Update on HIV Gene Therapy Clinical Trials

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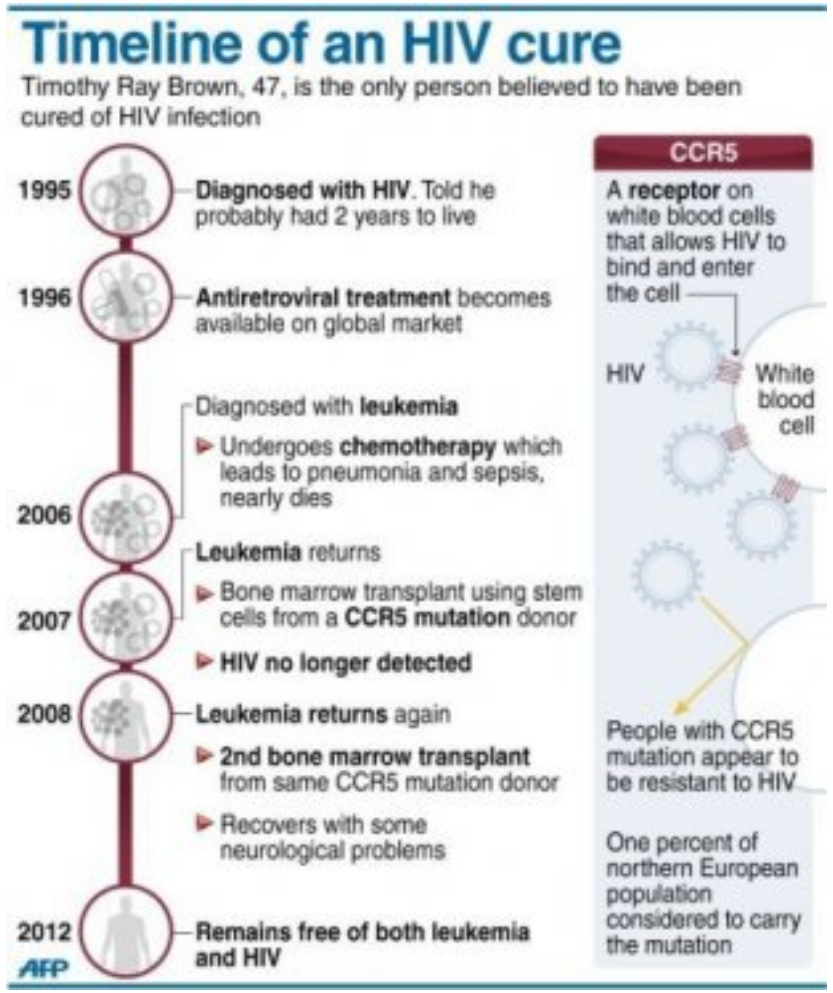
The University of Pennsylvania has determined that Dr. Riley has a FCOI as the data presented here has been licensed to a company (Tmunity) in which he has an equity interest. The University is actively managing this conflict.

Can HIV be Cured? At least 2-3 people says Yes!



Timothy Ray Brown, London patient and maybe Dusseldorf patient proves that HIV can be cured.

However

Challenging to repeat because every patient is different.

Several patients have been enrolled in similar protocols and cure rate is low

Very intensive and high risk protocol-hard to imagine how this could be employed on a wide

But….HIV can be cured!

Sheridan and Santini Alternet.org

What is Gene Therapy and why is it a promising approach for HIV Cure strategies?

- Through 40 years of HIV research, we have learned much about the virus.

- Through the study of HIV infected individuals, we have gained insight into why some individuals control HIV replication better than others.

- By directly altering a person's genome, we can attempt to convert someone who does not naturally control HIV replication to someone who does.

Active HIV gene therapy clinical trials

- A Study Evaluating the Safety of Cal-1 (LVsh5/C46) Drug Product in HIV-1 Infected Patient With High Risk Lymphoma
- Gene Therapy in Treating Patients With Human Immunodeficiency Virus-Related Lymphoma Receiving Stem Cell Transplant
- An Efficacy and Safety Study of shRNA-modified CD34+ Cells in HIV-infected Patients.
- VRC 603: A Phase I Dose-Escalation Study of the Safety of AAV8-VRC07 (VRC-HIVAAV070-00-GT) Recombinant AAV Vector Expressing VRC07 HIV-1 Neutralizing Antibody in Antiretroviral -Treated, HIV-1 Infected Adults With Controlled Viremia.
- CD4 CAR+ ZFN-modified T Cells in HIV Therapy
- CCR5-modified CD4+ T Cells for HIV Infection
- Safety of Transplantation of CRISPR CCR5 Modified CD34+ Cells in HIV-infected Subjects With Hematological Malignances

711 active cancer gene therapy clinical trials- NIH clinical trial.gov (https://clinicaltrials.gov/)

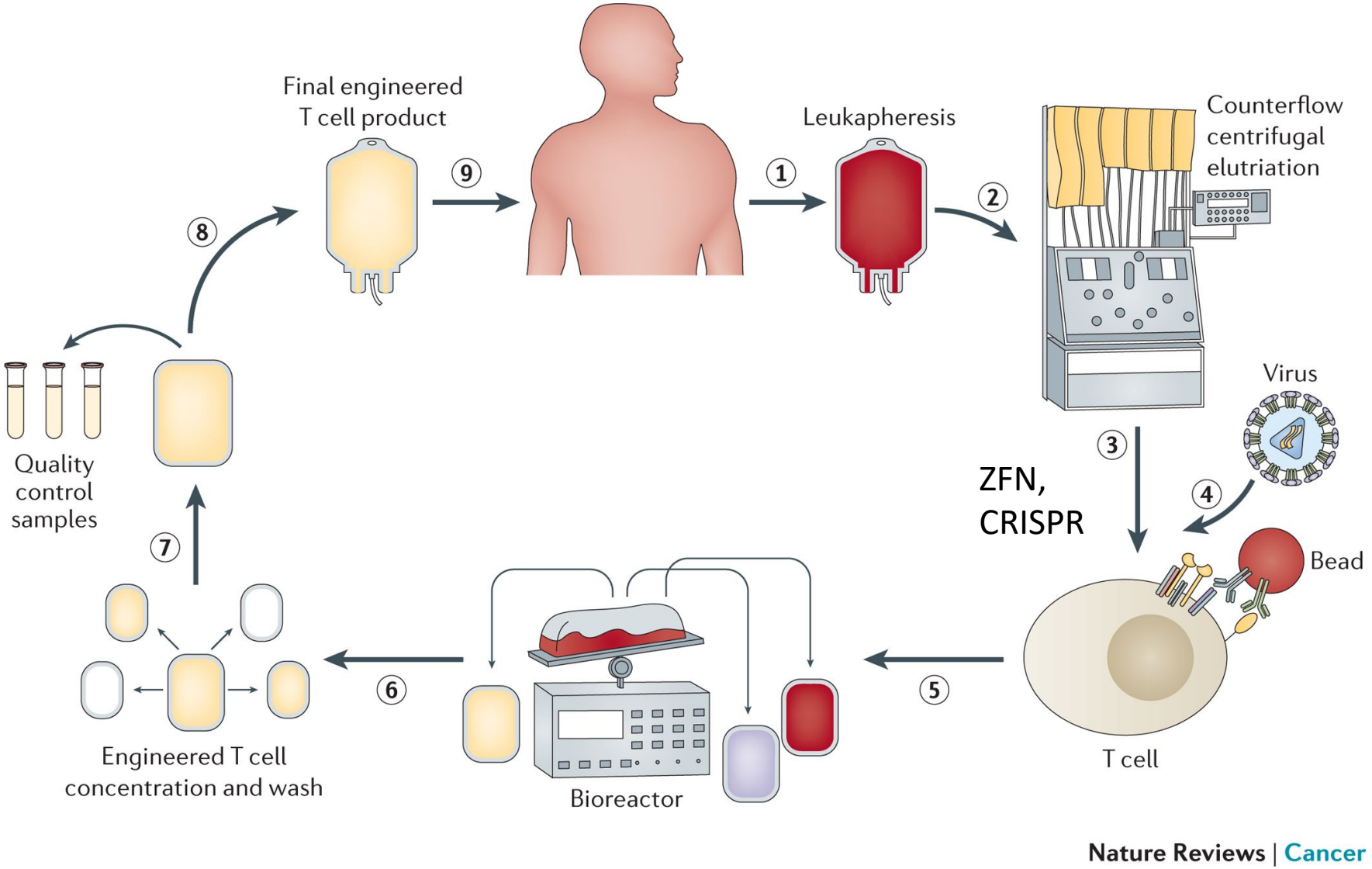
Rationale behind T cell based gene therapy

