18ª edición

POSTCROI 2021

Una actualización de la 28ª Conference on Retroviruses and Opportunistic Infections

Vacunas (VIH)

Beatriz Mothe Pujadas, MD, PhD
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Hospital Germans Trias i Pujol, Badalona
Uvic-UCC

FUNDACIÓN LUCHA CONTRA EL SIDA Y LAS ENFERMEDADES INFECCIOSAS

FLS SCIENCE

HIV Vaccine CT

Wednesday March 10th
O-10 HIV Reservoirs

160-AAV8-mediated Gene Transfer (VRC07)
Joseph Casazza Prev Vax

LB 161-AELIX002 RCT w/ HTI Vaccines in Early-ART
Beatriz Mothe Ther Vax

(NHP)
157-PD-1 blockade enhancement of vaccine-induced responses
Sheikh A. Rahman

Related Basic Science

Tuesday March 9th
S-05 Immune-mediating Killing of HIV Reservoirs

42 Initiating ART (not too) Early?
Lydie Trautmann

41 Intrinsic Resistance of Reservoir to Immune Killing
R. Brad Jones

Wednesday March 10th
Plenary

57 Elite Controllers
Xy Yu

CT design

Sunday March 7th
W-3 Clinical Trial Design & Analysis
Lori Dodd & Holly Janes

Wednesday March 10th
S-12 COVID19 Vaccine
74-Lessons & Challenges in COV-19 vaccine trials
Kathleen Neuzil

HIV Vaccine CT

Wednesday March 10th

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Human CT

- Challenge to induce bNAb by vaccination
- AMP trials (Passive Immunization w/ VRC01) partially effective in susceptible viruses

→ AAV can be used to transfer genes encoding the light & heavy chains from Ab (NHP).

- Transgene persists as episomal DNAs in the nucleos and are stable in post-mitotic cells

- VRC 603 study: Phase 1, non-randomized, parallel assignment, open label, dose escalation study in 25 HIV+ ART-suppressed of AAV8-VRC07 (CD4 binding site)

- Goal: determine dose to achieve at least 50 mcg/mL VRC07 concentration (4 wk post injection)

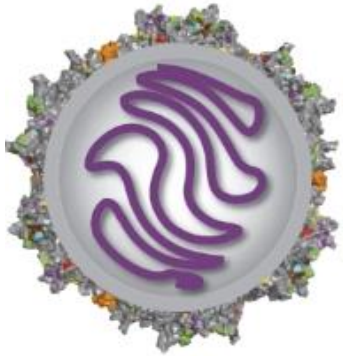
Wednesday March 10th

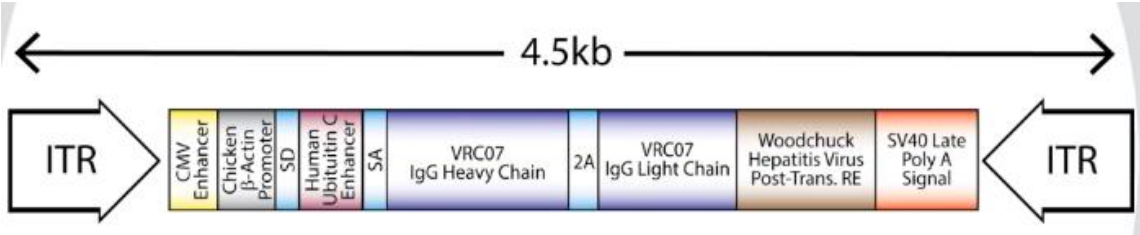
POSTCROI 2021

O-10 HIV Reservoirs

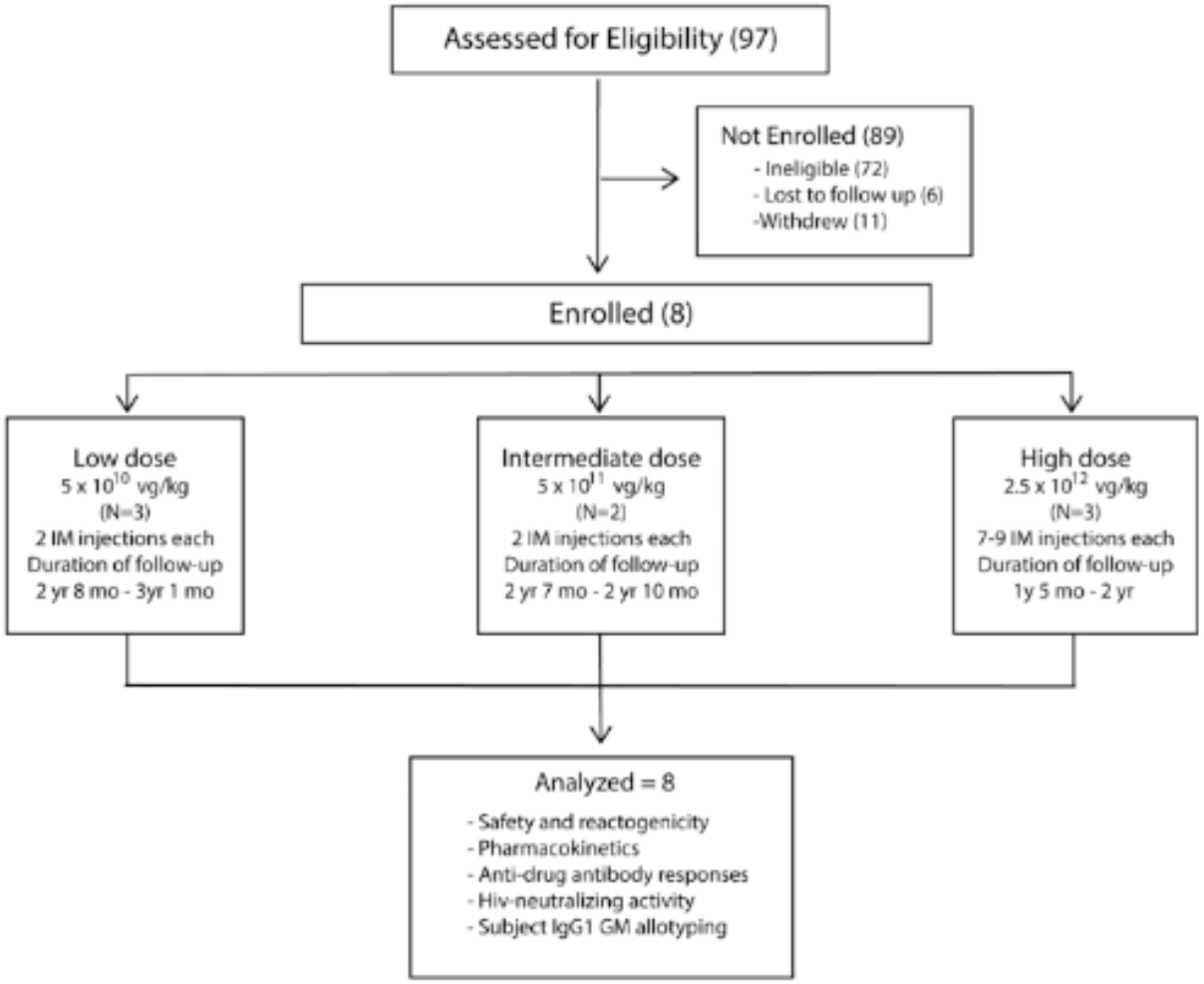
160 *12:35* **DURABLE HIV-1 ANTIBODY PRODUCTION IN HUMANS AFTER AAV8-MEDIATED GENE TRANSFER**

Joseph P. Casazza, Evan M. Cale, Sandeep Narpala, Laura Novik, Galina V. Yamshchikov, Bob C. Lin, Janardan P. Pandey, Adrian McDermott, Mario R. Roederer, Alejandro Balazs, David Baltimore, Richard A. Koup, Julie E. Ledgerwood, John R. Mascola, for the VRC603 Team





Human CT



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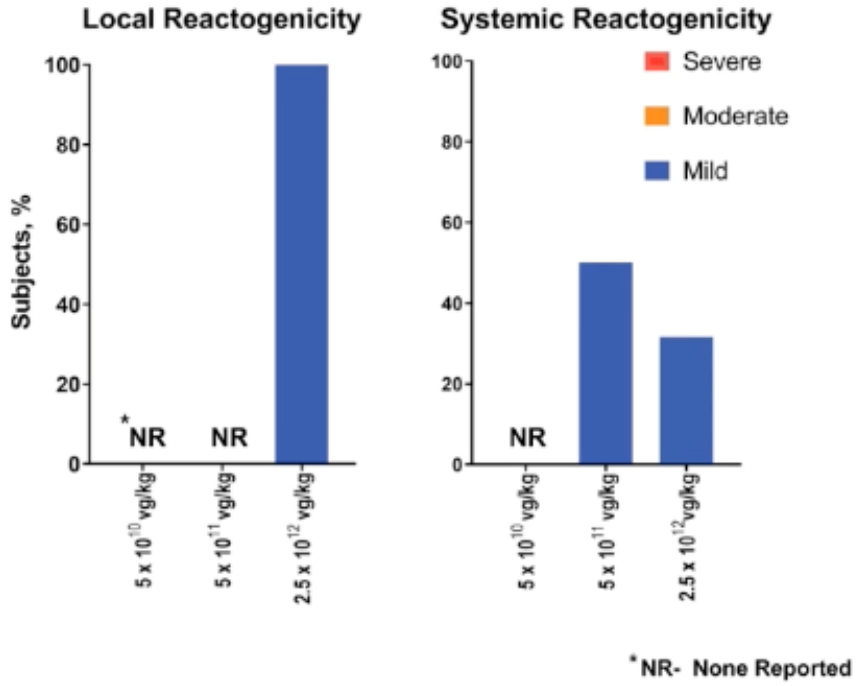

