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Question 3: What key questions were not addressed at the meeting or should have been discussed more in detail?

Barriers to Cure

- We didn't focus on the issues of drug toxicity as a bigger barrier to regulatory issues than treatment interruption.
- Future Forums should allow more discussion on the barriers the gut-lymph nodes-CNSmacrophages may present towards a HIV cure.

Basic Science and Preclinical Research

- What scientific dogma needs to be re-examined so that a HIV cure can be obtained? For example, cellular proliferation appears to be the intersection between cancer and infectious disease. Is it truly understood?
- 1. Molecules needed to activate latent proviruses. 2. Research path on methods to activate proviruses.
- Translational path and validation of animal models. Role of preclinical efficacy testing in drug and basic science advancement.
- Strategies to target the Brain reservoirs and potential neurological complications of current reactivation strategies.
- It would have been helpful to have context around the selection of immune therapies versus antivirals as we develop regimens for HIV cure. An over view talk of the biological and scientific approaches to achieving functional cure would have been helpful. For example, it was difficult to understand the relative merits targeting viral latency (Vorinostat vs Romidepsin) and immune modulation (VRC01 vs gene therapy (modified CD8 cells) vs CAR cellss

Clinical Trials

- While I realize it is still early in the stage of things, more detailed discussion on endpoints for definitive studies or what needs to be accomplished in order to come to resolution on endpoints would be appreciated.
- Case study on a combination of different vaccines
- I would have dedicated a brief session on the state of the art of current "remission" oriented strategies and ongoing trials.
- I think more examples of actual clinical trial protocols OR draft protocols from agencies, industry, or academics would be beneficial.

Treatment Interruption

- We kept coming back to discussing various aspects of treatment interruptions. It might be interesting, if further funding is obtained, to devote a meeting to this topic alone.
- A lot of discussion on ATI but did not address safety concerns with product itself and how best to study especially when multiple dose and longer duration are likely needed to show activity/proof of concept, etc
- What are people comfortable with in regards to viral load rebound during ATI 100, 200, 1000, 10,000? It would have been interesting to get feedback on the threshold to reinitiate treatment. Discussion on next steps for standardization of assays/biomarkers. How best do we generate

this data? It would have been interesting to discuss a case using an immune modulator such as anti-PD-1 or anti-PD-L1.

I still think questions relevant to patients remain underdeveloped. ATIs are informed mostly by studies (ie, SMART) that offer important clinical insights, but lack awareness of the social/cultural/behavioral context of pill taking. There is an implicit assumption that most people with HIV are taking their meds successfully, which we know is not true (CDC-2012 estimate only 25% are). There is a more nuanced and informed discussion that needs to take place. Also, the need for ATIs in Phase I safety studies seemed underexplored. Plus, I was surprised that a placebo group was proposed--the advocacy community has always viewed placebo trials with significant skepticism. Also, along similar lines, the segmentation of acceptable patient populations for which trials seemed underdeveloped. As a whole, people with HIV and their views felt underrepresented and under-empowered.

Ethics

- One question was whether the risks of cure research, including risks of optional procedures, can be justified given the uncertain social value of research at this early stage?
- I think that participants selection and informed consent process could have been discussed more in details, due to their important ethical and regulatory concerns, but actually the discussion we had during the meeting was greatly valuable
- The issue of partner participation in research. Partner counseling about risks and exposures will be extremely important during the consent process.
- How is respect being conveyed to clinical trial participants and the public by both domestic and international investigators that are conducting and/or presenting trial information given that a rationale clinical trial hypothesis may still result in unintended and/or unfortunate consequences for patients (i.e., STEP trial)? Given the growing, yet somewhat unstable knowledge base for HIV infectivity, is the collection of historical HIV-related trial misfortunes being provided to patients (as examples of adverse outcomes) who may not be aware of this type of information?

Collaboration

 Biobanking issues are crucial for present and future cure research. I would also like to hear more from industry on all categories/sessions presented. I would love some discussion on how the Forum could begin going about making ATI criteria and things like the VSOT definition uniform, accepted metrics for trail design.

Biomarkers/Assays

• Where is the field in developing new laboratory assays for measuring latent HIV reservoirs in potentially cured individuals? The viral outgrowth assay is not sufficient. Without a better assay, HIV-infected individuals are at-risk of viral rebound during cure trials.

International Issues

- International coordination efforts (included funding): review of ongoing projects.
- Vision for cure studies in resource-limited settings (Thai study aside)
- Research for cure in countries where HIV is endemic and the FDA's role in global health
- Involvement of investigators from developing countries

Regulatory Pathway for HIV Cure Survey Summary Session 2: Arriving at a Common Language

What questions or additional topics related to defining HIV cure, preclinical testing and biomarkers/assays need to be addressed in the future?

