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State of the ART: HIV Cure – where are we now and where are we going?

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Outline

- Is HIV cure possible?
  - HIV persistence
- Cure Strategies
- Ethical and social considerations

A Case of Cure

The Berlin Patient	
Off ART	6 years
Treatment	CCR5-/- bone marrow transplant
Mechanism	Make cells Resistant to HIV
Lesson	**Eliminate** **CCR5+/+ cells**

Hutter G, NEJM 2009; Allers K, Blood 2011; Yukl SA, Plos Pathogens 2013;

Transient but Encouraging HIV Remission

	Two Boston Patients[1,2]	The Mississippi Child[3]
Treatment	CCR5+/+ bone marrow transplant	Early ART
Off ART	3 months and 7 months	2.5 years
Lesson	**Delayed viral rebound is achievable But unknown biomarkers for HIV remission**	

[1]Henrich T, JID 2013; [2]Annals Internal Medicine 2014; [3]Persaud D, NEJM 2014

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Challenges to Eradication

- HIV persistence
  - HIV can exist in a resting state where it persists, even in patients on suppressive antiretroviral therapy

- Accurately measuring the reservoir
  - Inability to detect all of the HIV that can replicate (called replication competent virus)
  - No definitive way to measure if HIV is eradicated

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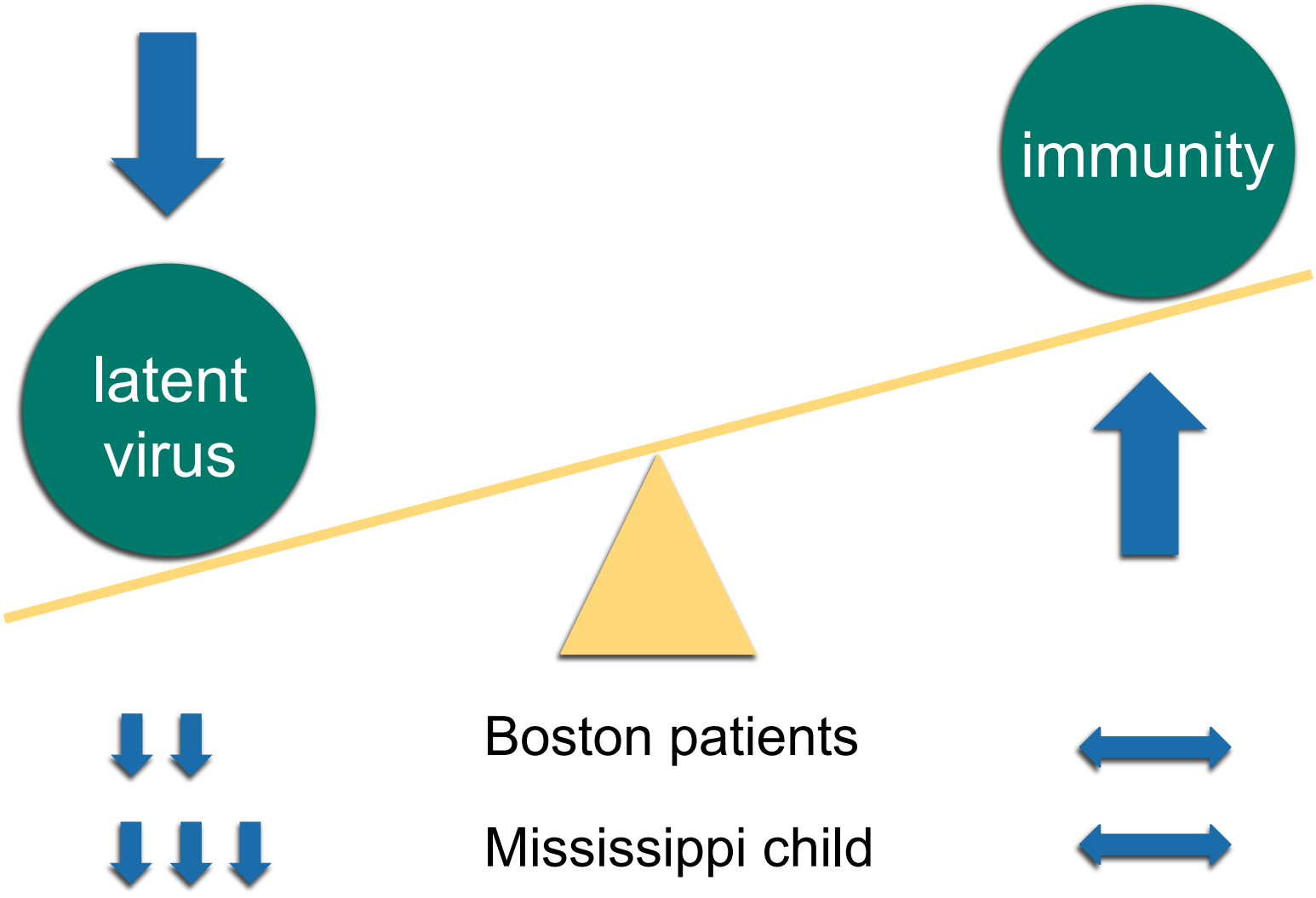
Reservoir and Immunity



