



**Forum for
Collaborative HIV Research**

WORKING GROUP#2: CLINICAL SCIENCE AND MANAGEMENT OF CURE TRIALS

FORUM HIV CURE PROJECT: FOCUS ON THE REGULATORY PATHWAY JUNE 17, 2014



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COMMENTS FROM CO-CHAIRS

JINTANAT ANANWORANICH AND JOE ERON



INTERVENTION-BASED SUBGROUPS

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- Cell Activation/Disruption of Latency
- Immune-modulating
- Gene Therapy



THANKS TO WORKING GROUP MEMBERS

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Cell Activation

Jose Arribas, Lynda Dee, Joe Eron, Charlie Flexner, Daria Hazuda, Sharon Lewin, Lars Østergaard*, Adam Sherwat, Neil Shortman*, Kim Struble

Immune-modulating

Chuka Anude, Ron Bosch, Guilio Maria Corbelli, Steve Deeks, Nicole Frahm, Carey Hwang*, Filip Josephson, Yves Levy, Julie McElrath, Jeff Murray, Rob Murphy*, Asier Saez-Cirion, Brian Woodfall

Gene Therapy

Gwen Binder-Scholl, Ilan Irony, Hans-Peter Kiem, Dan Kuritzkes, David A. Margolis, Ron Mitsuyasu*, John Rossi, Pablo Tebas*, Jeff Sheehy, Randy Tressler, Matt Sharp

* Subgroup co-leads



COMMON ISSUES ACROSS INTERVENTIONS – I

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- **Single agent proof-of-concept trials should:**
 - Demonstrate an acceptable safety profile and some measure of biological activity
 - Couple with pre-clinical data to address mechanism of action and proof-of-concept
- **Assessment of acceptable risk-benefit for initial trials**
 - Early studies mainly offer scientific and societal benefits, with little to no individual benefit
 - ◉ In terms of acceptable risk, virally suppressed participants can be considered similar to “healthy volunteers”
 - A more comprehensive delineation of the long-term risks associated with life-long suppressive therapy will help define risk-benefit and the control group’s risk



COMMON ISSUES ACROSS INTERVENTIONS – IIA

- **Short and long-term toxicities**
 - A risk mitigation plan is critical to address any known toxicities
 - Rigorous assessment of safety using standard grading and blinding (where possible)
 - The safety information on drugs approved for other indications being repurposed for HIV cure research (i.e. chemotherapeutic agents) will be more complete than that of drugs in earlier stages of development
 - Animal models may not fully address toxicities associated with interventions
 - potential carcinogenicity, teratogenicity, hematological toxicity, and genotoxicity or genome activation



COMMON ISSUES ACROSS INTERVENTIONS – IIB

- **Short and long-term toxicities**
 - Long term follow-up may be needed to fully assess potential long-term toxicities
 - gene therapy interventions or others with malignancy risk may require a 15 year follow-up (registry)
 - Toxicity issues will be further complicated by the combination of agents with unknown and potentially compounded effects
 - A shared registry/common database of short- and long-term toxicities would greatly help the field



COMMON ISSUES ACROSS INTERVENTIONS – IIIA

- **Safety, sample size and dosing of initial studies**
 - Protocol design and implementation should maximally reduce risk via
 - ◉ small number of participants in initial trials
 - ◉ stringent inclusion/exclusion criteria, with intervention-specific parameters for: HIV reservoir, age, CD4+ count and nadir, time on ART, salvage therapy options, viral load set point, and prior clinical conditions
 - ◉ single dose, dose escalation studies – especially for novel agents
 - ◉ staggered enrollment



COMMON ISSUES ACROSS INTERVENTIONS – IIIB

- **Safety, sample size and dosing of initial studies**
 - Clear stopping rules for individuals, cohorts and overall study population
 - Use of consistent and standardized adverse event grading scales
 - Consideration of drug-drug interactions
 - It may be critical to conduct interim reviews by an independent, unblinded review committee to monitor data, number of exposures and best tolerated dose etc.