Defining HIV Cure

- Ideally, a definition of cure would include some measurement of latently infected cells. However for a working definition for use in clinical trials, VSOT is a great start.
- If VSOT52 was achieved, what is next? What type of confirmatory trials are needed?
- Need agreed upon language moving forward that does not mislead patients and the public. What is the most efficient way in sharing samples from "cure" studies and prevent silos? What is the best way to evaluate different biomarkers and assays and to correlate these with clinical endpoints?
- Social aspect or behavior should also be addressed or eluded to, as it's part of the "cure
- Defining "cure trials" for potential participants (or alternate language to use)

Preclinical Testing

- We cannot forget about the important role of animal studies for studying safety. More safety related discussions might be helpful in the future.
- Summary of animal models and differences between models; how can animal models be used to test potential interventions
- Study designs to establish proof of concept
- The plan to write a position paper on the current knowledge available for the use of animals in cure research is a good one. Seemingly, the most significant difference between animals and humans is genetics. Will there be any emphasis on, or further research of, the effects of HIV (SIV, etc.) infectivity (and its accompanying inflammation) on genome activation or inactivation (i.e., DNA or histone methylation and/or histone acetylation/deacetylation, etc.) in for example, humans vs. monkeys or other animal species? If this information was obtained, perhaps it could be useful in discerning how well animal data might be able to predict human clinical trial outcomes.

Biomarkers/Assays

- In-depth discussion of potential biomarkers and the promises and pitfalls of the assays
- Discussion on validation of biomarkers in animal models or human studies.
- Biomarkers associated with non-lymphoid reservoirs such as macrophages, astrocytes and microglial cells.
- We need to push research towards new assays. We need a test that could predict the presence of expanded and functional proviruses before and after interventions to reduce the reservoir.
- Where is the field in developing new laboratory assays for measuring latent HIV reservoirs in potentially cured individuals? The viral outgrowth assay is not sufficient. Without a better assay, HIV-infected individuals are at-risk of viral rebound during cure trials.
- Updates on biomarkers/assays as these improve modification of the length of suppression as clinical trial data become available: increasing/decreasing as necessary; 1 years is a good place to start
- Identification of latently infected resting cells with superior diagnostic tools based on alternative surface expression

Question 5: A potential virologic endpoint for phase I/II clinical trials discussed in this session is "Virologic Suppression Off Therapy (VSOT)" followed by a number that indicates the duration in weeks (e.g., VSOT52 = 52 weeks, i.e. one year, of virologic suppression off therapy). VSOT can further be revised to include the method (lower limit of detection of the assay, LLD) used to define virologic suppression. For example, a VSOT that defined suppression using an assay with a lower limit of detection of 20 copies/mL and that lasted at least 52 weeks could be VS200T52. Is VSOT a reasonable and sufficient virologic endpoint for HIV cure trials? If no, why not?



Yes

- Yes, I believe VSOT is a flexible and reasonable endpoint. It must be combined, however, with maintenance of CD4 counts and no increase in immune activation/inflammation.
- Yes, there just has to be consensus on what is a clinically relevant and reliable endpoint (eg, 52 weeks)
- Yes. I thought it was very ingenious. But I would say HIV remission trials since cure connotates a very different ball game. The viral suppression metrics outlined does not really go to an HIV cure per se.
- As was discussed at the meeting, current antiretroviral therapy has set an incredibly high bar for success. I think VSOT is a reasonable and sufficient virologic endpoint, but it would also need to be combined with markers of inflammation.
- It's a very good start, quite analogous to terminology in cancer
- The endpoint may be good as a proof of concept but longer follow-up will be needed.
- I think it is reasonable and useful. As noted above, ideally a definition of cure would also include some measurement of reservoir but that will probably need to wait for better assays to measure this more accurately.
- Seems reasonable to explore further.
- Yes, VSOT is a reasonable virologic endpoint for HIV cure trials at this time. However, in the future we may need to revise this in order to truly define a cured individual.
- OK for now, but length of VSOT may be a moving target.
- It is probably the best endpoint. It quantitatively describes what the expected effect of a treatment is, and it could potentially be used as a basis for licensure. The described effect (VSOT) would be described in the product label.
- It is reasonable to define a functional cure. A sterilizing cure would require a different definition. It should be regarded as an interim definition until more data are available.
- It is certainly reasonable for early phases of development and may be a reasonable endpoint for Phase 3, but it will likely need to be combined with other evidence of benefit to patients, for any consideration of benefit risk.
- Yes, but time to VF also appears to be a decent endpoint statistically.

