

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Early intervention with an indoline CD4-mimetic compound that sensitizes HIV-1-infected cells to ADCC favors post-treatment HIV control in humanized mice

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Session: Antibody & Immune based Therapies, Date: 12/13/2024

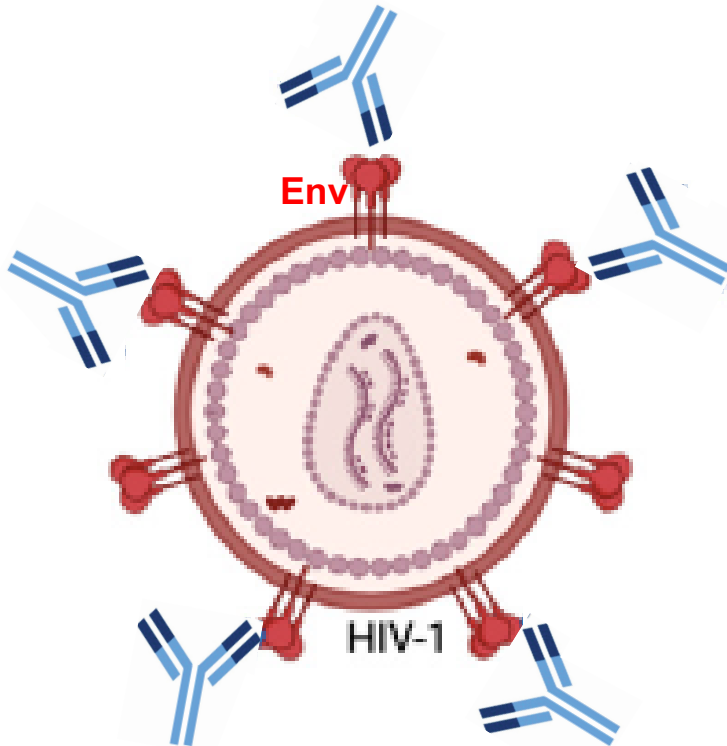
www.hiv-persistence.com

CONFLICTS OF INTEREST

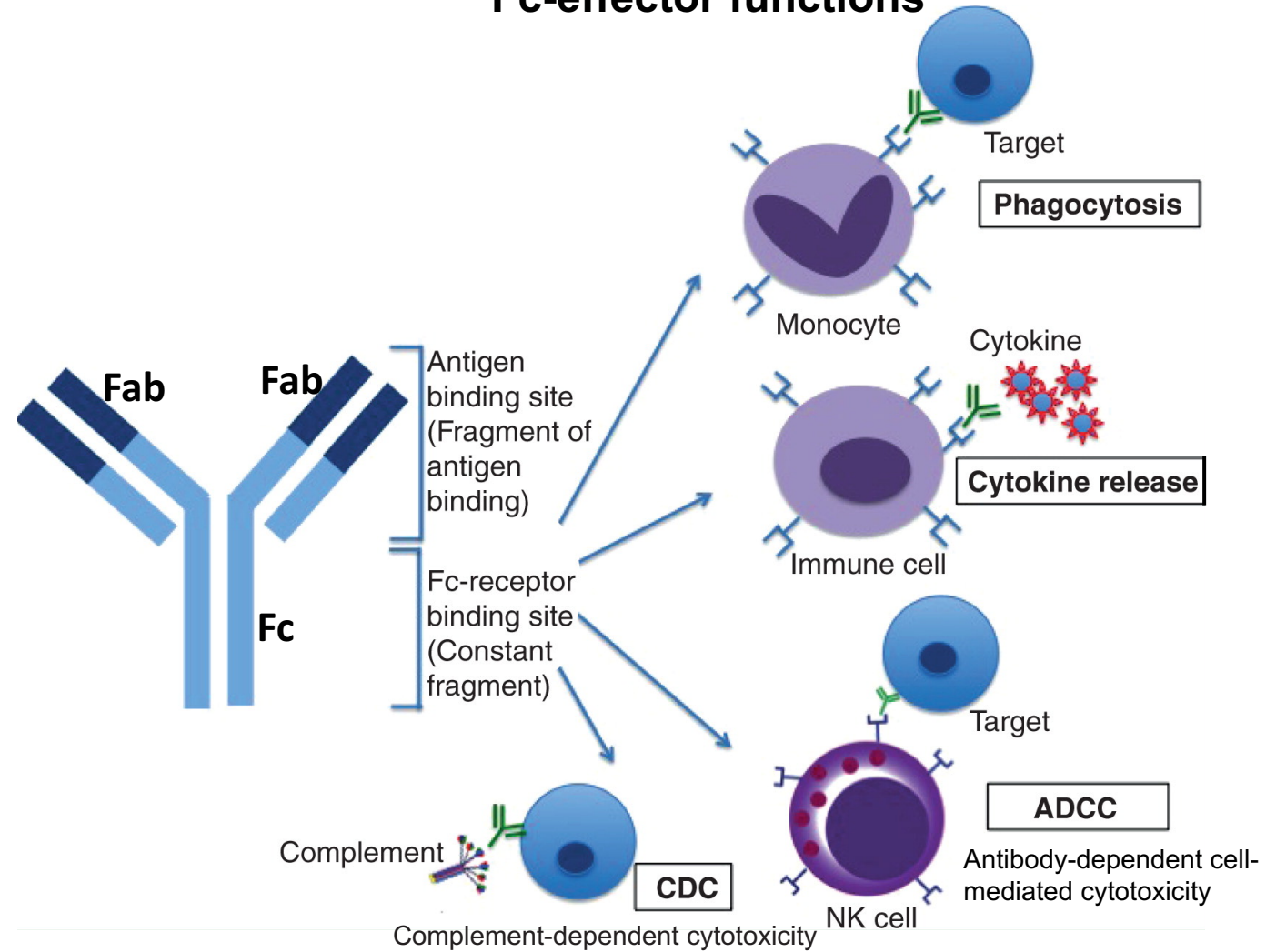
No conflicts of interest to declare.