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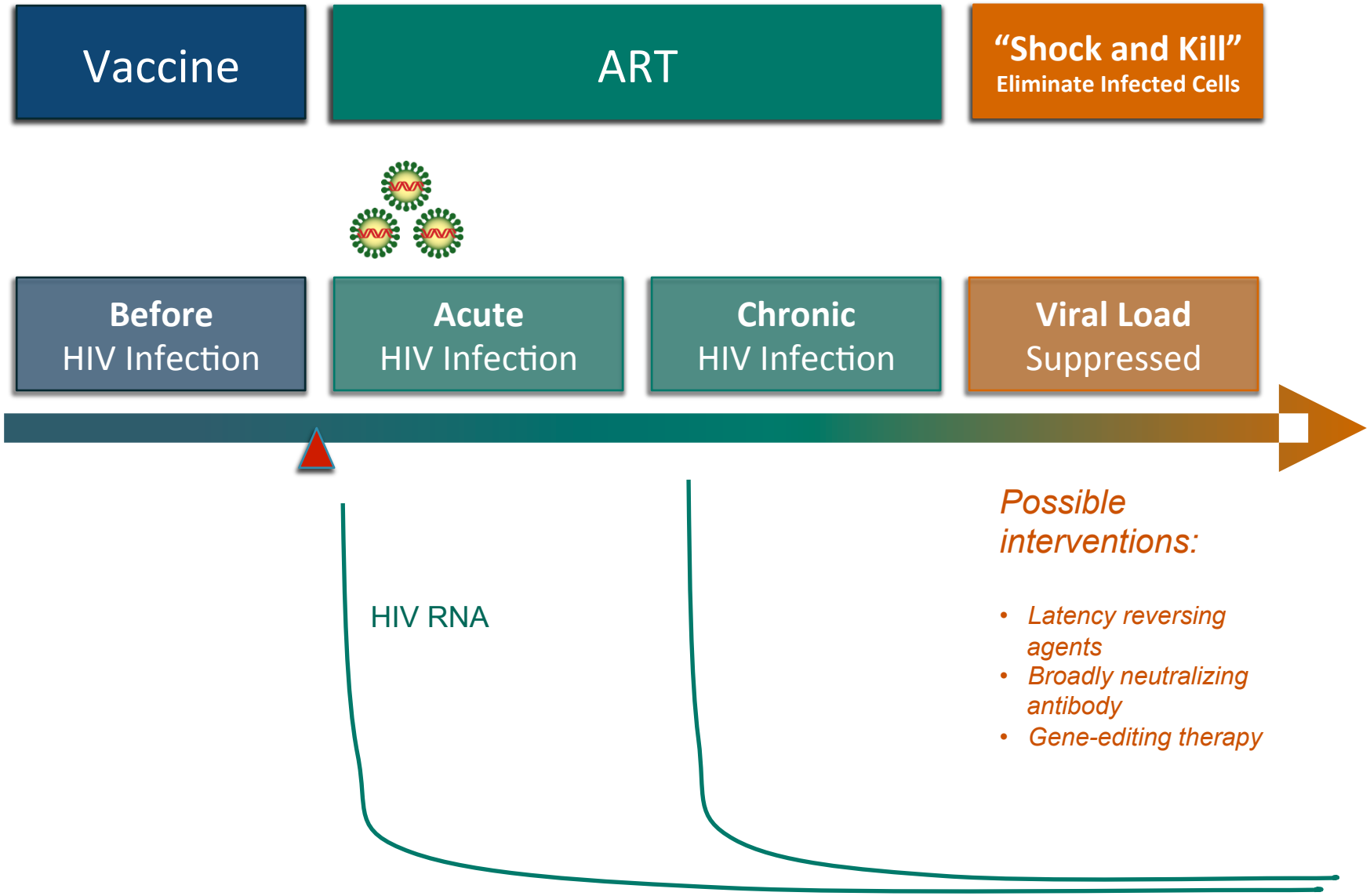