- Yes, this seems like a good term and a good initial endpoint. I do wonder whether this will be a good way to describe the goals of the research to study participants. As much as the research community loves acronyms, VSOT might be a confusing term for laypeople.
- It is a sufficient endpoint in the first Phase of studies, however must be again defined for the Long-term use
- Reasonable as virologic endpoint, but clearly does not encompass CD4 and clinical outcomes.
- This is reasonable for most studies using ATI as an end point. Needs correlation with other markers however, viral DNA, intracellular RNA, single copy assay, productive virus quantitation-co culture assays, etc.
- Yes I think it is better than other surrogate endpoints. but there should be someway incorporating elements of a slope. because as clinicians we are interested in the general trend not just one point value.
- This endpoint is reasonable and sufficient for early clinical trials which are looking for proof of concept, dosing, etc..., but more long term endpoints may be needed for definitive trials.
- VSOT is a great first step. It is something that can be easily measured in any study and has direct clinical relevance.
- This is a reasonable virologic endpoint for clinicians to use in trials. This language needs to be used careful for patients during the branding process. It could get complicated for participants to understand the difference between cVSOT or VSOT52.
- It is a reasonable endpoint but may be accompanied by additional measures depending on the intervention
- VSOT would be a reasonable term to communicate trial results (interim or final), but should not be used in combination with the word "cure" since it is not necessarily indicative of this outcome.
- Good starting point, should include additional tests for inducible virus if we get to a routine VSOT52.
- It is an excellent place to start. The best place so far. Sure, as assays become even more sensitive there may be other endpoints.
- It's ok, I guess. This discussion limits dialogue about providing new treatments for those who need it most, ie immunologic non-responders (as high as 1 in 5 treated patients in some clinical settings) who benefited from the Sangamo T cell trial and who could potentially benefit from pursuit of FDA approval for an INR indication sans VSOT are abandoned in this construct. Likewise, those failing ART and out of options. The "best", VSOT is pursued in the absence of what might be good, even very good, for patients in need. This again speaks to the weakness in representing people with HIV in the discussions.
- No
- No. There may be mother markers indicating damage done by even undetectable levels of virus, and they must be considered
- This is a tough question, but I would say no because there would need to be further evaluation of suppression including reservoirs, making sure that those reservoirs are FULLY suppressed also.

- While VSOT is one important measure to report, I do not believe this endpoint alone is
 reasonable and sufficient. Cure trials need to address virologic suppression + latent reservoirs.
 Otherwise, an HIV-infected individual may simply be existing in a state of "waiting" for the
 activation of latent HIV.
- not the best endpoint, if the VL is 200 copies and more importantly its derivation and use has not been explored in the setting of LMIC countries or in the context of confections. The role of residual HIV transmissibility based on VL in all bodily fluids or in the female genital tract should also be considered
- VSOT + CD4 would be better.

Other

- I think using "weeks" is a mistake. In my opinion we're not talking cure, functional or otherwise, if the patients can't be off therapy for AT LEAST a year, so I suggest that the number should indicate "years" not "weeks" off therapy.
- Not sure. This is a question that can only be answered by PLWHA.
- It is nice to redefine objectives and bring them to a more manageable frame. But at the end it is kind of semantic point.
- It is a reasonable interim measurement, but ultimately VSOT is not cure. There is growing evidence that natural elite controllers would probably still benefit from ART.
- I like VSOT but not use of LLD. What is a lower limit of detection? One either detects the target
 or doesn't. The correct term, limit of detection is also confusing as many individuals do not
 realize that there is a 95% likelihood of detection at the LOD. Undetectable or TND (target not
 detected) using an assay with an LLOQ of 40-50 copies/mL would be better and would be
 consistent with assay labeling;
- Does VSOT allow sufficient time to determine virologic endpoint for HIV cure trials. Is it months or years (and how many years) to show reasonableness of VSOT.
- It can be useful and reasonable, but probably not sufficient: we still have to understand whether a future "cure" will address the issue of inflammation and immune activation

Question 6: Ideally, HIV remission should be life-long, however this is not a practical endpoint for clinical trials. In this session, virologic suppression for one year (i.e. VSOT52) was suggested as a starting point that may have clinical relevance, especially from the context of virologic control. In your opinion, is the duration of virologic suppression for one-year (VSOT52) sufficient as an endpoint for HIV cure trials?



Question 7: How long should it be?

Days

• 2 days

Months

- 6-8 months. Coming data will help define an appropriate time period. Don't think it helpful to determine too restrictive a time period in the beginning.
- 6 months (1/2 year)
- 9 months
- Don't know 18 months at least (I would use months rather than weeks personally).

Years

- 2 years
- 2 years
- 5 years
- 260 weeks (5 years)
- 5 years
- 4-5 years
- 52 weeks is a good place to start, but ideally longer term follow-up studies will demonstrate years (3 or more?) of virologic suppression without disease progression due to the potential risk of poorly monitored virologic rebound
- 3 to 5 yrs
- One year of intense follow-up, 2 additional years of quarterly or biannual monitoring. The use of the term "endpoint" implies that after this outcome is achieved, the trial will end and results will be reported. Two concerns: 1) Individuals outside of the scientific community will perceive the reported results as evidence of cure/remission and may be tempted to stop therapy. 2) Funding for trials will be dependent on this outcome, meaning follow-up for clinical trial participants after the "endpoint" is reach may be compromised.
- 4-5 years
- 5 years
- Over a year. 2 years at least
- 5 years? 10 years? longer?
- so hard to know but 2 years would be preferable
- 2 years

Other

- Think it should be staged. VSOT52 might be a primary endpoint with longer durations as secondary endpoints.
- Until re-bound virus is detected.
- Six sentences.
- we should not define that at this stage. we should evaluate this in a continuous fashion without a set minimum. lets not set the bar too high initially.