Role of antibodies in viral infection

Neutralization

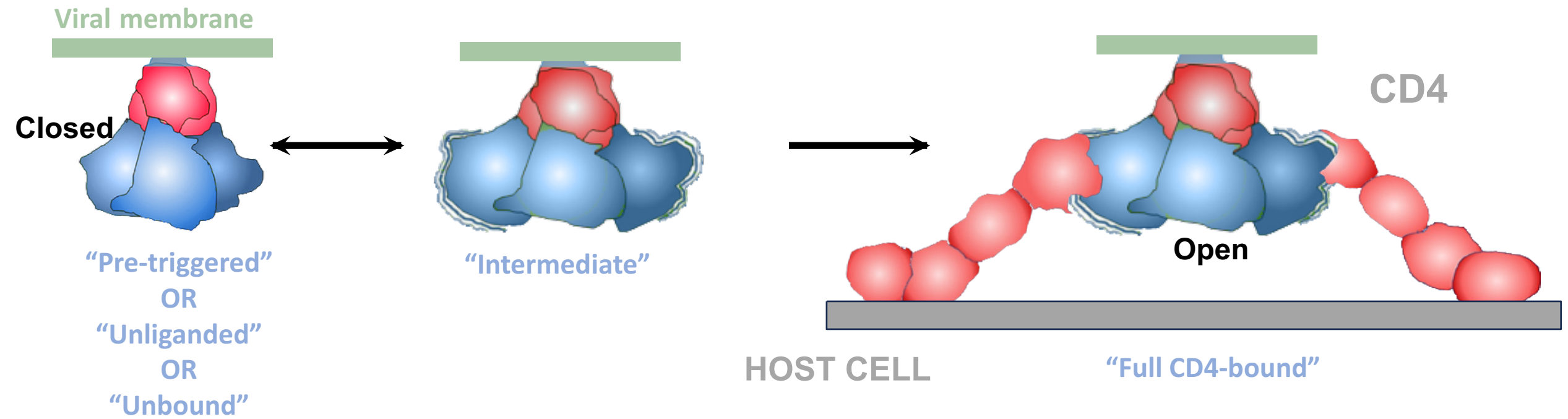


Fc-effector functions



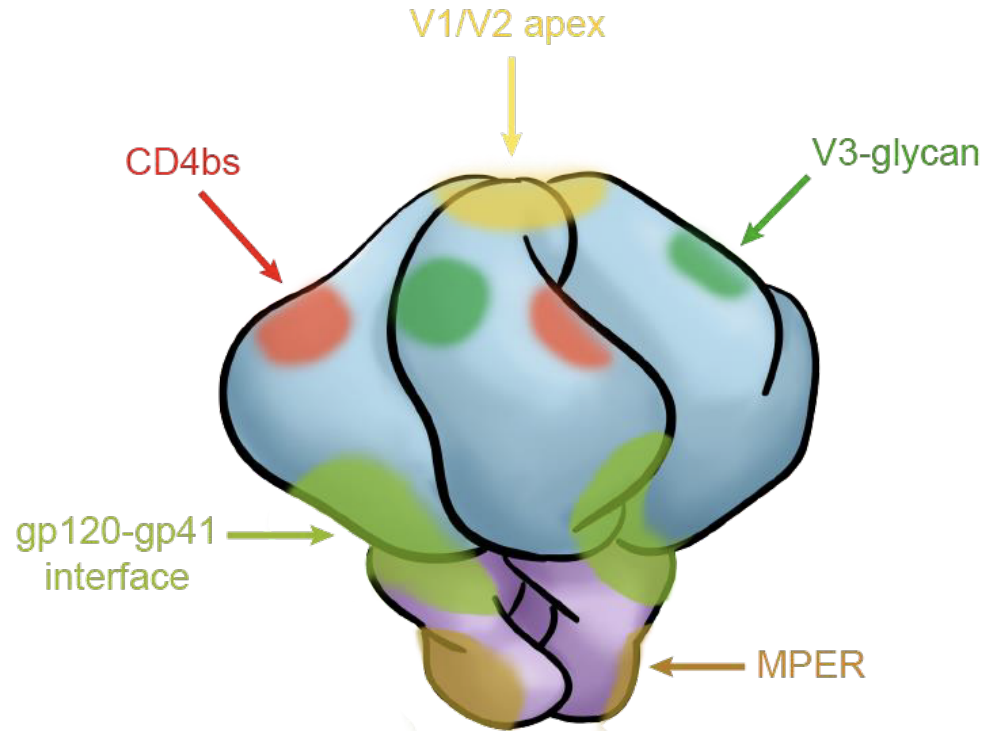
Thavarajah JJ et al., Viruses. 2024; Chan KR et al., Expert Rev Anti Infect Ther. 2015

Env Conformational States



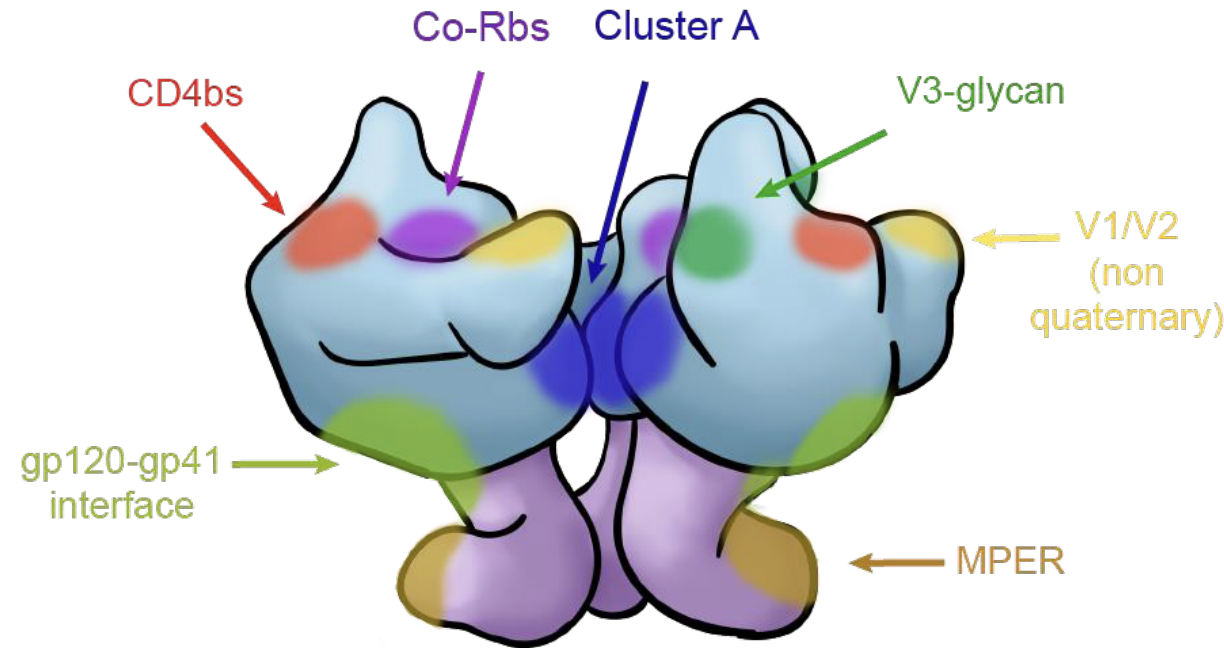
Antibody binding sites on the Env

Neutralizing Abs (easy escape)
Broadly neutralizing Abs (difficult to elicit, rare)



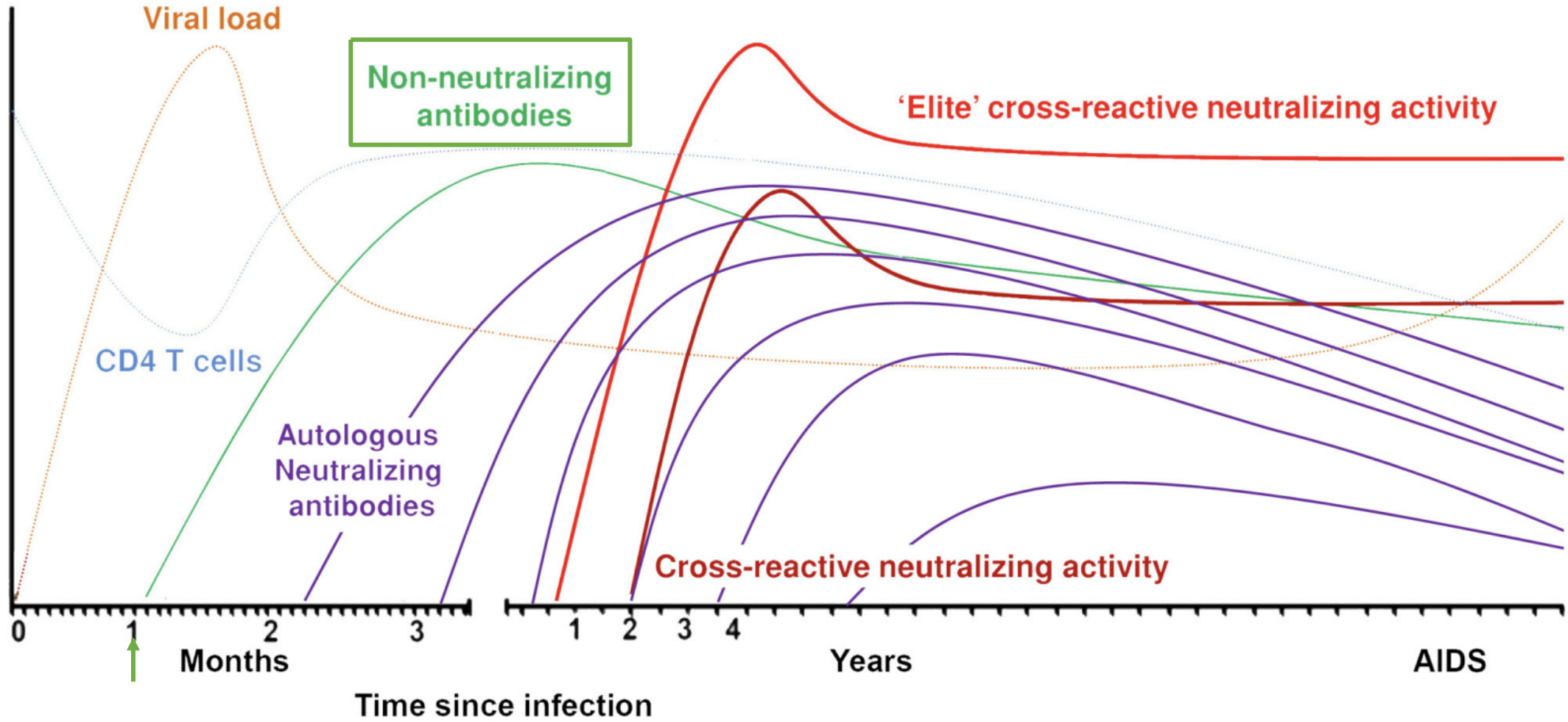
State1 "closed" conformation

Non-neutralizing Abs (easily elicited in PWH)