UNIQUE ISSUES – CELL ACTIVATION

- Given the mechanism of action of latency disrupting agents, multiple potential assays may be used to measure activity:
 - HIV RNA expression from resting cells
 - change in peripheral viremia (VL)
 - total and integrated cellular DNA
 - cellular HIV RNA to DNA ratio by PCR
 - flow-based RNA to determine proportion of activated latent cells
- ATI's may not be necessary in early cell activation trials
- Inclusion/exclusion criteria should select for the least vulnerable participants with normal laboratory markers
- To limit ongoing viral replication, patients should be on suppressive therapy past the 2nd phase of decay with consistent demonstration of plasma HIV suppression



UNIQUE ISSUES – IMMUNE-BASED

- Immune-based biomarkers for PK/PD are less developed than virologic measurements
 - Measures of activity will be intervention dependent, i.e. decrease in HIV-expressing cells, increase in CTL activity, neutralization, antibody dependent cell-mediated cytotoxicity, and/or delay of treatment resumption during an ATI
 - Due to the lack of an immune correlate of control/biomarker of activity, ATI will likely remain critical during initial trials
- The specific patient population for an intervention may alter the risk-benefit assessment
 - Acutely-infected participants may have a better response to immune interventions, but there may be greater consequences of a treatment interruption



UNIQUE ISSUES – GENE THERAPY

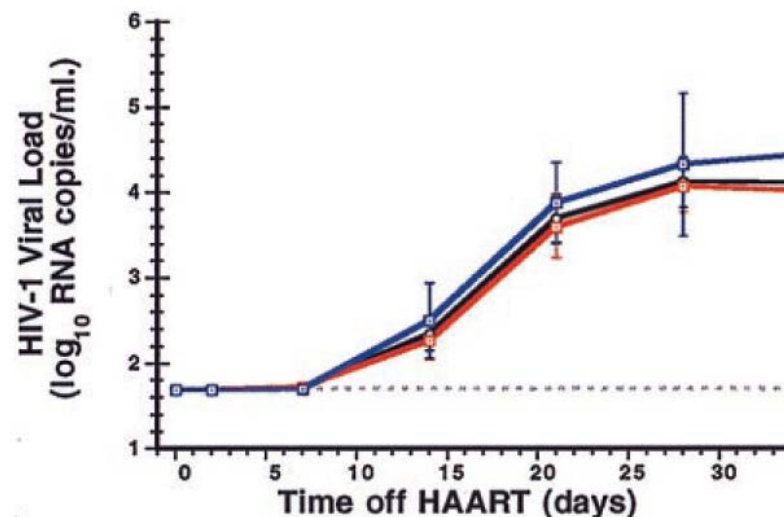
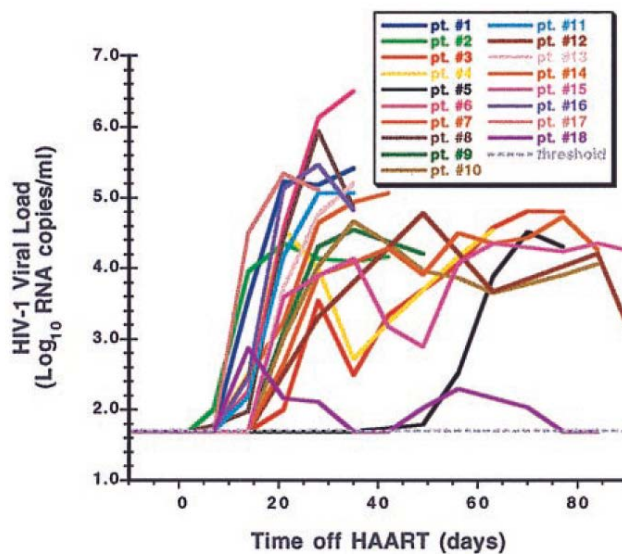
- The risks associated with gene therapy, especially stem cell modification; weighed based on proposed interventions and target populations
 - Potential risks and interventions may be more appropriate in certain populations than others i.e. virally suppressed individuals without complications versus HIV-infected individuals with malignancy or other conditions requiring hematopoietic stem cell transplantation
- Trial design, ATI endpoint, length of follow-up influenced by :
 - Mechanism of action of the intervention (CD4+ cell “protection” vs. increasing infected cell clearance)
 - Pre-ATI threshold level of modified cells in the trial participants
 - Ways to address off-target effects, cytokine release syndrome, genotoxicity, retrovirus-mediated toxicity, late 2nd stage malignancy