*NR- None Reported

Human CT

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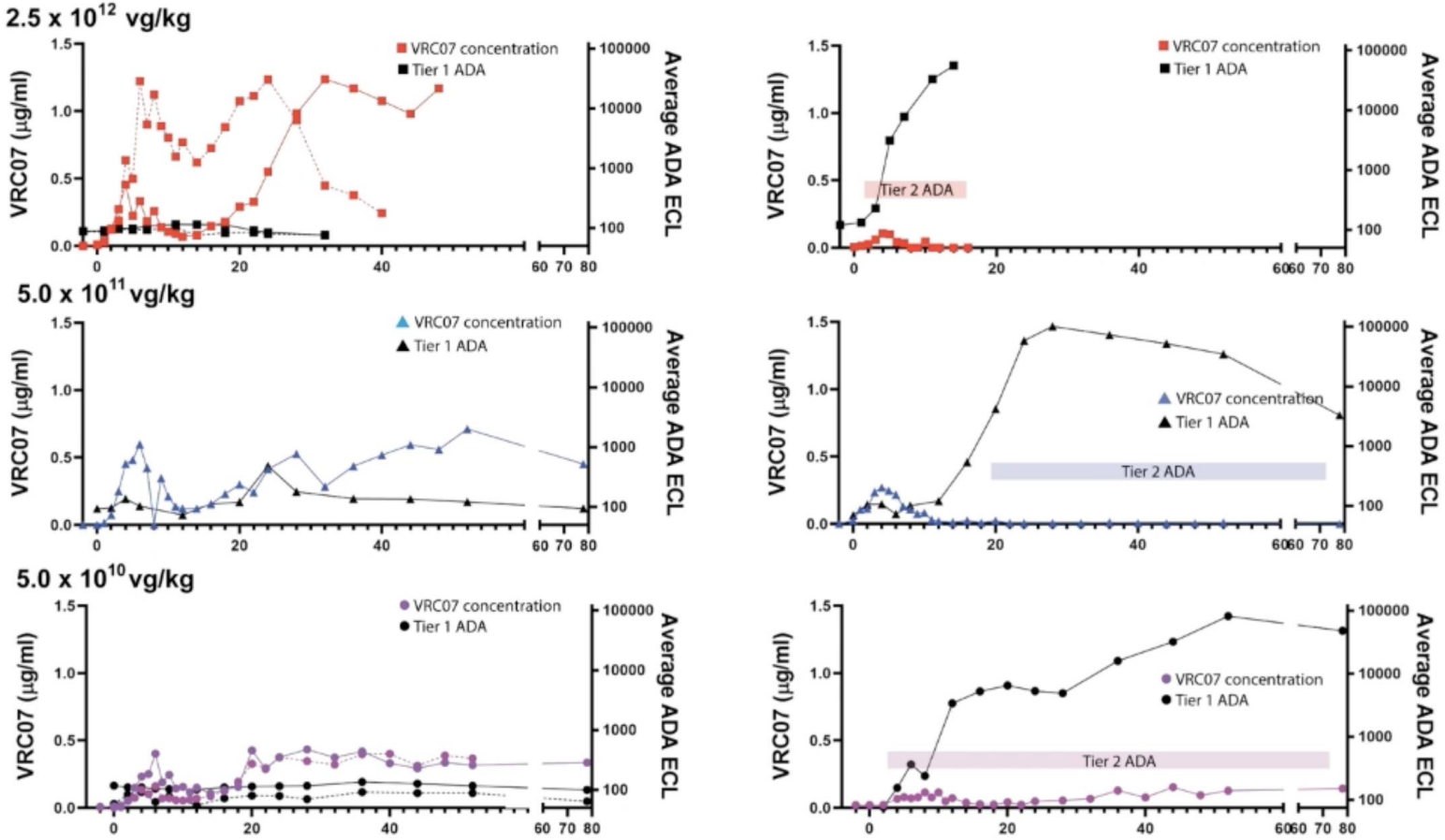


- AAV safe to induce functionally difficult Ab
- Understading the causes of induction of anti-drug antibodies will help to increase efficacy in production of Ab by AAV.

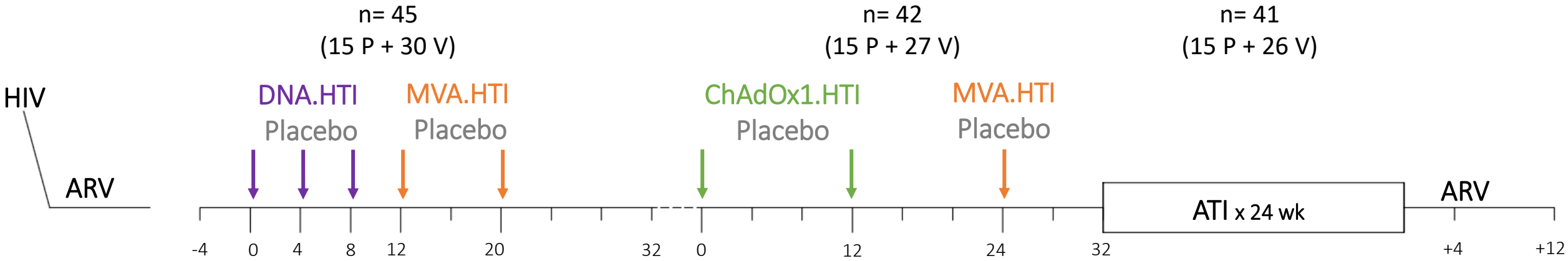
Human CT

Wednesday March 10th
POSTCROI 2021
O-10 HIV Reservoirs

161 **A PLACEBO-CONTROLLED ATI TRIAL OF HTI VACCINES IN EARLY TREATED HIV INFECTION**

12:45

Lucia Bailon, Anuska Llano, Samandhy Cedeño, Miriam B. Lopez, Yovaninna Alarcon, Pep Coll, Àngel Rivero, Anne R. Leselbaum, Ian McGowan, Devi SenGupta, Bonaventura Clotet, Christian Brander, Jose Molto, **Beatriz Mothe**, for the AELIX-002 Trial Group



MAIN INCLUSION/EXCLUSION criteria

- **Early-ART with 3-drug regimen**
  <6months after documented HIV acquisition
- **Virological**
  >1y pVL undetectable
- **Immunological**
  CD4 count >400 cells/mm^3 for 6m
  Nadir >200 cells/mm3

ART RESUMPTION CRITERIA DURING ATI

- **Clinical**
  ARS
- **Virological**
  pVL of HIV-1 RNA >100,000 copies/mL
  pVL of HIV-1 RNA > 10,000 copies/mL for 8 weeks
- **Immunological**
  CD4 count <350 cells/mm^3 for 2 consecutive determinations

Human CT

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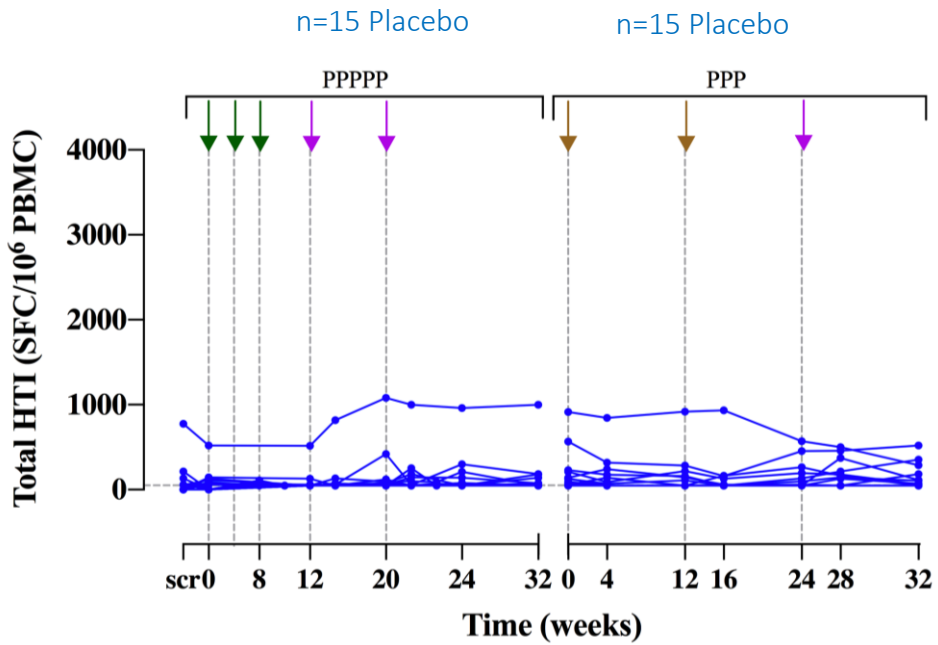
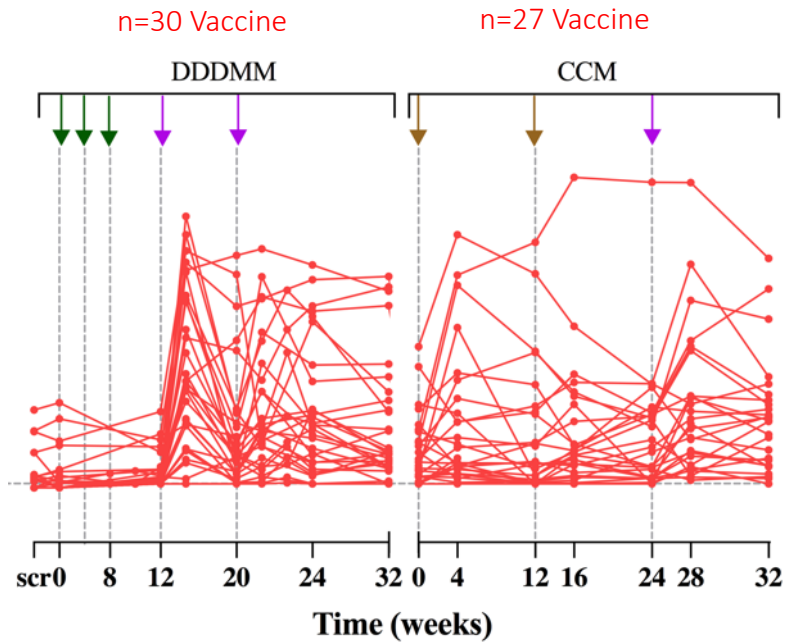
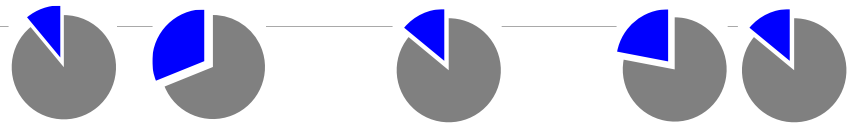
- Strong, broad and functional T cells.







HTI Dominance over total HIV

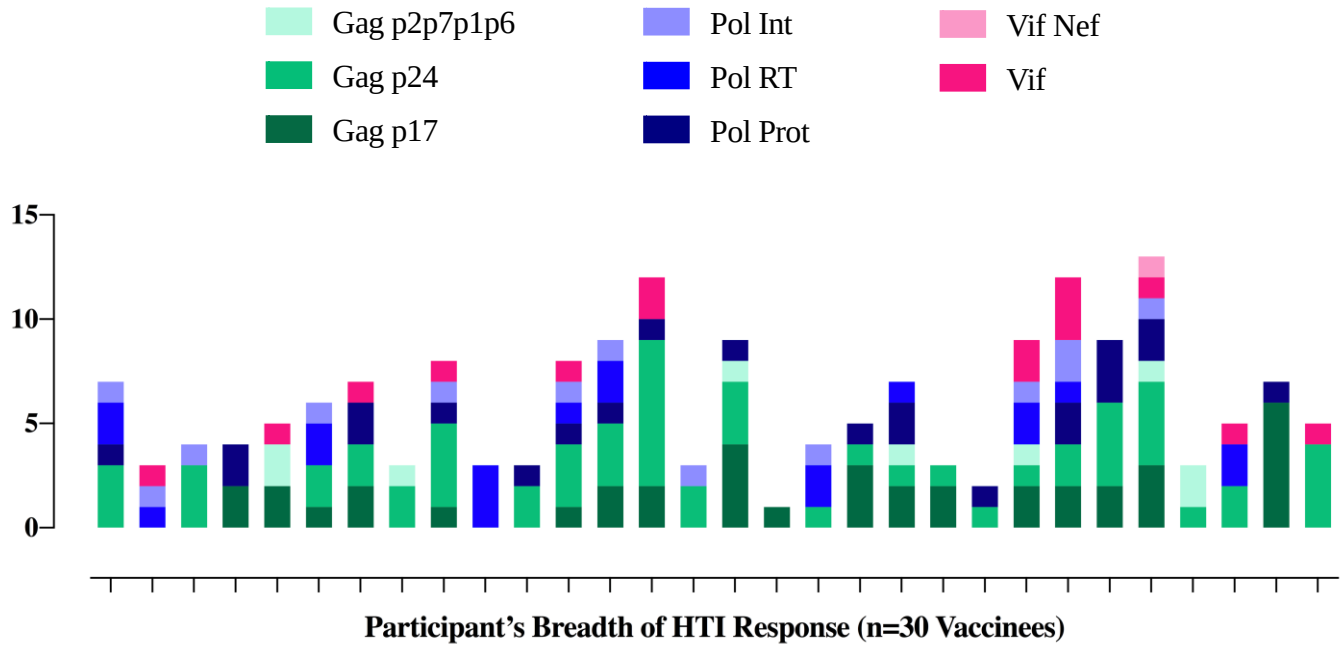
11% 28% 14% 22% 14%

21% 88% 44% 78% 67%

High HTI dominance at ATI start

Human CT

- Strong, broad and functional T cells.
- Not impact on the viral reservoir (same decay)