- T cells are a white blood cells whose job is to eliminate viruses and tumors.
- T cells are absolutely ingenious and are able to customize their activity based on the type of pathogen they are trying to elimininate.
- T cells are designed to be unique. The T cells you have to fight HIV are different from the ones that fight the flu (or coronavirus).
- HIV preferentially kills HIV-specific CD4 T cells. This causes a lot of problems
  - Poorly functioning HIV-specific CD8 T cells
  - CD4 T cells are really important to producting effective antibody responses

Rationale behind T cell based gene therapy (cont)

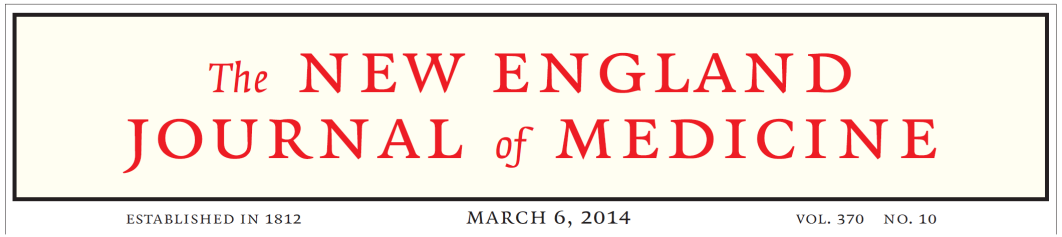
- Thus, the goal of T cell gene therapy approaches is two-fold
  - Can we protect T cells so that they resistant to HIV infection?
    - CCR5 targeting
    - Fusion inhibitors
  - Can we take T cells that were specific to something else and now make them specific for HIV?
    - Chimeric antigen receptors (CARs)

Manufacturing CAR T cells



Modified from Feswick, Levine and June

A Phase I Study of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 in HIV-Infected Patients



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., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., 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.

10B CCR5
ZFN treated
CD4 T cells
Are expanded

Of which only
5-10% CCR5
defective

Infused in a human
that has between 300B
and 600B CD4 T cells

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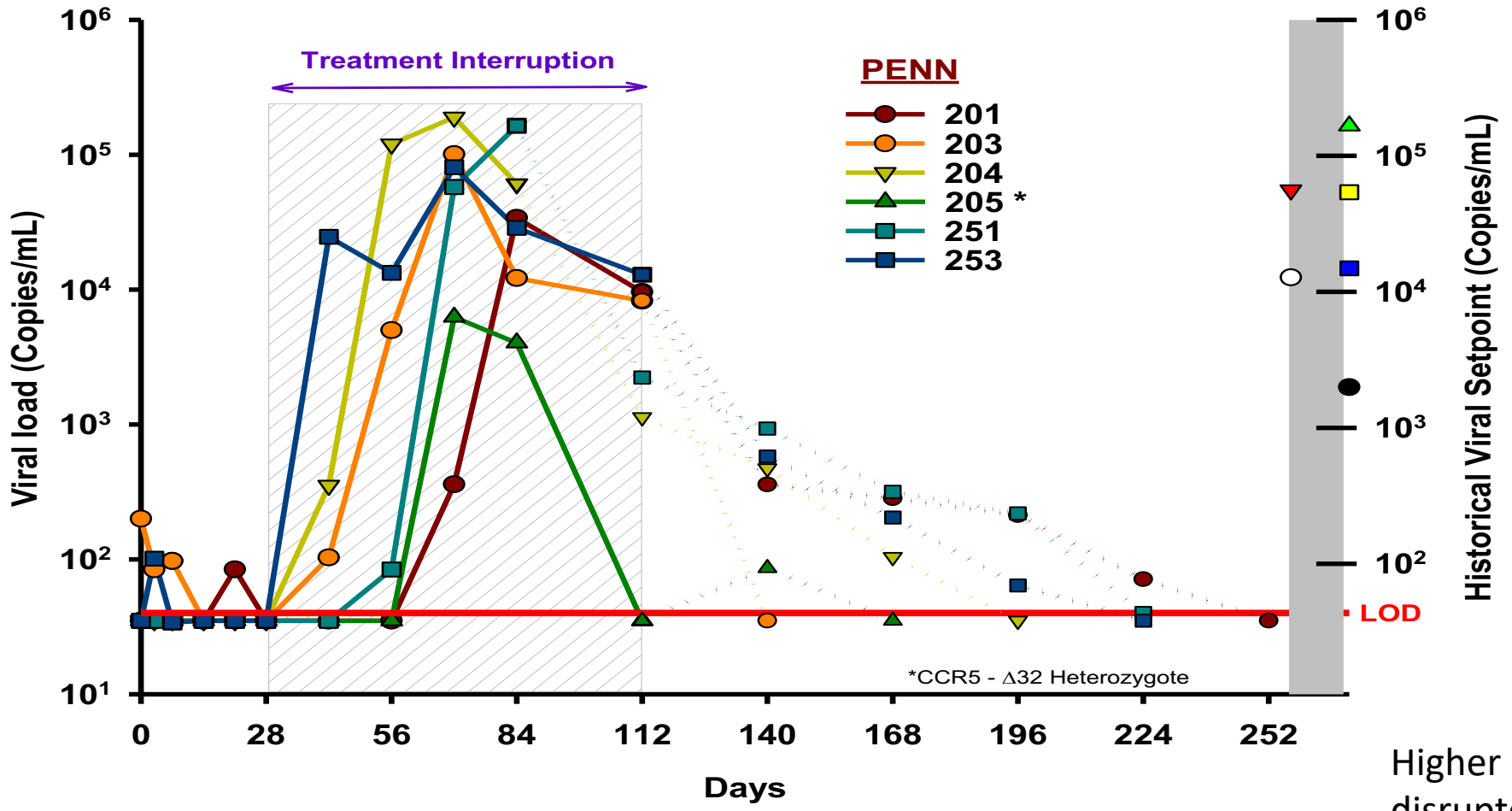
HIV-1 RNA Decreases During STI After Reaching Peak



Sangamo reported other Δ32 CCR5 heterozygotes (2) treated with CCR5 ZFNs demonstrated sustained control of HIV-1 in the absence of HAART. Control is some individuals was observed for more than 300 days

Higher CCR5 ZFN disrupted engraftment Correlated with time to Rebound and resetting a lower viral set point

