether in vivo measurements such as delayed-type hypersensitivity (DTH) might prove useful in future studies. Alan Landay reported that an ongoing study led by Mike Lederman is evaluating whether DTH can be used to assess HIV-specific immune responses.

Returning to ethical issues, Mark Harrington expressed his concern that STIs in chronic infection are being characterized as unethical prematurely, and that this will cause funding agencies to cease supporting new studies. Harrington stressed the need to better understand the basic immunology underlying STIs, particularly in terms of whether truly new, primary HIV-specific immune responses can be induced in chronically infected individuals. Several discussants reiterated that some individuals do seem to respond to autovaccination approaches in chronic infection, and emphasized the importance of understanding why this occurs.

It was suggested by Julianna Lisziewicz that the issue may be one of focus, with unembellished autovaccination studies perhaps deserving of less priority than those involving additional IBTs. Steve Deeks added that "immunosuppressive" drugs such as hydroxyurea and MPA may need to



be considered IBTs in this context, since they have been employed with some success in pilot STI trials.

Deeks went on to raise the question of why STIs do not work well as an autovaccination strategy in chronic infection. Mark Dybul responded that researchers at the NIH (and indeed many other groups) are looking for answers to this question, and suggested that phenomenon such as immune escape and original antigenic sin may be to blame (see the report from the 3rd International STI Workshop for a more detailed discussion of these issues). Dybul also noted that there is an in-between category of individuals who show short-term improvements in control of viral load off therapy in response to STIs.

James Demarest from GlaxoSmithKline offered an industry perspective on the discussion. He agreed with Mark Dybul that analyzing immune responses to autologous virus in large cohorts of individuals is "not realistic" due to the complex nature of the assays involved. Perhaps most important for companies developing immune-based therapies is the selection of study endpoints. Demarest stated that the use of Delta viral load seems reasonable, as long as the assays used to measure the pre-treatment viral load are compatible with those used to measure the setpoint off therapy. He also asked whether correlates of effective HIV-specific immunity could be uncovered by analyzing individuals who do respond to STIs in chronic infection (Mark Dybul pointed out that studies of long-term non-progressors should also offer useful insights into this question).

Switching to non-profit sources of funding, Alan Landay suggested that NIH could put out an Small Business Innovation Research (SBIR) program announcement for autologous virus assays if there is limited commercial interest in this area. He also asked Jeff Safrit from the Elizabeth Glaser Pediatric AIDS Foundation whether he might consider issuing a program announcement to support the development of these assays. Safrit expressed uncertainty, given that for practical reasons, the use of such technology would likely be relegated to a small number of patient samples.

David Sahner from Chiron shared his view that the concept of autovaccination is worthy of additional study. He suggested that researchers focus on those individuals most likely to respond or introduce additional immune-based therapies in order to try and tease out correlates of success. He also raised the possibility of conducting a meta-analysis of STI trials in chronic infection as a means of gaining insight into this question. Sahner argued that, in the absence of immunological correlates, viral load off therapy is currently the best read-out of functional HIV-specific immunity. He felt it would be useful to evaluate the prognostic significance of baseline viral load on the eventual outcomes in STI trials.

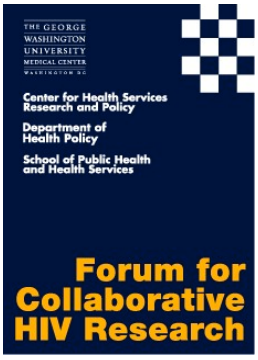
Alan Landay followed up with some questions regarding how the field should proceed. He highlighted the need to know what various investigators are doing, and asked whether it might be possible to set up a database of STI trials (both national and international) as a "clearinghouse for information." Landay wondered if there is an optimal STI trial design that has yet to be explored, but cautioned: "we've got to stop sometime and move ahead." He suggested that some of the areas of research raised in the discussion – such as the basic immunology of STIs - may be appropriate topics for smaller meetings, citing the Forum for Collaborative HIV Research's workshop on therapeutic vaccines as an example.

Access to new in vitro reagents was brought up by Jeff Harris, who complained "if you want to get your hands on something, it's really difficult." Alan Landay inquired as to the status of IL-18, a cytokine being considered for commercial development by GlaxoSmithKline. James Demarest reported that IL-18 is currently undergoing toxicology testing, and that availability is limited. He noted that different companies have differing approaches when it comes to making such reagents available to researchers.

Gregg Gonsalves asked if the Forum for Collaborative HIV Research could help facilitate efforts to address this concern. Veronica Miller responded that a list of desirable reagents would be a starting point and that the Forum could support workgroups to work on such issues, but the funding of research studies would be outside of the Forum's remit. Miller polled participants for suggestions as to potential sources of funding, noting that support for a meta-analysis might be obtained via a supplement to an existing NIH grant.

Luis Montaner suggested advocating that the NIH amend their recent "hyperaccelerated grants for new immunological endpoints" to include HIV research. Gregg Gonsalves added that the Office of AIDS Research offers grants for human immunology research, which might be an appropriate source of funding for some STI studies. David Sahner from Chiron reported that his company is making awards for genomics research, which might under some circumstances support analyses of data from STI trials.

Veronica Miller concluded this part of the discussion by stressing the need to come up with recommendations for funding agencies (such as the Division of AIDS at the NIH) to help them evaluate and prioritize STI research proposals.



<u>Topic 2</u>: STIs as drug sparing strategies

Summary

What research gaps exist and which questions need answering?

