Pablo Tebas. University of Pennsylvania

Towards an HIV Cure
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The Philadelphia patient*

*I did not pick the title

AIDS 2022

Affiliated Independent Event

The 4 HIV cures have been "gene therapy"

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	Berlin Patient	London Patient
Primary Malignancy	Acute Myeloid Leukemia, diagnosed June 2006	Hodgkin's Lymphoma, diagnosed December 2012
Therapies Prior to CCR5Δ32	Induction (2X), and consolidation (1X) chemotherapy	First line and salvage chemotherapies including anti-CD30
Stem Cell Donor	10/10 HLA match + CCR5Δ32	9/10 HLA match + CCR5Δ32
Transplant #1	February 2007. Conditioning included fludarabine, cytarabine, amsacrine (FLAMSA), cyclophosphamide, rabbit antithymocyte globulin (ATG), 400-cGy TBI	May 2016. Conditioning included lomustine, ara-C, cyclophosphamide, etoposide (LACE), and anti-CD52
ART Discontinued	Day of transplantation	16 months post-transplantation
Transplant #2	March 2008. Conditioning included cytarabine, gemtuzumab ozogamicin (anti-CD33), 200-cGy TBI	N/A
Immunosuppression	Cyclosporine A, methylprednisolone, mycophenolate mofetil, ended 38 months post-transplantation. >3 years treatment.	Cyclosporine A, short-course methotrexate. <1 year treatment.
GVHD	Grade I following first transplant	Grade I, 77 days post-transplant
ART-Free HIV-1 Remission	Over 12 years	18 months

They tend to be named after the city where the intervention was done

Peterson CW, Kiem HP. Cell stem cell. 2019;24(5):685-7.

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The Philadelphia patient is not a “cure”

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CCR5 modification.

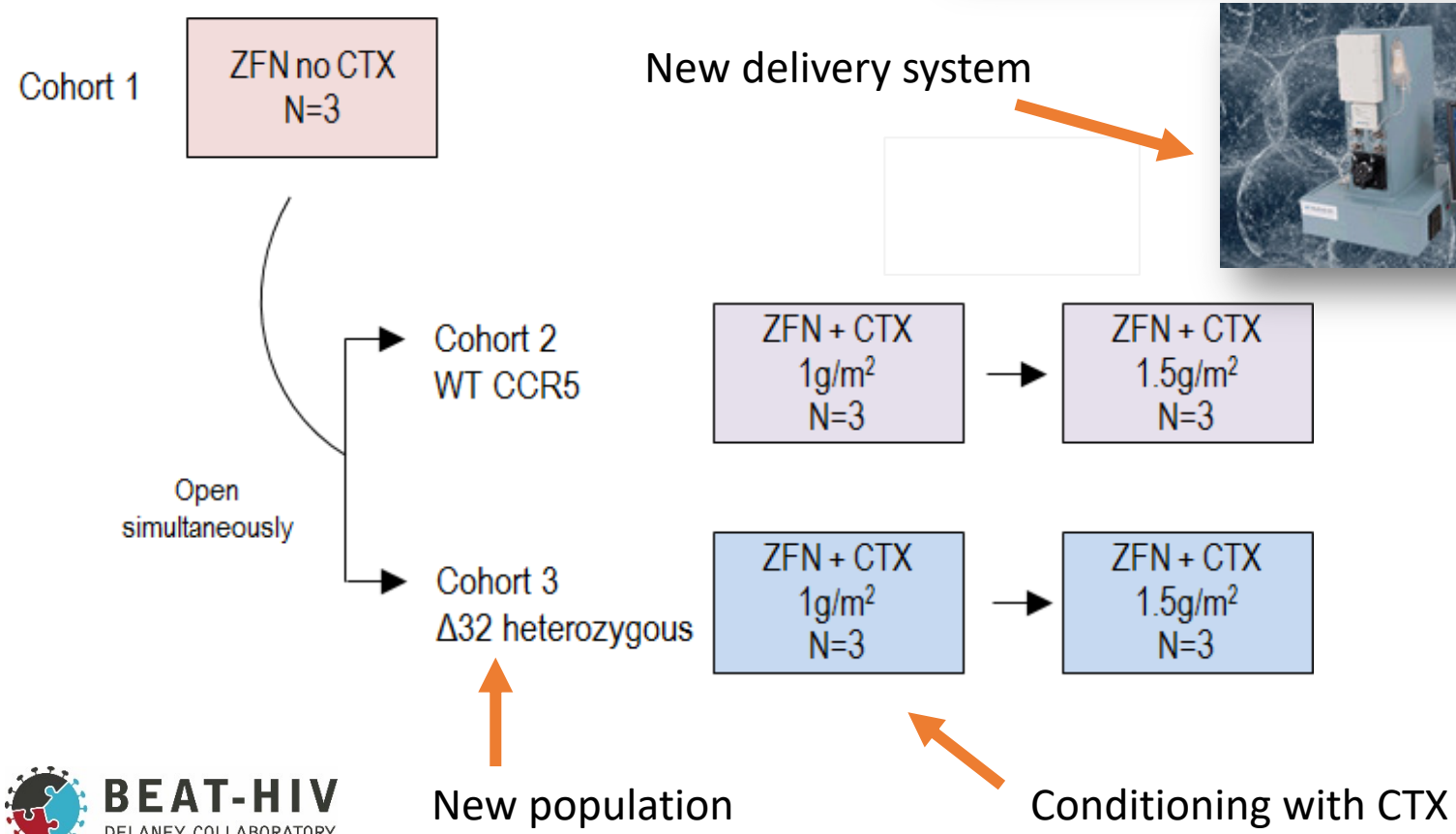
Can we do better, increase the engraftment of genetically modified cells by conditioning with CTX? Can you avoid AD5 vectors?

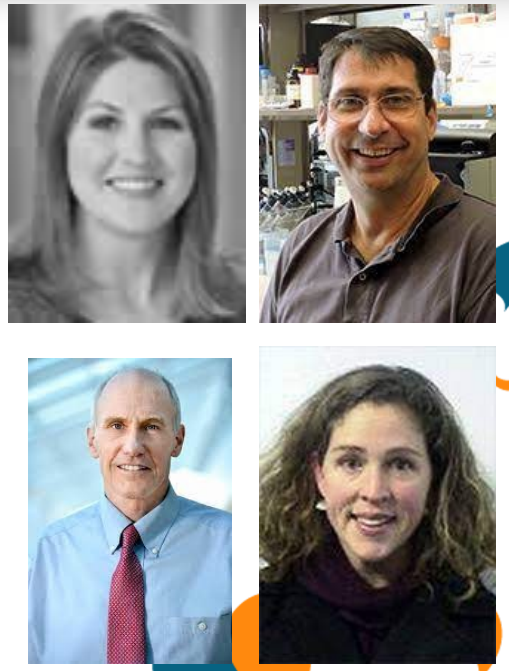
JCI The Journal of Clinical Investigation

CCR5-edited CD4⁺ T cells augment HIV-specific immunity to enable post-rebound control of HIV replication

Pablo Tebas, … , Carl H. June, James L. Riley

J Clin Invest. 2021;131(7):e144486. https://doi.org/10.1172/JCI144486.