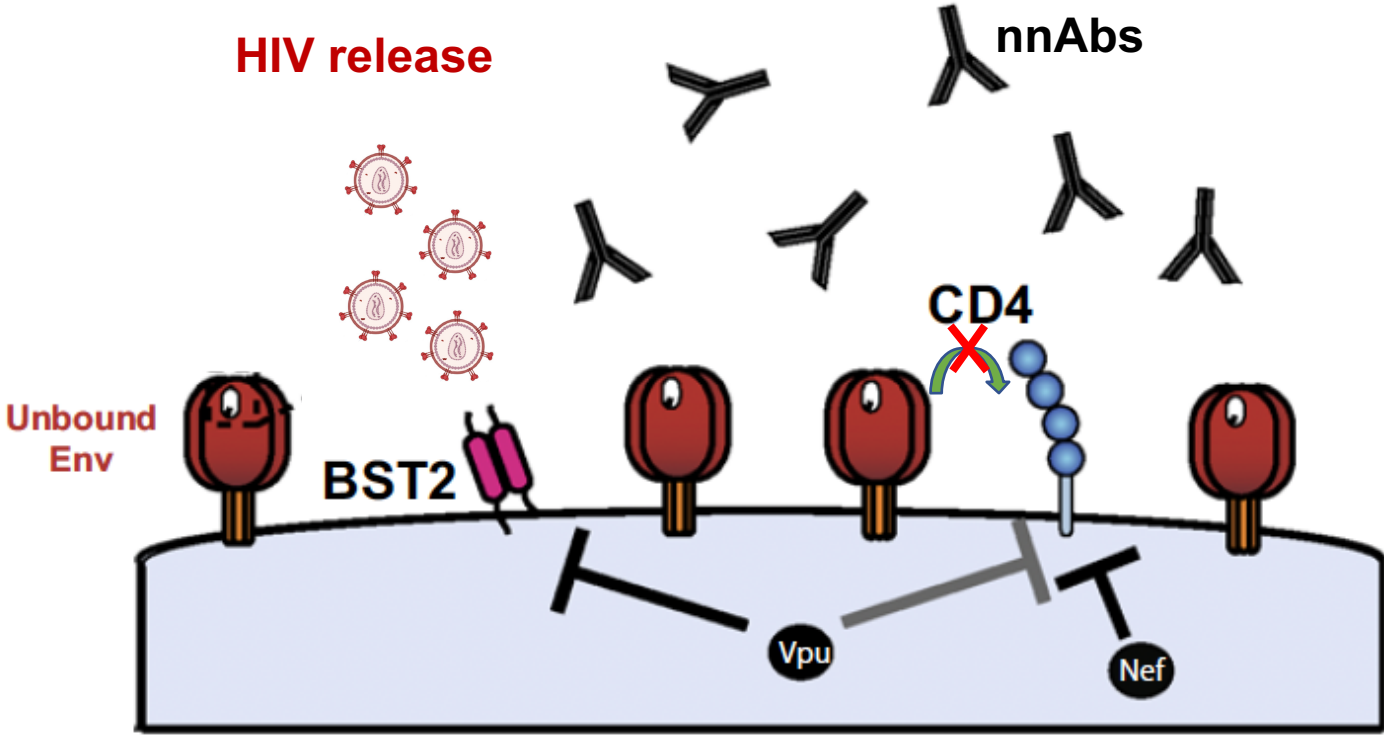


State2/3 "open" conformation

Antibodies elicited to HIV-1 envelope over the course of the untreated infection

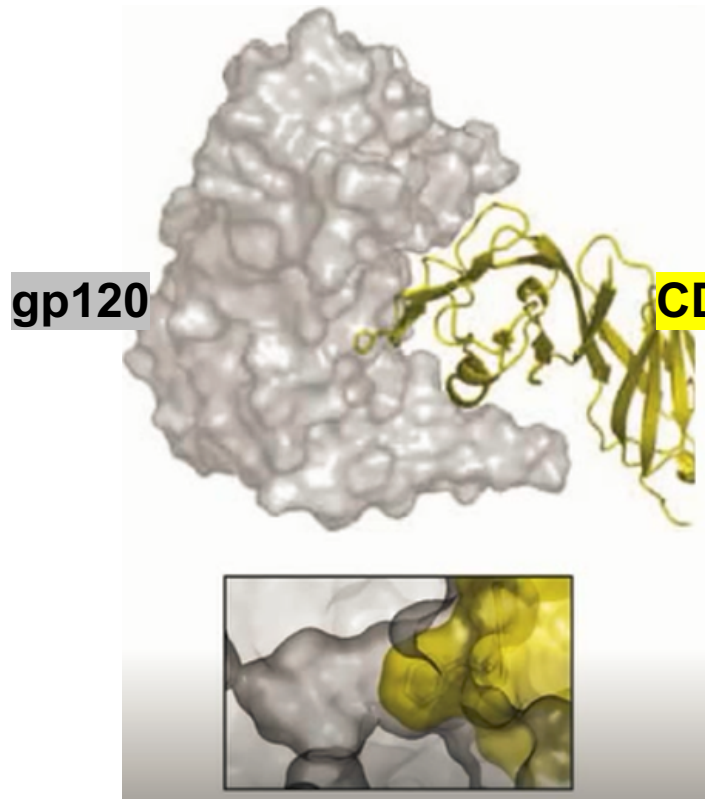


Protection from ADCC

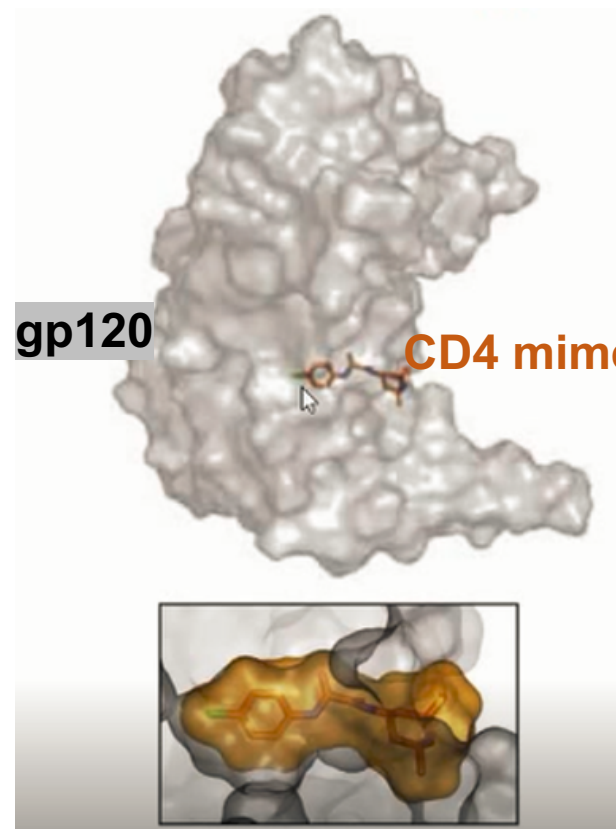


Richard J et al., AIDS Res Ther. 2017

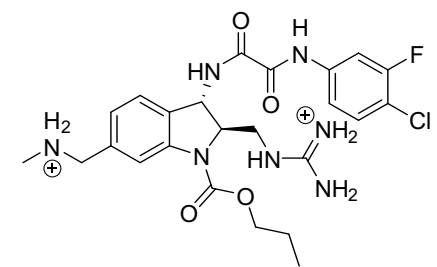
CD4-mimetic compounds (CD4mcs) bind in the highly conserved CD4-binding site of gp120 and induce Env conformational changes



Kwong et al., Nature, 1998



Madani et al., Structure, 2008; Lalonde et al., Bioorganic & Med Chem, 2011



CJF-III-288
(indoline CD4mc)



Dr. Amos B. Smith III
University of Pennsylvania

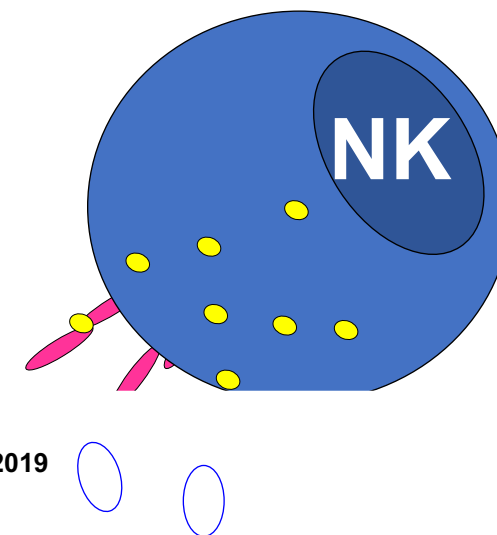
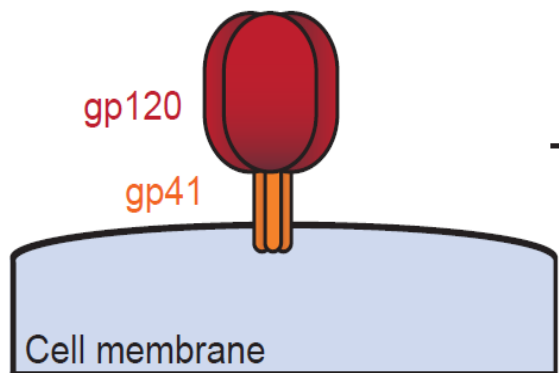