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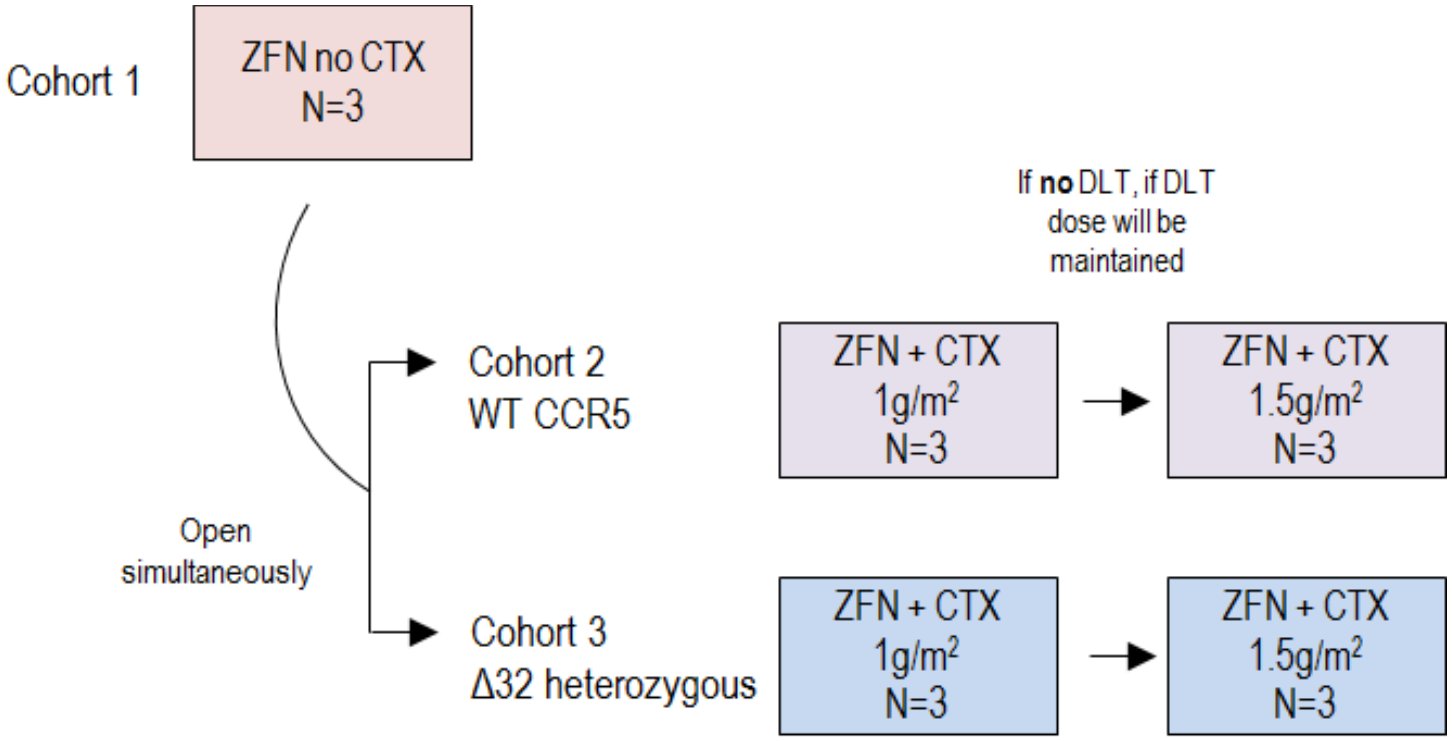
If delay in viral rebound correlates with the number of CCR5 disrupted alleles, then if we engraft more T cells, will we see improved control of viral rebound?