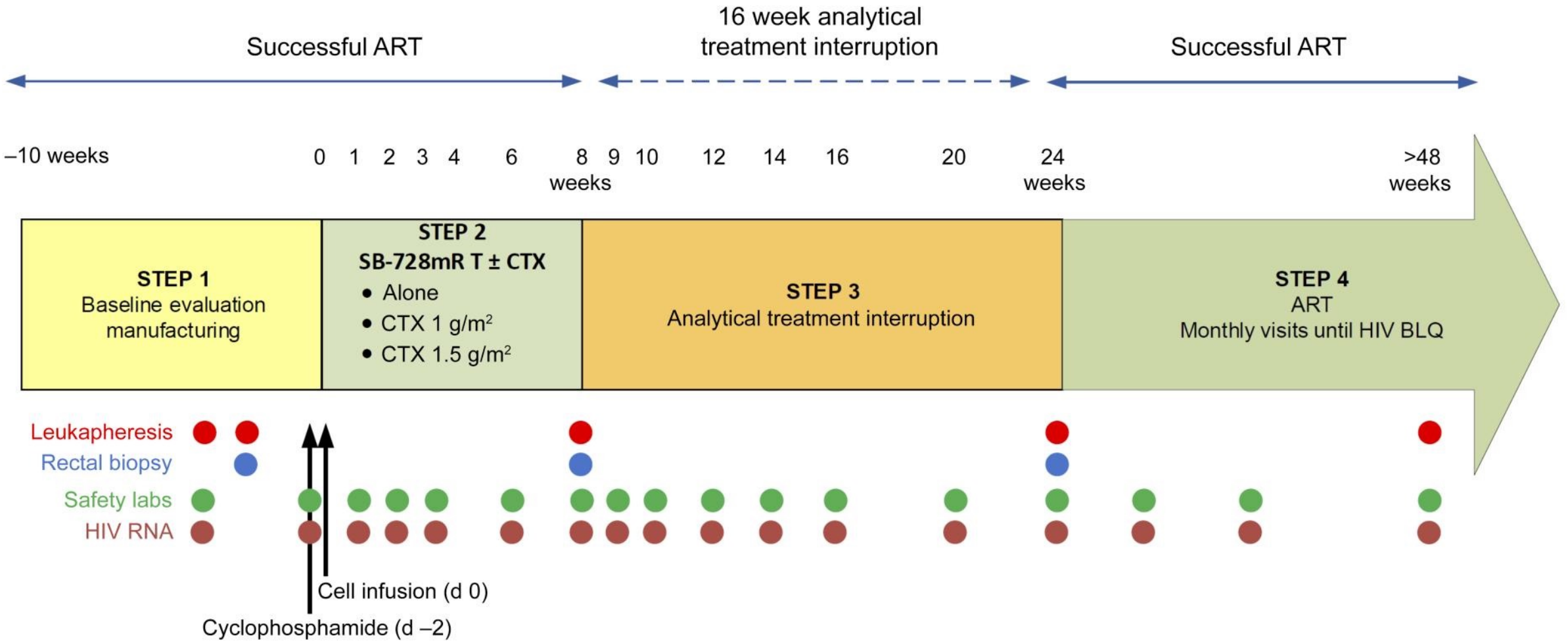




BEAT-HIV DELANEY COLLABORATORY

Schedule of Events

Towards an HIV Cure



BEAT-HIV DELANEY COLLABORATORY

J Clin

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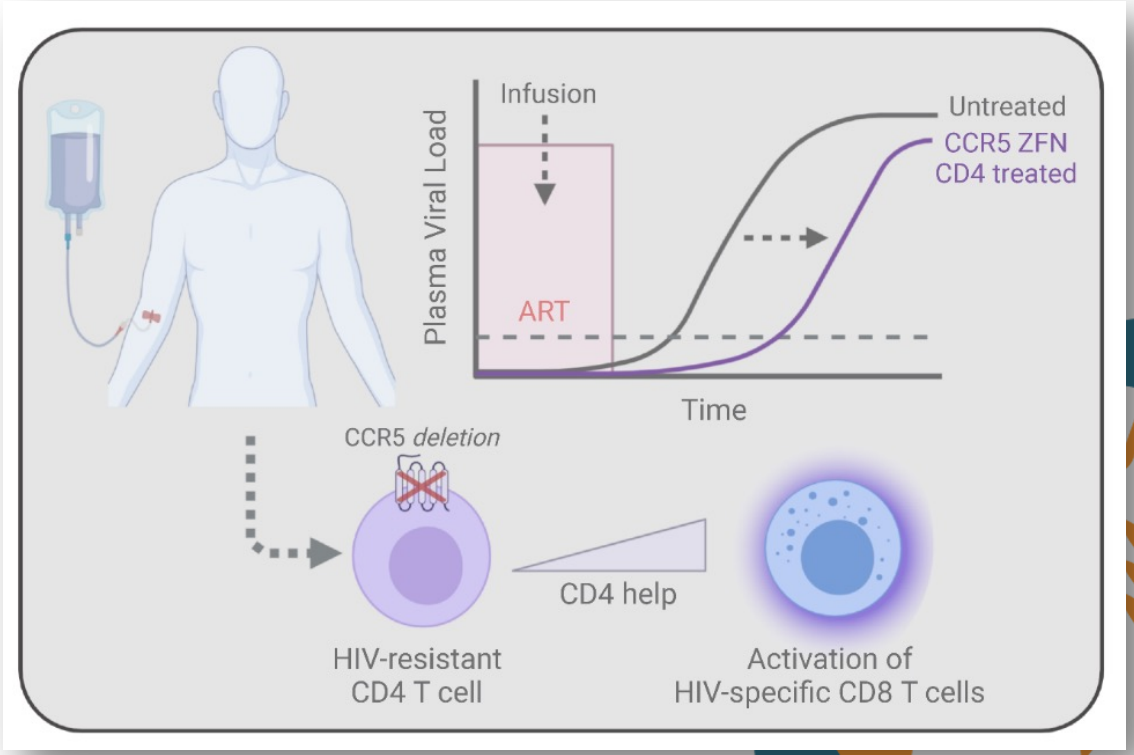
Table 1. Patient demographics and cell manufacturing

Cohort and patient no.	Age (yr)	Race or ethnicity	Sex	Duration of HIV infection (yr)	Baseline $CD4^+$ T cell count per mm^3	Baseline $CD4^+/CD8^+$ T cell ratio	SB-728mR-T dose	SB-728mR-T $CD3^+CD45^+$ (%)	SB-728mR-T cell modification (%)	ART regimen prior to ATI	Class
Cohort 1											
101	32	White	M	5.3	563	1.25	1.00×10^{10}	95.2	14.32	TDF/FTC/EFV	NNRTI
102	49	White	M	12.8	870	0.93	1.00×10^{10}	99.0	24.12	TDF/FTC/ATV/r	PI
103	41	Black	F	13.8	1081	1.62	1.00×10^{10}	98.6	28.63	TDF/FTC/DTG	INSTI
Cohort 2											
201	37	White	M	10.3	1179	1.14	1.00×10^{10}	98.2	26.81	TDF/FTC/ATV/r	PI
202	60	White	M	24.1	512	0.74	1.00×10^{10}	98.5	27.27	ABC/3TC/DTG	INSTI
203	54	Black	M	21.1	513	0.29	1.00×10^{10}	95.0	16.11	TDF/FTC/EVG/c	INSTI
204	49	Black	M	6.7	457	1.38	0.66×10^{10}	95.2	10.66	TDF/FTC/EVG/c	INSTI
205	45	Black	M	6.0	456	0.69	1.00×10^{10}	95.6	26.47	TDF/FTC/ATV/r	PI
206	43	Black, Hispanic	M	5.0	1421	1.55	1.00×10^{10}	99.2	21.51	ABC/3TC/DTG	INSTI
Cohort 3											
301	54	White	M	6.2	1535	3.27	1.00×10^{10}	95.0	33.87	TDF/FTC/RPV	NNRTI
302	50	White	M	7.5	456	1.62	1.00×10^{10}	98.6	23.04	TDF/FTC/EVG/c	INSTI
303	30	Black	M	1.7	763	1.28	1.00×10^{10}	96.6	24.20	TDF/FTC/RPV	NNRTI
304	19	Black	M	2.2	690	1.19	1.00×10^{10}	98.9	24.70	TDF/FTC/EVG/c	INSTI
305	39	Black	M	6.5	695	1.48	1.00×10^{10}	98.2	25.99	TDF/FTC/EVG/c	INSTI
Median	44			6.6	693	1.27	1.00×10^{10}	98.2	24.45		

M, male; F, female; TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; ATVr, atazanavir/ritonavir; DTG,dolutegravir; INSTI, integrase strand transfer inhibitor; ABC, abacavir; 3TC, lamivudine; EVGc, elvitegravir/cobicistat; RPV, rilpivirine.