Dr. Joseph G. Sodroski
Harvard Medical School

Opening of Env is required to allow binding of CD4i Abs involved in ADCC responses



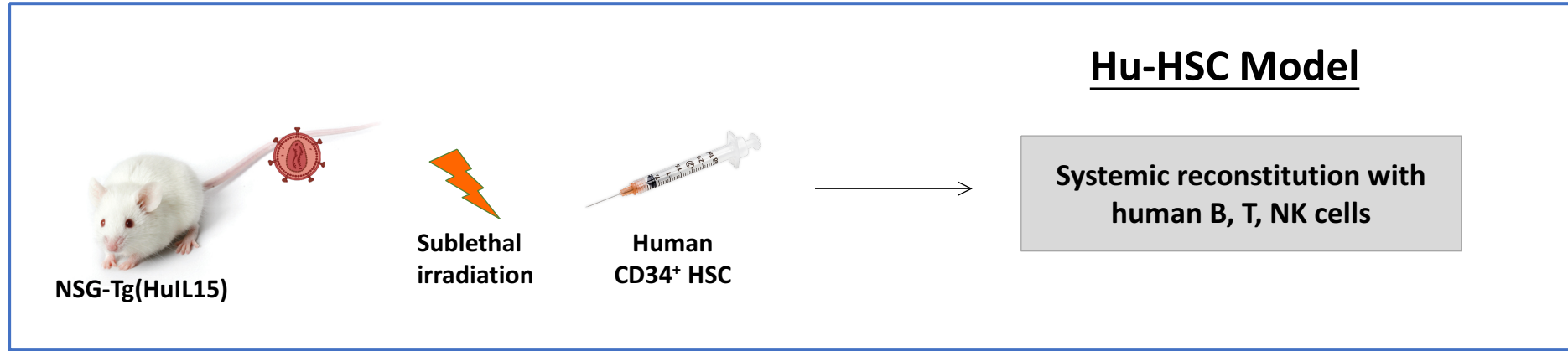
Dr. Andrés Finzi
CRCHUM, Montreal CA



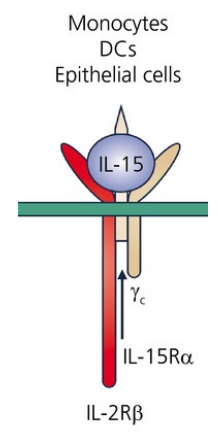
Anand et al., JVI 2019

CJF-III-288/CD4i Abs are currently being tested in NHPs as part of the ongoing studies in ERASE collaborators.

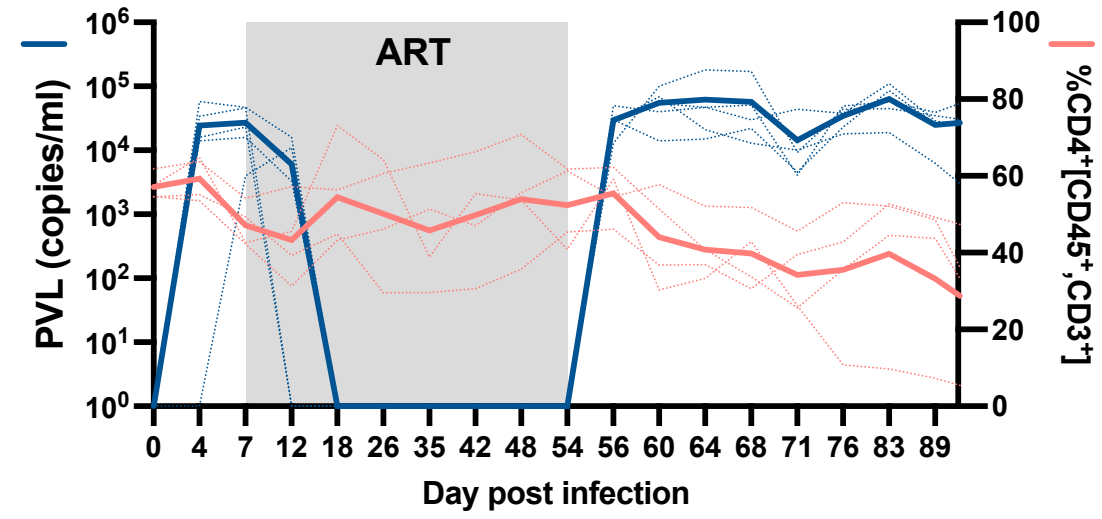
Humanized mouse model for HIV-1 that supports antibody effector function



IL-15

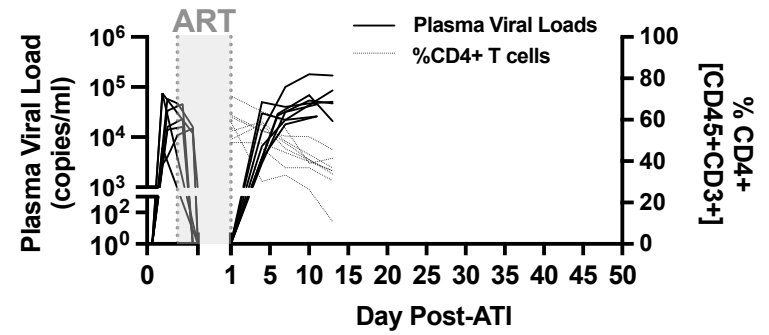


**NK Cells
 T Cells**

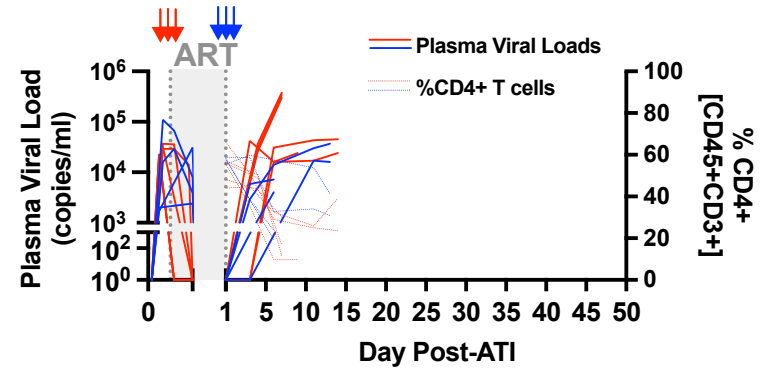
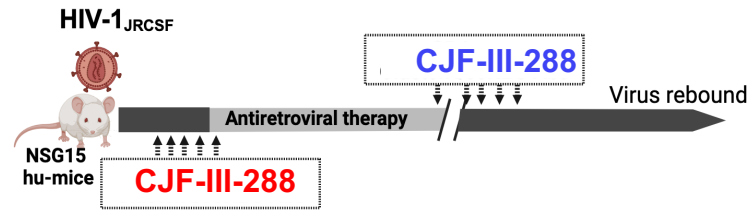


Treatment with CD4mc/CD4i Abs

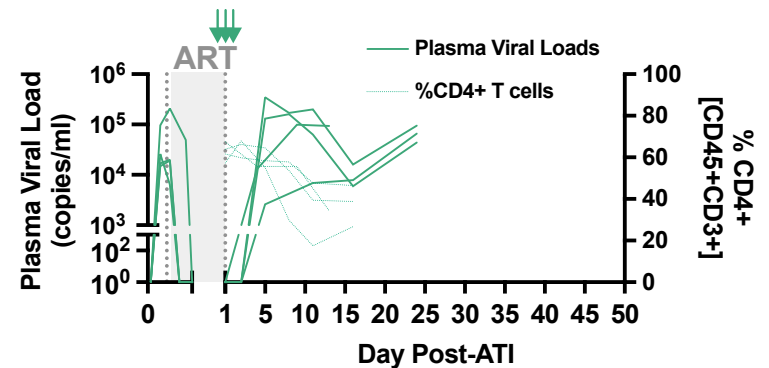
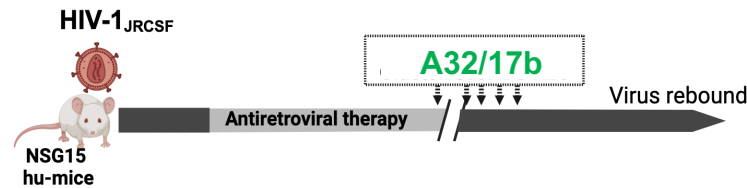
1. Mock treatment



