HIV Cure Research: CROI 2017 Update

TAG
Treatment Action Group

Therapeutic vaccination + romidepsin in early HIV infection

- Presented by Beatriz Mothe, IrsiCaixa-HIVACAT, Hospital Germans Trias i Pujol, Badalona, Spain
- 15 individuals (14 men, one woman) who started ART within three months of HIV infection
- Previously participated in a trial of two therapeutic HIV vaccines (MVA and ChAd) designed to induce T cell responses to conserved parts of the virus
- Recruited into a follow up “kick & kill” study that gave additional shots of the MVA-based therapeutic vaccine and a course of three infusions of the HDAC inhibitor romidepsin

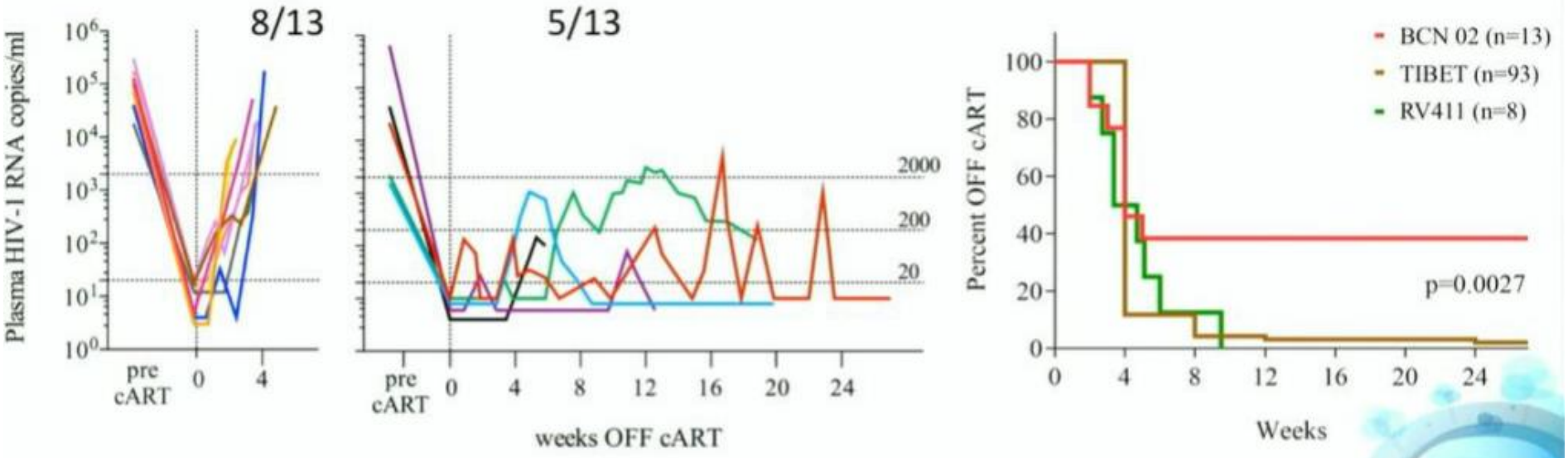
Therapeutic vaccination + romidepsin in early HIV infection

- Antiretroviral therapy (ART) interrupted eight weeks after the final MVA immunization
- At the time of the CROI presentation, 13 participants were in the interruption phase and 5/13 (38%) had maintained viral loads below 2,000 copies/ml (the criteria for restarting ART) – longest follow up a little over six months
- Frequency of post-ART control appears higher than prior studies of early ART alone (~0-15%)

Monitored Antiretroviral Pause (MAP)

n=13
Feb 15th

- 13 participants have interrupted cART to date.



[15]Ruiz, 2007; [16]Colby, #124; [16]Leal, #336; [17]Genevieve, 2017; [18]Saez-Cirion, 2013; [19]Rosenberg, 2010; [20]Cockerhan, 2016

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Therapeutic vaccination + romidepsin in early HIV infection

- Evidence of stimulation of latent HIV after romidepsin infusions and MVA vaccine administrations (viral load blips during ongoing ART), but no HIV DNA reduction beyond that achieved by ART
- Vaccines well tolerated, romidepsin infusions associated with an array of side effects mainly grade 1/2 headaches, fatigue and nausea. One participant developed sepsis after the final dose. The drug also caused transient declines in peripheral blood CD4 T cell counts
- Follow up ongoing to try and better understand outcome, vaccine-induced T cell responses targeting conserved parts of HIV (not recognized prior to vaccination) may be contributing

Very early ART and post-treatment viral load control

- Presentation by Jintanat Ananworanich, US Military HIV Research Program
- Eight individuals (seven men and one woman) who initiated ART at Feibig I, estimated to represent the period ~10-17 days after HIV acquisition
- Median 2.8 yrs on ART
- All experienced viral load rebound a median of 26 days after ART interruption, slightly longer than seen in studies of chronic infection (median 14 days)

Very early ART and post-treatment viral load control

- Measures of the HIV reservoir increased during ART interruption but returned to baseline after restart
- 6/8 were HIV seronegative at study entry, but 4/6 seroconverted after ART interruption, representing a potential social harm in Thai context where HIV screening applied to employment
- Jintanat Ananworanich also delivered an excellent plenary presentation overview of HIV cure research