- To what extent are reductions in drug costs offset by increases in monitoring costs?
- Will prolonged STIs lead to increased HIV transmission (and potentially increase overall treatment costs)?
- Is the incidence of HAART-related toxicities reduced by STIs? Can any HAART-related toxicities be reversed by STIs?
- Is it possible to design an intermittent therapy trial (similar to CPCRA's SMART) using higher CD4 count thresholds (e.g. a count of 1,000 as the trigger for stopping therapy, a count of 500 as the trigger for restarting)?
- For how long can STIs be extended in this context?
- Could a trial be designed to evaluate earlier intermittent vs. later continuous therapy in a developing world setting?
- What is the relative risk of developing drug resistance on intermittent vs. continuous HAART?
- Can composite toxicity endpoints be developed?
- How do prolonged interruptions affect adherence during on-therapy periods?

What collaborations, new initiatives or other activities are necessary for this agenda to move forward?

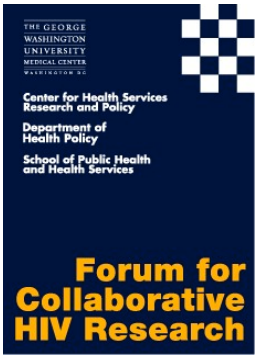
- A forum for discussions between investigators working on STI trials in resource poor settings.
- Standardizing of toxicity definitions.

What funding mechanisms need to be put into place for the agenda to move forward?

Discussion

Moderator: Ben Cheng

Ben Cheng from the Forum for Collaborative HIV Research introduced the second topic, the use of STIs as a drug sparing strategy in the clinical management of HIV infection. This approach looks promising from the perspective of preserving immunological and clinical health but, as Cheng articulated, concerns remain regarding a potential impact on adherence and public health. Based on the assumption that antiretroviral therapy reduces risk of transmission, the extended periods of detectable viremia



seen during prolonged STIs have led to the speculation that such strategies might end up exacerbating the epidemic (thus increasing overall treatment costs despite reducing individual expenditure on antiretrovirals). Cheng asked Mark Dybul to start the first part of this discussion, focusing on cost issues.

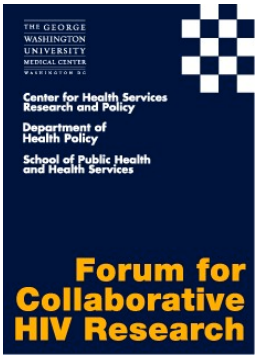
Dybul began with the observation that monitoring costs might also increase during drug-sparing STIs, and that this possibility is being assessed in ongoing trials. He noted that drug cost is less of an issue in the US, and that the primary goal in this setting is reducing toxicity. Dybul outlined planned trials of a novel drug-sparing STI strategy being pursued at the NIH, involving short cycles of 7 days on/7 days off or 5 days on/2 days off compared to continuous HAART. One potential advantage of this approach is that, in studies conducted to date, viremia remains controlled despite the treatment interruptions. A clinical trial is currently underway in Uganda to evaluate the feasibility of short cycle STIs in the developing world setting. The primary endpoint will be equivalence between the STI and continuous therapy arms in terms of viral load and CD4 count outcomes.

In terms of the use of longer STIs in the developing world, Dybul cited the DART study led by Charlie Gilks (Imperial College, London) described in detail at the Montreal workshop[1]. The DART study is funded by the MRC, Rockefeller Foundation and DFID (UK Government), and carried out in three sites: Kampala, Entebbe (Uganda) and Harare (Zimbabwe). Ben Cheng asked how the issue of monitoring costs was being addressed; Dybul responded that the NIH was looking for equivalence between the continuous therapy and short cycle STI arms of their study, while Gilks's study will assess disease progression or death in patients randomized to laboratory and clinical monitoring or clinical monitoring alone.

Comments added *post hoc* by Charlie Gilks: In the DART study, a second randomization is planned for patients whose CD4 count has been restored to > 200 cells/mm3: continuous treatment or 12 weeks on/off cycles. The DART study will include a costings and health economics core which will assess the costs in the different arms in addition to establishing quality of life indices appropriate for the developing country setting.

Continuing the discussion, Dybul provided more details regarding the Ugandan studies. He reported that both abacavir (Ziagen) and nevirapine (Viramune) will be excluded due to concerns about hypersensitivity and p450 enzyme induction, respectively. All participants will be on at least three drugs, provided not by the study but through Uganda's generic antiretroviral program in Kampala (where 4,000 individuals are currently

[1] See www.hivforum.org/projects/3rd-STI.html



receiving therapy). Dybul stated that an important question for this study to answer is whether the higher immune activation status associated with living in Africa will cause a more rapid HIV rebound during STIs. He explained that the trial does not include an arm employing prolonged STIs because participants in the Ugandan antiretroviral program typically receive treatment at CD4 T cell counts of 100-200, and about 40% have an active opportunistic infection, making the risks of longer interruptions greater.

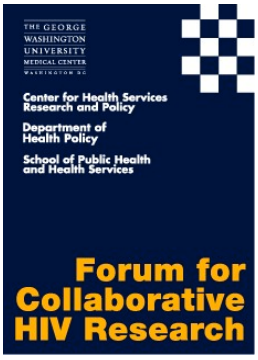
Comments added *post hoc* by Charlie Gilks: the short-cycle STI explored in the Ugandan studies -- if "equivalence" to continuous therapy can be established" – may lend themselves to a directly observed therapy (DOT) approach. This interrupted treatment/DOT approach is being used by many TB programs but has not been used in HIV treatment yet due to concerns regarding efficacy. Simple "implementation packages" are of crucial importance in many communities and may significantly improve adherence rates.

The Ugandan site is investigating abacavir hypersensitivity and nevirapine toxicity in blinded substudy involving 300 patients. The issue of abacavir hypersensitivity is of great practical importance in Africa, especially in malaria endemic areas where symptoms of malaria are common and overlap drug toxicity.