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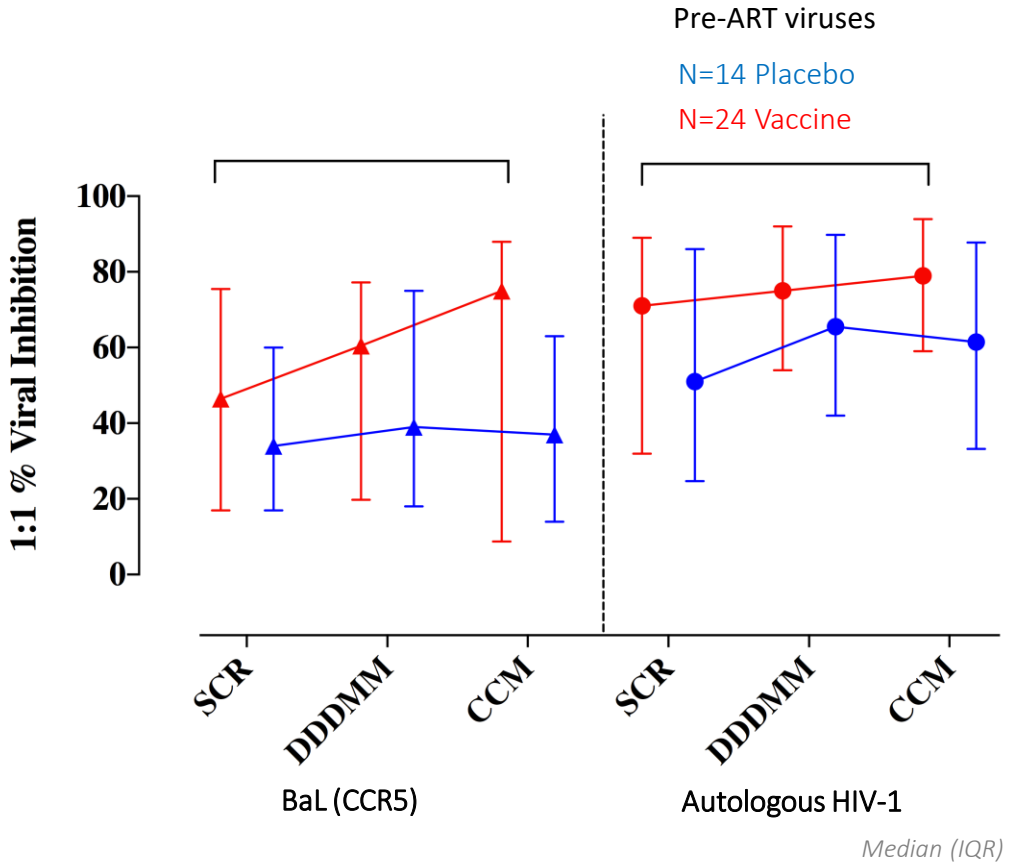

Human CT

- Viral Kinetics during the ATI

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O-10 HIV Reservoirs

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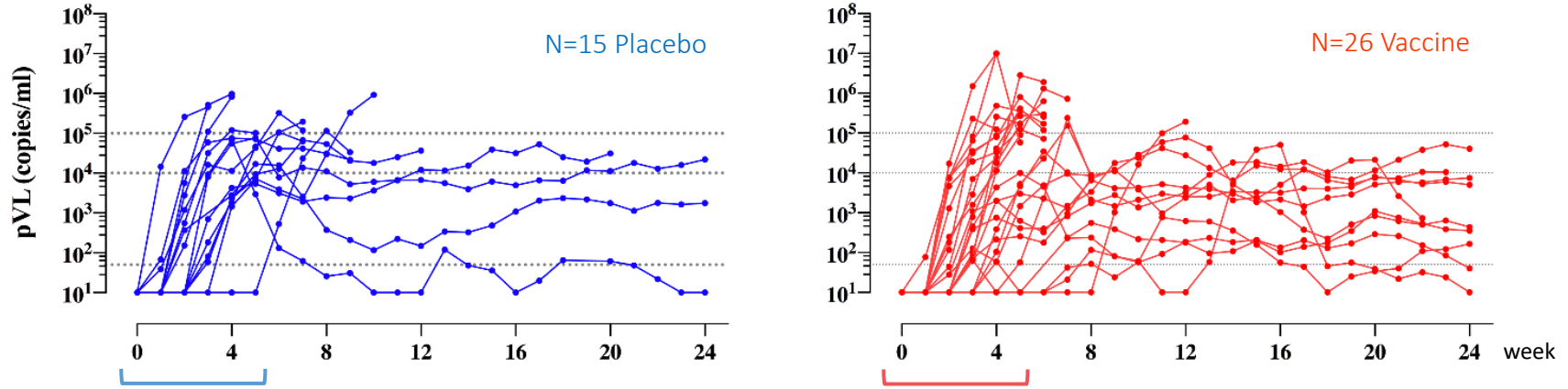
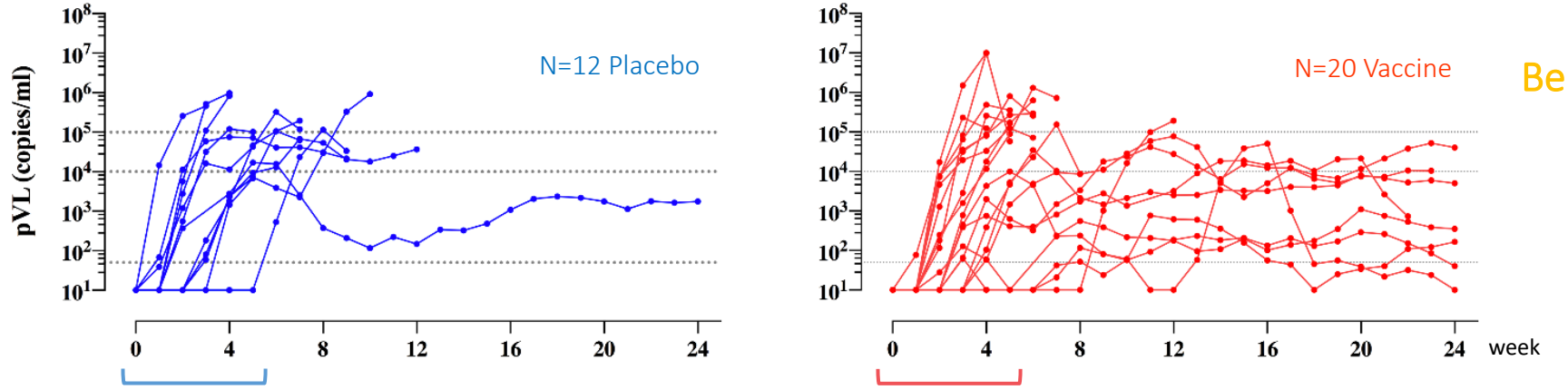


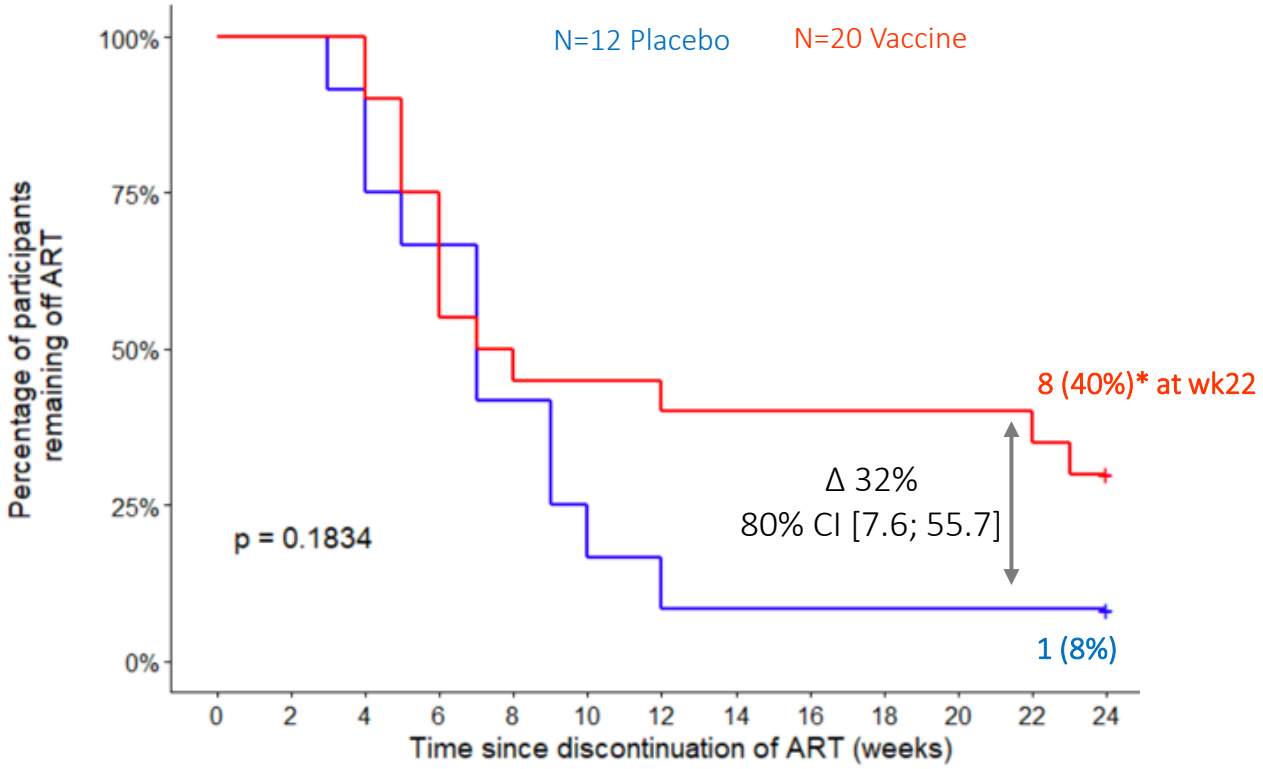
All Cohort (n=41)



Participants Without Beneficial HLA class I alleles (n=32)

Human CT

- Higher proportion of vaccinees off ART for longer periods of time.