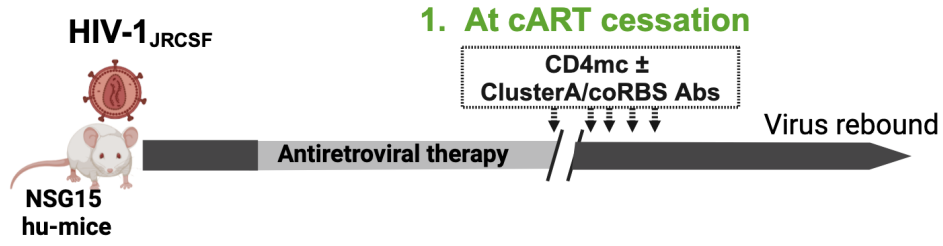
2. CD4mc (CJF-III-288) alone



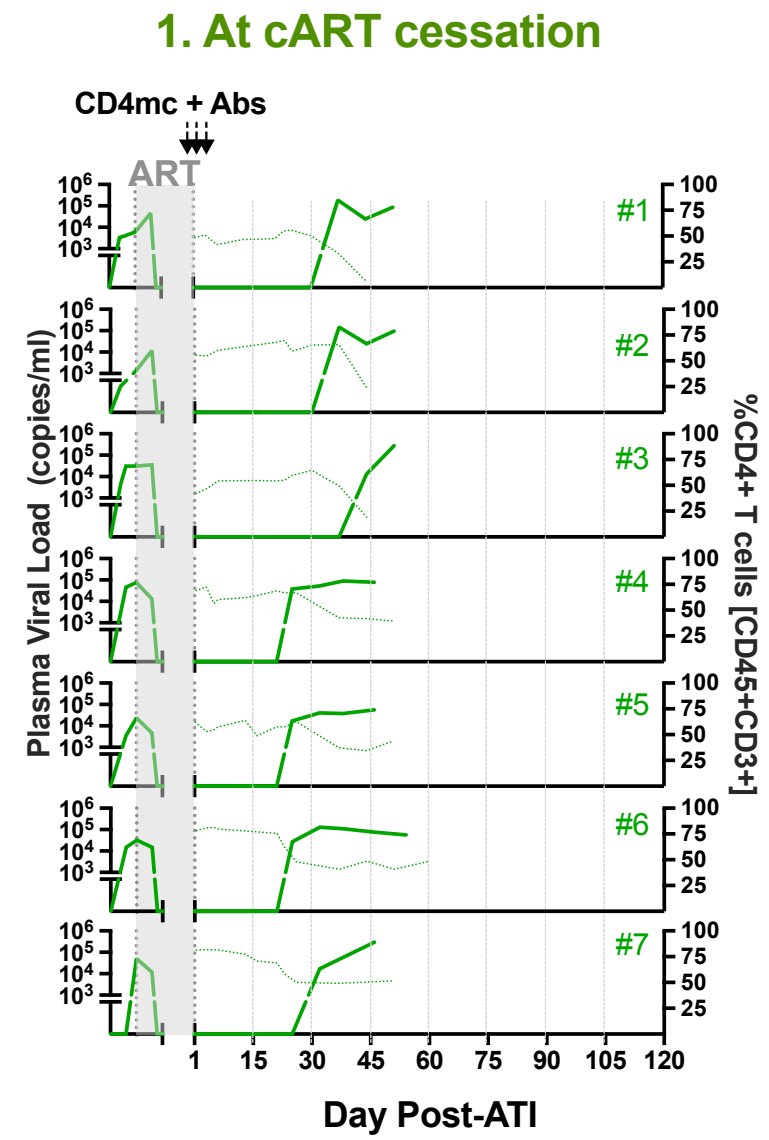
3. CD4i Abs (A32/17b) alone



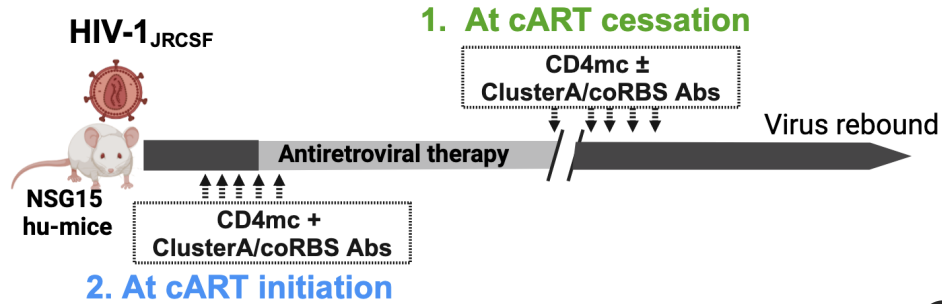
Effects of CJF-III-288/CD4i Abs cocktail on viral rebound