The frequency of modification is similar using mRNA



Is the delay related to effects on the reservoir?

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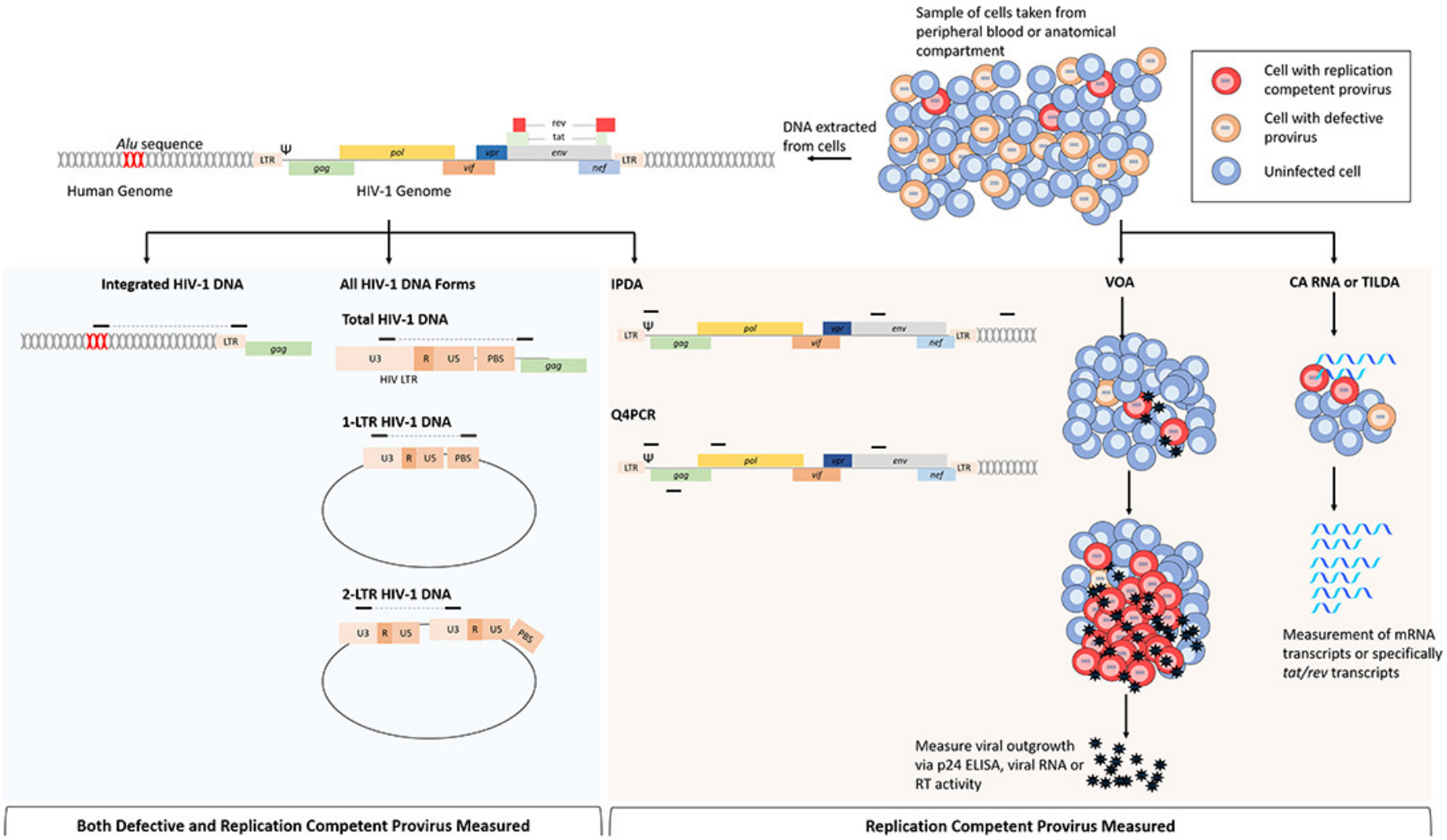
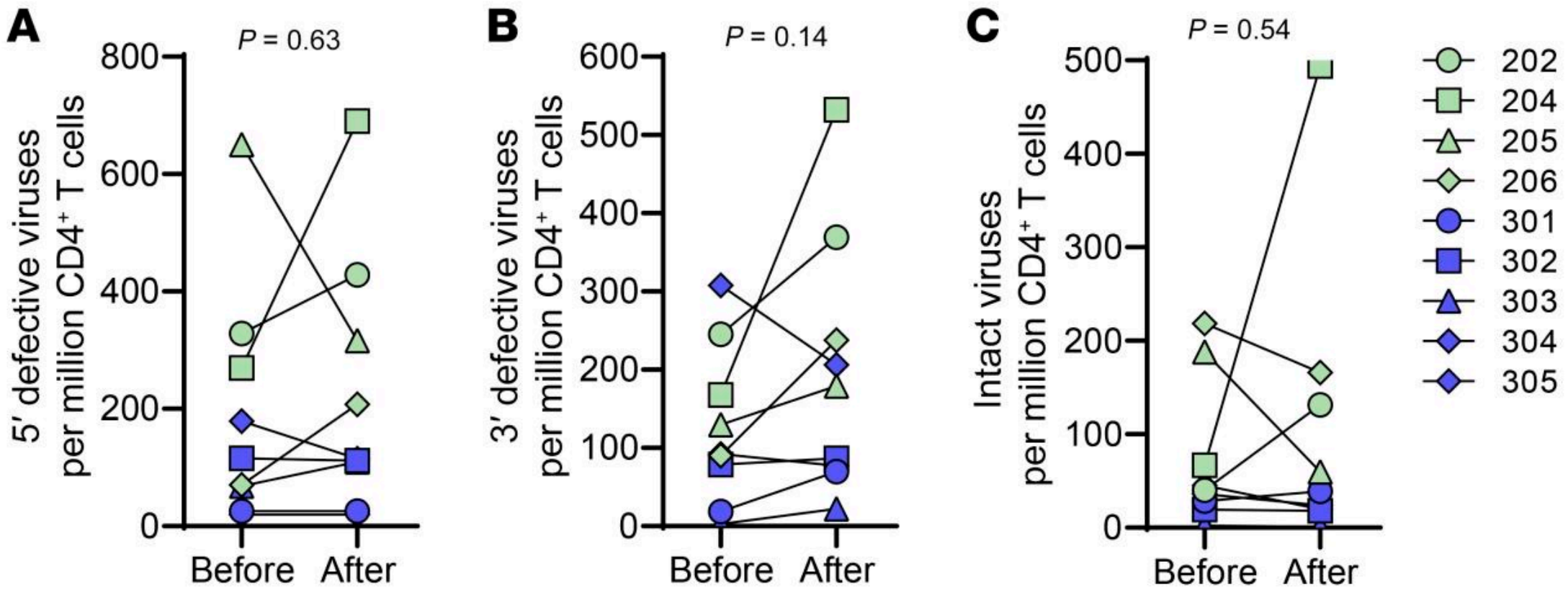


Effects on the HIV reservoir (IPDA, Accelavir)



If there are no effects on the reservoir, why there is a delay in rebound?