** 2 last vaccinees dropped out due to COV-19 without meeting pre-specified ART resumption criteria*

O-10 HIV Reservoirs

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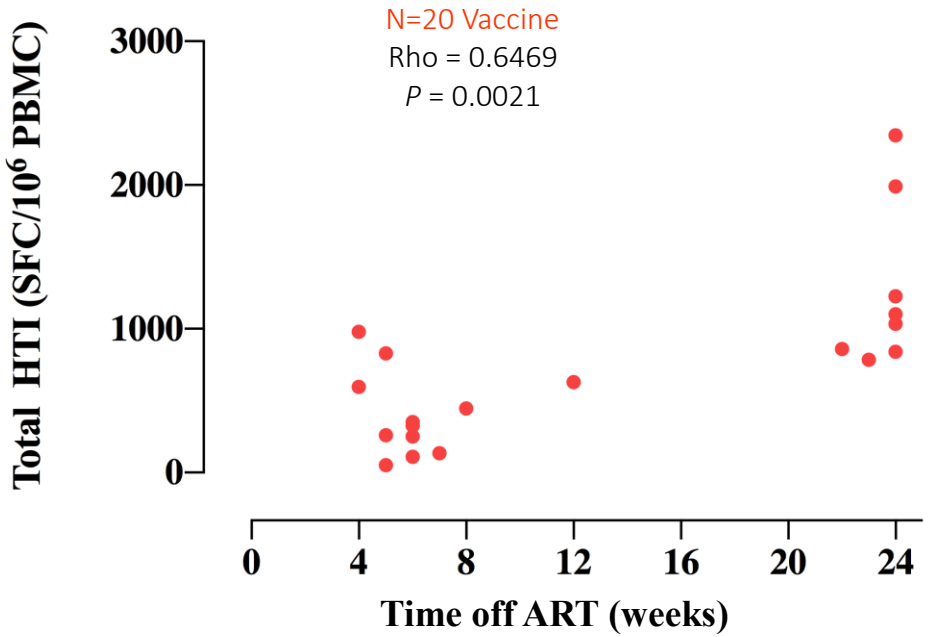
HTI Magnitude at ATI



Human CT

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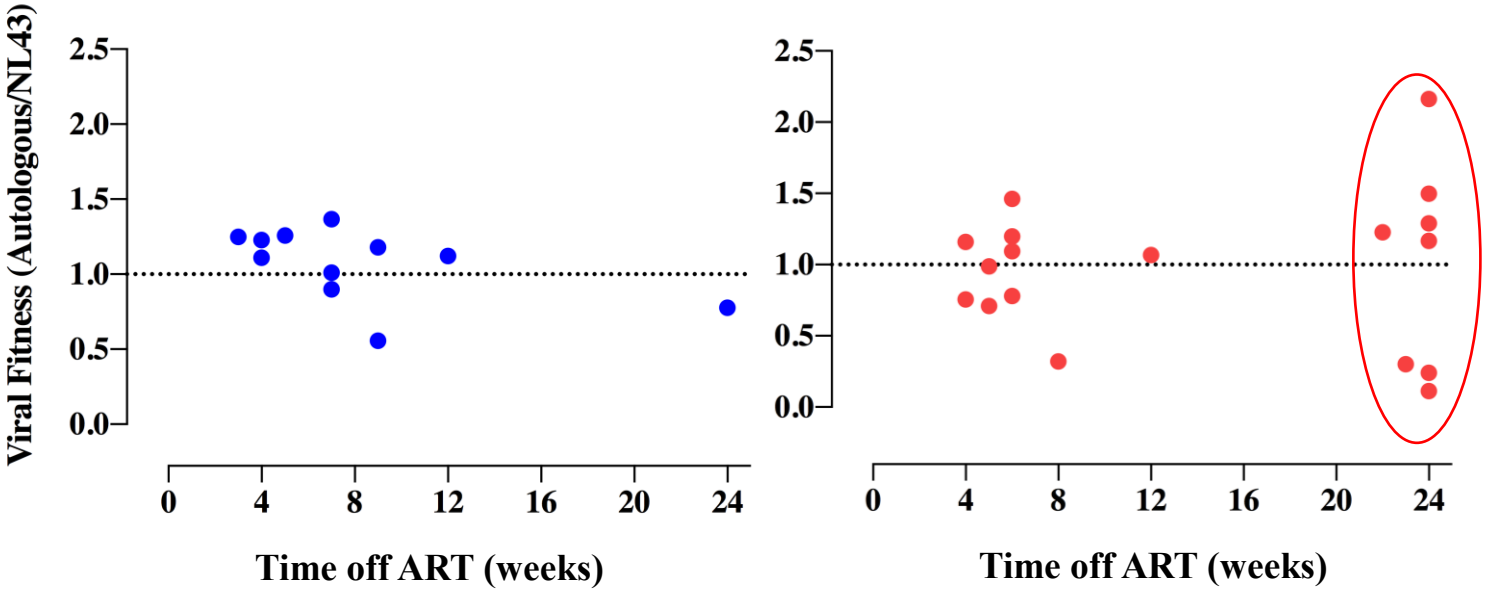
Viral Fitness (pre-ART)

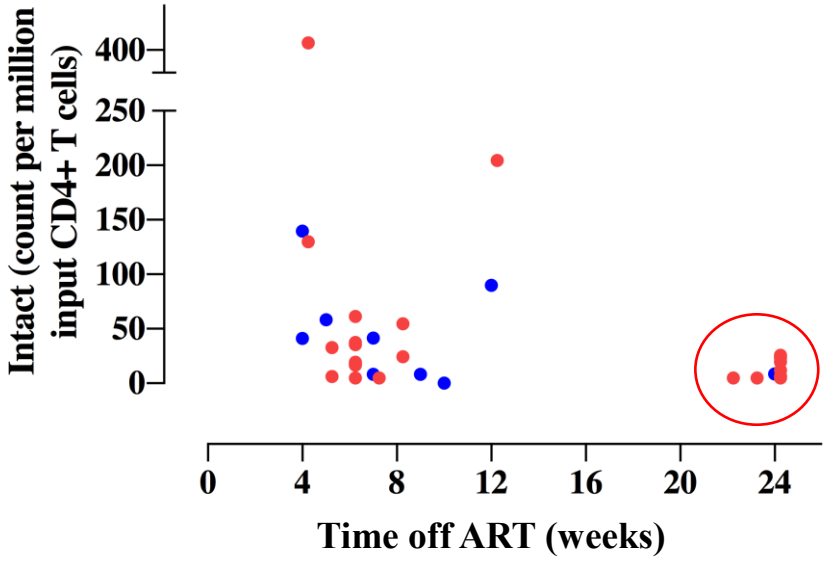
N=11 Placebo
Rho = - 0.5208
P = 0.1035

N=18 Vaccine
Rho = 0.1460
P = 0.5632



Viral Reservoir at ATI

N=9 Placebo N=17 Vaccine
Rho = -0.4768
P = 0.0138



Human CT

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POSTCROI 2021

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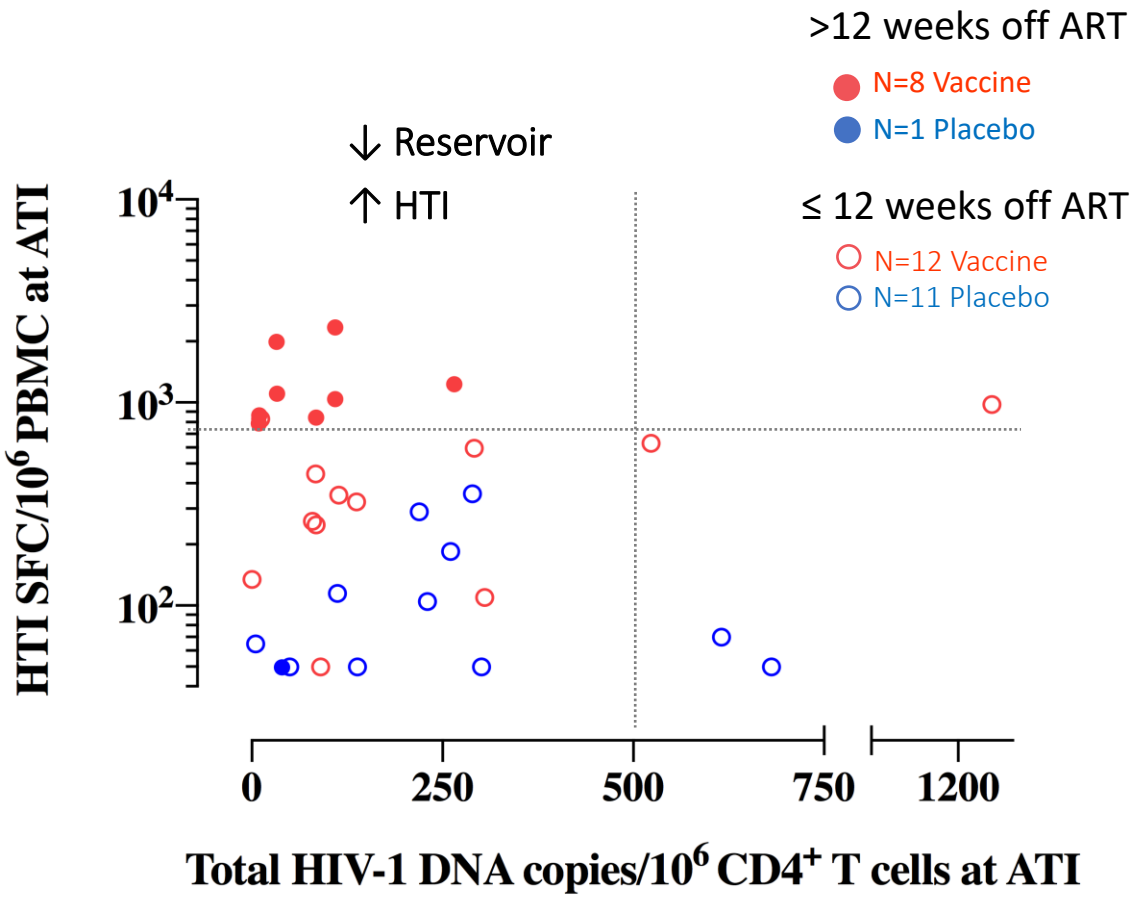

- In the context of a limited viral reservoir in the AELIX-002 trial, HTI vaccine induced responses contribute to a prolonged viral control
- Future use of HTI-based vaccines as the backbone of combination cure regimens, such as the one currently being explored with the TLR7 agonist vesatolimod in AELIX-003 (NCT04364035)