CJF-III-288/A32/17b Ab

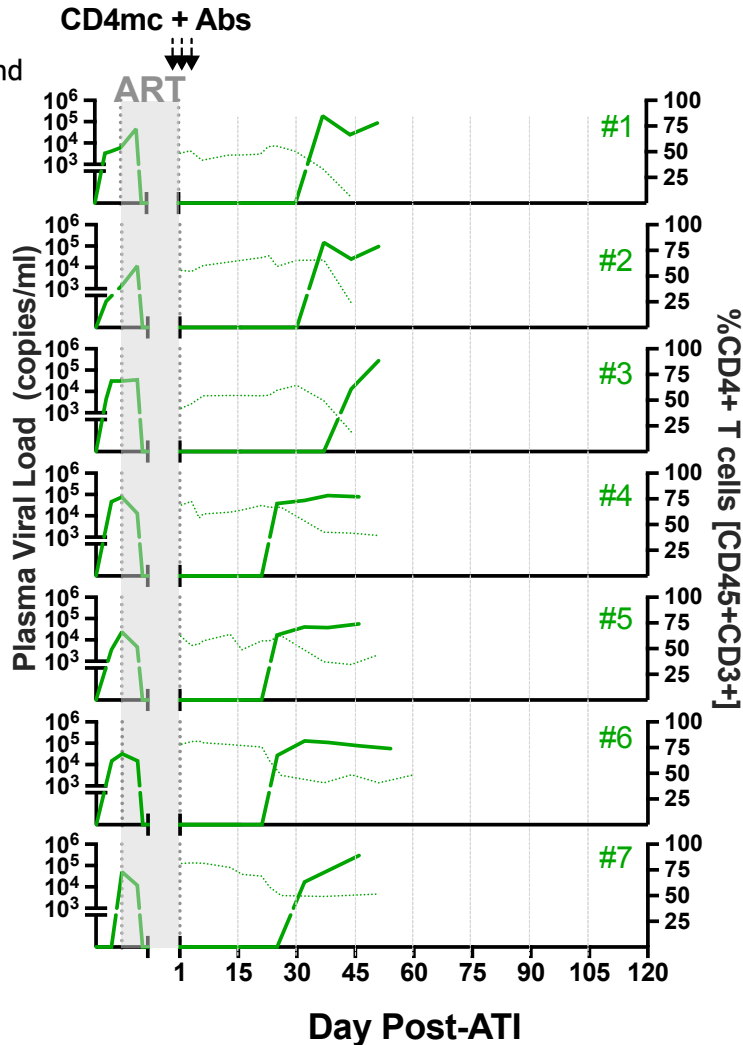


Effects of CJF-III-288/CD4i Ab cocktail on viral rebound

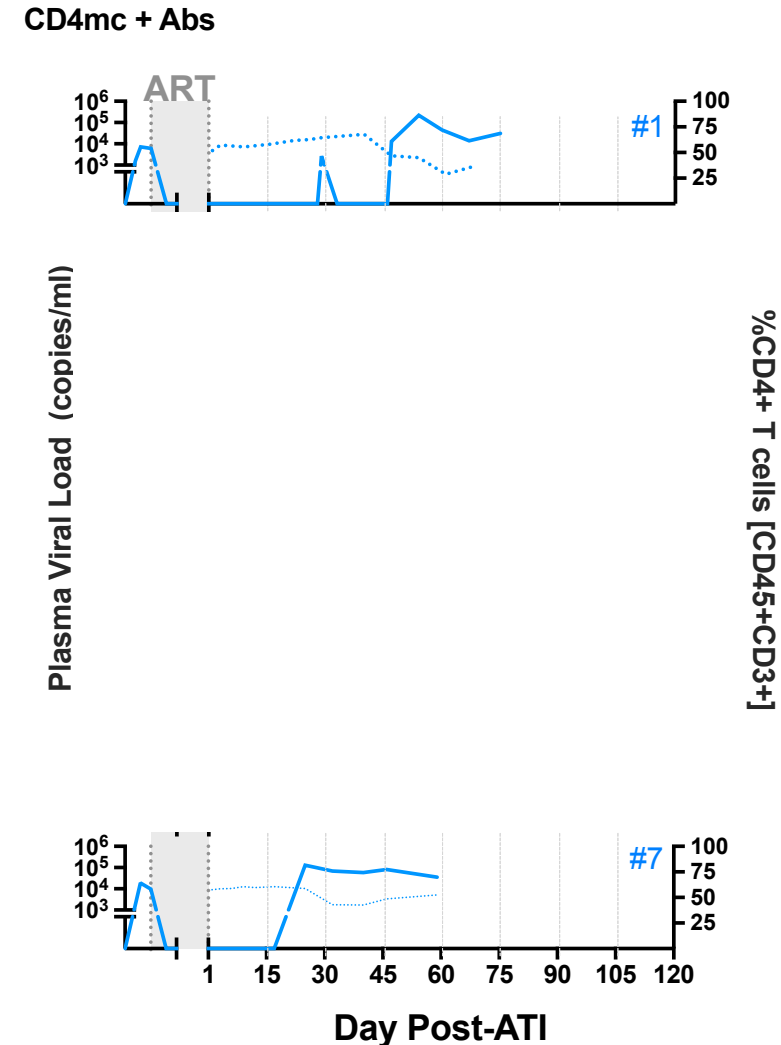


CJF-III-288/A32/17b Ab

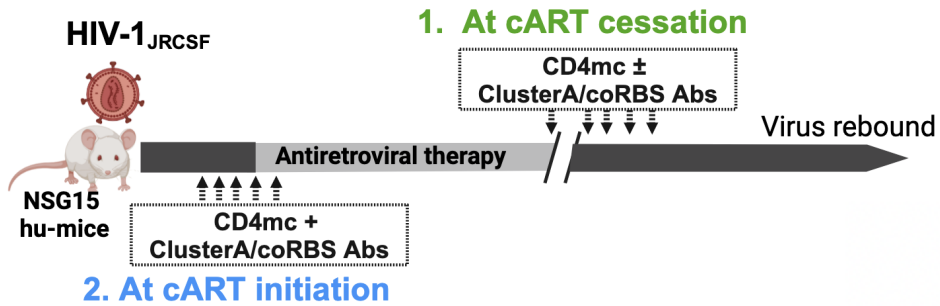
1. At cART cessation



2. At cART initiation

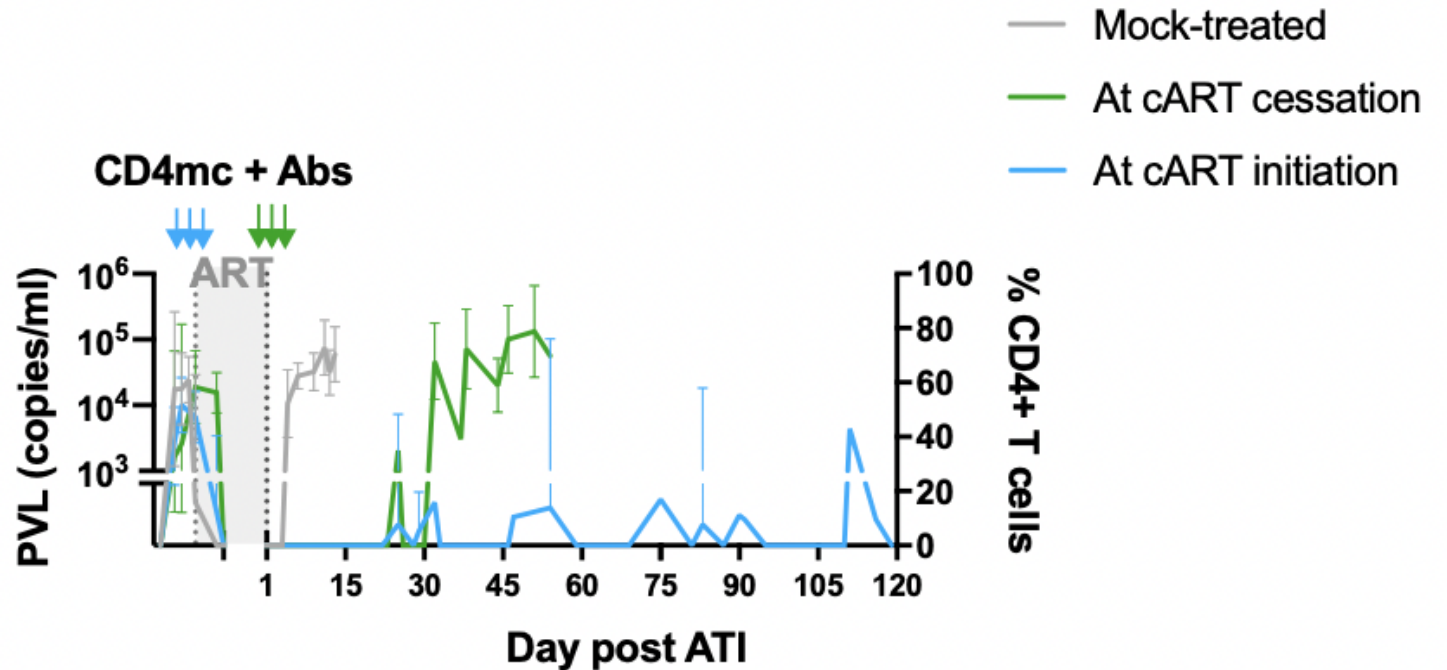


Effects of CJF-III-288/CD4i Ab cocktail on viral rebound

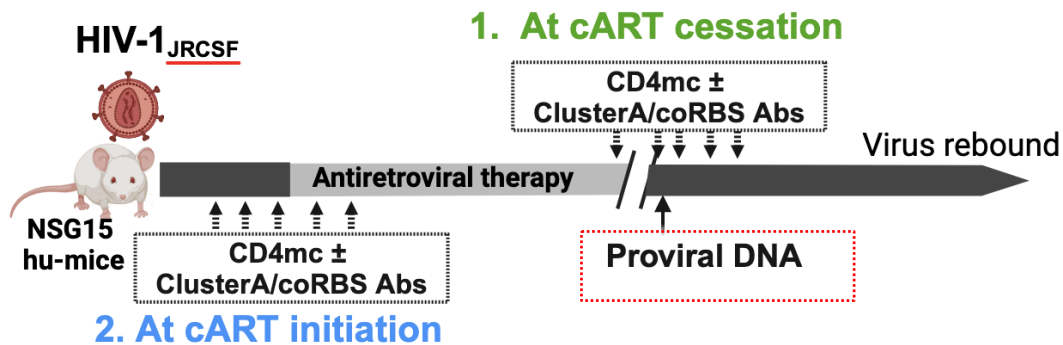


CJF-III-288/A32/17b Ab

Durable control.....