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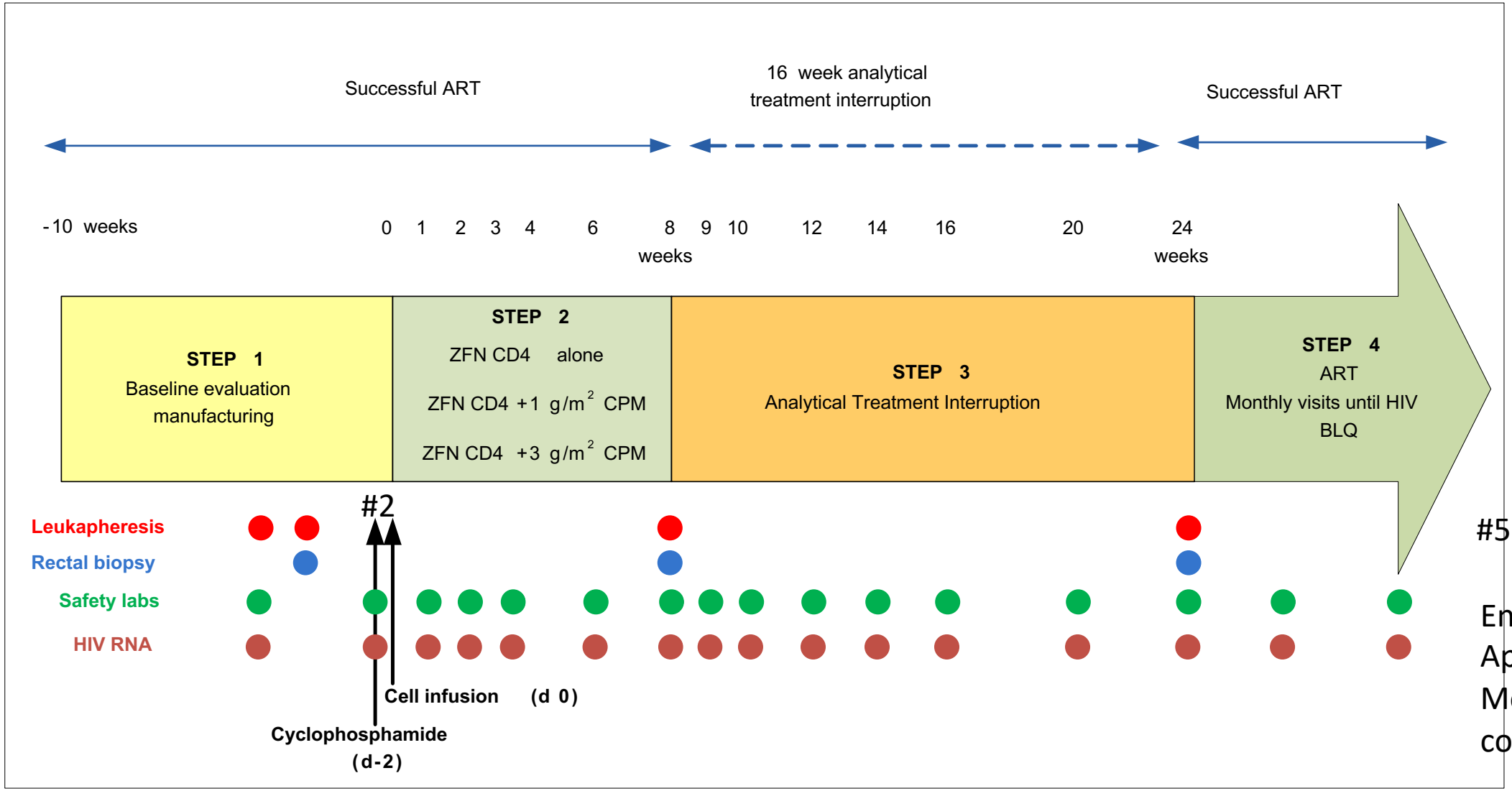
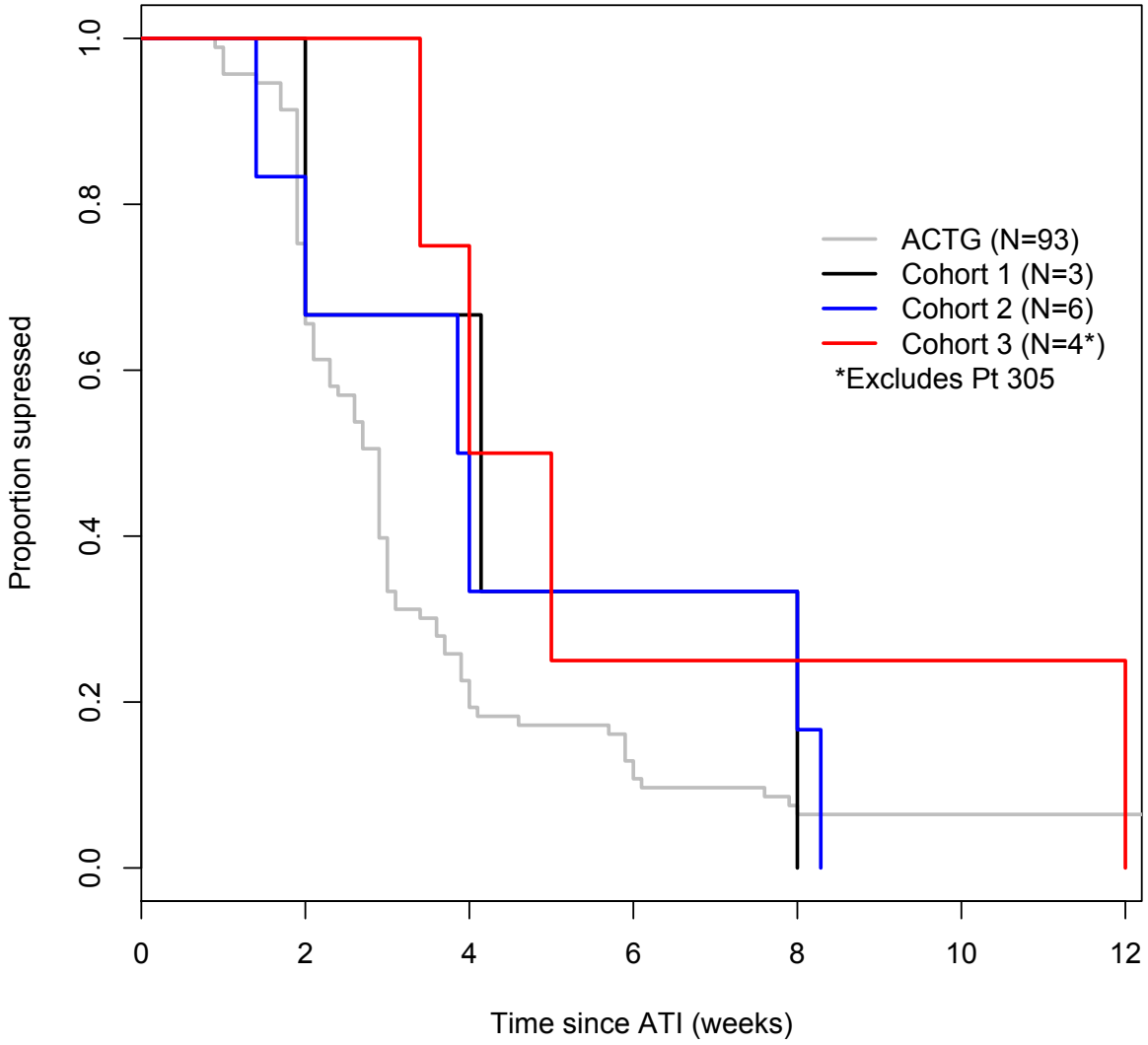
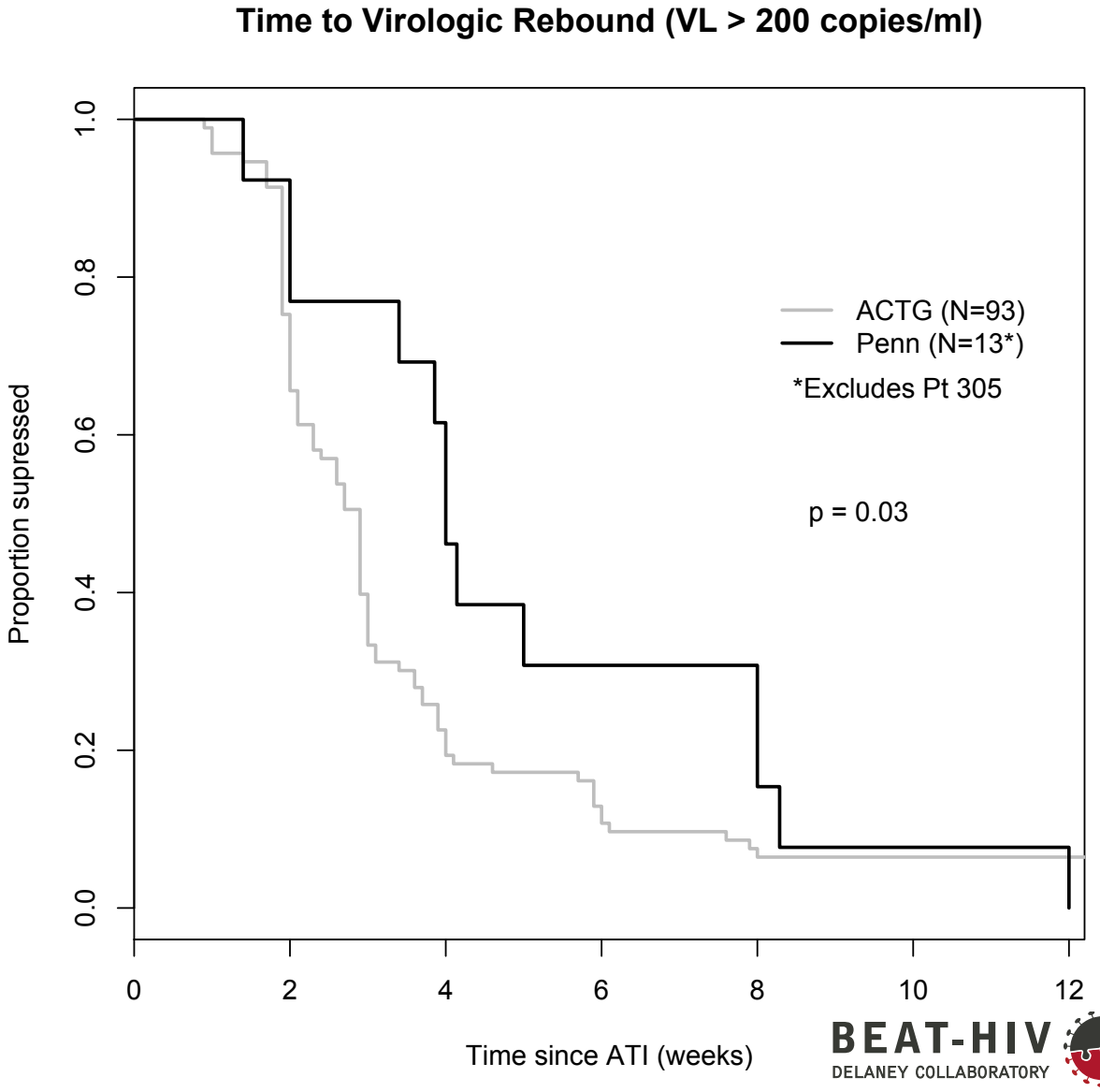
Schedule of Events