Human CT

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POSTCROI 2021

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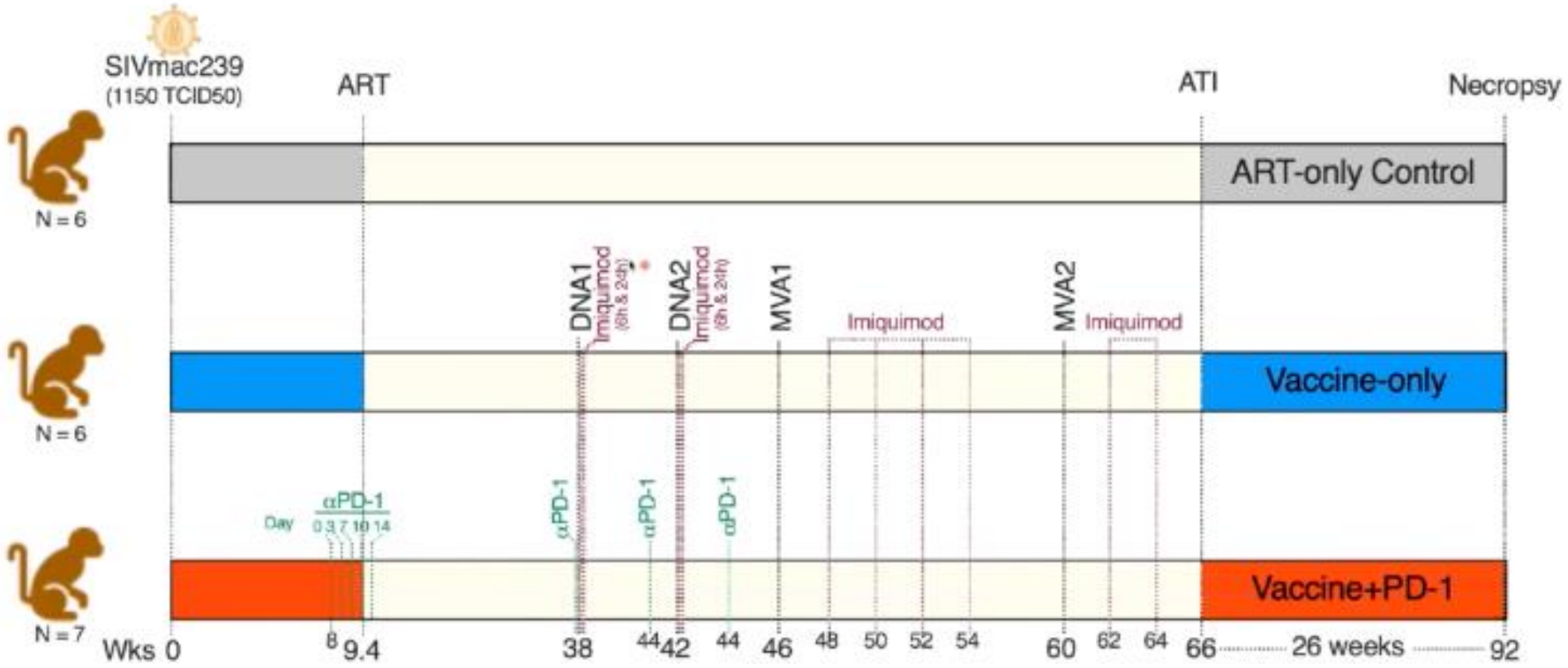
O-10 HIV Reservoirs

157 *11:50* **PD-1 BLOCKADE ENHANCES THERAPEUTIC BENEFITS OF VACCINE IN A CHRONIC SIV/MACAQUE MODEL**

Sheikh A. Rahman, Bhrugu Yagnik, Alexander P. Bally, Kristen N. Morrow, Wang Shelly, Thomas H. Vanderford, Gordon J. Freeman, Rafi Ahmed, Rama R. Amar

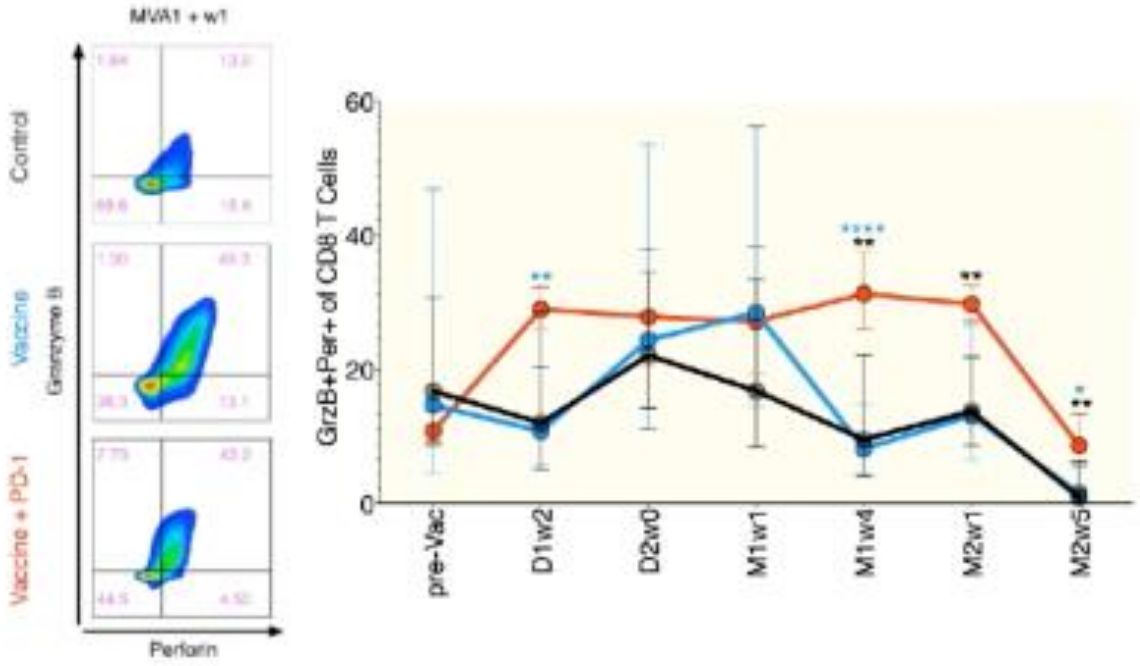
NHP

- Immune Checkpoint Blockade might improve vaccine response & preserve anti-viral immunity +/- might help to purge latent reservoir



DNA.SIV239
MVA.SIV239
(Gag, PR, RT & Env seq)
Non-heterologous SIV infection

NHP



- Better persistence of CD8T cells Granzyme B+

O-10 HIV Reservoirs

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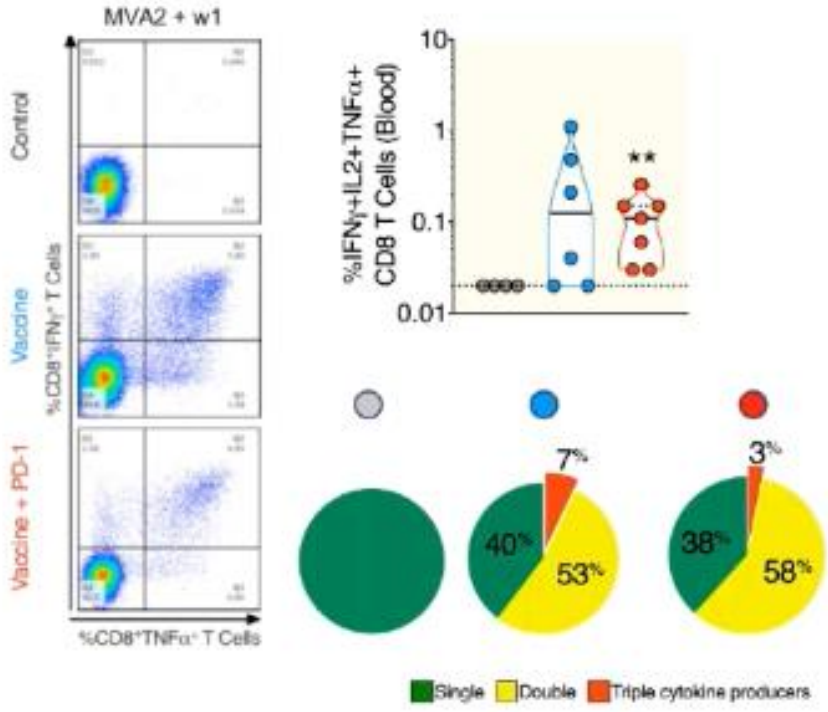

- Better persistence of Antigen-specific CD8 T cells

NHP

O-10 HIV Reservoirs

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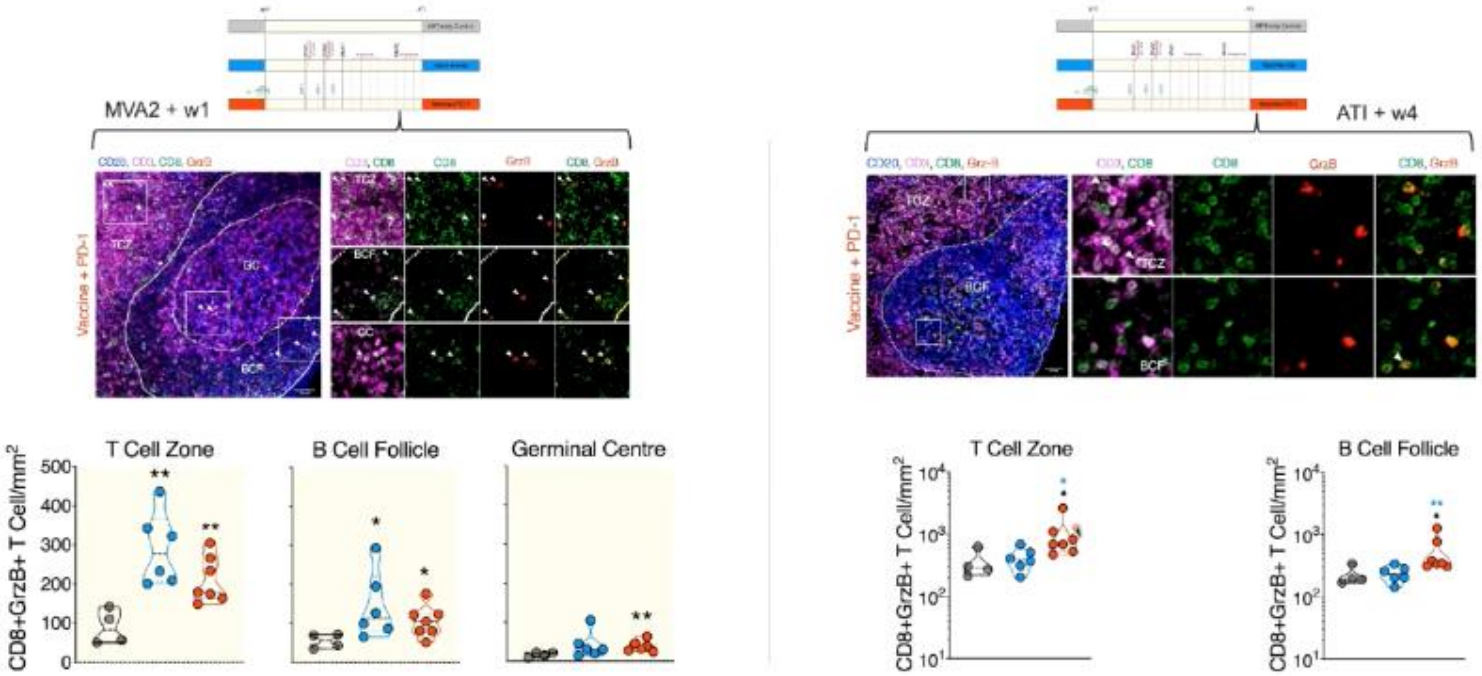
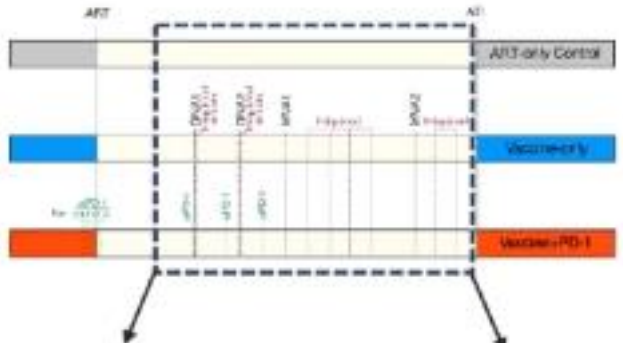
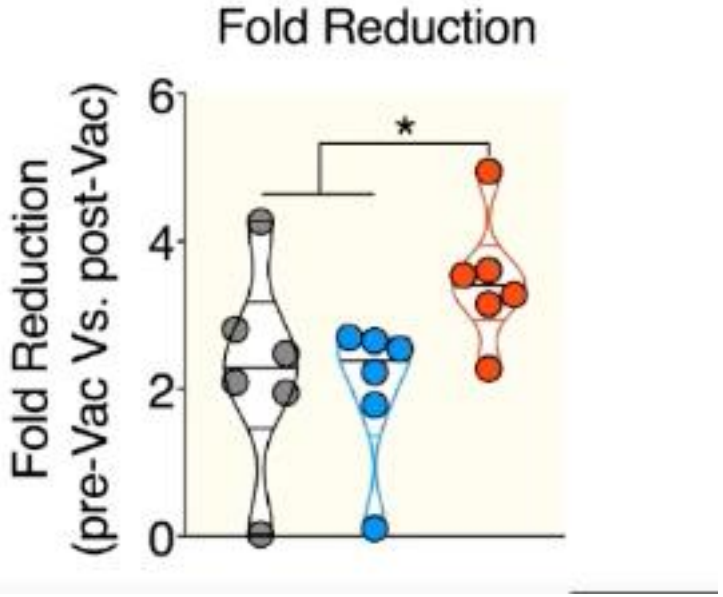