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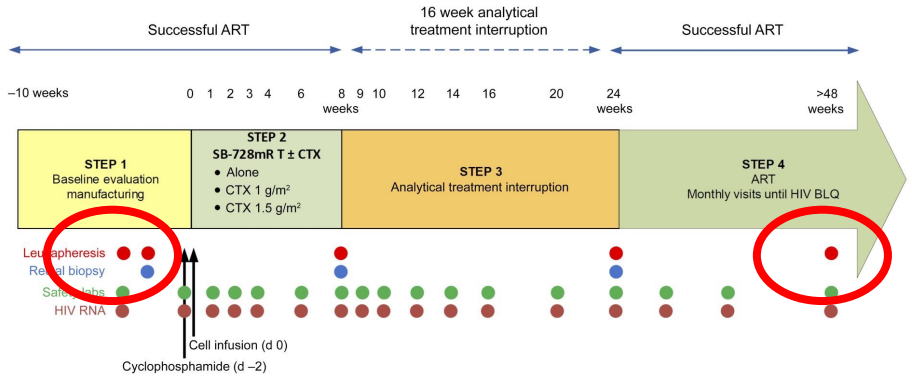
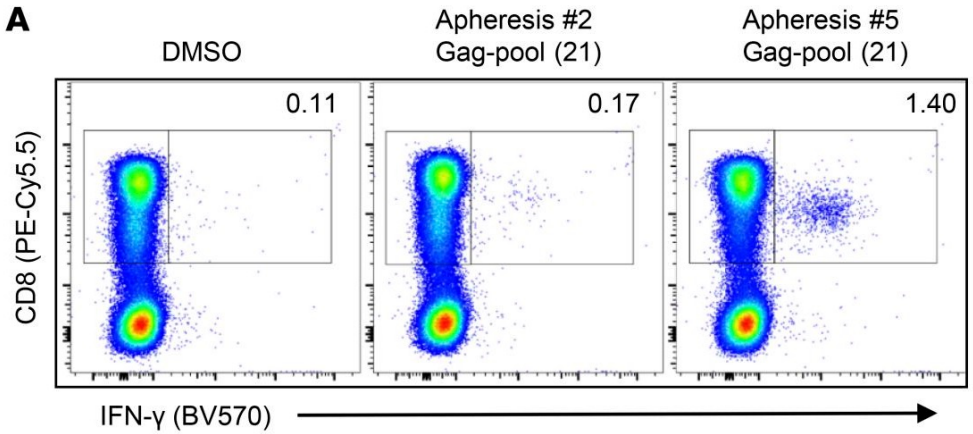
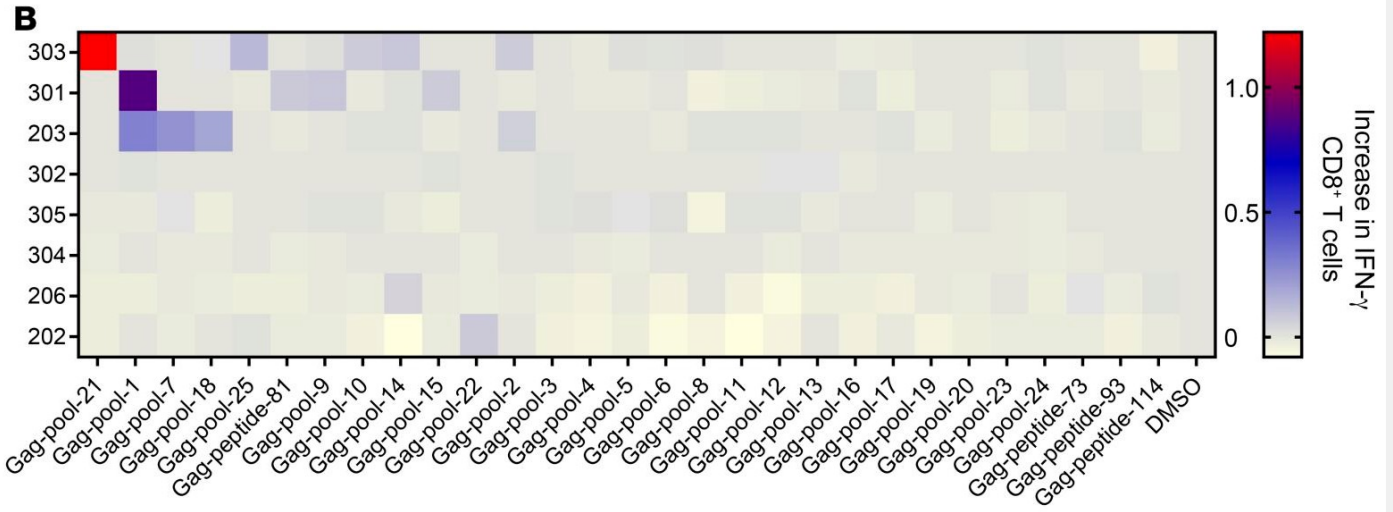
We looked at the HIV-specific CD8+ T cell gag responses before and after against multiple peptide pools