Drugs for the DART study are provided by GSK (6000 treatment years of combivir for first line, 600 treatment years of abacavir plus placebo), Gilead (7000 treatment years of tenofovir) and Boehringer Ingelheim (10000 treatment years of nevirapine). Study funds will be used for second-line drugs in line with the WHO treatment guidelines. The Ugandan and Zimbabwean Ministries of Health have committed to looking after these patients after the end of the trial, inclusive of antiretroviral treatment, thereby enabling both industry and sponsors to commit to a time-limited trial period.

Julianna Lisziewicz recommended that Diana Dickinson from Botswana present on the topic of STIs in Africa at the next meeting. Dickinson has been treating individuals in Gaborone with antiretrovirals for several years now, and has some data on the impact of unplanned treatment interruptions that occur due to the inability of individuals to afford a regular supply of drugs.

Cal Cohen expressed optimism that a 5 days on/2 days off regime could play a useful and likely popular role ("a weekend off," as he described it), and noted that this would be unlikely to affect adherence, at least in cultures where weekend breaks are the norm. He also reported that the



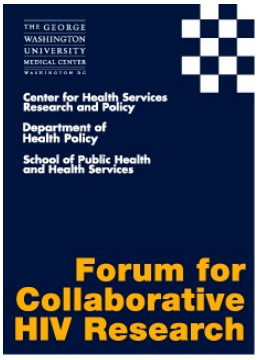
CPCRA SMART study is attempting to assess changes in transmission risk behaviors during STIs, since while there is potential for increased risk; it is also possible that individuals might be more careful about avoiding transmission during interruptions.

Steve Deek raised the issue of virological control prior to starting short-cycle STIs; Dybul responded that entry criteria for the Ugandan trial requires a viral load of <500 copies for three months prior to screening, and <50 copies at study entry. Although Dybul would like to conduct a study where individuals are naïve to treatment and undergo six months of therapy prior to starting short cycle STIs, this has not been feasible with current resources. He has been involved in several other pilot studies of alternative on/off schedules, including 3 days on/4 days off, 4 days on/3 days off and (most recently) 5 days on/2 days off, but data is so far preliminary. The only clear failure has been the 3 days on/4 days off protocol, where 3/5 individuals experienced virologic breakthrough after 6-8 months on study.

Mark Harrington ventured that randomized studies of longer interruptions, while currently difficult in the developing world setting, are still likely to be important in the developed world where there is a great deal of interest in the approach among patients. He added that such strategies might become more applicable in the developing world setting as CD4 T cell count monitoring becomes more accessible.

Julianna Lisziewicz described an ongoing Italian study (FROG, run by RIGHT and Policlinico S. Mateo) exploring fixed schedule 1 month on/1 month off STIs compared to continuous therapy. Although no evidence of an autoimmunization effect has been uncovered, preliminary results indicate a reduced incidence of toxicities although the long term risks and benefits remain unclear. Jeff Harris and Lidia Ruiz questioned which toxicities were evaluated. Ruiz reported observing decreases in cholesterol and triglycerides in her STI trials, but no improvement in lipodystrophy even after one year. In some cases, lipodystrophy has worsened when individuals restart HAART. Lisziewicz responded that FROG has also documented decreases in blood lipids, but data on lipodystrophy so far only includes one case of apparent improvement.

Before turning the discussion over to toxicity issues, Veronica Miller asked discussants whether there were additional trials planned in Africa that had not yet been mentioned. Luis Montaner reported that CIPRA grants for Durban and Johannesburg have recently been announced, and that Glenda Gray has a proposed pediatric STI trial (funding status not known). Bruce Walker's group is also considering an STI trial in sex workers in Durban, and Montaner has a protocol for a randomized STI trial in adults located in Johannesburg that is currently undergoing revisions prior to



resubmission to the NIH R01 grant program. Mark Dybul reported that another group in Johannesburg is combining short cycle STIs with directly observed therapy by treating children on the days they are in school.

Comments added *post hoc* by Charlie Gilks: The DART group is in the process of setting up a "Baby Dart" trial in children, investigating both the role of laboratory monitoring as well as STIs in this population. Could the concept of autovaccination in children be explored in a subset of babies in this trial?

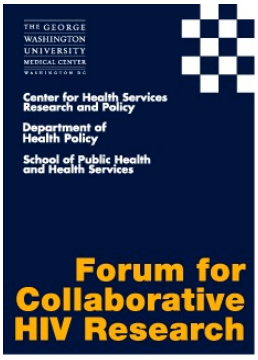
Veronica Miller asked if there would be value in convening an ongoing forum for discussions between investigators involved in these trials, and discussants agreed that this would be a useful resource.

Switching back to toxicity, Mark Dybul shared the experience at the NIH. In their 2 months on/1 month of study, blood lipids declined during the off therapy periods but returned to baseline after HAART was restarted. One potential marker of cardiac problems, HRCSP, remained stable throughout the study. Although DEXA scans were not done in these studies, these analyses are being conducted in newer trials.

Luis Montaner raised the importance of studying the incidence of toxicities prospectively in addition to looking for cases of reversal. But he pointed out that this can be a problem when selecting a sample size for prospective STI trials in treatment-naïve populations, if the incidence of the toxicity in question is relatively low.

Gregg Gonsalves argued the case for large studies looking at prolonged interruptions in individuals with good CD4 T cell recovery on HAART, which could assess the full range of toxicities including some – such as diarrhea and fatigue – that are typically regarded as quality of life issues. Mark Dybul suggested that the CPCRA SMART study – which plans to enroll 6,000 participants – may fill this role.