Very early ART leads to SIV cure/remission in some macaques

- Presentation by Louis Picker from Oregon Health Sciences University
- Six macaques started on ART four or five days after SIV infection didn't experience viral load rebound when ART was interrupted ~600 days later
- Large volumes of cells from these animals unable to transfer SIV infection to uninfected macaques and only traces of SIV genetic material detectable at necropsy
- Out of 35 macaques started on ART at later time points, only one (initiated on day 6 post infection) displayed a similar lack of rebound, but viral load reappeared after eight months

Very early ART leads to SIV cure/remission in some macaques

- Picker concluded that there may be a very small window of time after infection when the viral reservoir is not permanently established and can decay away during ART
- But even a day delay can be associated with the formation of a viral reservoir that can linger in an inactive state for long periods before causing viral load rebound
- Macaque that rebounded after eight months similar to human cases of HIV remission e.g. the Mississippi baby, Boston patients
- Picker cited case of an individual treated with ART within days of HIV acquisition (described by Hiroyu Hatano at CROI 2014) who interrupted ART last year and displayed no sign of HIV activity for 220 days before viral load rebound (this case will likely be described in full at the upcoming IAS conference in July)

Temporary HIV remission after stem cell transplant

- Poster presentation by Nathan Cummins From the Mayo Clinic in Rochester
- 55 yr old HIV+ man diagnosed in 1990, started ART in 1999, underwent stem cell transplant in late 2013 to treat acute lymphoblastic leukemia
- HIV reservoir measures declined post transplant
- ART continued until analytical interruption a little over 2 yrs later
- Viral load remained undetectable for 288 days at which point rebound to 60 copies/ml detected, ART restarted five days later with viral load 1640 copies/ml

Evidence ART stops HIV replication

- Presentation by Mary Kearney from the National Cancer Institute
- Looked for evidence of HIV evolution in 10 children started on ART soon after birth and followed for at least seven yrs
- In two children with lapses in viral load suppression, HIV evolution readily detectable
- No evidence of HIV evolution in the eight children with continuous suppression
- Kearney suggested widely-publicized 2016 *Nature* paper describing ongoing HIV replication despite ART may have used incorrect analysis

Evidence ART stops HIV replication

- Poster presentation by Morgane Rolland from the US Military HIV Research Program
- Analyzed the eight participants in the early ART study described by Jintanat Ananworanich
- Looked for evidence of HIV evolution comparing pre-ART baseline samples and samples taken after ART interruption (median 2.8 yrs later)
- No evidence of HIV evolution found

Sex differences in HIV persistence

- Poster presentation by Eileen Scully from Johns Hopkins University School of Medicine
- Study compared measures of HIV persistence in carefully matched cohorts of women and men
- HIV reservoir levels not significantly different as measured by HIV DNA
- Levels of HIV RNA being expressed by the HIV reservoir significantly lower in women compared to men
- Consistent with prior work from Jonathan Karn indicating estrogen affects HIV expression from reservoir
- Scully concluded that biologic sex is an important consideration in cure research

Canakinumab reduces inflammatory biomarkers

- Presentation by Priscilla Hsue from the University of California at San Francisco
- Study of canakinumab, an antibody against pro-inflammatory cytokine IL-1β, in 10 HIV+ people on ART
- Significant declines in inflammatory biomarkers:
  - IL-6 levels declined by 30%
  - High sensitivity C-reactive protein declined by 41%
- Imaging studies showed a 10% reduction in arterial inflammation
- Larger trial now enrolling, effect on HIV reservoir also being evaluated
- Canakinumab is FDA-approved for some autoimmune conditions and under evaluation for cardiovascular disease in large trial for HIV- people

Dual bNAb combo in macaques

- Michel Nussenzweig from Rockefeller University described a study that gave a short course of two broadly neutralizing antibodies (10-1074 & 3BNC117) to macaques, starting three days after infection with a SIV/HIV hybrid virus
- The intervention led to sustained immune control of the virus in six animals for >2 yrs, mediated at least in part by CD8 T cells
- The study was published in *Nature* after CROI
- A clinical trial of the combination of 10-1074 & 3BNC117 is ongoing at Rockefeller University

Additional cure-related presentations

- Jeff Lifson from the National Cancer Institute gave the Bernard Fields Memorial Lecture on the topic of macaque models in HIV research, including cure research
- Carl June from the University of Pennsylvania delivered a plenary on the topic of cellular and gene therapies for HIV, highlighting the progress that has occurred with these approaches in cancer
- Several presentations from the annual pre-CROI community workshop on HIV cure research are available online

Community-based sources of CROI reporting

- AIDSMap
- AVAC
- i-Base
- HIVandHepatitis.com
- NATAP
- TAG

Potentially important post-CROI studies

- CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses
  - Identifies a cell surface marker, CD32a, that is expressed by a significant proportion (26.8% to 86.3% in the individuals studied) of CD4 T cells containing latent HIV
  - Should facilitate easier sorting of CD4 T cells containing latent HIV from people on ART for studies at the single-cell level
  - May offer a means to better target the HIV reservoir
- Levels of HIV-1 persistence on antiretroviral therapy are not associated with markers of inflammation or activation
  - Large longitudinal ACTG study that found inflammation, immune activation and measures of HIV persistence during long-term ART were correlated with pre-ART levels