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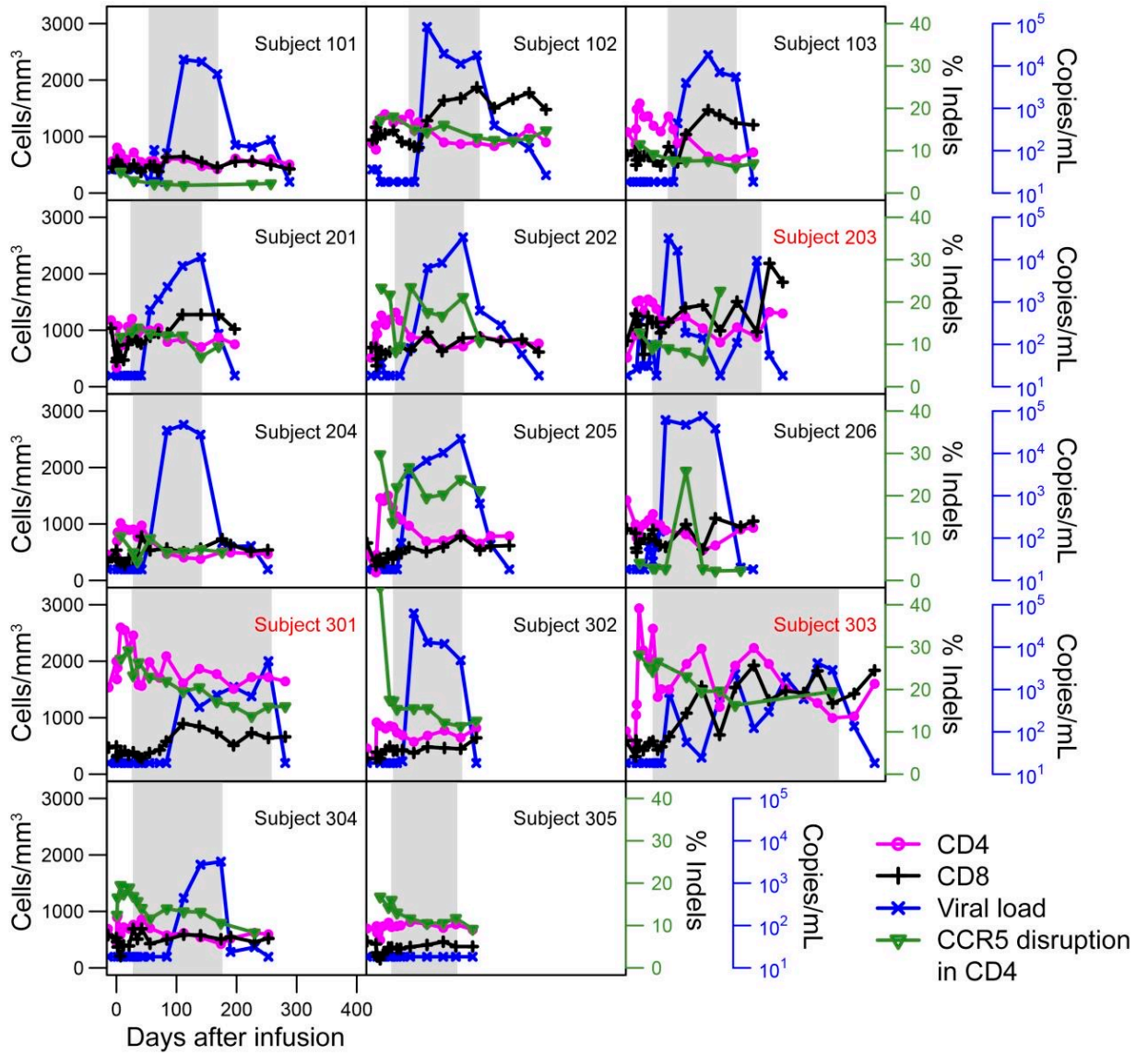
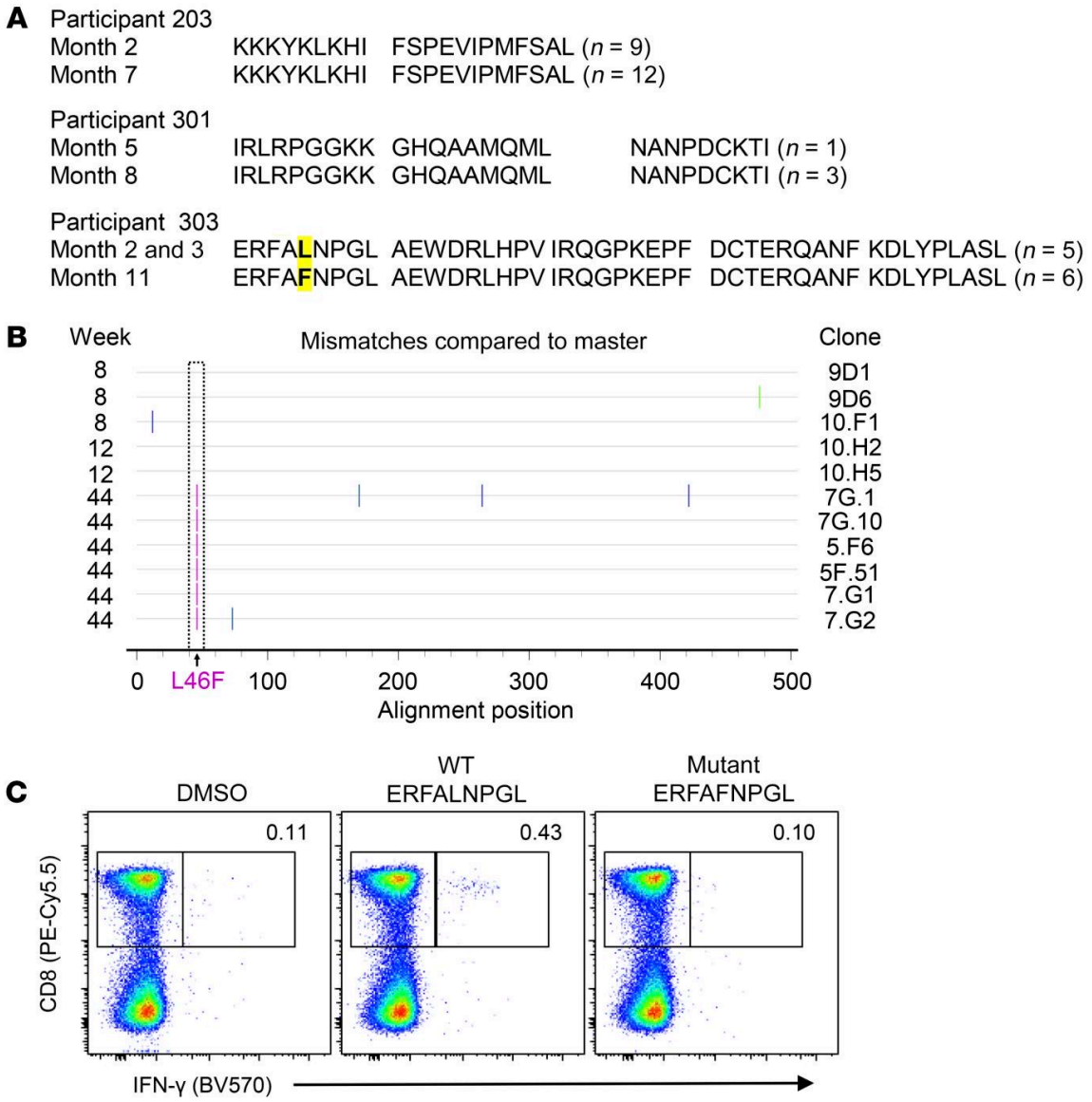
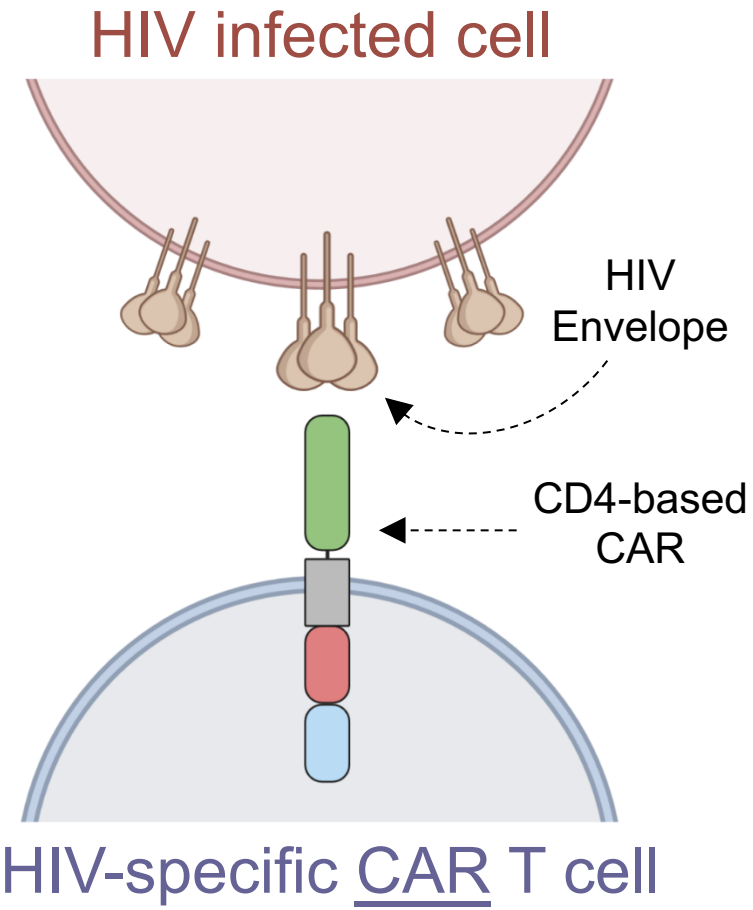
Lower viremia
Greater ATI duration



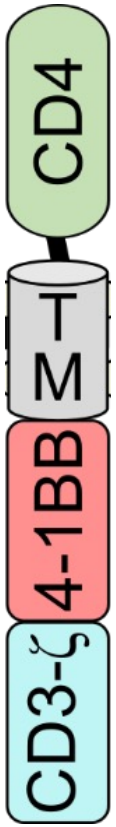
Are the modified CD8 putting pressure on the virus?