Cal Cohen brought up the potential role of immune activation in lipodystrophy, which might complicate analyses of the effect of STIs on this condition, due to the immune-activating effects of viral load recrudescence during treatment interruptions. Cohen is hoping to help address this question by employing DEXA scans in a short cycle 5 days on/2 days off study - where viral load remains controlled during the brief off-drug periods – and in the SMART study where the STIs are of an extended duration. Following up on Gonsalves's point, Cal Cohen noted that the SMART study does leave room for another large drug-sparing STI trial in individuals with higher CD4 T cell counts. He observed that some individuals are uncomfortable with the trigger for restarting therapy in SMART (a CD4 count of 250), but would be willing to participate in an STI

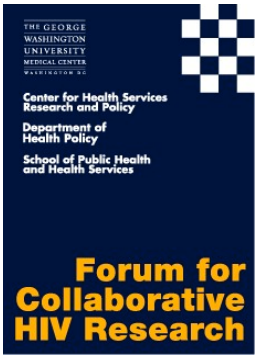


trial if the threshold for restarting was higher (e.g. a CD4 count of 500). Mark Dybul suggested that there is also a rationale for studying this type of approach in the developing world, in order to ascertain whether starting intermittent therapy early (at a CD4 count between 350 and 500, for example) could offer more prolonged clinical benefits than continuous therapy initiated at a more advanced stage of disease. But he added the caveat that it would be "an enormous study."

In terms of measuring toxicities, Rob Murphy shared his view that CT scans can often be a more sensitive method for assessing changes in body habitus than DEXA scans. Although these measures are difficult to standardize across multi-center trials, Murphy reported that the ACTG has taken up the challenge and that "it's doable." In response to a question from Ben Cheng, Mark Dybul stated that these techniques are not being employed in the Ugandan STI trial – the technologies are simply not available - but blood lipid levels will be assessed. He added that physicians such as Peter Mugyenyi in Uganda have not yet seen much evidence of lipodystrophy and lipoatrophy in their patients, and speculated that this could possibly relate to differences in dietary factors or the later initiation of therapy.

Due to the potential difficulties associated with using toxicity outcomes as primary study endpoints, Luis Montaner made the case that viral load and CD4 count equivalence between STI and continuous therapy arms will be the more useful primary outcome measure, with toxicity assessments as secondary endpoints. Mark Dybul added that viral load – as measured on therapy at the end of a trial – may be the more convenient primary endpoint due to individual variations in CD4 count (which can necessitate an increase in study sample size of CD4 counts alone are used). This does not preclude CD4 counts being employed as a secondary endpoint, which is the approach taken by Dybul's Ugandan study. Rob Murphy asked if CD4 percentages were also being assessed, since they tend to be more stable than absolute counts, and Dybul responded that both measures are being employed.

Steve Deeks continued on the topic of endpoints, arguing that while equivalence is important there remains a need to define the benefit of using STIs as opposed to continuous HAART. He cited ongoing work by Victor De Gruttola which aims to create a novel endpoint that assesses the ability of an STI strategy to avoid drug resistance and thus preserve future therapeutic options. Deeks also stressed the need for validated measures of toxicity that might enable the advantages of STIs - if any - to be more clearly discerned. Mark Dybul agreed, noting that while it may be assumed that reductions in parameters such as blood lipids are a good thing, it is entirely unknown whether such changes are clinically beneficial in the long term. Rob Murphy reported that the ACTG is conducting a



"huge" one-year project that will attempt to define a comprehensive range of standardized toxicity endpoints. Murphy bemoaned the lack of clarity surrounding definitions of even well known toxicities such as pancreatitis, let alone more recent concerns such as cardiovascular problems, and meeting participants agreed that it will be vital to address this issue so that toxicity reduction can be evaluated with confidence in future STI studies.

Gregg Gonsalves put forward adherence as another potential endpoint in drug-sparing STI trials, since it remains unknown whether intermittent use of HAART makes it easier or harder for people to adhere when compared to taking the drugs continuously. Cal Cohen acknowledged that this an open question, and reported that the SMART study is evaluating adherence among participants.

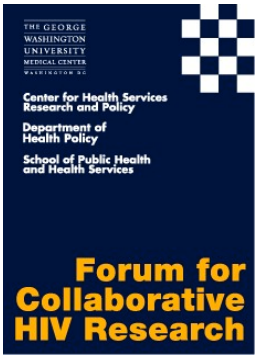
Following up on Rob Murphy's concern regarding toxicity definitions, Veronica Miller asked Cal Cohen how SMART was addressing this question. According to Cohen, the toxicity data collection forms are from the Division of AIDS, and are currently the standard tools used in CPCRA trials. Rob Murphy expressed his feeling that these forms are useful, but noted that they could use improvement in defining cardiac toxicity, pancreatitis and drug-induced liver disease. He added that DAIDS has been working closely with the ACTG on improving these instruments.

Veronica Miller also raised the continuing controversy regarding the definition of lipodystrophy, particularly given recent data presented by Carl Grunfeld from the Fat Redistribution and Metabolic Changes in HIV) FRAM study. The Forum Collaborative HIV Research is sponsoring a roundtable to try and help resolve this issue[2].

Ben Cheng then shifted the discussion to the risk of developing drug resistance during drug-sparing STIs. He asked Lidia Ruiz to share her experience regarding this issue. Ruiz reported that mutations have been documented in some patients in her STI trials – primarily the M184V substitution that confers 3TC resistance – but that this was associated with use of suboptimal mono- or dual-nucleoside therapies prior to the initiation of HAART. Despite the emergence of these mutations, Ruiz noted that viral load has been successfully resuppressed in these individuals after STIs, without a change in the drug regimen. The only exception was an individual with prior nevirapine experience who developed the K103N mutation on study and subsequently failed to resuppress viral load after STI, necessitating a change of drug therapies.