<u>Session 3: Ethics and Fairness in Trial Recruitment, Participant Education and Informed Consent</u> Question 8: What questions and/or additional topics related to patient education, recruitment and informed consent need to be addressed in the future?

Diversity of Patient Population

- The exploration of these questions and phase 1 trials for novel and not yet approved interventions should be undertaken in LMIC countries not the US.
- There needs to be a discussion of the ethics of doing trials in third world countries with very different ethical and legal rules
- It is critical that patient education and engagement at all phases reflects diversity of the affected population. Focus group information may determine where the need for information varies with different ethnic, racial or age groups.
- Engagement efforts to involve more women and minorities in the process of research. Engaging these populations beyond just research participants but in the full spectrum of research. Patient education needs to include raising the literacy level for all stakeholder groups, not just potential participants.
- Subject understanding greatly depends on location, socioeconomic status, psychiatric comorbidities, and culture. How do we make sure each subject understands the informed consent independent of the factors listed above? What roles can key stakeholders play in patient education and what are the best modalities for educating patients? These will be different in different parts of the country/world.
- It is now clear that these initial trials may not be suitable for everyone; participant selection is an important issue that affects both protocol design and informed consent process. Finding a way to balance the need to protect most vulnerable people and to respect their right to choose is crucial.

Patient Medical Literacy/Understanding

- We need to discuss the actual informed consent process, as none of these issues are new. What we need is a new process for ensuring that people actually know what they are getting themselves into.
- The idea of a video IC was good as long as it was not considered a total tool the individual has to be considered; including a nurse or outreach worker with the PI during IC process is important to ensure the discussion is clear to all
- Is there a role for a patient/participant advocate for women who have just given birth? Recruiting and enrolling HIV-infected neonates within days of birth is a significant psychological burden to mothers. Can they fully comprehend potential risks of trial participation during this period, or are they "blinded" by learning their new baby is HIV+?
- Patients should be informed about the study results of the previous studies in an understandable way. Perhaps the Forum can create a Patient-related Information site in the web in order not to leave interpretations of study results to the public media alone.

Language

- A benefit, risk and language to describe treatment interruption template would be useful
- It would be great to understand how best to harmonize heterogeneity in informed consents and then provide this information to IRBs - to try and minimize IRB-specific changes

- Favor not using the word "cure" but instead using "remission" as "remission" seems less likely to cause confusion to potential trial participants. Especially since "cure" may lead to unrealistic expectations for trial participants.
- I think we need more data on how patients react to terms like "cure", "functional cure",
 "sustained virologic remission", etc.--both in terms of whether these terms are more likely to
 induce therapeutic misconception and whether they help make the social value and objectives
 of the research clear. I suspect that there are both advantages and disadvantages to using the
 term "cure", but we tended to focus on the disadvantages.

• Need to come to some kind of consensus about use of the term "cure" in describing these trials. Conveying Risk

- Provide patient with frank description of toxicities of current reactivation strategies.
- Risk in different settings, especially early Fiebig vs later stage disease.
- Theoretical risks are always hard to discuss with participants. In particular, the theoretical risk of "reseeding the reservoir" during treatment interruption is a difficult concept to convey and unclear whether or how it should be discussed with participants.

• Availability to subjects of any clinical trial results that may impact their future treatment Learning from Other Fields

- Approaches to integrating decision-making research into cure trial protocols
- More concrete suggestions for collaboration with other fields (HIV prevention, cancer) would be helpful

Community Involvement

- Community buy-in to allowing patient protocols where dormant virus can be reactivated
- What are the conflicts of interest between the patients and the HIV Cure Research clinical trial investigators? Having clinical trial participant advocates was mentioned. If this is a practical idea, could these individuals assist participants with informed consents? I would like to hear more about the utilization of clinical trial participant advocates. I also felt as though additional community representation (i.e., 2 individuals vs. only one) on the Forum HIV Cure Project panels would have been useful as the comments provided were great, but at times, seemingly almost overrun by all the other stakeholders.

Compensation and Patient Records

- Make sure they are well compensated for their participation
- Many HIV infected people participate in clinical trials just to earn money
- Some patient don't want the redaction of their records so how can we get them in involve them in the discussion

Question 9: Should trial participants receive their clinical results administered during a trial, even if there is no direct, known implications for the individual's future prognosis or treatment?



Maybe Responses

- Mode of Deliverance
 - o Only if delivered at the end
 - Group, rather than individual, data delivered at a meeting of participants might provide the best chance for understanding the results
 - Patients should receive summary results accompanied by an adequate interpretation of the data; the benefit of getting individual results is questionable.
- With Adequate Information
 - With CLEAR description of the known implications or frank admission that implication is unknown
 - o Extensive information as to interpretation of results is key
 - I think many participants will be interested in receiving results related to measurement of reservoir and these can be given with proper disclaimer/explanation.
 - As long as all individuals, regardless of outcomes, are highly educated about AND COMPREHEND the potential for viral rebound after therapy cessation.
 - Needs to be given in a fashion which does not overstate or understand its meaning or significance. So tell patients limitations of the assays.
- If it doesn't affect trial
 - Only if it doesn't unblind the study
- Only the pertinent information
 - Clearly people should be told VSOT status
 - o I would exclude markers/parameters that are not clinically validated
- Patient Characteristics/Preferences
 - If it's something participants are really interested in, the information is not likely to mislead them or cause them to engage in risky behavior, and if it can be conveyed clearly that the information has no clear clinical relevance.
 - Depends on the patient and the data (some can understand uncertainty and the idea of a non-validated assay).
 - o If they desire so
- Depends on Trial Type, Size and Results