ANALYTICAL TREATMENT INTERRUPTION (ATI) ISSUES IN HIV CURE TRIALS

HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression

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ANALYTICAL TREATMENT INTERRUPTION (ATI) ISSUES IN HIV CURE TRIALS

- The kinetics of viral rebound are well described in chronic patients
 - Typically, rebound is detected 1-4 weeks after ARV interruption and plasma HIV RNA tends to return to pre-therapy set point.
 - Time to rebound will be influenced by ARV pharmacokinetics
- Risks associated with an ATI
 - Clinical events due to treatment interruption
 - Risk of transmission
 - Risk of viral resistance
 - In AHI treated patients additional risks may include
 - ◉ Repopulation of the reservoir
 - ◉ Virus diversification
 - ◉ Impairment of HIV-specific immune response

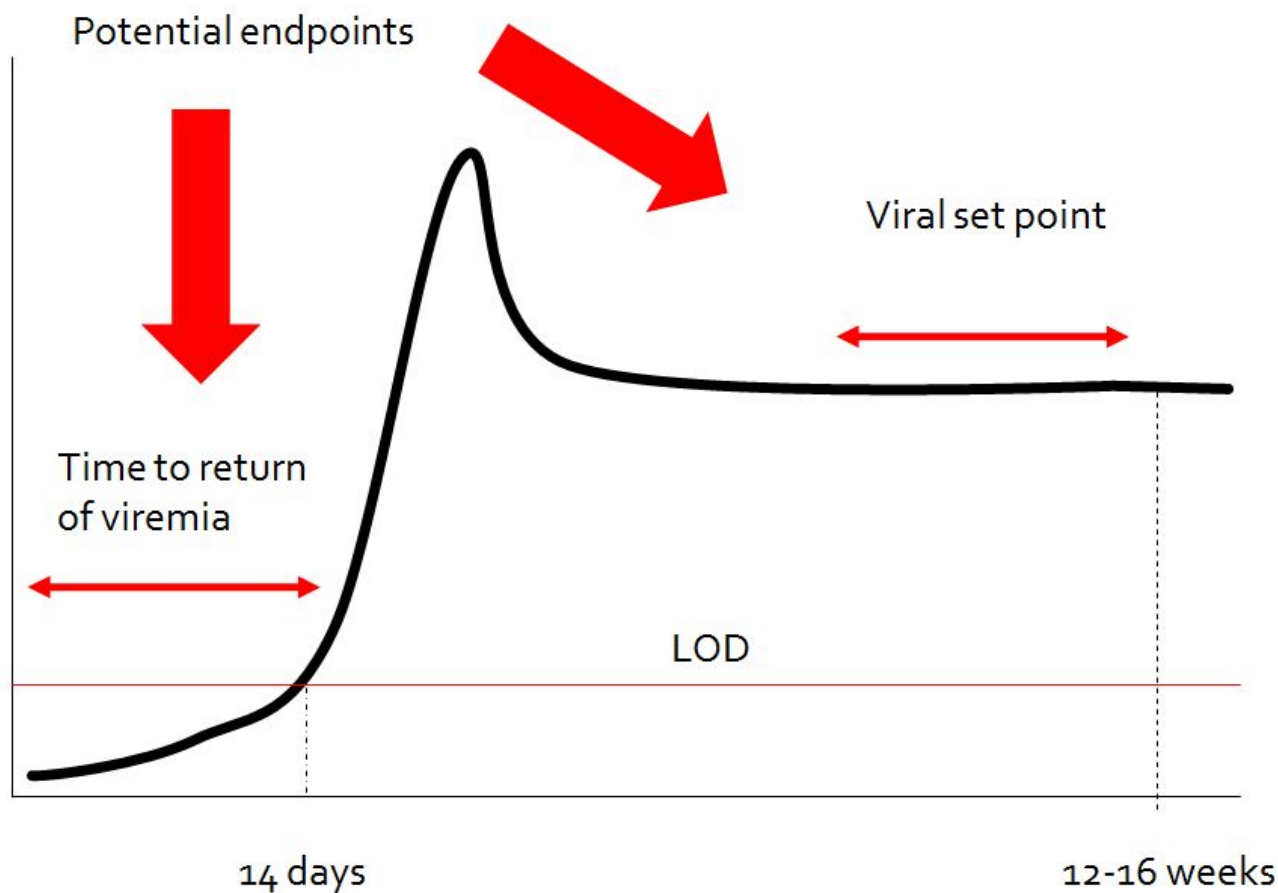


KEY PARAMETERS IN ATI STUDIES – I

VIRAL REBOUND VERSUS VIRAL SET POINT

The endpoint chosen may depend on the intervention's mechanism of action

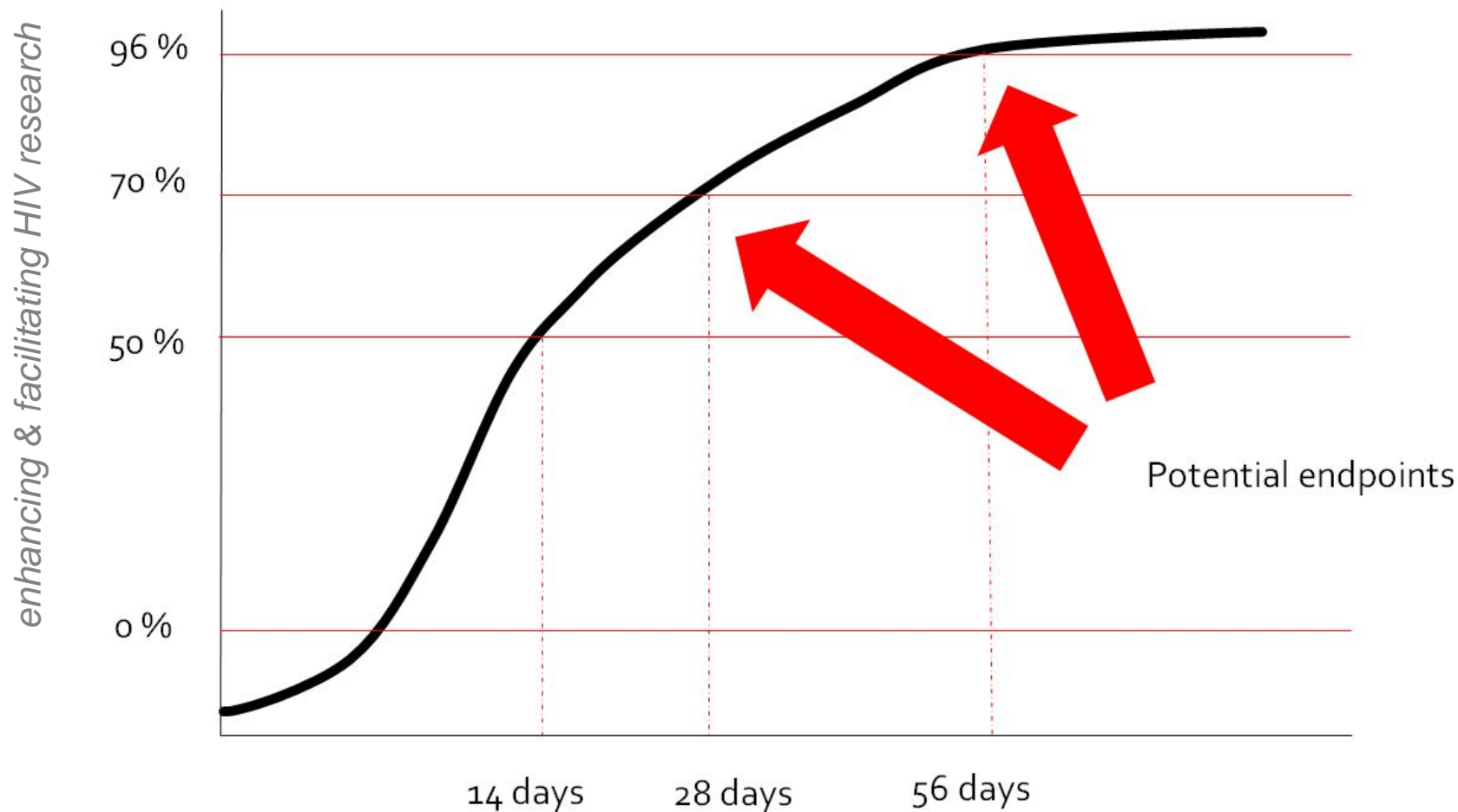
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KEY PARAMETERS IN ATI STUDIES – II