Jeff Harris posed the question of when sampling for resistance should be conducted during STI trials. He expressed concern that if samples were taken after 3 or 4 weeks off therapy, any resistant virus would be masked

[2] see www. hivforum.org/publications/Lipodystrophy.pdf

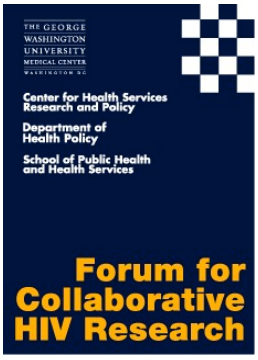


by wild-type due to the absence of drug-induced selective pressure. Harris speculated that a week after HAART reinitiation might be a more appropriate time point for resistance analyses. Mark Dybul countered that, paradoxically, the amount of resistant HIV quantitatively declines almost immediately after drugs are reintroduced. In his experience, which he reported has been echoed by several other groups, 3 or 4 weeks into an STI remains the ideal time to catch the presence of resistance using standard genotypic assays. Dybul also stressed that at earlier timepoints after stopping drugs, the viral load is typically too low to allow reliable amplification of resistant clones.

Julianna Lisziewicz described her experience with a randomized trial that compared indinavir/ddI/d4T and hydroxyurea/ddI/d4T taken either continuously or on an intermittent schedule of 3 weeks on/3 weeks off. In this study, the only documented cases of drug resistance occurred in the continuous therapy arm. Based on these data, Lisziewicz suggested that discussants bear in mind that the risk of developing drug resistance is in no way restricted to STI strategies – the important question is the relative risk compared to continuous HAART. Several discussants cited SMART as a study that will help answer this question. Mark Dybul offered the cautionary note that, while the data showing resuppression of viral load despite resistance mutations is encouraging, it remains possible that treatment failure will occur during longer follow-up and this needs to be closely monitored in ongoing and future STI trials.

Steve Deeks wondered if STI trials are simply opening a window onto the presence of resistant viruses that may also be lurking unseen in many individuals on continuous HAART. He cited data from Joe Eron showing that, when searched for intensively, 3TC resistance mutations could be found in 50% of individuals whose viral loads were suppressed to less than 50 copies. However, the presence of these mutations was not associated with eventual treatment failure. Deeks suggested that STIs may, at least in some circumstances, allow such cryptic reservoirs of resistant virus to be more easily detected. In his opinion, there is as yet no compelling evidence that STIs select for resistance to a greater degree than ongoing treatment.

Martin Delaney voiced his concern that these issues were being poorly articulated and widely misunderstood by the larger researcher and patient communities. He stressed that reported cases of resistance mutations appearing in STI trials were being interpreted simplistically as meaning "STIs cause drug resistance." Returning to Jeff Harris's earlier point that IRBs were beginning to perceive STI trials as unethical, Delaney suggested that there needs to be an effort to articulate the complexities and unknowns – as described in this discussion – in order to make it clear that STIs per se have not been shown to increase the risk of drug

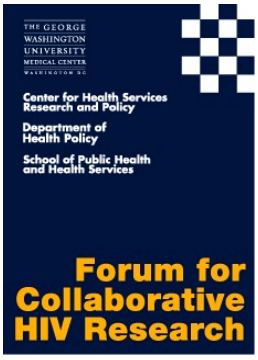


resistance beyond that already documented in individuals on continuous HAART. Cal Cohen seconded this viewpoint, noting that the perception is often that "all (treatment) stops cause resistance so stop stopping."

Although Mark Dybul's data has at times been cited in this context, Dybul agreed that it has probably been over-interpreted. He pointed out that there has as yet been no apparent cases of de novo resistance to protease inhibitors emerging as a result of STIs (one case of nelfinavir resistance in the Swiss-Spanish Intermittent Treatment Trial appears to have been the result of a mutation present prior to study entry), and even though his data has shown the emergence of resistance to efavirenz during STIs, it appears that this risk can be minimized or even eliminated by ensuring that treatment is not interrupted until viral load is suppressed below 50 copies. Dybul also emphasized that his resistance data derives from a 2 months on/1 month off protocol, and that the risk should be lessened in studies involving longer STI cycles.

There was a discussion of whether "optimal" drug regimens for STI studies might be recommended, with Julianna Lisziewicz expressing a preference for ddI over 3TC due to the potentially higher genetic barrier to resistance. Cal Cohen noted that participants in the SMART study have the option of switching to a regimen of drugs with short half-lives for a week prior to therapy interruption. Luis Montaner reported that an initial plan to exclude use of NNRTIs in his STI protocol was dropped by the IRB after an individual switched regimen but then failed to resuppress due to intolerance. Rob Murphy backed up this point, observing that around 10% of recipients can be expected to develop intolerance to any given HAART regimen. Mark Dybul reiterated that a viral load below 50 copies at the time of HAART interruption appears key in preventing the development of drug resistance during STIs.

Due to pressing time constraints, Ben Cheng closed out this section of the meeting and turned the discussion over to topic #3, STIs in patients with multi-drug resistant virus.



<u>Topic 3</u>: STIs in patients with multi-drug resistant virus

Summary

What research gaps exist and which questions need answering?

- What explains the divergent outcomes seen in different studies in this setting?
- Can STIs be used to optimize the response to new drug classes?
- Can the safety of STIs in advanced disease be improved by the use of broader opportunistic infection prophylaxis?
- Can pre-STI use of IL-2 improve the safety and efficacy of the approach?
- How does the duration of STI influence outcome?
- Do the pharmacokinetics (including intracellular half-lives) of particular antiretrovirals influence outcome?
- Can novel IBTs play a role in this setting?

What collaborations, new initiatives or other activities are necessary for this agenda to move forward?