Engineering T cells to redirect specificity from peptide/MHC to HIV Envelope



Chimeric **A**ntigen **R**eceptor



HIV entry receptor

Mitigate the possibility of HIV escape

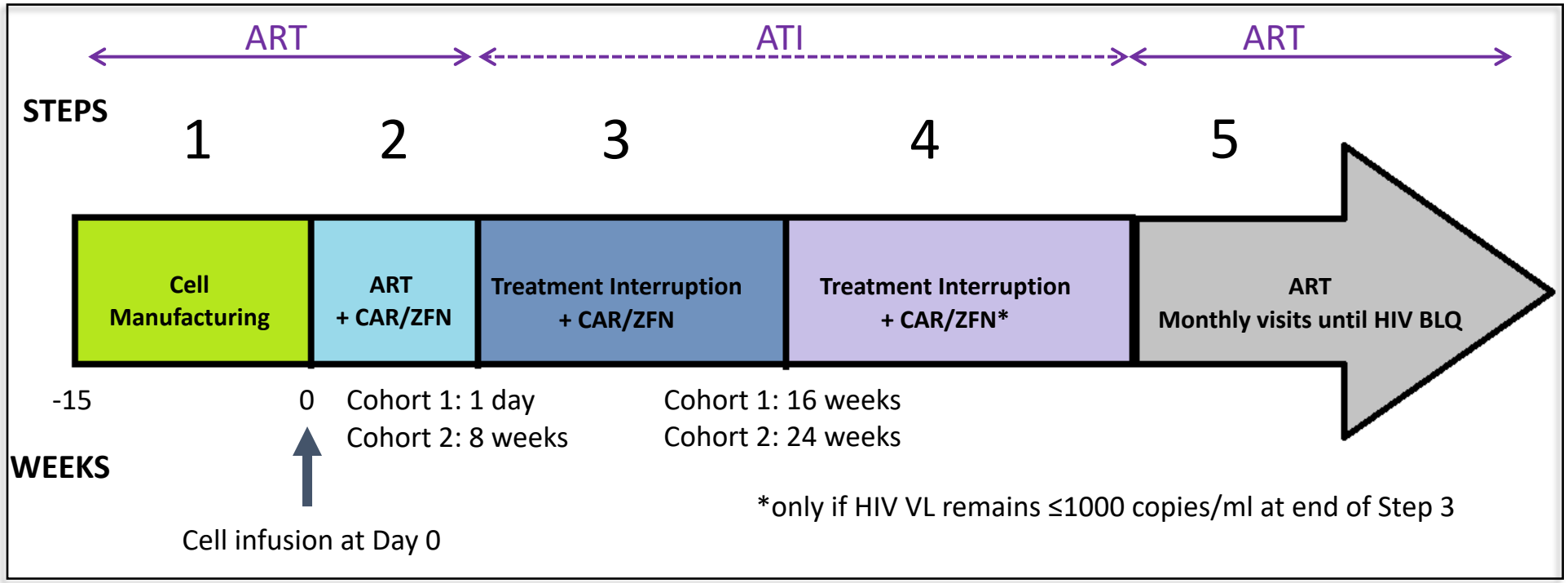
Avoid MHC downregulation

Costimulation (4-1BB, CD28)

TCR signaling component

Rachel Leibman

A Pilot Study of T Cells Genetically Modified by CCR5-specific ZFNs and CD4 Chimeric Antigen Receptor in HIV-infected Subjects (NCT03617198)



1: To what extent does ongoing HIV replication contribute to the maintenance of the HIV reservoir?

2: Can engineered T cells restore functionality to endogenous HIV-specific T cell populations?

3. Can engineered T cells provide durable control of HIV replication?

4. When is the best time to do the ATI?

Cohort 1- engraftment (step 2) of 1 day before ATI
Cohort 2- engraftment (step 2) 8 weeks before ATI

Results

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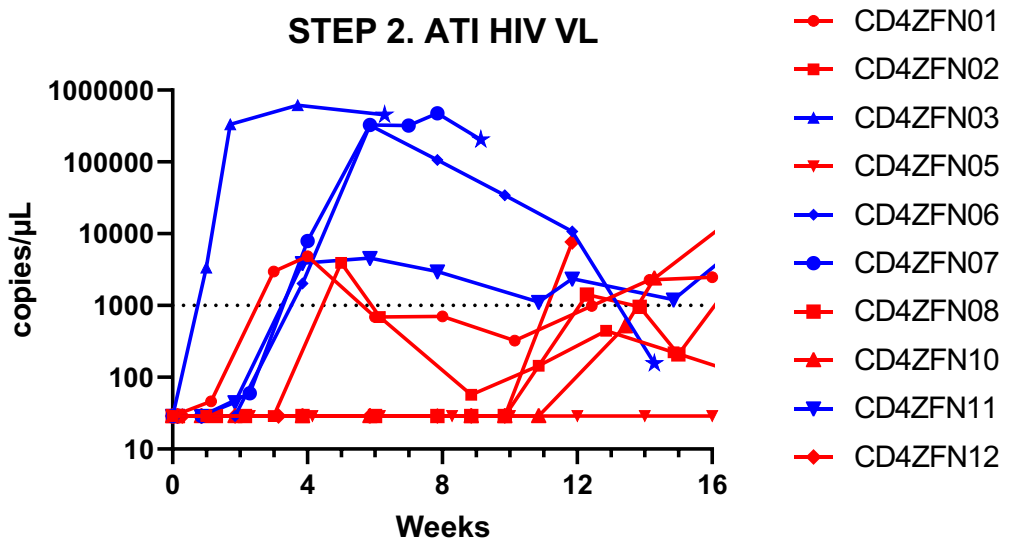

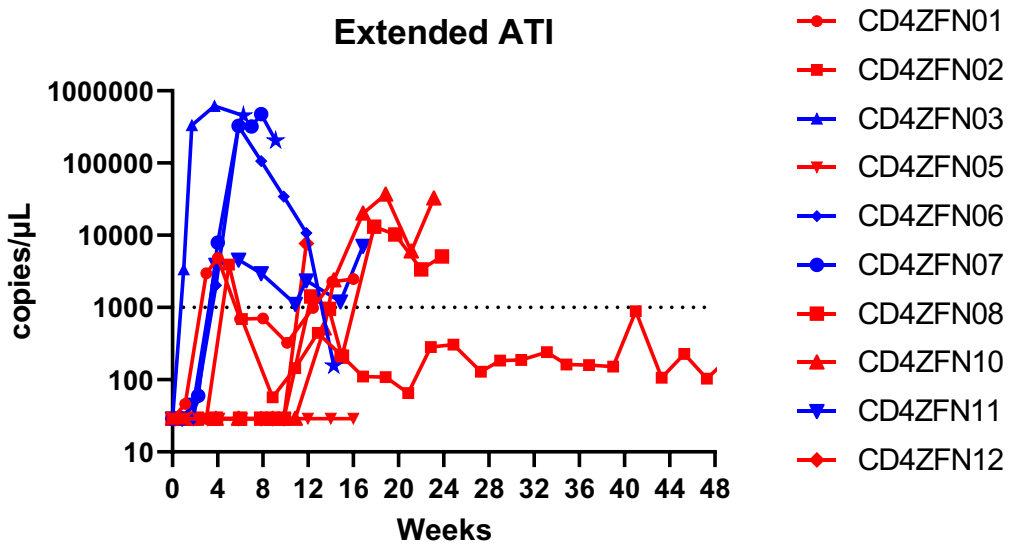

In **blue** participants that started ATI 1 day after the infusion
In **red** participants that waited for 8 weeks