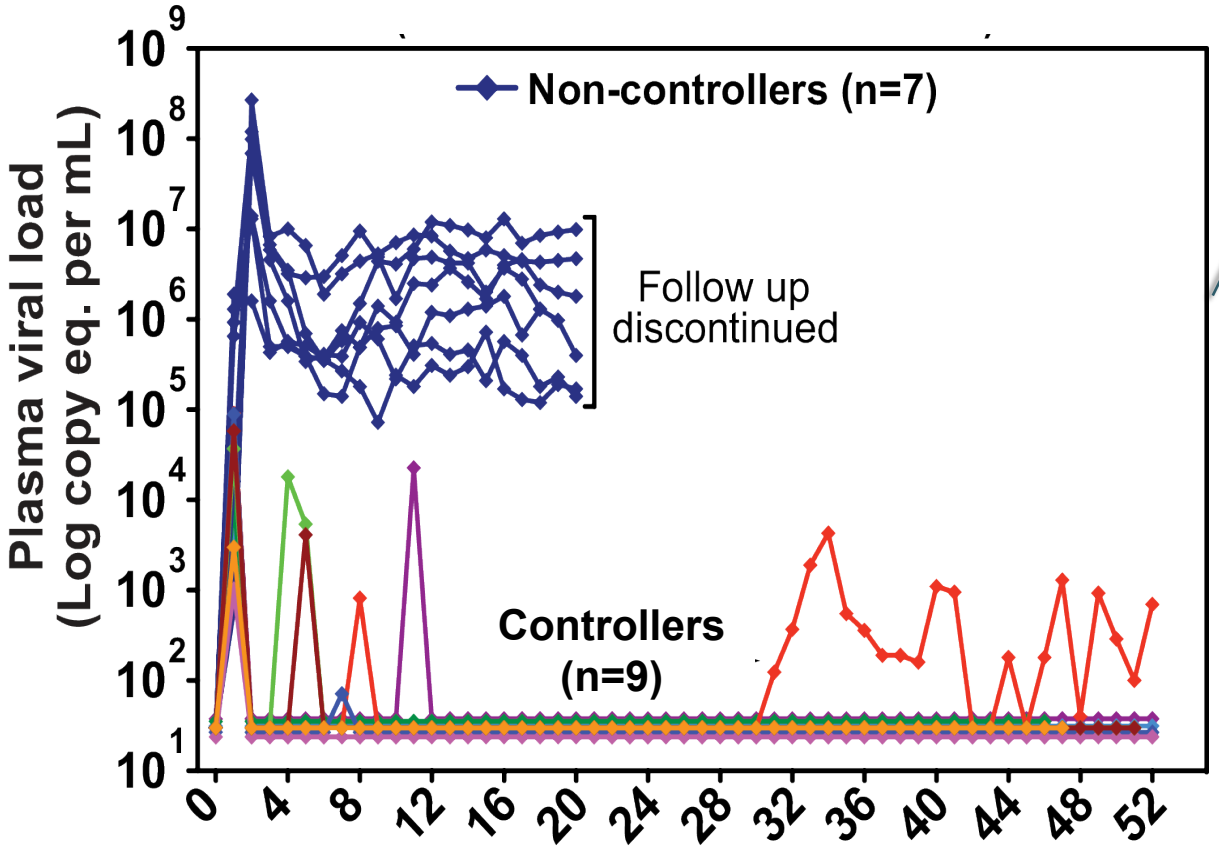
Strategies to Eliminate HIV Persistence