End of study Apheresis- 6 Months after ART control

Infusion of CCR5 ZFN Treated Cells Results in a Delay of Viral Rebound





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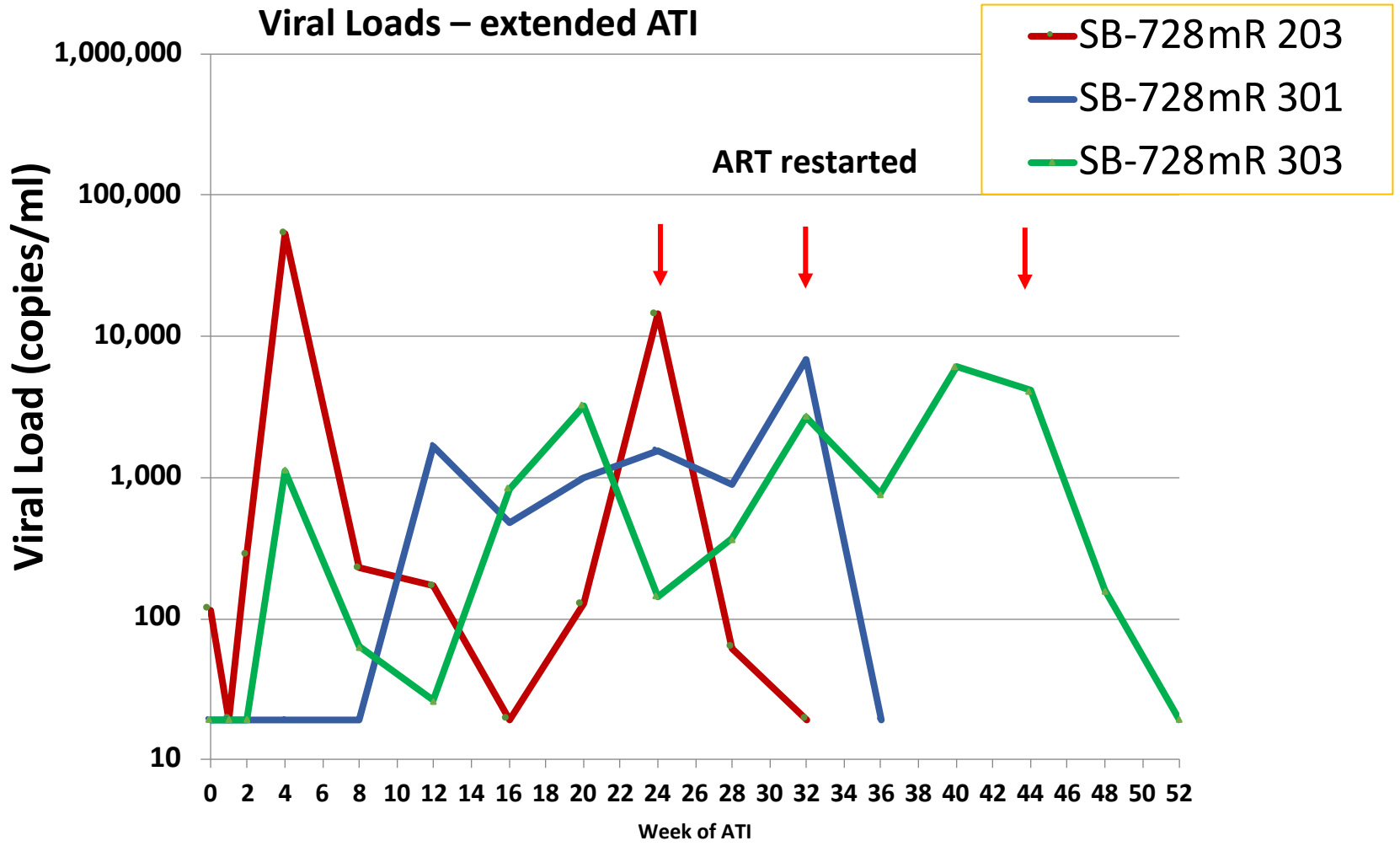
Three Individuals had sustained ATI with interesting viral load peaks and valleys



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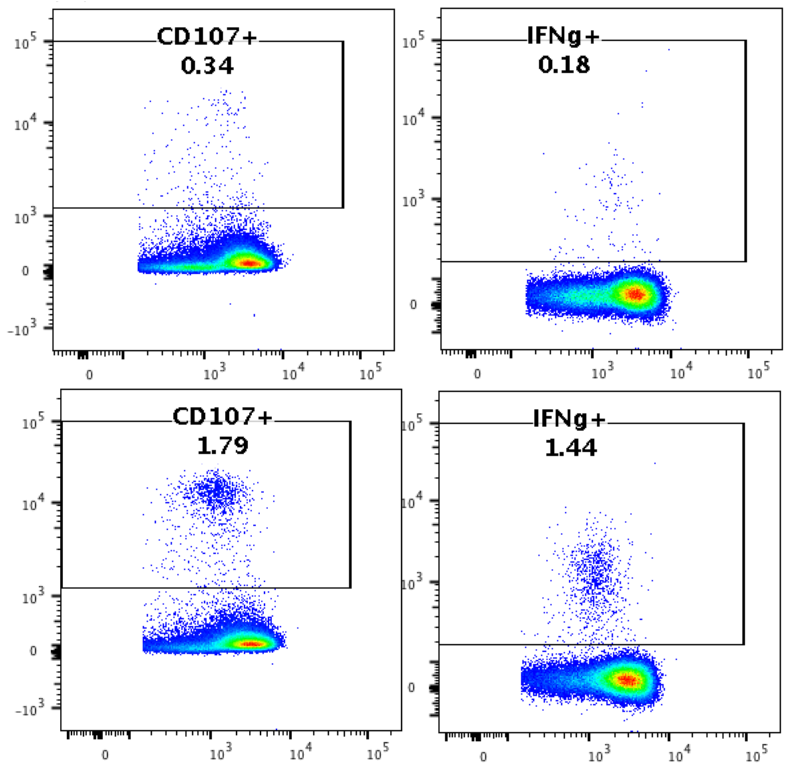
Improved HIV-specific immune after infusion of CCR5 ZFN treated CD4 T cells