Results

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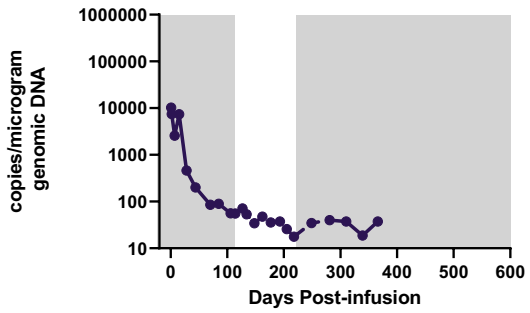
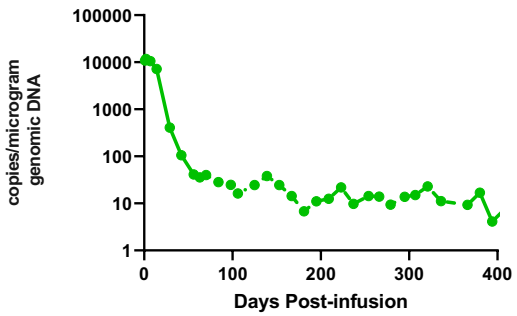
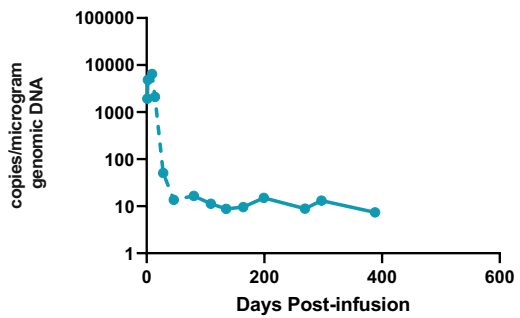
CAR Persistence: CD4ZFN-01



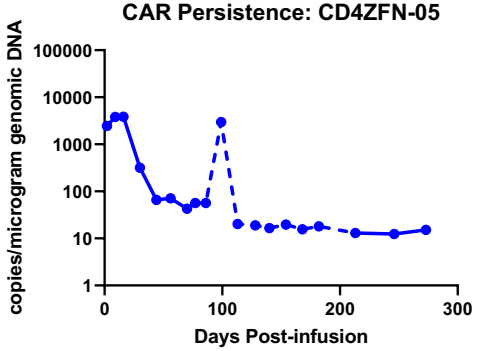
CAR Persistence: CD4ZFN-02



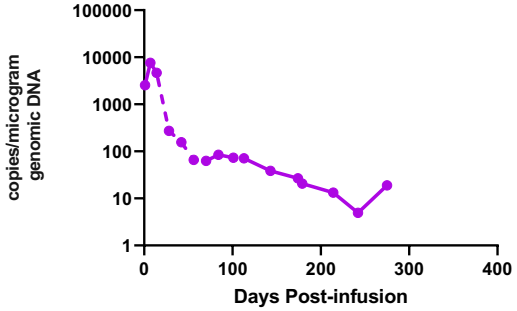
CAR Persistence: CD4ZFN-03



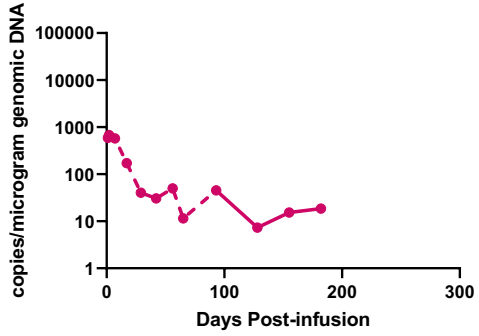
CAR Persistence: CD4ZFN-05



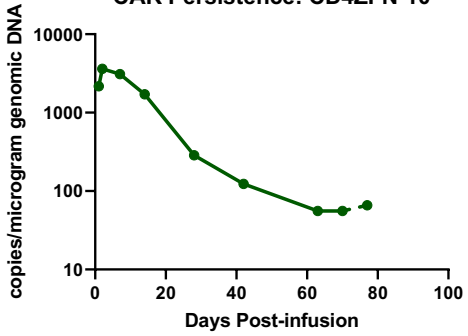
CAR Persistence: CD4ZFN-06



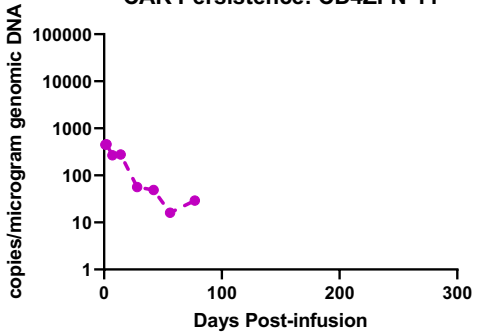
CAR Persistence:CD4ZFN-07



CAR Persistence: CD4ZFN-10



CAR Persistence: CD4ZFN-11



Participant 205, 301 and 2-third time is a charm?

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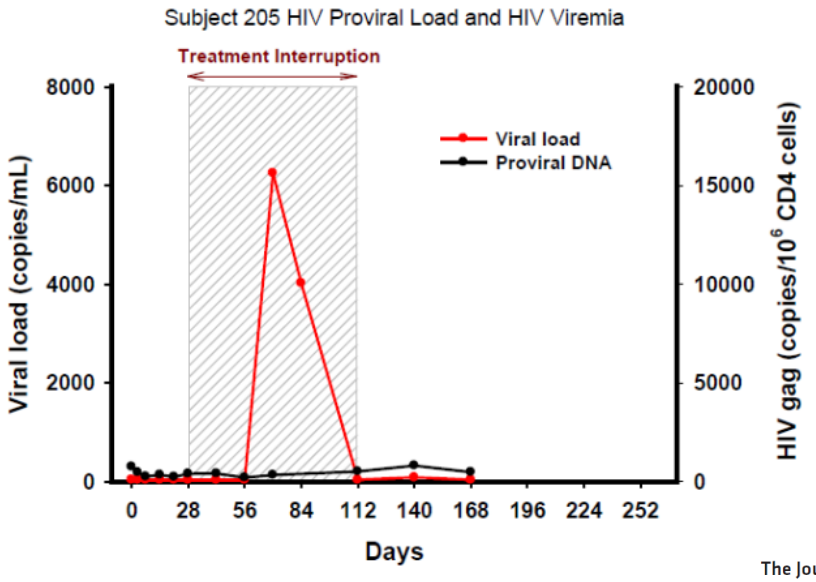
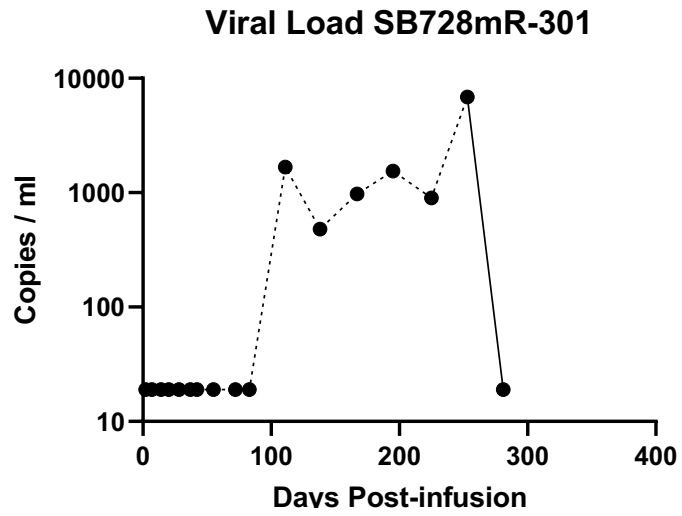
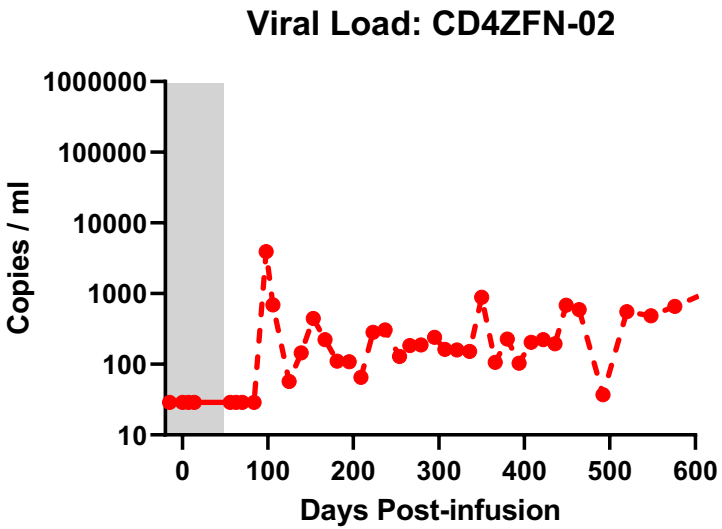
Study ID#	Sex	Race	Age at Consent	Historic VL copies/ml)	Historical VL Date	Years HIV infection (at the time of enrollment)	Screening CD4 abs (cells/uL)	Viral Load Set Point
CD4CAR-ZFN-02	M	Caucasian	58	165,810	08/24/2009	10	1785	165,810