- Better homing of GrB+ CD8 T cells into BCF during ATI

NHP





- Higher reduction of the viral reservoir

O-10 HIV Reservoirs

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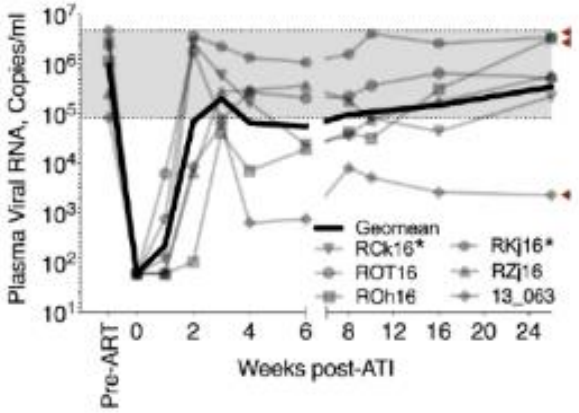
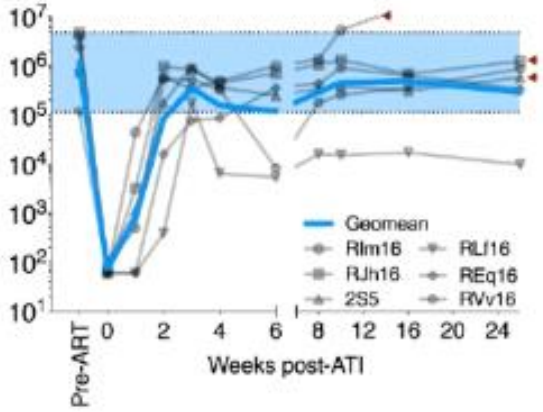
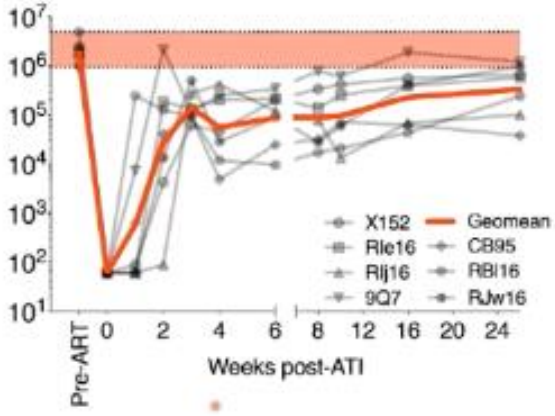






- Better HIV control after ATI (ATI setpoint < preART setpoint)

Related Basic Science

Tuesday March 9th

S-05 Immune-mediating Killing of HIV Reservoirs

42 Initiating ART (not too) Early?
Lydie Trautmann

41 Intrinsic Resistance of Reservoir to Immune Killing
R. Brad Jones

Wednesday March 10th

Plenary

57 Elite Controllers
Xy Yu

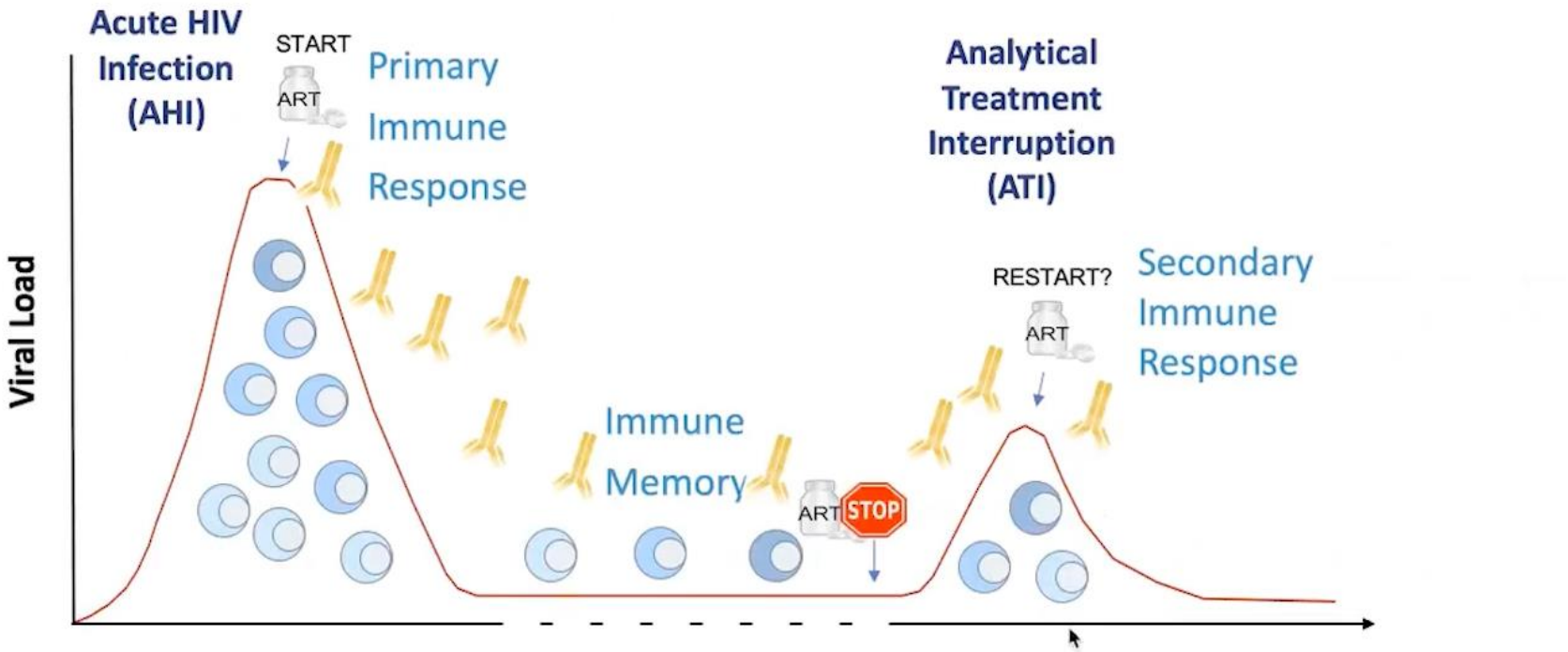
Related Basic Science

S-05 Immune-mediating Killing of HIV Reservoirs

42 HOW TO GENERATE GOOD KILLERS BY INITIATING ART (NOT TOO) EARLY?

Lydie Trautmann, *Oregon Health Sciences University, Portland, OR, USA*

Hypothesis



Early initiation of ART preserves the capacity of CD8 T cells and NK cells to efficiently eliminate HIV infected cells and control viral rebound post-ART

Related Basic Science

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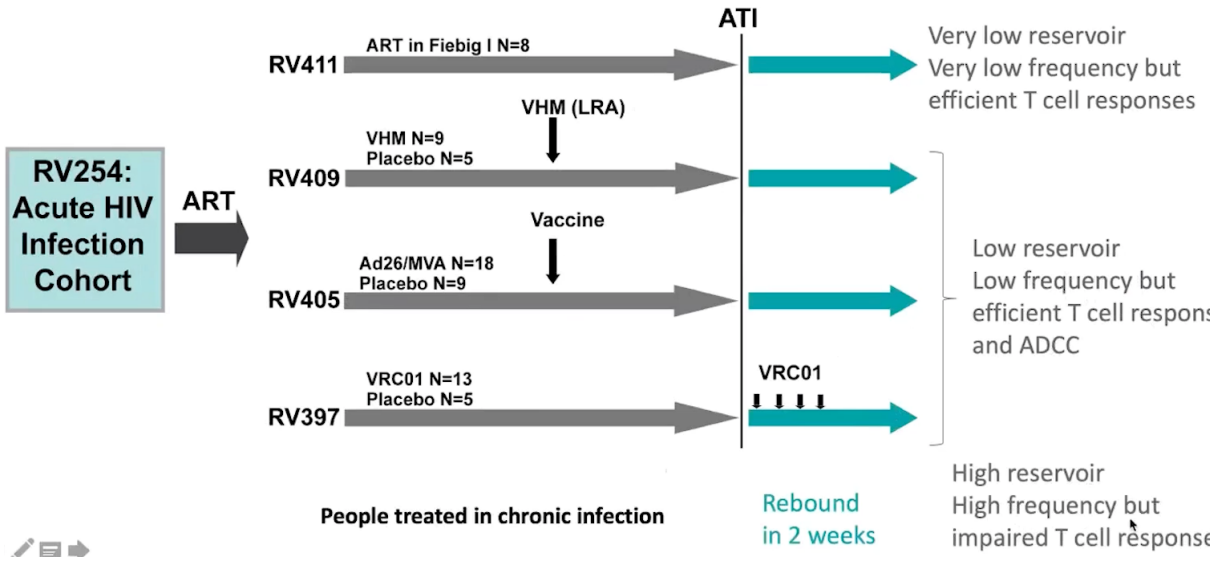
42 HOW TO GENERATE GOOD KILLERS BY INITIATING ART (NOT TOO) EARLY?

Lydie Trautmann, *Oregon Health Sciences University, Portland, OR, USA*

RV254 Analytic Treatment Interruption (ATI) sub-studies



Can we generate good killers by treating early?

Are anti-HIV immune responses developing early enough in acute HIV infection?

- ✓ CD8 T cell responses are detected even in Fiebig I but not antibody responses

ADCC after FI

Do they have enough breadth of anti-HIV immune responses in acute HIV infection?