Novel vaccine given before exposure may aid in viral control: SIV/macaque model



No protection

but

Virus **eradicated** in 50%

Hansen SG and Picker LJ, Nature 2013

VISCONTI Cohort of Post-Treatment Controllers

Why are these patients able to control HIV without ART?

HIV reservoir amount and location?

- ✔ Low HIV DNA
- ✔ In shorter-lived CD4 cells

Saez-Cirion A, Plos Pathogens 2013

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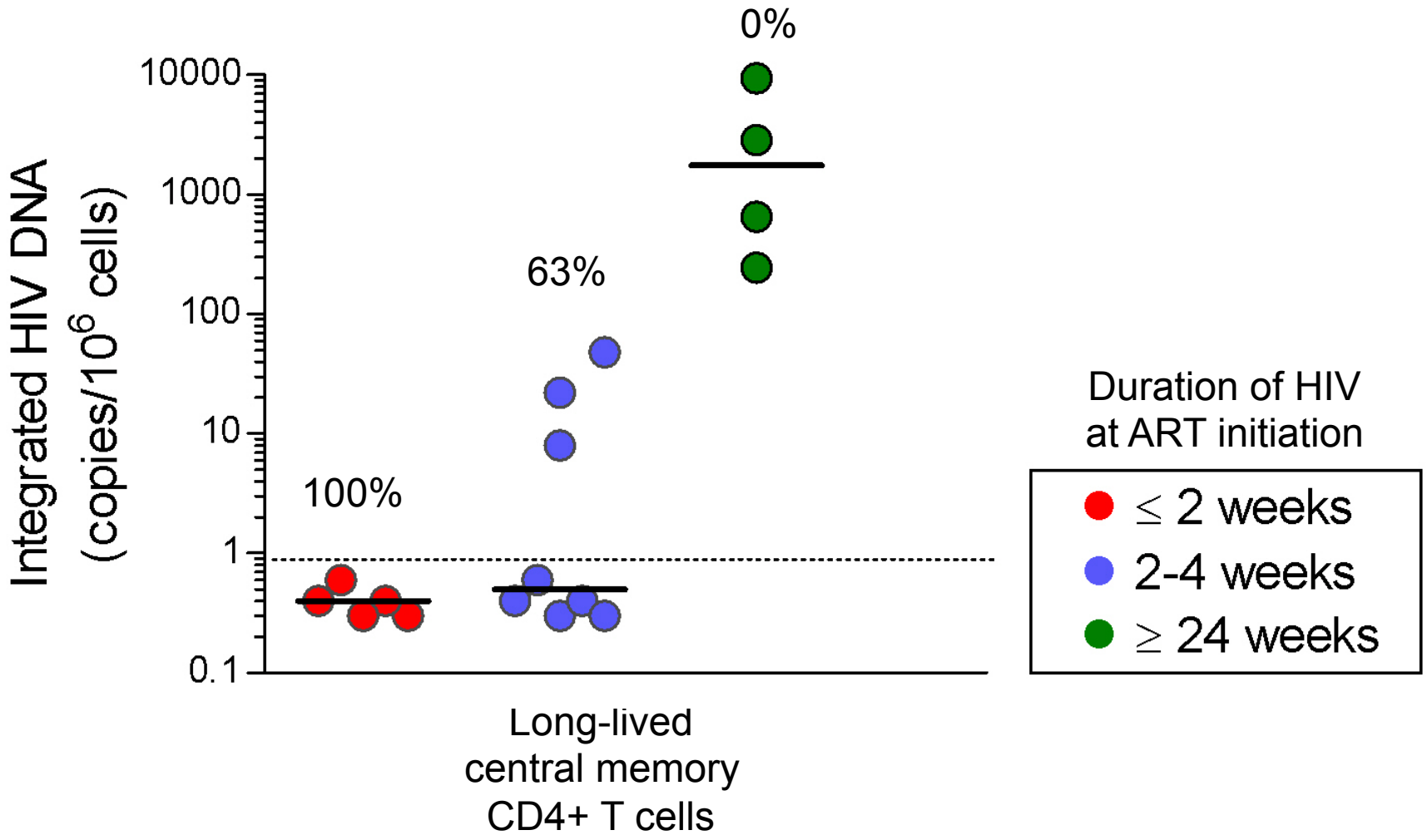
Early ART limits persistence of HIV reservoir