The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

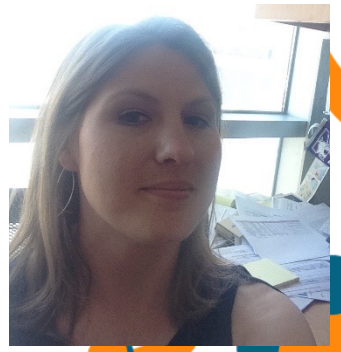
Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gar S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.[Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph. Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

The Journal of Clinical Investigation CLINICAL

CCR5-edited CD4+ T cells augment HIV-specific immunity to enable post-rebound control of HIV replication

Pablo Tebas,[1] Julie K. Jadlowsky,[2] Pamela A. Shaw,[3] Lifeng Tian,[4] Erin Esparza,[4] Andrea L. Brennan,[4] Sukyung Kim,[1] Soe Yu Naing,[1] Max W. Richardson,[2] Ashley N. Vogel,[4] Colby R. Maldini,[2] Hong Kong,[2] Xiaojun Liu,[4] Simon F. Lacey,[4] Anya M. Bauer,[1] Felicity Mampe,[1] Lee P. Richman,[1] Gary Lee,[5] Dale Ando,[5] Bruce L. Levine,[4] David L. Porter,[1] Yangbing Zhao,[4] Don L. Siegel,[4] Katharine J. Bar,[1] Carl H. June,[4] and James L. Riley[2]

Pablo Tebas



Julie Jadlowsky

Conclusions and questions

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Safety: So far so good

Persistence: this is a big problem in the absence of antigen

How can we expand the CAR T cells?

Trafficking

Protection. A CD4 CAR makes the cell susceptible to HIV. Best strategy for protection

Best methods for genome editing

Best CAR signaling

Improving CAR persistence and effector function: Dual CARs

Future directions: ACTG proposal: Dual CAR plus vaccination

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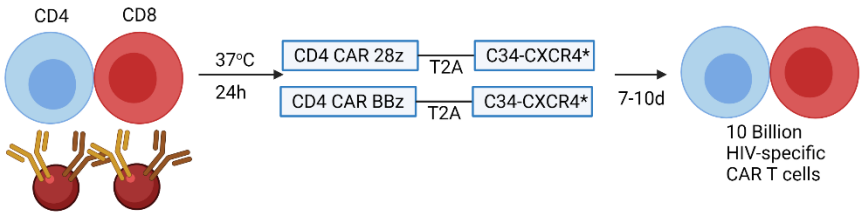

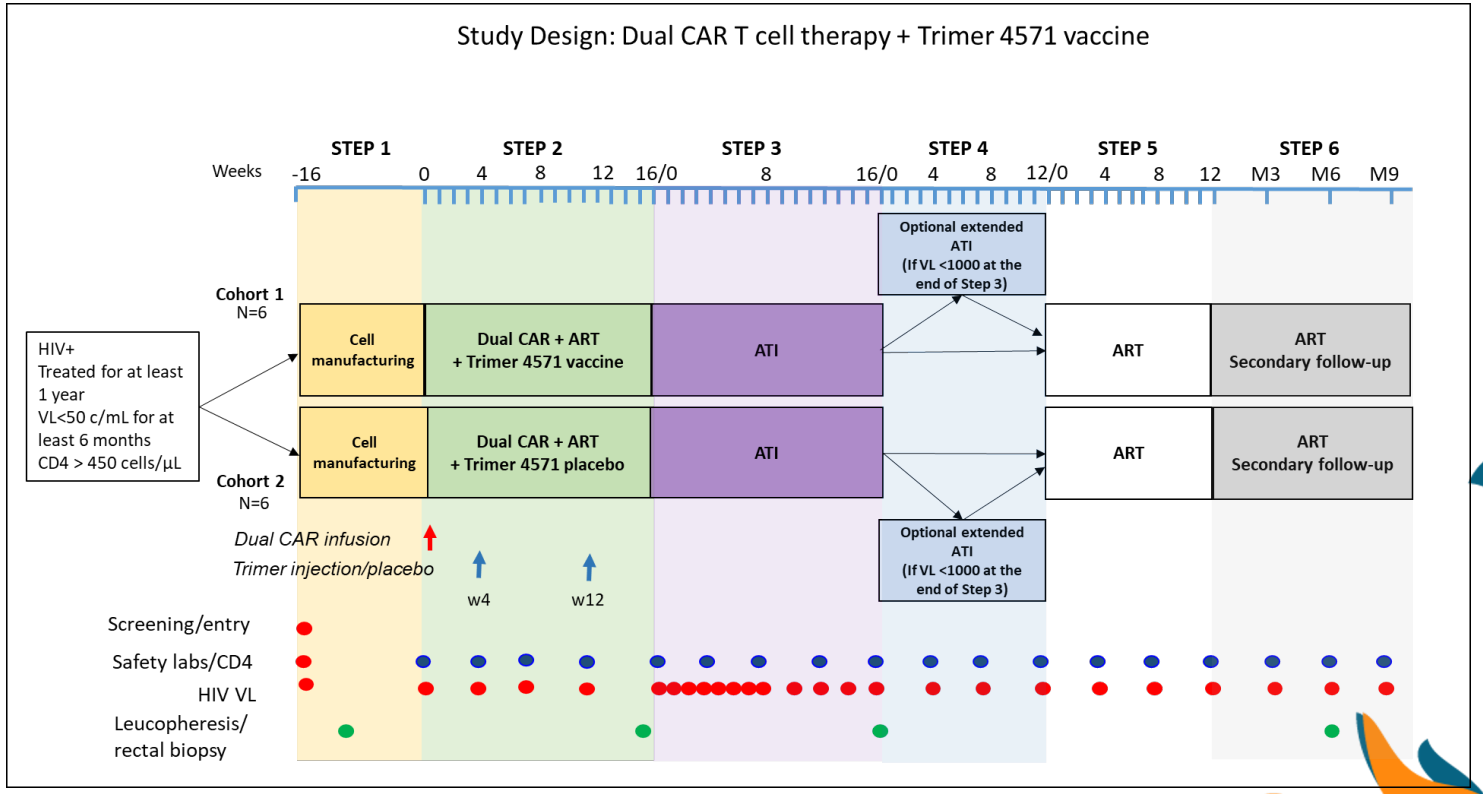

Acknowledgements

Penn ACTU

Larisa/Amber/Jenna/Mark/Su Kim

Joe Quinn/Eileen Donaghy/Jamie

Rob Roy MacGregor

Jacoby Medical Center

David Stein

Angelo Seda

U. Penn Abramson Inst.

Carl June

Bruce Levine

Jim Riley

Richard Carroll

Julie Jadlowsky

Liz Veloso

Wistar Institute

Luis Montaner

Penn CFAR

Clinical Core

Ian Frank

Immunology Core

John Wherry

Hong Kong

Kevin Gayout

Viral/Molecular core

Farida Shaheen

Katie Bar

Ron Collman

Rick Bushman

Jim Hoxie

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