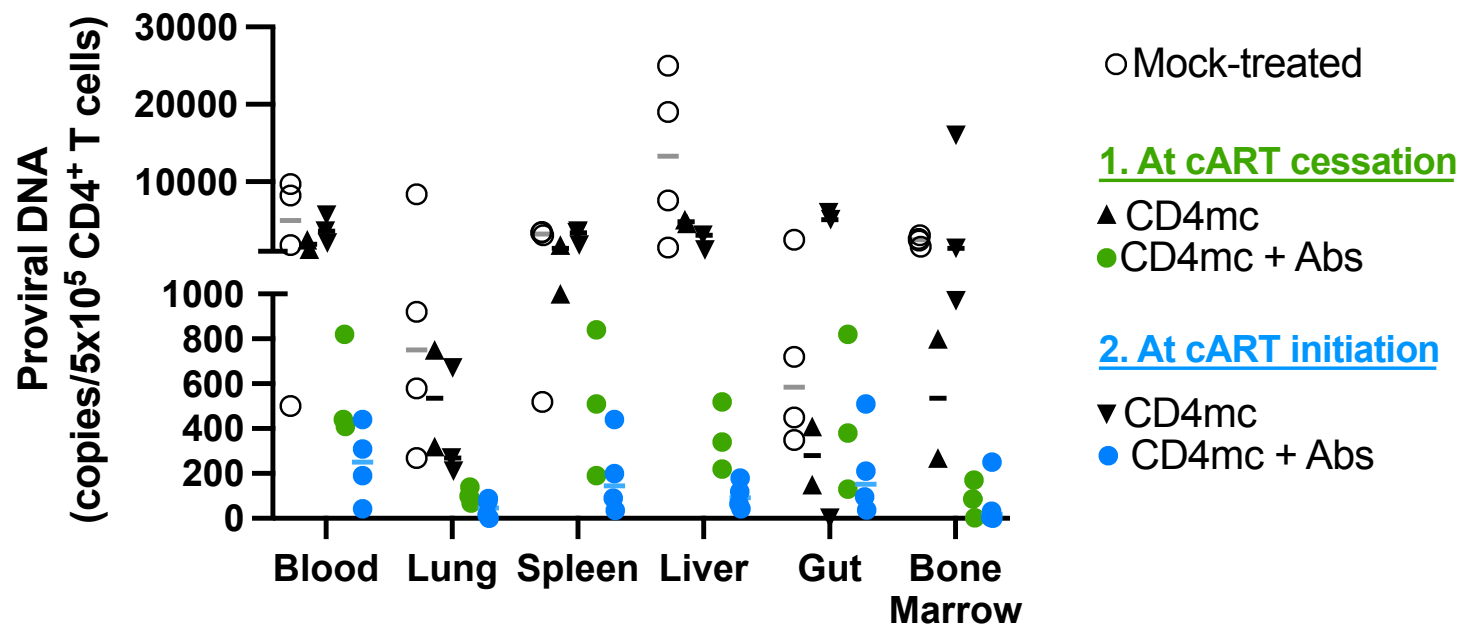


Effects of CJF-III-288/ CD4i Ab cocktail on the HIV-1 reservoir

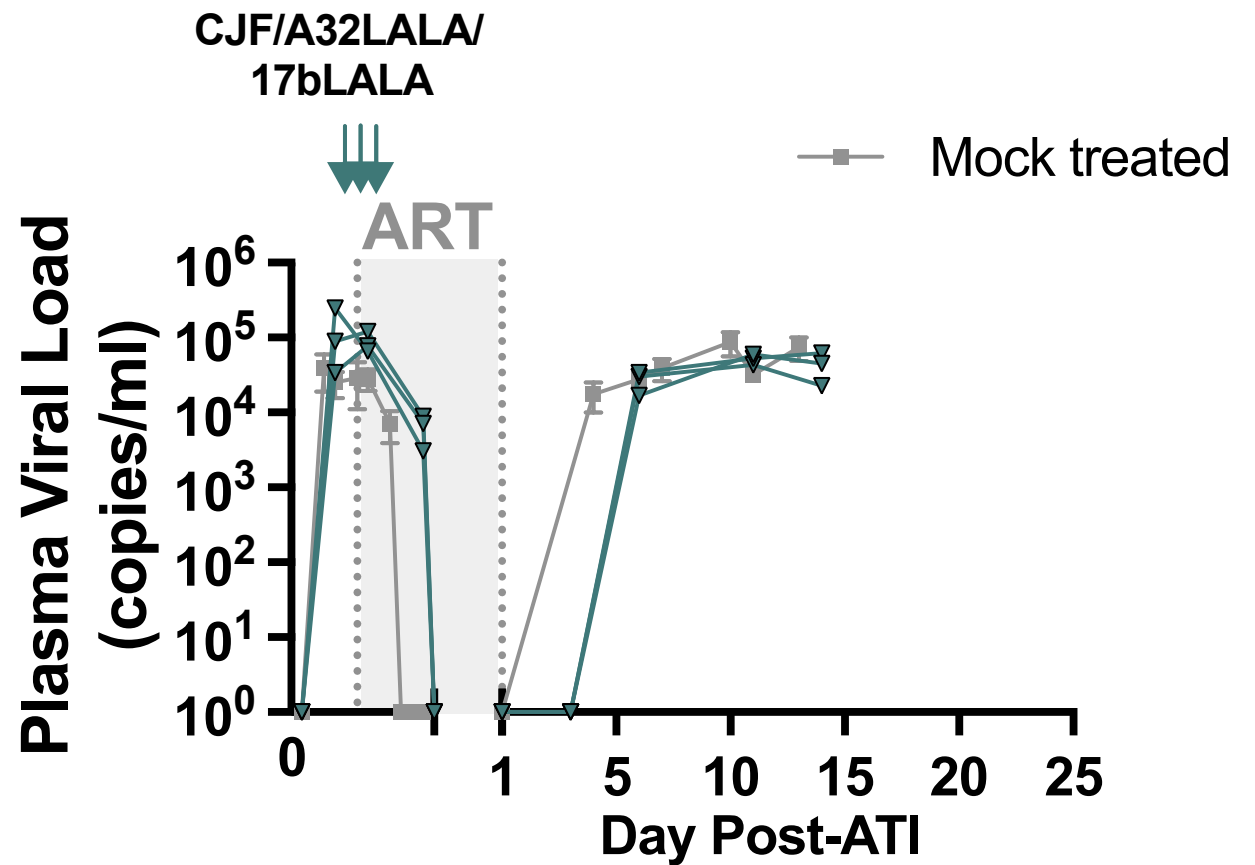
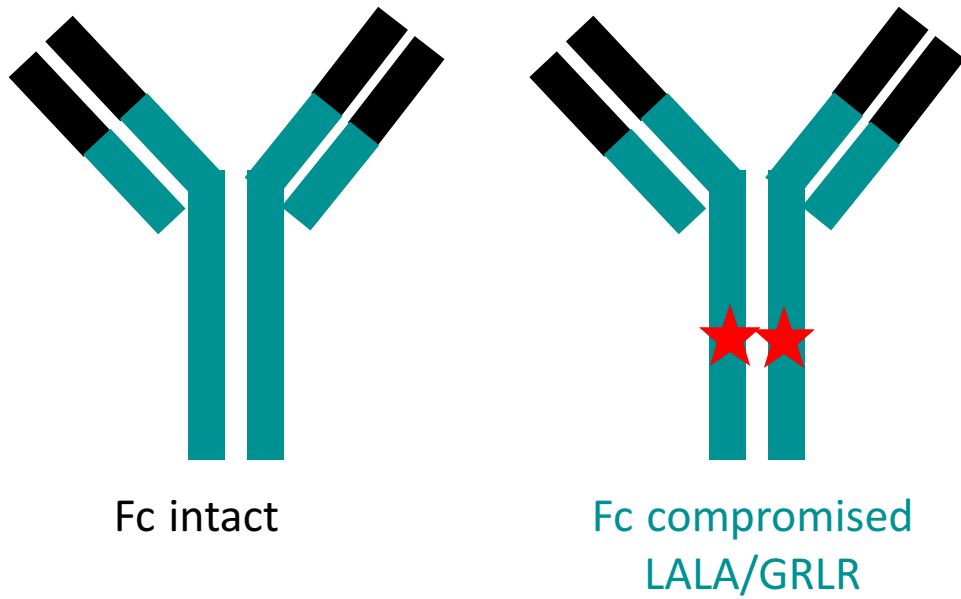