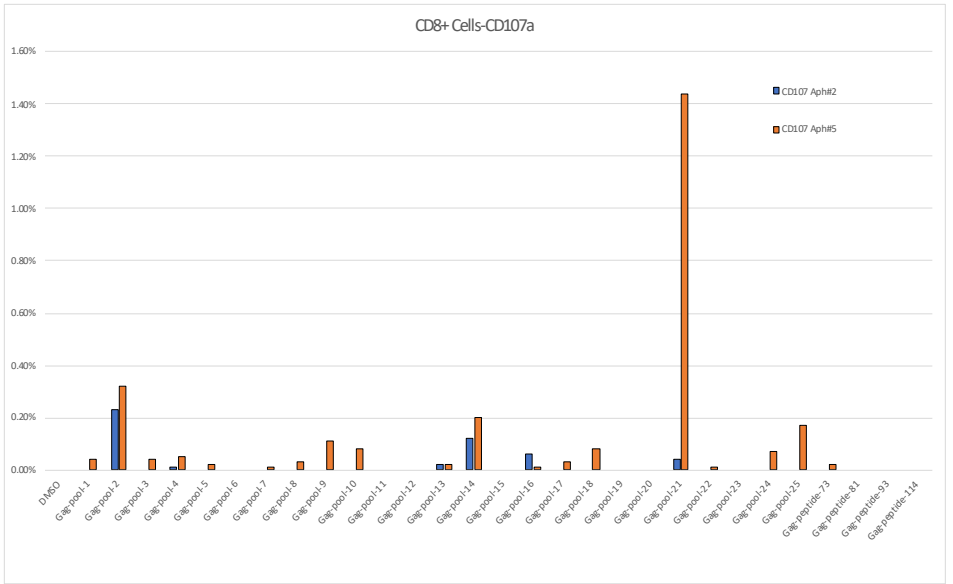
Before
After

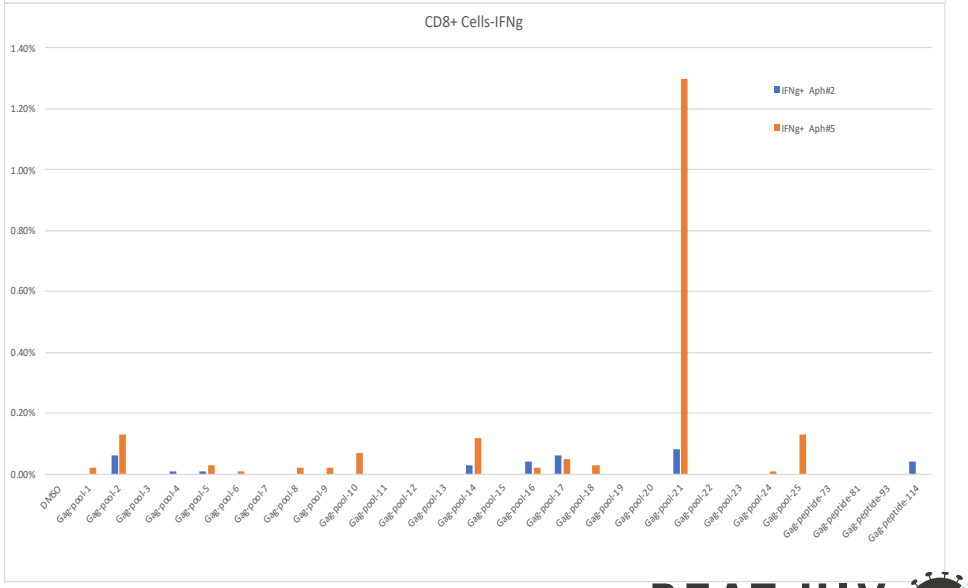


Pre-infusion

Post-infusion
~6 months after ART

Gag pool 21; #303





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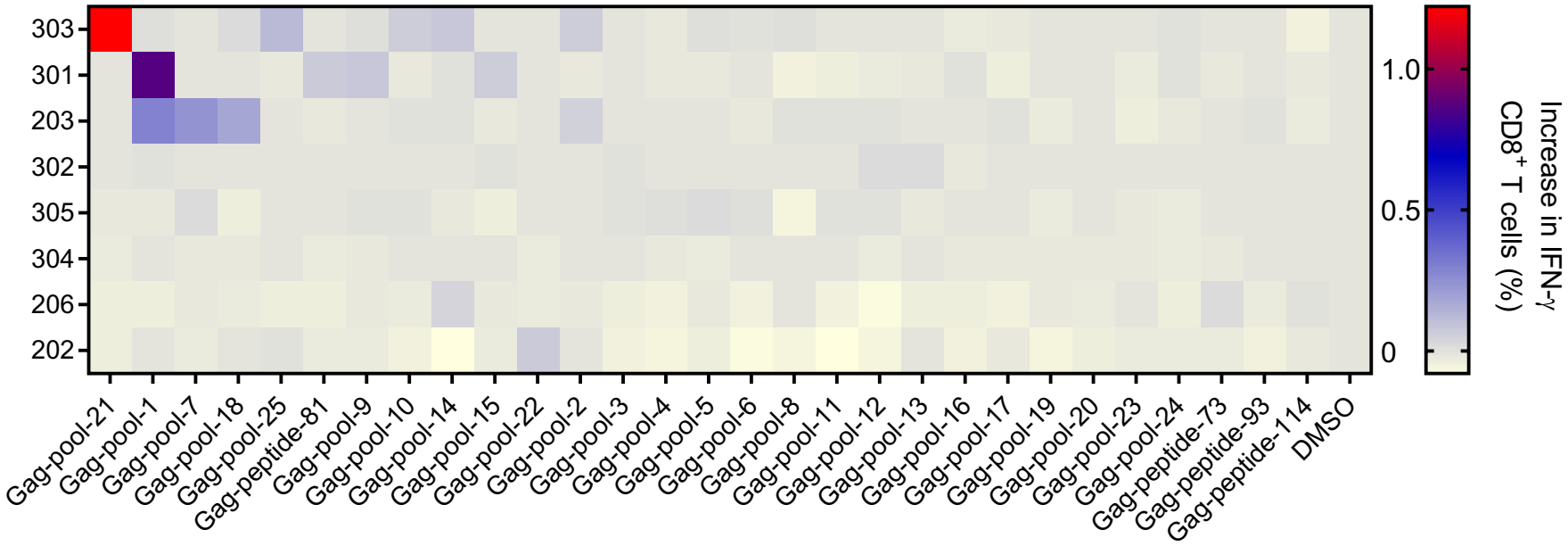
Three Individuals (203, 301, 303) had sustained improvement in CD8 HIV-specific immune response



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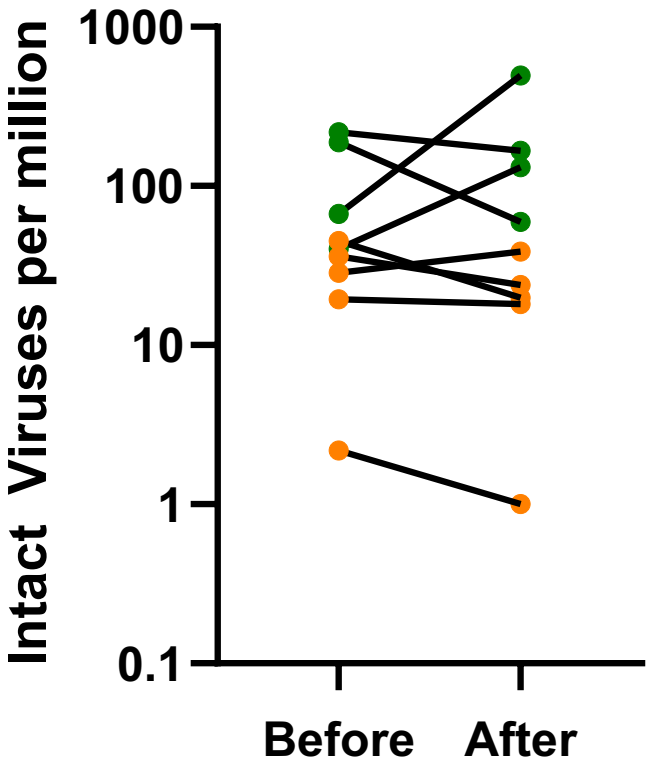
Number of replication competent HIV is unchanged by infusion of CCR5 ZFN treated T cells



p=0.54

IPDA assay run by Accelevir

Conclusions:

1. Manufacturing T cells with ZFN disrupted alleles is feasible and can be safely infused into HIV infected individuals.

2. Infusion of CCR5 ZFN T cells can delay viral rebound.

3. These cells stably engraft. Some individuals from our initial trial still maintain >1% of T cells with CCR5 ZFN disrupted alleles. CTX helped engraftment but the effect was modest.