- Releasing data could bias the research, but in very long studies it may be necessary to motivate the subjects.
- Depends on the actual clinical trial results.
- If the results are based on clinical assays they may be shared, but if they are based on non-certified assays they should not

Yes Responses

• If there is no harm to the patient in knowing these results and if knowing the results will not influence the outcome of the study, then I think erring on the side of more information sharing is preferable.

Question 10: In your opinion, is the word 'cure' misleading to potential trial participant understanding of risks and benefits to describe trials seeking to achieve long term ART free remission or eradication?



Question 11: What additional mechanisms for communication among those conducting HIV cure research are needed to effectively communicate and share best practices?

Shared materials and information in a central location

- Online shared educational materials on "cure" research with chat capabilities/intranet forum
- Perhaps have a web portal that serves a source of new information that is useful for academia, private sector and the community with web-based updates
- National open-source databases for clinical trial data generated during these early HIV cure studies would be extremely beneficial to help guide investigators in the design of new clinical trials and potential new therapy design
- Common list-serves and conference tracks at major ID conferences.
- Newsletter with updates on studies being planned and active
- An electronic library of (historical) clinical trial informed consent documents might be beneficial to investigators.

Templates/Standardization

• Common terminology and consider bringing in already used guidelines, like the Good Participatory Practices produced by UNAIDS and AVAC, to learn and share best practices.

Community involvement

- Help and engagement from the community
- Community involvement COB's ASO's and community health care centers.....

Researcher to Patient Communications

- If possible, researchers could steer away from using the word "cure" but instead using "remission" as "remission" seems less likely to cause confusion to potential trial participants. ("Cure" may lead to unrealistic expectations for trial participants.)
- Proper language translation and back translation
- More figures, diagrams, pictures. Most trial documents attempt to explain complicated science in layman's terms. Putting an emphasis on schematics like figures or diagrams will ease the burden on participants to read several pages of text. Moreover, comprehension will likely improve
- I like the word remission, since it indicates that the virus is no longer measurable but also that it may recur or relapse or maybe descriptive just like VSOT
- We need universal language, which includes cure, into all protocols
- 'Cure' is a misleading term. Prevent remission or maintain suppression may be better terms to sue with patients than 'cure'.
- Do you mean communication with researchers and patients? Videos. The Martin Delaney National CAB is working on cure education modules/slides. We are planning to develop a clinical trial module. Maybe that would help. I like the idea of a very short, very directed quiz before consent is established.

• Recommend an assessment of understanding at the end of the informed consent process Researcher to Researcher Communications

- Discussions of issues that have arisen in communication with volunteers and how these were resolved, or could be better dealt with
- Hard to say. I would be especially worried about clinical studies with very limited number of subjects, but at the same time finding other similar (never identical study) elsewhere. We are losing power by doing that
- I don't think the researcher must evaluate the reasons why a person wish to participate in a trial, but a strict and as objective as possible evaluation of his/her understanding of the trial procedures should be done at every step of participant involvement
- F2F meetings of those involved in shaping the informed consent document with others that have experience in research that is highly unlikely to benefit the participant directly (e.g. HVTN)

• More information on patient risk and decision-making

The Forum

- Messaging is key. Researchers and the lay press have to be very careful in how they represent results. More harm can potentially be done. I think the Forum is an excellent mechanism to effectively communicate and share best practices.
- The conference is a good way to share the information. Update in 2-3 years
- The Forum could facilitate the development of consensus template language and consent approaches. The Forum could go a step further and suggest draft guidance language revisions to FDA

Session 4: Cure Research in Maternal/Pediatric Setting

Question 12: What questions and/or additional topics related to HIV cure research in the maternal/pediatric setting need to be addressed in the future?

Physiology

- How the pediatric immune system differs from adults and how this lends itself to cure studies (or not)
- What are the key immunological differences between pediatric and adult patients that affect acquisition of HIV infection? What is the plan to identify them?
- Tissue sampling and HIV latency in pediatric patients versus adult patients

Treatment and Diagnosis

- Advocacy for global early diagnosis, treatment and very regular monitoring during breastfeeding
- If remission is obtained in adult patients with chronic/established HIV, the same therapies should be evaluated in pediatric patients with chronic disease.
- Assays for detection of infected infants at the POC in order to enroll into early treatment trials as soon as possible.
- Discussion on what 'cure' would mean for use of ART during pregnancy -would risk for vertical transmission dictate ART during pregnancy even among 'cured'? When would risk for vertical transmission be considered negligible enough to let the pregnant 'cured' woman get off ART?
- I'm not certain this session was explained fully in the context of FDA's role; in this case there's no new agency approval of the ART compounds? The issue for FDA is development of surrogate biomarkers or diagnostics?
- Plans for follow up of high risk infants who test negative at birth for HIV using qualitative HIV nucleic acid detection assays