- Larger collaborative or network (ACTG, CPCRA) trials are needed to evaluate whether STIs can optimize the response to new drug classes (e.g. fusion inhibitors).
- The FDA should be approached regarding the possibility of a hearing on appropriate trial designs and endpoints for STI or STI plus IBT trials in heavily treatment experienced patients.

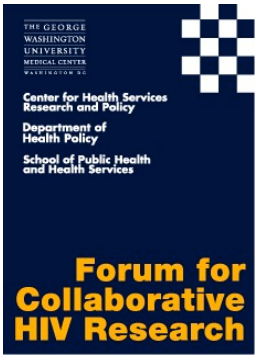
What funding mechanisms need to be put into place for the agenda to move forward?

Industry sponsored clinical research (new drugs, IBT agents)
Large agency funded clinical networks (ACTG, CPCRA)

Discussion

Moderator: Veronica Miller

The third and final topic of the day's meeting was introduced by Veronica Miller, who pioneered this area of research several years ago while at the Klinikum der Johann Wolfgang Goethe-Universitaet in Frankfurt, Germany. Miller started by acknowledging that treatment interruptions in the setting of advanced HIV disease and multi-drug resistance will sometimes be a "matter of necessity" due to issues such as accumulated drug toxicities and lack of viable therapeutic options. She stressed the difficulty of designing treatment strategies appropriate for this population

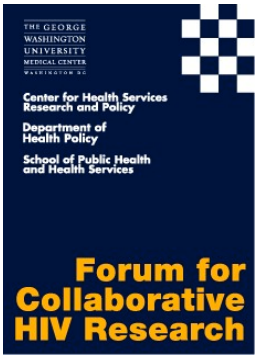


and the importance of carefully evaluating the risks and benefits of any intervention, including STIs. Miller asked Cal Cohen to share information regarding the status of CPCPRA's MDR study, which was evaluating whether STIs could improve the response to salvage regimens in individuals with multi-drug resistance, before being stopped by the Data Safety Monitoring Board (DSMB) in the summer of 2002.

Cohen described the design of MDR, which enrolled around 250 individuals with low CD4 counts and experience to all three antiretroviral drug classes (NRTIs, NNRTIs and protease inhibitors). The study randomized participants to either directly switch to a new salvage regimen or undergo a four-month STI prior to changing therapies. According to Cohen, the DSMB stopped the trial due to both the greater drop in CD4 counts and increased number of clinical events seen in the STI arm. Cohen noted that participants will continue to be followed, so it perhaps remains possible that a longer term benefit could emerge. He added the additional caveats that this was a population with very low CD4 counts and no new drug options. As regards to other similarly designed studies, Cohen cited the Retrogen study (led by Lidia Ruiz) as also showing no virological or immunological benefit to a 12-week STI prior to starting salvage therapy. In contrast, Christine Katlama's GigHAART study (described in detail at the Montreal workshop) did show a virological benefit from an 8-week STI in the setting of multi-drug resistance. Cohen argued that the weight of evidence suggests that, in individuals with triple-class drug experience and low CD4 counts, STIs are not beneficial, at least over the short term. Cohen asked about the fate of a similar ACTG study, and Steve Deeks reported that this has been closed as a result of the termination of the CPCPRA trial.

Mark Harrington queried Cal Cohen about the number of clinical endpoints seen in the trial; although Cohen could not provide the exact number he reported that the difference between the continuous and STI arms was enough to convince the DSMB that the trial should be stopped. However, Cohen added that – in retrospect - it might have been possible to employ a broader range of prophylactic therapies and thus improve the safety of the STI. He underscored that "this study doesn't answer all the questions."

Mark Dybul asked if anyone could offer explanations for the difference between Christine Katlama's results and those obtained in the CPCRA and Retrogen trials. Veronica Miller responded that timing could be a key issue, both in terms of the duration of STI and the duration of follow-up. Cal Cohen also mentioned that there might have been a greater availability of Kaletra to individuals in the STI arm of the GigHAART study, although Katlama has denied that this played a role in her results.



Cohen went on to suggest that one way to provide a cushion against the CD4 cell loss seen in the CPRCA study might be through the pre-STI use of IL-2. He also emphasized that the availability of a new class of antiretroviral drugs – in the form of the fusion inhibitor T-20 – means that the question should be revisited to assess whether STIs improve the response to a regimen that includes this new drug.

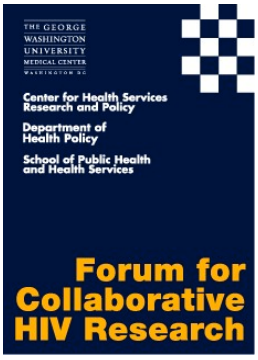
Veronica Miller asked Cal Cohen to clarify whether he feels that the CPCRA study demonstrates a definite risk to the use of STIs in multi-drug resistant individuals; he responded affirmatively but pointed out that these risks had been documented previously, and could potentially be addressed by using more prophylactic drugs than is currently the typical standard of care. Cohen also stated that while toxicities were not an endpoint in the CPCRA trial, he agreed with Miller's conclusion that the message for individuals in this situation that need to interrupt therapy due to drug intolerance is: "if you have to stop, stop, but prophylax."

Steve Deeks articulated his sense that, if there is a benefit to STIs in salvage therapy, it will be in "a well defined group of patients." He agreed with Cal Cohen that this is likely to be individuals that have the option to add one new drug (to which their virus is not resistant) to a combination regimen. Deeks expressed the opinion that benefit is unlikely to be demonstrated for individuals with no new options, and individuals with two or more new drugs to add to a regimen will likely do well without an STI. He reported plans for a 30-person randomized trial which will evaluate the value of an STI in individuals whose only new option is T-20.