(RV254/SEARCH010)

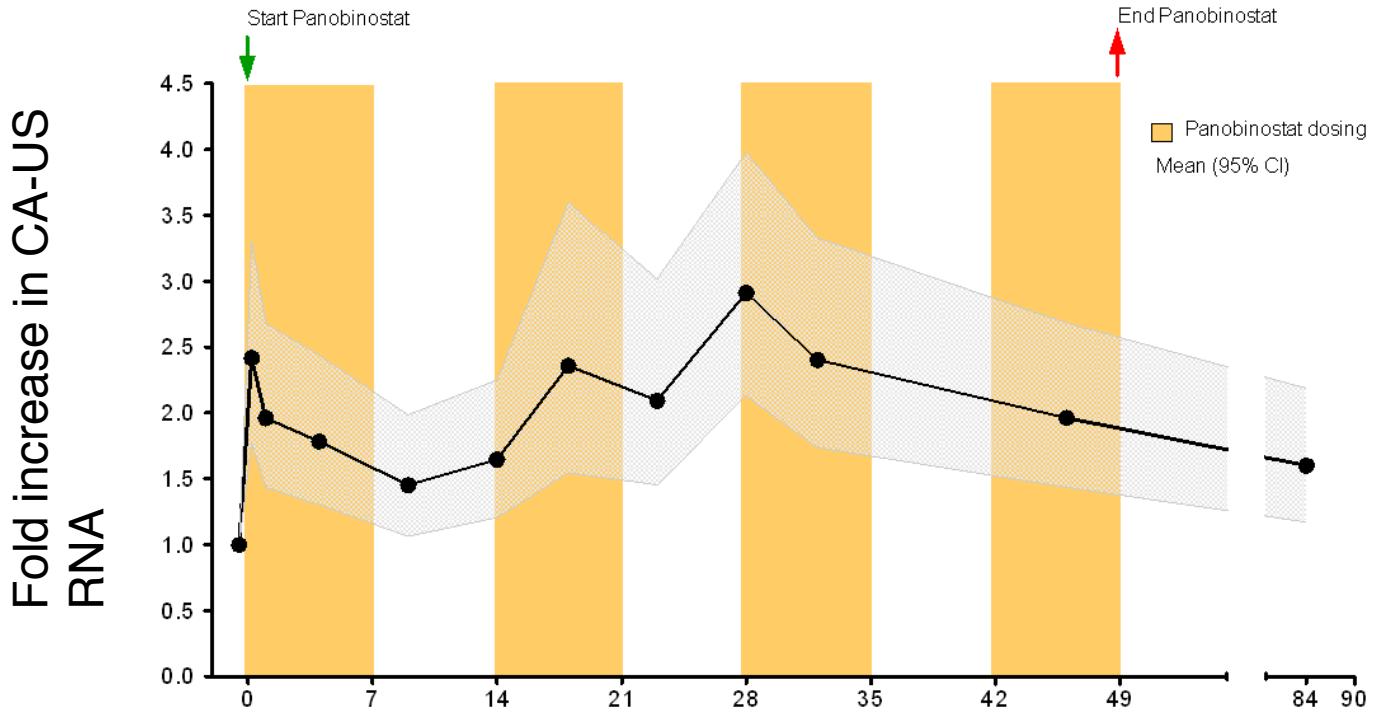


Nicolas Chomont (VGTI-Florida)
Updated from Ananworanich J, 2013 CROI

Shocked but not Killed

HDACi Panobinostat

n=16



ANOVA p<0.0001

Goal: Force the hidden HIV "out into the open" and expose them to the immune system to eradicate them