Ethics

- What are potential consent issues as well as structural social/behavioral questions and barriers
- I would love to learn more info on their consent process. It might be helpful for adult trials
- What are the ethical issues surrounding continued reservoir studies in placebos and treatment failures after studies are over in these pediatric cohorts?
- Is there a role for a patient/participant advocate for women who have just given birth? Recruiting and enrolling HIV-infected neonates within days of birth is a significant psychological burden to mothers. Can they fully comprehend potential risks of trial participation during this period, or are they "blinded" by learning their new baby is HIV+? The conduct of pediatric and adult trials in parallel. What are the justifications and implications of this? Ethical issues? This desperately needs to be outlined
- Patient acceptability of interventions
- Women need to be involved in study design, not subjects but participants

Trial Design

- We need to follow up after the data from ongoing trials is available to be sure our time points for when to stop and start treatment and what is the optimal treatment
- Generalization to all infants, not just those infected in utero
- Additional attention to evaluating and monitoring for the potential for NVP resistance in studies using NVP-based regimens.

- Next trials, like P1115, are trying to reproduce the case of the Mississippi Baby. We should go beyond that and assess the impact of early ART on infants, even if therapy is started later
- What the criteria are for interrupting ART? More debate is needed to formalize criteria
- There will be studies proposed with pediatric subjects who have achieved some measure of VSOT through treatment, that include treatment interruptions. The topic in this regard relates to how many subjects can be tested to get meaningful results and what are the decision processes to use placebos in such studies.

Regulatory Pathway for HIV Cure Survey Summary Session 5: Managing Risk Benefit in Clinical Trials

Question 13: What questions and/or additional topics related to clinical trial design, risk mitigation strategies and analytical treatment interruptions need to be addressed in the future? Clinical Trial Design

- As highlighted during discussions, many participants enroll in trials to benefit themselves as well
 as others. Therefore, standard trial designs may not be appropriate in this setting because
 participants may not be motivated to enroll in a study where they do not receive treatment
 (they perceive it as a risk of serving as a control subject). Innovative trial designs, such as a single
 cross-over after safety assessment where controls cross-over to treatment if adverse events are
 not detected, can bypass these potential problems and also enhance scientific results.
- Discussion was good here. Think Network physicians have a good handle on these issues but individual researchers trying to do Cure trials do not seem to have thought trial design through. More discussion of design issues would be useful for these individuals.
- Most efficient design (inclusion of a control group or individuals as their own controls) and more information on safety of ATI
- Are control groups necessary in cure trials? Are there more efficient adaptive designs that can be used? More data needs to be generated for short duration treatment interruptions. What is the best way to combine drugs from different companies? Are there mechanisms to facilitate contracts?
- Phase 1 safety study should be conducted in real patients, not in healthy human volunteers
- Frequency of VL test during ATI. Monitor HIV-RNA in plasma during re-suppression.
- What length of ATI is justified for early phase trials? How much data should there be about the efficacy of an intervention before an ATI is employed? How much monitoring should occur during an ATI?
- Sample size calculations were not discussed
- What constitutes an HIV Cure intervention or HIV Cure clinical trial vs. a regular HIV intervention or clinical trial?

Risk Mitigation Strategies

- Patient population segmentation to identify those who may be at less risk or with a greater likelihood of benefit. At present, there seems to be acute and chronically infected, both with assumptions of good pill taking and viral suppression. Plus, no real discussions of other patient populations like INRs and those who have ceased therapy.
- The need for regular follow-up, and discussion of risk of treatment break to patient and to public
- Pharmacology of study design, side effects. Management and mechanisms to anticipate unexpected new side effects
- Does resistance develop during ATIs; can resistance be minimized by changing drugs with a long half-life to drugs with a short half-life prior to an ATI
- How to best be assured that participants have realistic expectations
- Continued discussion regarding the safety and risks of drugs and biologics used in research, especially oncologic products

Regulatory Pathway for HIV Cure Survey Summary Other/General

- Would such studies be indemnified?
- I'd like to know from a wider audience what researchers think of the community's ideas on ATI recommendations. And once again, more discussion on when to start and ATI. I think we could use more opinions from industry here to. I liked the way Pablo asked Janssen his opinion in a later session. We need to be sure to get industry's take on these issues as well.
- Treatment for research related injury

Question 14: In many HIV cure trials, trial participants undergo an analytical treatment interruption (ATI) where he/she discontinues antiretroviral therapy after administration of the cure research intervention in order to test the safety and effectiveness of the intervention. Although ATI's will need to be flexible and study driven, what are potential mechanisms to standardize and coordinate how ATI's are conducted across cure-related trials?