PROPORTIONS OF INDIVIDUALS WITH RETURN OF VIREMIA





KEY PARAMETERS IN ATI STUDIES – III

TIME TO REBOUND

- Advantages
 - Continuous variable
 - Less time with detectable viremia = less risk for patients
 - Rapid answers (4-6 weeks)
 - Characterization of rebounding virus may be important
- Disadvantages (plus those inherent to all ATI)
 - Limited variability in chronically-infected individuals thus requiring increased sample size
 - Influenced by pharmacokinetics of ARV (e.g. efavirenz half-life)
 - Relevance of small changes
 - Frequent visits for precise measurement, impacting feasibility
 - Will miss any influence of intervention on set point
 - Studies in acute patients will likely need untreated control



KEY PARAMETERS IN ATI STUDIES – IV

VIRAL SET POINT

- Advantages
 - Continuous variable increases power to detect differences
 - Requires less frequent visits for precise measurements
 - Variability in chronically-infected individuals
 - Critical if viral rebound is required (cell protection)
- Disadvantages (plus those inherent to all ATI)
 - More time with detectable viremia = more risk for patients
 - Slow answers (12-16 weeks)
 - Information on pre-therapy set point may be needed
 - Small changes, while statistically significant, may have limited importance
 - Profound effect in small number of participants may be difficult to distinguish from chance (need for control group?)



KEY PARAMETERS IN ATI STUDIES – V

PROPORTION OF INDIVIDUALS WITH DETECTABLE VIREMIA AT WEEK 4 OR 8

- Advantages
 - Dichotomous variable similar to ARV therapy
 - Very predictable in chronically-infected individuals, a control group may not be needed
 - Requires less frequent visits for precise measurement
 - Intermediate time with detectable viremia = intermediate risk for patients
- Disadvantages (plus those inherent to all ATI)
 - Limited power in controlled trial – much larger sample size
 - Likely only useful if there is a large effect size



ATI STRUCTURE WILL NEED TO BE FLEXIBLE AND STUDY DRIVEN

- A single ATI design for all studies is unlikely
- Specific interventions may require different endpoints
 - Time to rebound may be appropriate for interventions that target the reservoir
 - Set point studies needed for
 - ◉ Immune based- interventions, that require boosting of HIV-specific response provided by return of viremia
 - ◉ Gene-therapy that relies on “protection” of uninfected CD4+ cells which expand as vulnerable cells are infected and lost



HOW TO PROTECT TRIAL PARTICIPANTS DURING AN ATI

- Trial participant safety must be the priority and treatment interruptions should be as short as possible
- Frequent monitoring during treatment interruption of viral load and CD4⁺ counts
- Enrollment of subjects with:
 - high CD4⁺ counts (>350 or >500 cells/mm³)
 - CD4⁺ nadir of >200 cells/mm³
 - Additional ARV treatment options
 - Exclude previous OI, malignancy and CV, liver, kidney risk
- Consider the PK and half-life of ARV therapy before ATI
- Minimize risk of developing viral resistance
- How to mitigate risk of transmission to partners?



WG RECOMMENDATIONS

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- Common registry of trial participants to track and compile short and long-term toxicities of early cure-related clinical trials
- Interim reviews by an independent, unblinded review committee to monitor data, number of exposures and best tolerated dose etc.
- Standardization and coordination of how ATI are performed across trials, with appropriate biobanking of samples to allow testing for potential surrogate markers predictive of ATI



RISK MITIGATION STRATEGY DISCUSSION

- Jintanat Ananworanich (MHRP)
- Joe Eron (UNC)
- Lynda Dee (AAB)
- Ron Mitsuyasu (UCLA)
- Rob Murphy (Northwestern)
- Adam Sherwat (CDER/FDA)
- Neil Shortman (ViiV)



QUESTIONS

- Single dose, dose escalation studies with staggered enrollment and interim monitoring take a long time – are there alternative strategies?
- Are controls groups necessary for time to rebound ATI studies in chronically infected patients – do we have enough data on time to rebound?
- For “set point” ATI studies are controls needed if pre-therapy set points are known?