- ✓ CD8 T responses have breadth early and antibodies develop for 6 month after ART

Do they persist long term on ART? Are they functional?

- ✓ CD8 T cell responses can be detected for at least 5 years after ART initiation, expand well and are good killers

Are they numerous enough? Are these responses contributing to control viral rebound in HIV remission trials?

- ✓ These functional responses are too low and too late to intercept the rebounding virus
- ✓ In SIV: CD8 T cells with preserved function after early ART initiation can reduce viral set point but not rebound after ART cessation (Picker, Okoye, unpublished)

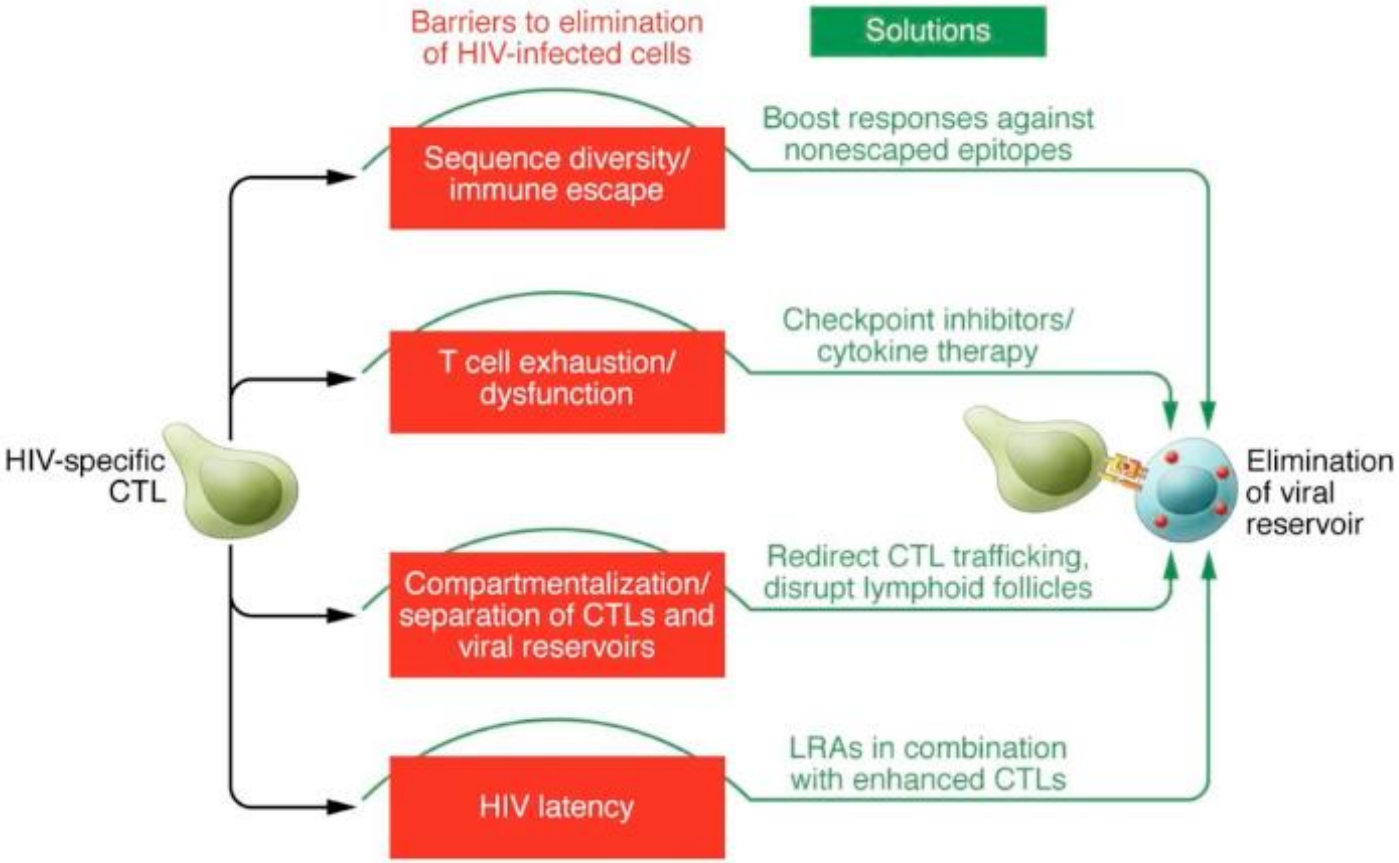
Memory Recall & Cytotoxicity assay (M-REACT)

Related Basic Science

S-05 Immune-mediating Killing of HIV Reservoirs

41 INTRINSIC RESISTANCE OF RESERVOIR CELLS TO IMMUNE KILLING

R. Brad Jones, *Weill Cornell Medicine, New York, NY, USA*



Jones and Walker, *JCI*, 2016

- LRA show increases in viral RNA but no decreases in reservoir
- There is substantive in vivo recognition of Ag by HIV-infected cells

→ Latent HIV reservoir exhibit inherent resistance to elimination by CD8 T cells (JCI 2018)

Related Basic Science

Tuesday March 9th

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S-05 Immune-mediating Killing of HIV Reservoirs

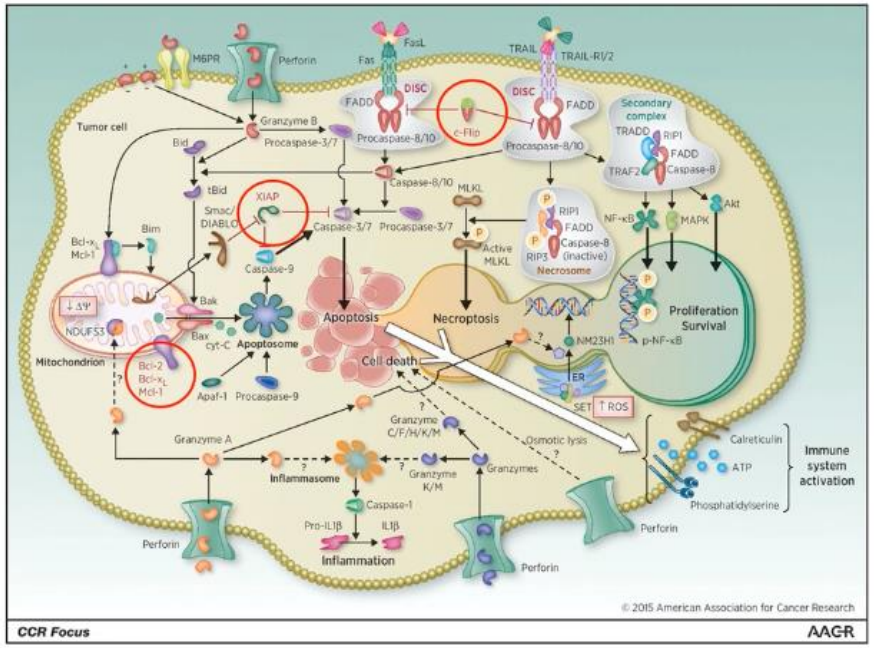
41 **INTRINSIC RESISTANCE OF RESERVOIR CELLS TO IMMUNE KILLING**

R. Brad Jones, *Weill Cornell Medicine, New York, NY, USA*

"Target Cells"
Are active and self-regulating partners in 'killing'

Examples of known inhibitors of killing

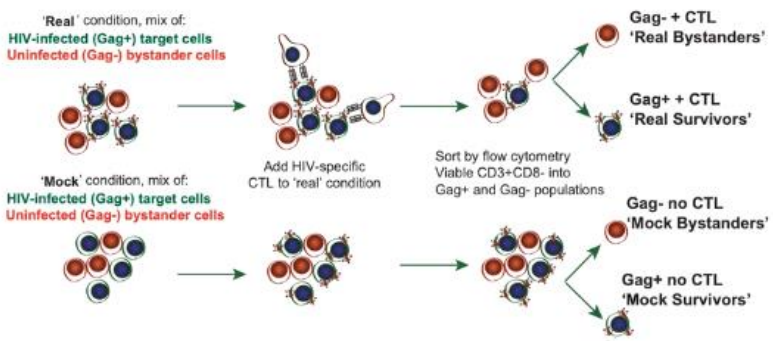
- HIV persistence on ART is tied to the properties of reservoir-harboring cells
- Do cells that over-express CTL resistance factors preferentially survive to form the reservoir? Undergo clonal expansion?

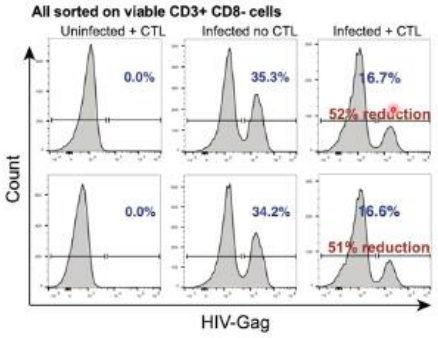


Luis Martinez-Lostao et al. *Clin Cancer Res*, **2015.**

Identifying Mechanisms of CTL Resistance in T_{CM} Cells

- Target cells synchronized to T_{CM} phenotype





- Isolate surviving HIV+ cells from a killing assay for RNA seq

→ Distinctive Transcriptional signatures that would allow identify CTL resistance targets?

Related Basic Science

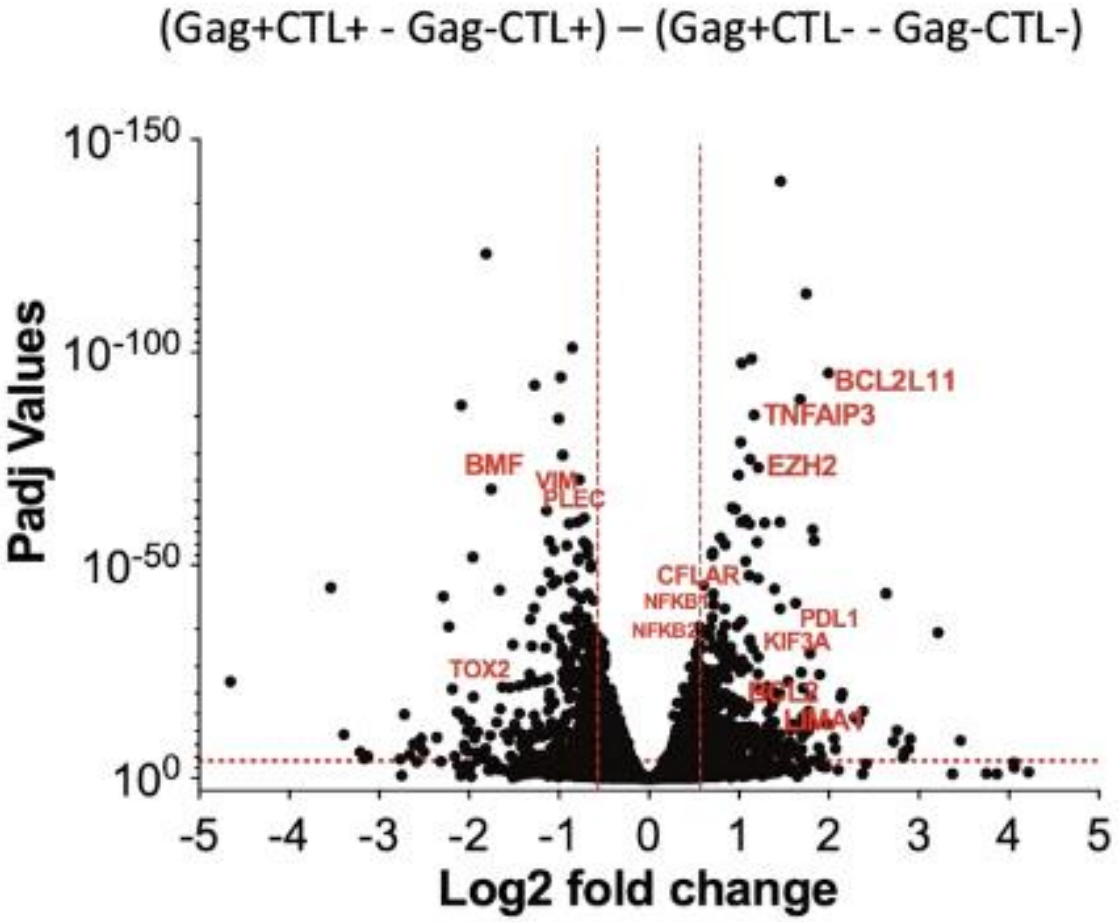
Tuesday March 9th

POSTCROI 2021

S-05 Immune-mediating Killing of HIV Reservoirs

41 INTRINSIC RESISTANCE OF RESERVOIR CELLS TO IMMUNE KILLING

R. Brad Jones, *Weill Cornell Medicine, New York, NY, USA*



- EZH2 inhibitor upregulates MHC-I & sensitize HIV-infected cells to CTL killing

→ Validate hits of CTL resistance → potential therapeutic agents to **reduce reservoir resistance**