General Comments on Standardization

- Many research groups consider ATI in their clinical trial. Could it be feasible to define a consensus protocol? This could obviously be modified later on, but my impression is that ATI will be unavoidable but we need to do them with the best criteria.
- Guidance for how to think about when ATIs are justified that can be adapted for different study phases and designs.
- Open and collaborative discussion of pre-defined ATI criteria prior to study initiation.
- Studies should be conducted to determine when and how often a lumbar puncture should be conducted after ATI to determine presence of HIV in the CNS/CSF.
- Would make attainment of undetectable HIV RNA by SCA a requirement for ATI.
- Restart Tx when viral load rebounds above a specific threshold with careful monitoring seems like a reasonable approach (as opposed to waiting for set point).

Sharing Data/Results

- Ensure broad discussion of trial designs across the various groups doing cure research and have the study designs posted on a common website.
- While an FDA Guidance is optimal, I think the Forum's Cure Meeting is a great start for this as well as things like the VSOT definition. Maybe a good start would be a new Forum WG in this regard that includes participation from each Collaboratory, the ACTG as well as other national and international cure researchers
- This might be a subject for trials networks to consider and develop a consensus approach. It would be useful in the field to have some level of harmonization of data collection and analytical methodology and data sharing
- Develop consensus panels to define endpoints
- Create more standardized, "cure" language like VSOT for the purposes of communication among investigators.

Patient Follow-up/Monitoring

• Frequency of follow- up and standardization of assays used to monitor outcome

- Should be frequent sampling for virologic endpoints and patients followed for prolonged periods off therapy. Not sure there needs to be VL cap for restarting therapy, as some agents may require some time to have a measureable effect.
- Good reservoir management and viral sequencing and treatment history clear patient understanding and vigorous follow-up very low threshold for recommencement no mixed messages in the community

Resuming Therapy and Biomarkers

- Agreement on trigger for restarting therapy and on eligibility for treatment interruption
- Do a pilot study with ATI to investigate which are the biomarkers to be measured before the ATI and the proper frequency of VL measurements to catch the rebound as early as possible and the decay curve when patients are put back on ARVs.
- Standardization and coordination can be achieved using validated markers and endpoints which the HIV community has reach a consensus about.
- It would be great to standardize timing/frequency of blood/biomarker collection so results can be analyzed across different studies. A guideline for ATI would be a great first step.

Risk

- Trials need to identify risk of re-seeding reservoirs and mitigation strategies (use of entry inhibitors)
- Difficult to standardize across different trials, but the pause should be kept as short as feasible, and screening of subjects should take risks into account.

No Standardization

- Needs to be tailored to the question being asked. No one size fits all. Should consider standard of care.
- Since the interventions will likely be different, it is likely that the ATIs may also differ, which is probably acceptable.
- Standardization may be difficult at this point. Depending on results from current and near future trials, we may learn how to more appropriately standardize going forward.
- ATIs should be directly relevant to study outcomes, which can vary significantly.

Other

- I think the field is moving forward with more frequent monitoring during ATI's and restarting rules of 1,000 or so copies of virus, at least for early proof of concept studies, though there is not yet a standard model that all agree upon.
- Very important question. FDA should be the gate-keeper here. More and stronger participation from FDA would help in future Forum on the Cure.

Regulatory Pathway for HIV Cure Survey Summary Session 6: REDUC Trial Case Study

Question 15: Please share additional comments or questions regarding the REDUC trial case study presentation and panel discussion.

Risk/Safety

- Numerous very good points were raised about deficiencies in the trial design of the study. While NIAID network studies may be a bit conservative, the REDUC study did not consider a number of important issues. Open discussions like the one that was had regarding this protocol should be encouraged so that important safety issues are reinforced, particularly during this period where definitions are still being made and assays are not yet routine.
- In the Clear study, several subjects' viral load was allowed to reach high levels increasing the diversity of virus and potentially impacting future treatment. This should be avoided in future trials.
- This is the type of study we DO NOT want to see: high risk for participants because of unjustified dose selection (rather than dose escalation) and lack of avoidance of known PK interactions (allowing boosted PIs). Also, under-powered for safety.

Need more Explanation

- The studied dose and administration frequency of romidepsin was poorly justified
- Pharmacological Problems, especially Pk Needs to be addressed in this Trial.
- This strategy will require repeated administration followed by a treatment interruption to assess its efficacy.
- Lack of PK data collection and adjustment for DDI. Need to consider range of doses/exposures for safe use
- I thought there was great discussion. It also illustrated how individual studies that are designed may not have considered other factors such as pk and drug-drug interactions and perhaps a more rigorous/independent review process may be helpful.

Regulatory Pathway for HIV Cure Survey Summary Session 7: RV397 Protocol Case Study

Question 16: Please share additional comments or questions regarding the RV397 protocol case study presentation and panel discussion.