Returning to the differing outcomes seen in studies to date, Lidia Ruiz brought up baseline CD4 counts as another factor to bear in mind. In her Retrogen study, the average count was around 350 cells compared to just 27 in the GigHAART trial. Baseline viral loads were also somewhat higher in GigHAART, and – as Steve Deeks added – the continuous therapy control group fared better in Ruiz's protocol. Cal Cohen further observed that participants in GigHAART used an average of around eight drugs, compared to five in Retrogen and four in the CPCRA MDR trial.

Martin Delaney questioned why prophylaxis wasn't required in the CPCRA trial. Cal Cohen explained that the average CD4 count of participants was around 150 so prophylaxis for infections other than PCP was not indicated. He also said the most commonly reported infection was candida, so - with hindsight - a broad recommendation for fluconazole prophylaxis during the STI might have been a good idea.

Citing older data, Rob Murphy reminded discussants that around 20% of individuals that stop HAART may experience a rapid drop in CD4 counts. He mentioned a study where the average CD4 count was around 600 at



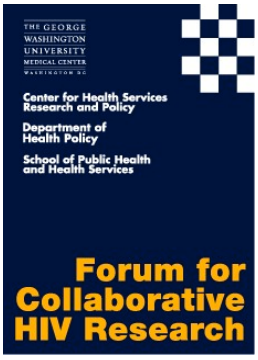
the time of interruption, which documented several outbreaks of herpes simplex and zoster among participants. Murphy cautioned that, in some circumstances, CD4 counts may drop below prophylaxis thresholds more quickly than can be caught by even fairly frequent sampling.

Veronica Miller asked the group whether they felt that the CPCRA study had answered the question regarding whether STIs are beneficial in the salvage setting, at least when no new drug options are available. Mark Harrington responded that "it's hard to know without seeing the actual data." Martin Delaney added: "based on the limited amount of data in front of us, I wouldn't see this question as being answered at all."

Steve Deeks came back to Christine Katlama's GigHAART trial, noting that while the results were very positive, the underlying cause did not appear to be a shift from resistant to wild-type virus as a result of the interruption (eight weeks is typically too short a period to allow such a shift). Veronica Miller agreed, since in her trial a low CD4 count reduced the likelihood of such a shift and counts were extremely low in GigHAART participants. Deeks also pointed to Katlama's argument that the duration of the STI is critical, and only GigHAART has used an eight week interruption; the less successful studies employed longer STIs. He rued the lack of any putative mechanism to support Katlama's thesis, however.

Attempting to tease out the practical implications for pursuing this research, Veronica Miller questioned how future studies can address these questions if trials are difficult to enroll and risky in terms of clinical health. Mark Harrington suggested that small, specifically targeted studies (such as Steve Deeks's T-20 trial) may be one option. Gregg Gonsalves wondered if, instead of longer interruptions, short cycle STIs might be appropriate in the setting of advanced disease, simply to reduce drug exposure while perhaps lessening risks. Steve Deeks concurred that this might be one way to maintain individuals on a regimen and thus preserve future options.

Julianna Lisziewicz returned to the issue of how different drug regimens may have affected study outcomes. Courtney Fletcher offered that there may be some interaction between the regimens used and the duration of STI, with some drugs better used in conjunction with brief interruptions and others appropriate for longer breaks, due to their pharmacokinetics. In response to a question from Steve Deeks, Fletcher stated that the intracellular half-lives of many antiretrovirals remain unknown, let alone whether half-lives vary in different body compartments (as is the case for aminoglycosides, for example).



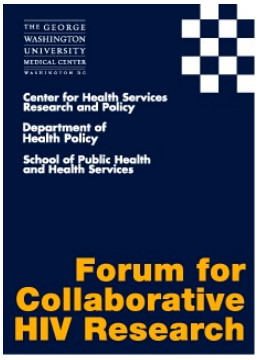
Veronica Miller then steered the discussion to the role of STIs in optimizing new drug classes, asking "what would be the best way to set up studies in this area."

Steve Deeks provided the background to this question, which arose when he found that individuals whose only new option was an NNRTI responded better virologically if they underwent an STI prior to adding the drug to a new regimen. Deeks noted that these studies can be relatively easy to enroll when the new drug is experimental and unavailable outside of clinical trials. Although Deeks is conducting such as study with T-20, he emphasized that this will not have the statistical power to answer questions about the role of STIs definitively and argued that the large trial networks need to pursue the question.

In response to a query from Veronica Miller, discussants were only able to cite one other study investigating whether an STI can improve the response to adding T-20 to HAART, which is being conducted by Lidia Ruiz in Europe and involves only 20 patients. Miller gleaned a recommendation from the group that larger controlled trials are needed to properly address this question.

The discussion moved onto whether viral fitness can be manipulated in ways that will benefit the health of patients who have run out of therapeutic options. As described by Steve Deeks, the idea is to maintain a population of drug resistant virus with impaired fitness, in the hope that this will be less damaging to the immune system than wild-type HIV. Deeks stated that ideally, the maintenance of less-fit virus should be accomplished with the simplest and least toxic regimen possible. He cited one 100-person study in France, described by Francoise Clavel at the Montreal workshop, which is looking at the efficacy of the dual combination of nelfinavir and 3TC in this regard.