4. We observed improved CD8 T cell responses after CD4 T cell infusions and this correlates with durable control of HIV replication during ATI

5. The HIV reservoir was unaffected by these cell infusions

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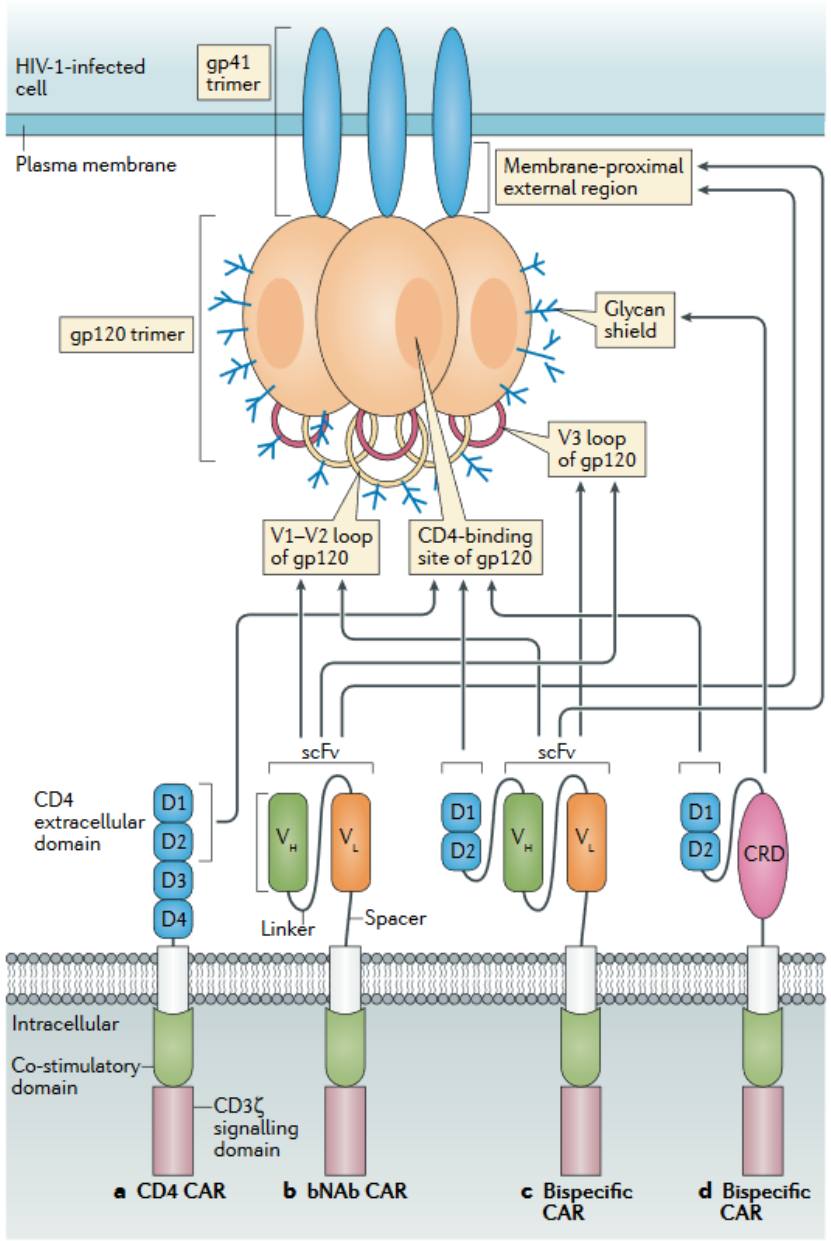
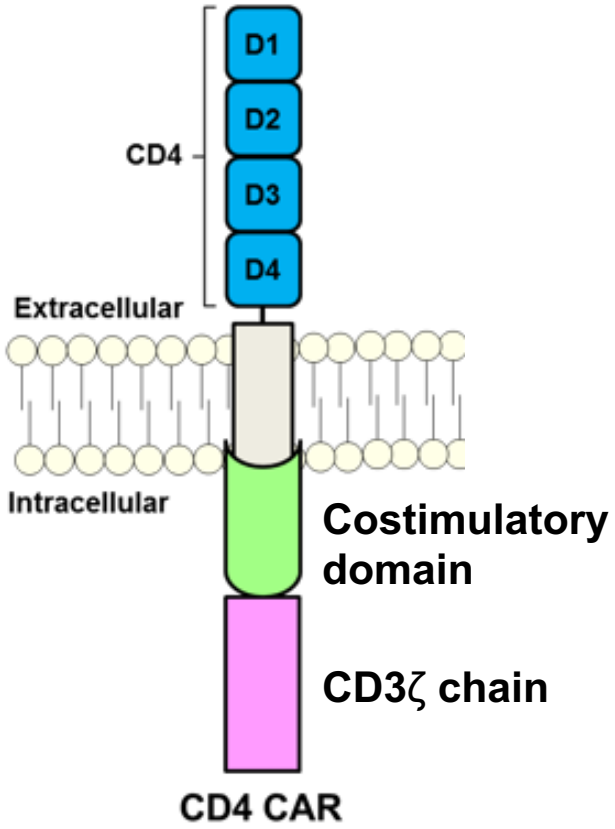
CD4-based chimeric antigen receptor confers HIV Envelope specificity





- Avoid MHC restriction & downregulation
- Unlikely that HIV will adapt
- Safety profile
- Mediates HIV entry

Maldini *et al* 2018 NRI

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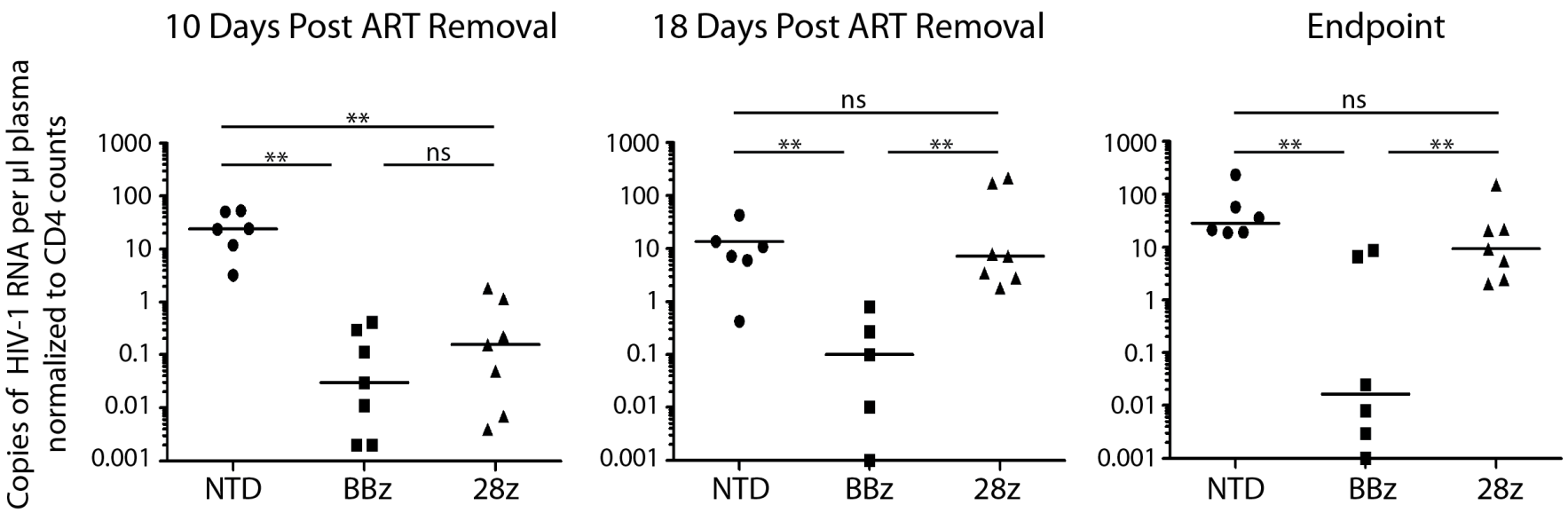
4-1BB promotes CD4 CAR T cell to durably control HIV replication