General Case Study Comments

- This seems to be an example of non-harmonization across clinical trial research programs. To my knowledge there are at least 4 phase 1 studies of the antibody, with each protocol making assumptions without data, and designing under-powered studies in an inappropriate path without a development plan for the molecule in the first place. RV397 and the other phase 1 protocols are an example of how not to do efficient clinical study of a new entity.
- The patients will not re-start therapy until they have a confirmed viral load of greater than 1000. In effect, this study endpoint is a VS₁₀₀₀OT₂₄. I think that level may be too high. If patients were followed clinically and had 2 or 3 consecutive viral loads of 500 to 1000, I think most physicians would recommend the patient switch to a new regimen to re-suppress. In this study, they would be kept on the ATI for 24 weeks.
- I don't understand the basis for the placebo arm in this study of well-controlled persons who were treated early in the course of their HIV infection.
- I also agree that this is a long lasting monotherapy trial as opposed to VSOT.
- Not really a study of the impact of VRC01 on persistent HIV reservoirs. Rather it is a study to determine if VRC01 can prevent rebound.

Regulatory Pathway for HIV Cure Survey Summary Session 8: Hypothetical Case Study

Question 17: Please share additional comments or questions regarding the hypothetical combination protocol of vorinostat and CAR-modified CD8+ T cells case study presentation and panel discussion. Issues with the Protocol

- Combination therapy seems premature without demonstrating POC for either agent alone as well as dose optimization
- It was a nice presentation and a worthwhile idea, but it will take a long time before either part of the combination can be seriously considered as contributing to the cure agenda.
- I think Tebas is right that CART need to be dose escalated. The placebo arm made no sense. And, I didn't get the need for an ATI in any arm. Isn't the CART supposed to kill the kicked virus? It was suggested that there be a plan to distinguish kicked virus vs emergent/ATI-released virus. Why not keep patients on drug? What is the safety endpoint? I also think that there should be an arm or arms using other kick therapies, ie romidepsin with CART.
- Did not take much away from this presentation. Agree with the comment that CARs for HIV are not ready for prime time. Maybe this scientific area should be revisited in a future Forum. Inclusion was good but this type of a combination is premature.

Question 1: Which of the following describes your role (check all that apply):



Question 2: Would you agree that The Forum HIV Cure Project: Regulatory Pathway for HIV Cure Research meeting was valuable to your education, work and/or career advancement?



Regulatory Pathway for HIV Cure Survey Summary Question 18: How did you attend this meeting?



Question 19: How would you rate the quality of the webcast technology for this meeting?



Question 20: Please provide any comments or suggestions on meeting format, structure, venue and overall meeting experience.

Venue

- I know we needed a larger venue and the Barbara Jordan Center was very nice, but I did not feel the informality of most of our other meetings. Maybe if less people wish to attend in the future, we can have a more intimate venue. More informality often promotes more open discussions.
- The format was good- allowed for good discussions on topics that were well thought out. The venue was good, but the room was too cold, and it would have been nice to have tables to sit down for lunch. Overall meeting experience was good.

Format

- The Meeting was simply great, however more time for discussion would be good.
- The meeting went really well. I thought the right people were in the room for conversation. I wish there was more time for discussion. If possible, it would have been nice to have a day and a half meeting to allow for more robust debate.

- I thought that the meeting in general was very well run and very inclusive. My main comments are that it seemed like many of the panelists (myself included) weren't sure what their roles were supposed to be, which made some of the sessions a little uneven. I also thought the case discussions were a good idea, but three case discussions were a bit too much, and a more focused and better moderated discussion of the cases might also have helped keep the energy up.
- Very nice venue, and I liked the format although some of the "panel discussions" were really not panels, rather short talks from some panel members. Having a more clear timeline for the main presenter (i.e. shorter in most cases) to allow for more discussion would be helpful.

Diversity

- I got the impression (but I was not there to say for sure) the audience was mainly US attendees, not many internationals. Different countries bring diverse experiences in the topics discussed in the meeting.
- Excellent gathering. Really good to hear from regulators and patient advocates. Would have liked to see some broader representatives from resource-limited settings. Would be very keen to participate in future meetings and consensus guideline writing/discussion.

Audio/Visual

- I required considerable tech assistance to access webinar on Apple lap top. Apple users should have been given specific instructions in advance!
- With regard to the video cast, there was a fair amount of freezing up of the video but I'm not sure that anyone else does better. Perhaps the technology is not yet perfected.
- Hard to say. I was listening remotely and the sound dropped out repeatedly during all of the afternoon sessions. At times, I had no audio feed for 15 min stretches. The audio loss occurred with every speaker.
- Webcast OK most of the time, but local issues apparently caused lags that completely interfered with comprehension for some of the talks. Not sure if others had similar problems.
- Only issue with webcast was that I was frequently disconnected from the live stream and had to rejoin. Sometimes it took a while to rejoin. The webcast would freeze.

Meeting Materials

- The speaker notes/slides for this meeting were OUTSTANDING. I attend many meeting and was just so pleased to be able to review nearly all of the slides prior to the presentation. It also provided and format for note and comment recording. Is there a way to get an audio feed of this meeting that is not interrupted? Many thanks to the hard work and planning.
- Very good meeting with good discussion. Nicely coordinated and executed. I would try to get the white paper of the deliberations and recommendations out as soon as possible, since this is a very timely issue with a great deal of interest and research focus currently. Thank you for organizing this. I enjoyed my participation greatly.