Result: Replication competent virus did not decline

Rasmussen et al, 2014 CROI

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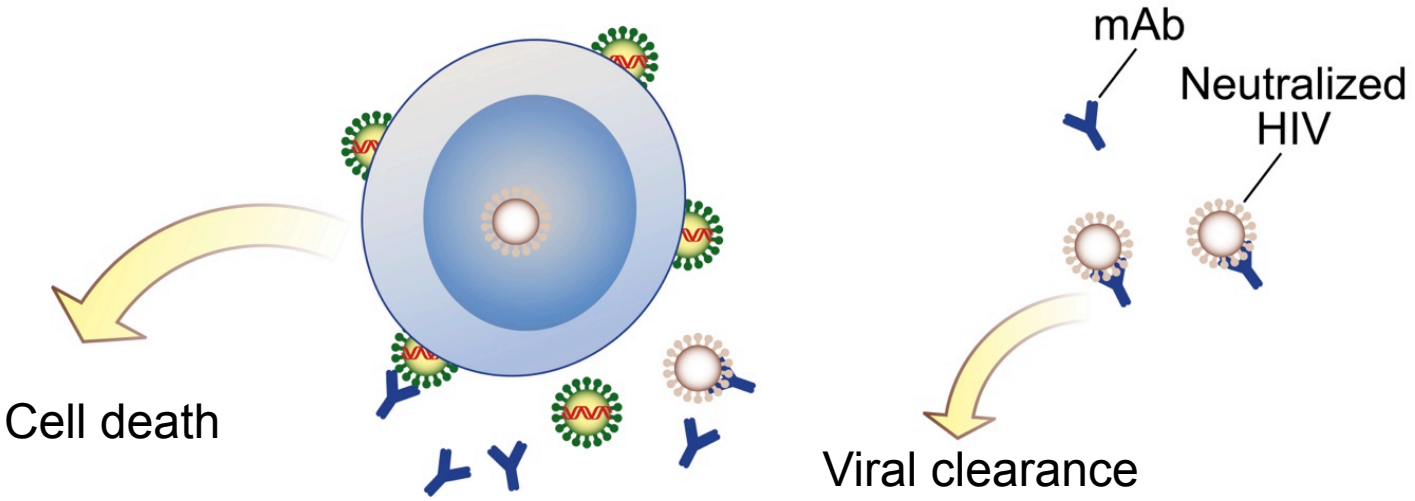
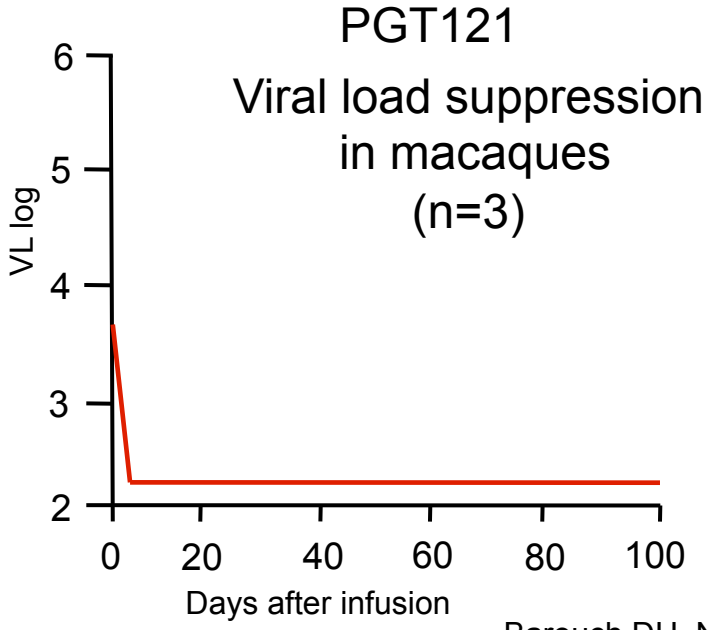
Broadly Neutralizing Antibody