=cytophatic enhancing agents (CPA, as BCL-2/EZH2 inhibitors)

Related Basic Science

Wednesday March 10th

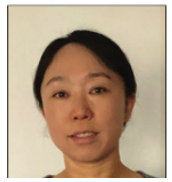
POSTCROI 2021

Plenary

57 *10:10*

ELITE CONTROLLERS: A MODEL FOR A FUNCTIONAL CURE OF HIV-1 INFECTION

Xu Yu, *Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*



HIV-1 Elite Controllers

	Elite Controllers (EC)	ART-Suppressed People (ART)
Number of patients	73	41
Age in years	57 (31 - 75)	55 (34 - 73)
Female (%)	20.54%	21.95%
CD4 counts	902 (450 - 2282)*	726 (316 - 1649)
Viral loads	undetectable	undetectable
Time since diagnosis (year)	18 (1 - 34)	17 (5 - 35)
Known duration of undetectable viremia (year)	9 (1 - 24)	9 (2 - 19)
ART treatment	NO	YES

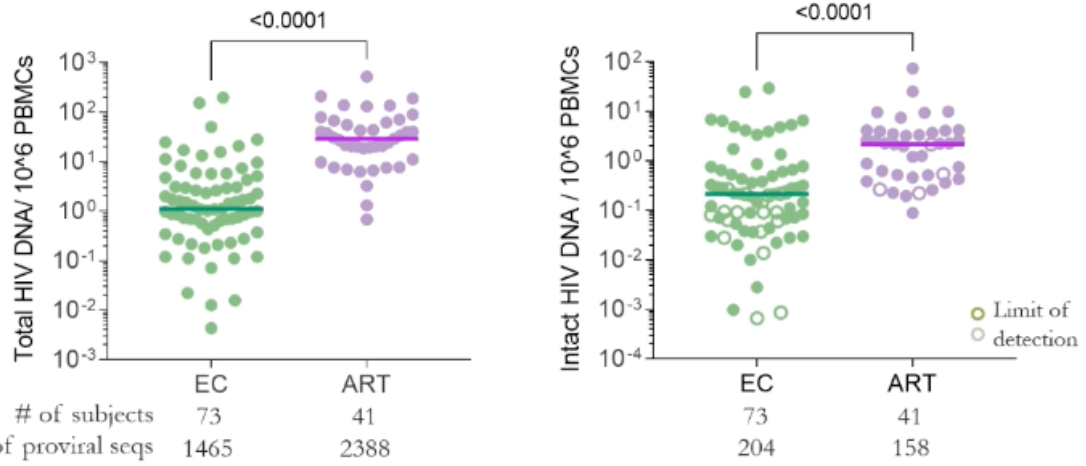
- > 60% with no viral blips;
- <40% with blips, typically only one blip with <100 copies/ml

Bruce Walker, Steven Deeks, Tae-Wook Chun, Ezequiel Ruiz-Mateos, Natalie Laufer

Lian, unpublished data

Jiang, Lian, Gao, *Nature*. 2020

Wide Variations of Intact HIV-1 Proviral Reservoir Sizes in Elite Controllers



Lian, unpublished dat

Jiang, Lian, Gao, *Nature*. 202

- Elite Controller-like reservoir profile as a model for Functional Cure or Long-Term Remission
- How can these EC maintain spontaneous control despite large intact proviral reservoirs?

→ Quality rather than quantity of viral reservoirs can be an important distinguishing feature

Related Basic Science

Wednesday March 10th

Plenary

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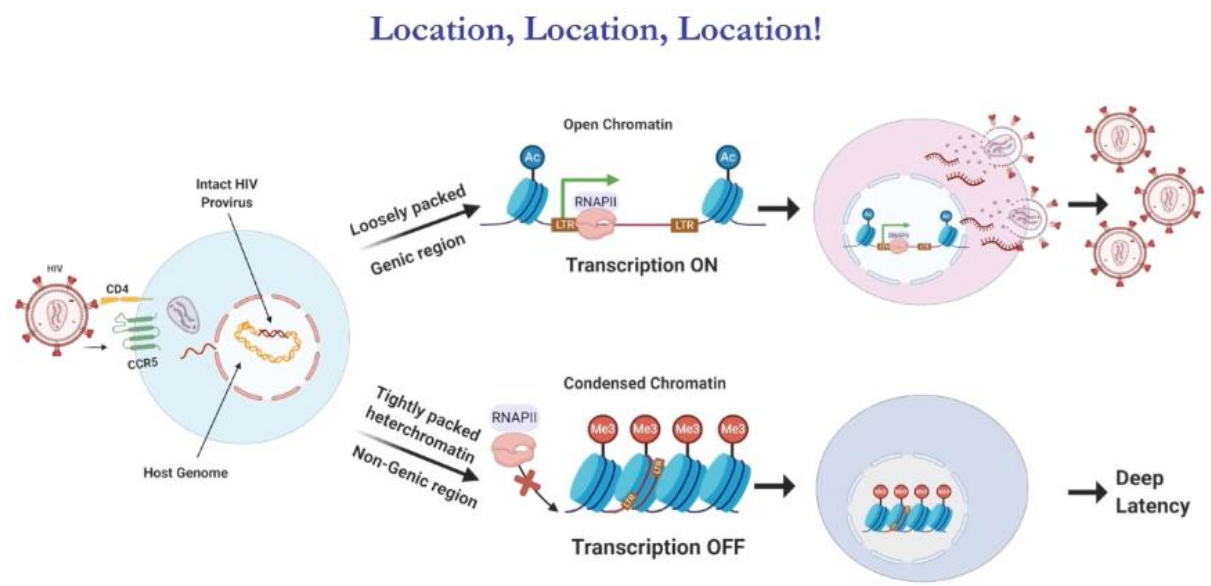
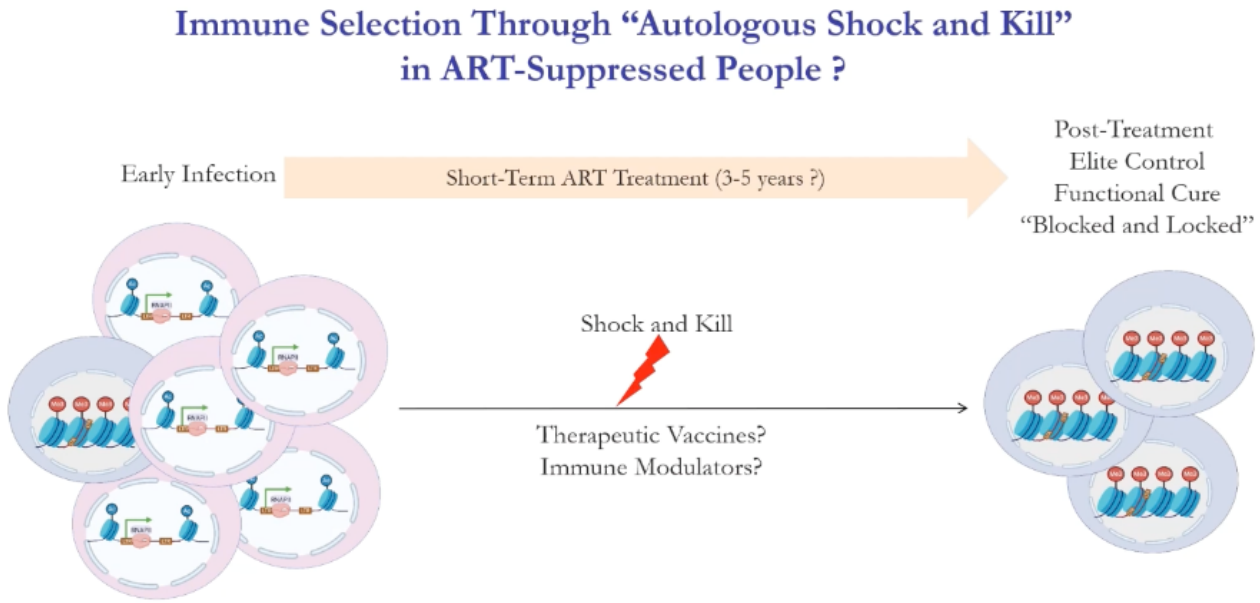
Xu Yu, *Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA*





Siliciano & Greene, *Cold Spring Harb Perspect Med.* 2011; Sherrill-Mix et al., *Retrovirol.* 2013; Lewinski et al., *J Virol.* 2005

- Implementation of assays to analyze qualitative reservoir profiles to evaluate effects of immune interventions aiming for a functional cure of HIV-1

Science Spotlights

D3 Novel Vaccine Concepts

267 VSV-based EBOLA/HIV.1 vaccine (NHP)
Eric J. Arts

268 V3-Glycan Epitope-focused Nanoparticles for HIV vaccines
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271 Protection with Immune-Complex vaccines (NHP)
Qingbo Liu

D4 Neutralizing Ab during Infection

275 Ab profiling identifies Ab targets associated with natural Control
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276 Autologous Neutralizing Ab increase with Early ART and shape HIV rebound
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295 Venetoclax reduces HIV vl in vivo and In vitro
Aswath Padmanabhan

296 Autologous Neutralizing Ab delay viral rebound in infant SHIV model
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297 Virus Remission with and optimized early ART (NHP)
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298 GH on reservoir (CTN 298)
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299 PD-1 Blockade on Reservoir
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309 Dynamics of intact Proviral HIV-1 DNA in PTC
Xiadong LIan

310 Cell-free DNA predics HIV rebound in ATI
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311 Immune Markers & Time to rebound during ATI (ACTG A5345)
Bernard Macatangay

312 Mathematical modeling of predictors of posttreatment control in HIV cure trials
Gesham Magombedze

¡MUCHAS GRACIAS!

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