CJF-III-288/A32/17b Ab

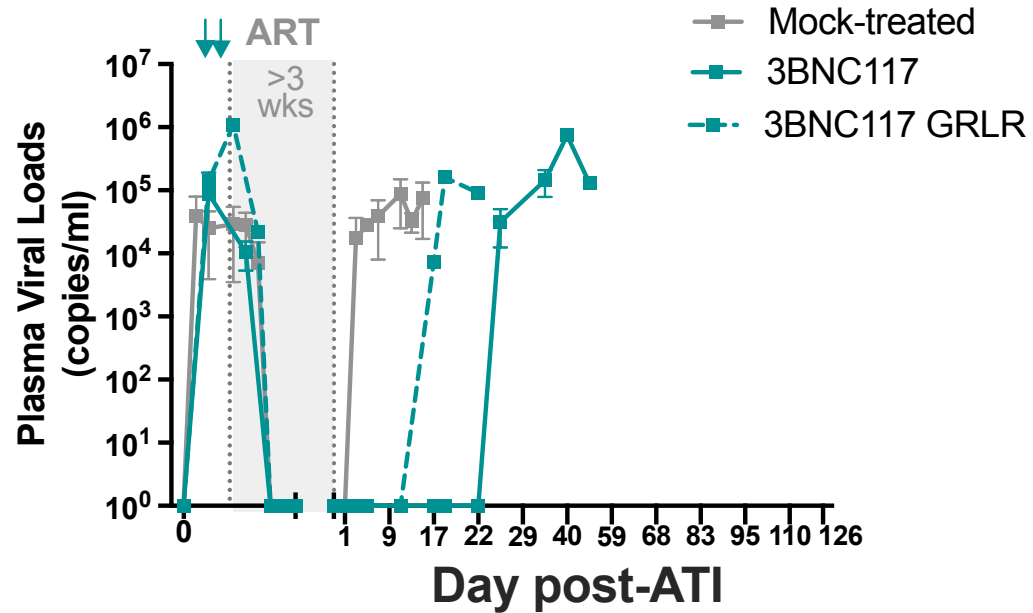
HIV-1 Proviral DNA



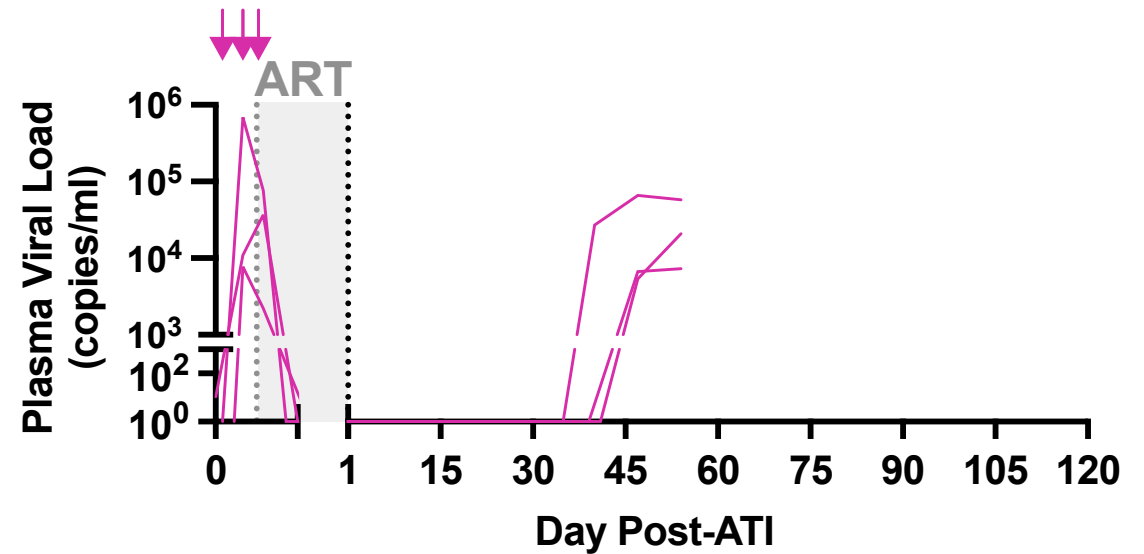
Impact of Ab Fc-effector function



Effects of the broadly-neutralizing antibodies



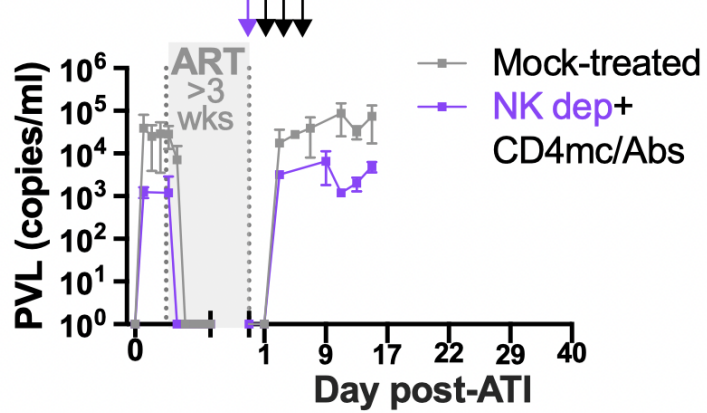
3BNC117/10-1074/PG16



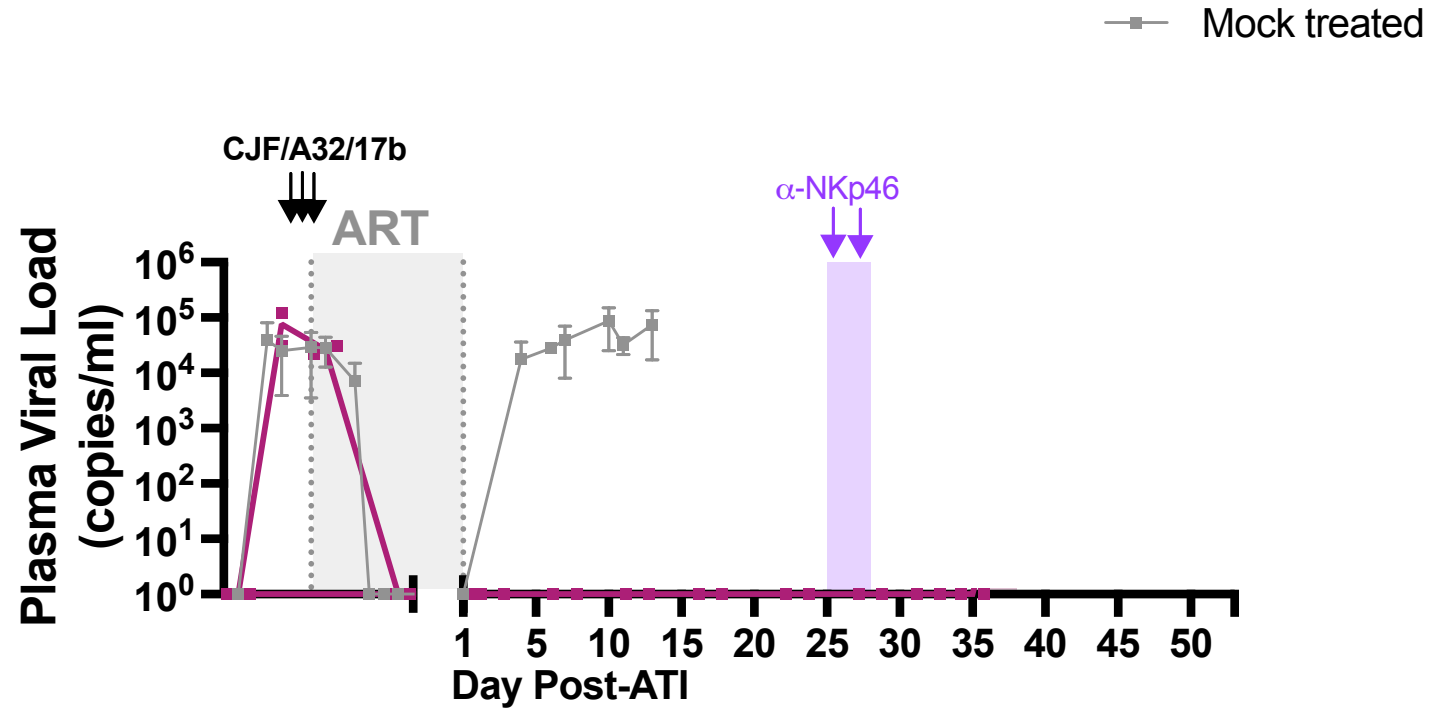
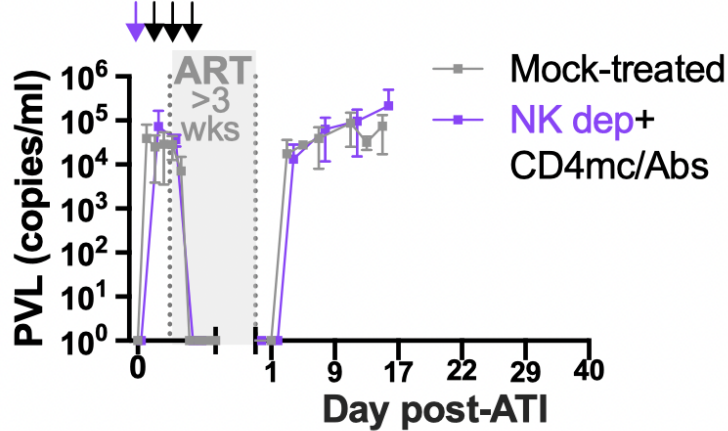
Role of NK cells

.....and CD8 T cells

1. At cART cessation



2. At cART initiation



Summary

- Treatment with CJF-III-288/CD4i Abs at the time of cART initiation results in durable control of plasma viral loads after cART interruption.
- NK cells played a primary role, supporting ADCC effects; but CD8⁺ T cells contributed to continued viral suppression and control of rebound.

Acknowledgements

Kumar Lab

Hongil Kim
Srilaksmi Tejaswi Boodapathi
Natalia Salazar-Quiroz
Shawkat Alam Muhammad
Jyothi Rajashekar
Rashi Jindal
Yaping Sun
Irfan Ullah



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Fritschi, Derek Yang, Hung-Ching
Chen, Ta Jung-Chiu)
Beatrice Hahn (Frederic Bibollet-
Ruche, Weimin Lu)

Dana Farber Cancer Institute

Joseph Sodroski

Gladstone Institutes

Nadia Roan (Julie Frouard)

Jackson Laboratories

Lenny Shultz

U Mass Med, Worcester

Michael Brehm, Dale Greiner

Caltech

Pamela Borkman

The Rockefeller University

Michel Nussenzweig

Yale University

Kurt Schalper (Kishu
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Pradeep Uchil
Walther Mothes
Ya-Chi Ho

Richard Flavell

Emory University

Mirko Paiardini (Leonardo
Sorrentino, Laurence
Marchand, Justin Harper)



National Institute of
Allergy and
Infectious Diseases



Martin Delaney Collaboratories for
HIV Cure Research: **UM1AI164562**