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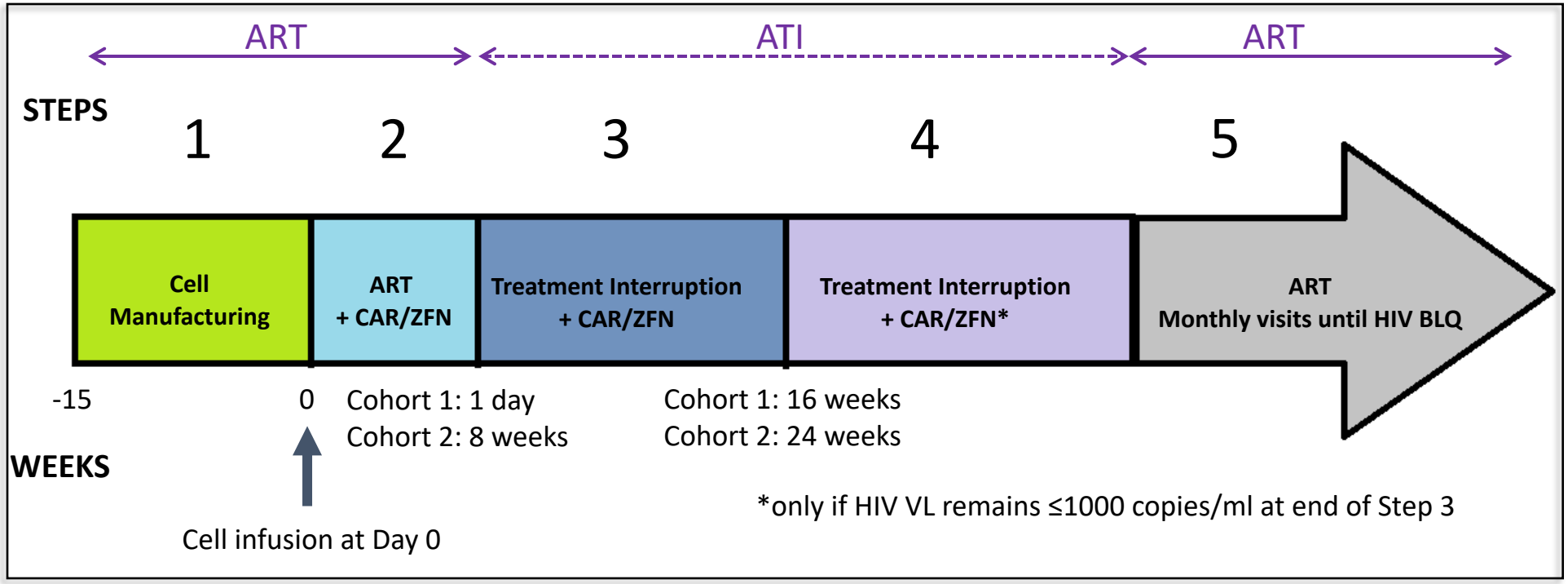
A Pilot Study of T Cells Genetically Modified by Zinc Finger Nucleases SB-728mR, and CD4 Chimeric Antigen Receptor in HIV-infected Subjects (NCT03617198)



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

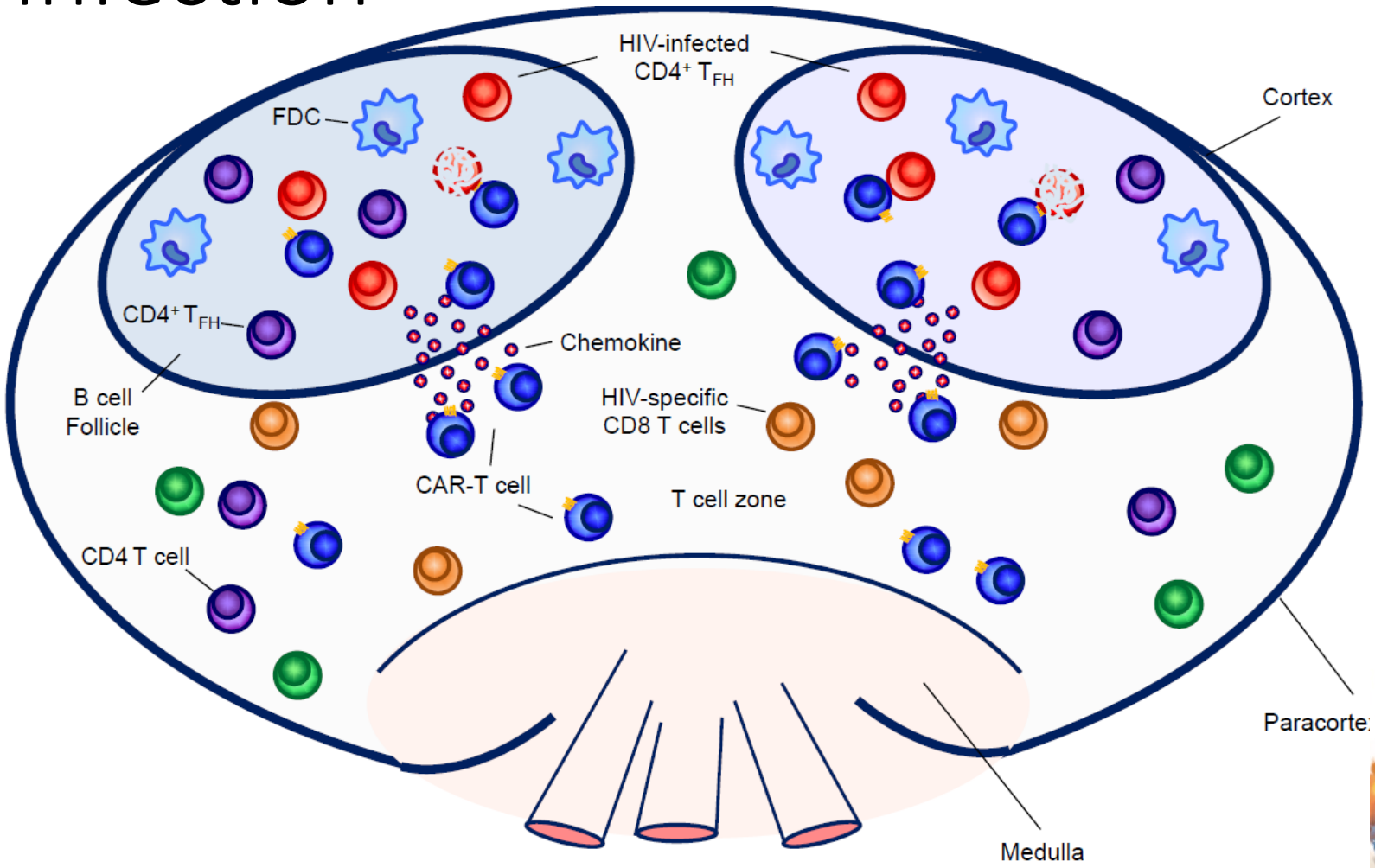
2: Can engineered T cells restore functionality to endogenous HIV-specific T cell populations?

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

Challenges of CAR-T cell Therapy for HIV Infection



Latent reservoir can remain Latent for a long time. Can HIV-CARs persist long term in presence of minimal antigen?

Can HIV CAR-T cells traffic to all places HIV is hiding?

Can HIV-CAR T cells remain resistant to HIV infection?

How long does someone need to have an undetectable viral load before they are pronounced cured?

Maldini et al NRI

HIV Cure, under any definition, is a high hurdle to jump

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