Mark Harrington asked if any study had compared the outcomes of staying on a failing regimen compared to switching regimens or undergoing an STI and then switching. Deeks responded that this has not been done, to his knowledge. Veronica Miller raised the issue of risk, in terms of HIV evolving to become increasingly fit in the presence of drugs. Deeks answered that, although this clearly occurs, the virus still remains less fit than wild-type. He added that while it is often assumed that protease inhibitor resistance plays a key role in diminishing viral fitness, in his experience nucleosides are critically important. Provocatively, he suggested that the ability of dual nucleoside therapy to achieve prolonged partial suppression of viral load may not have been fully appreciated, given that such combinations were only briefly considered standard of care in the mid-90s. Deeks noted, however, that studying partial suppression strategies in the current research climate is difficult, since



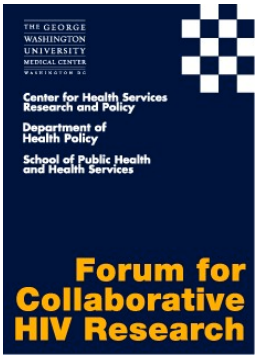
viral load cannot be used as the endpoint and other factors such as tolerability will need to be taken into account.

Veronica Miller quizzed discussants about the role of immune-based therapies (IBTs) in the context of multi-drug resistance. Julianna Lisziewicz argued that therapeutic vaccines and immunomodulators should be considered as new classes of drugs, but that study endpoints may need to be adapted. As an example, it might be possible for an IBT to improve the safety (and perhaps extend the duration) of an STI by preserving higher CD4 counts and/or enhancing immunologic control of viral replication. Lisziewicz asked how the FDA will deal with endpoints for IBTs; Alan Landay responded that in his discussions with the agency, they have made it clear that an impact on viral load would definitely be acceptable. In terms of the degree of effect, Landay stated that something equivalent to licensed antiretrovirals (e.g. a 0.5 log decline or better) would probably be adequate. He added the caveat that some IBTs might exert their activity via indirect mechanisms, citing the plight of IL-2 which - despite a dramatic effect on the surrogate marker of CD4 counts – has not been considered for licensure in the absence of evidence of clinical benefit.

Attempting to focus on salvage therapy, Landay reminded discussants that IBTs are often ignored in this context, noting that even 15 years ago the late Jesse Dobson (the driving force behind Project Inform's Immune Restoration Think Tanks) argued that researchers need to try and design IBTs that might benefit individuals with advanced HIV disease. Mark Dybul argued that IL-2 is perhaps the only known therapy that might play a useful role, given that it has been shown to raise CD4 counts even when the baseline levels were low. Given the concerns relating to rapid CD4 T cell loss and clinical events as a result of STIs in multi-drug resistant patients (as seen in the CPCRA MDR trial); Dybul made the case for studying whether pre-STI administration of IL-2 could ameliorate these complications. He also pointed out that such a trial could quickly answer the longstanding question of whether IL-2-induced increases in CD4 counts are clinically beneficial. Dybul outlined what a study design might look like, suggesting three arms:

1) Switching regimens without interruption
2) STI prior to switching
3) IL-2 followed by STI prior to switching

David Sahner agreed that "in principle that sounds like a great idea." He added the qualifier that there have been no IL-2 trials in individuals with CD4 counts of less than 50. Mark Harrington questioned whether such a trial design is ethical, which discussants felt depended on the ability (if any) of the STI to improve the response to the salvage regimen – a

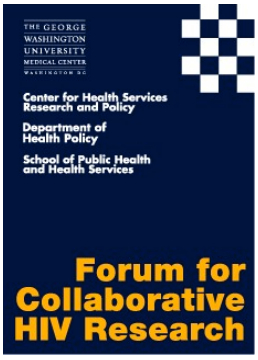


question that had earlier been characterized as still unanswered given the conflicting trial results to date.

James Demarest offered the reminder that, while there is clearly a rationale for examining the role of immunomodulatory agents in salvage therapy, a distinction probably needs to be made for vaccine approaches since an advanced degree of immunosuppression may limit or preclude an ability to mount a T cell response to vaccination.

Pondering the implications of these discussions for regulatory agencies, David Sahner wondered if it might be possible to convene an advisory committee – involving both community and academia - which would attempt to come up with “rational endpoints” for STI trials. He suggested that the findings of this committee could then be submitted to the FDA for consideration. Courtney Fletcher reported that there have been long discussions at the FDA antivirals committee about the need for novel trial designs in the context of multi-drug resistant patients, and he cautioned against pre-judging opinions at the agency. As a member of the committee himself, Fletcher stressed that the FDA appeared very open to being approached with new and innovative ideas in this area, regardless of whether those approaches are made by an individual sponsor or coalitions of representatives from community and academia.

Veronica Miller encapsulated the priorities in terms of issues for the FDA, noting that the two separate topics had emerged: one relating to these use of immune-based therapies and STIs in heavily treatment experienced patients, the other relating to endpoints for therapies aiming to enhance HIV-specific immunity (as discussed in the first session of the meeting). Miller then brought the meeting to a close by noting that additional comments and input will be sought from individuals unable to attend the meeting, and follow-up will be conducted regarding discussions with FDA advisory committees.



Discussion Participants

Ben Cheng
Forum for Collaborative HIV Research

Cal Cohen
CRI New England

Steven Deeks
University of California San Francisco

Martin Delaney
Project Inform

James Demarest
GlaxoSmithKline

Mark Dybul
NIAID

Courtney Fletcher
University of Colorado

Gregg Gonsalves
GMHC

Mark Harrington
Treatment Action Group

Jeff Harris
Gladstone Institute of Virology & Immunology

Richard Jefferys
Treatment Action Group

Alan Landay
Rush Presbyterian

Julianna Lisziewicz
RIGHT

Veronica Miller
Forum for Collaborative HIV Research

Luis Montaner
Wistar Institute, Philadelphia

Robert Murphy
Northwestern University Medical School

Lidia Ruiz
IrsiCaixa Foundation

Jeff Safrit
Elizabeth Glaser Pediatric AIDS Foundation

David Sahner
Chiron Corporation

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