(bNABs) neutralize multiple HIV-1 viral strains

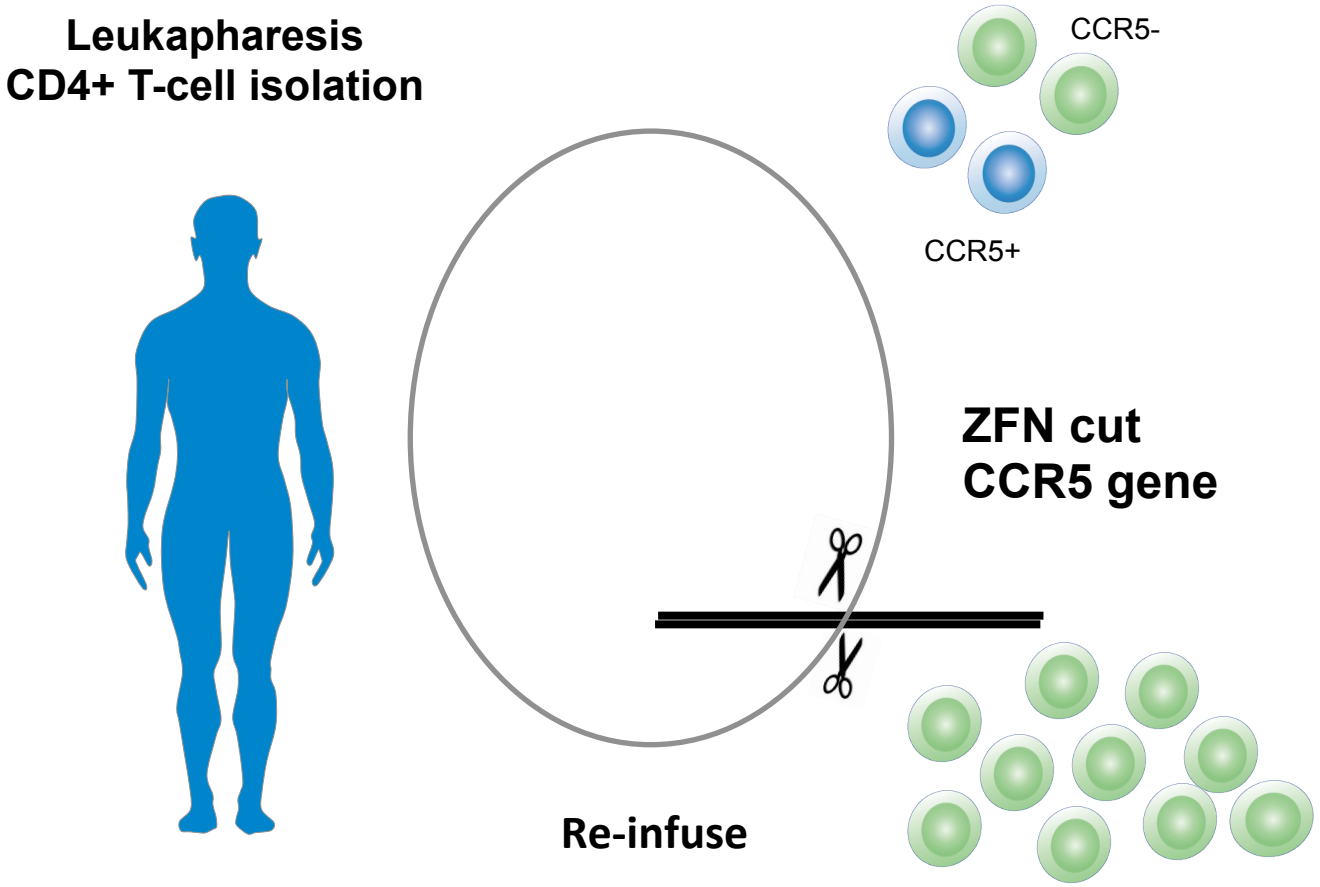




Barouch DH, Nature 2013

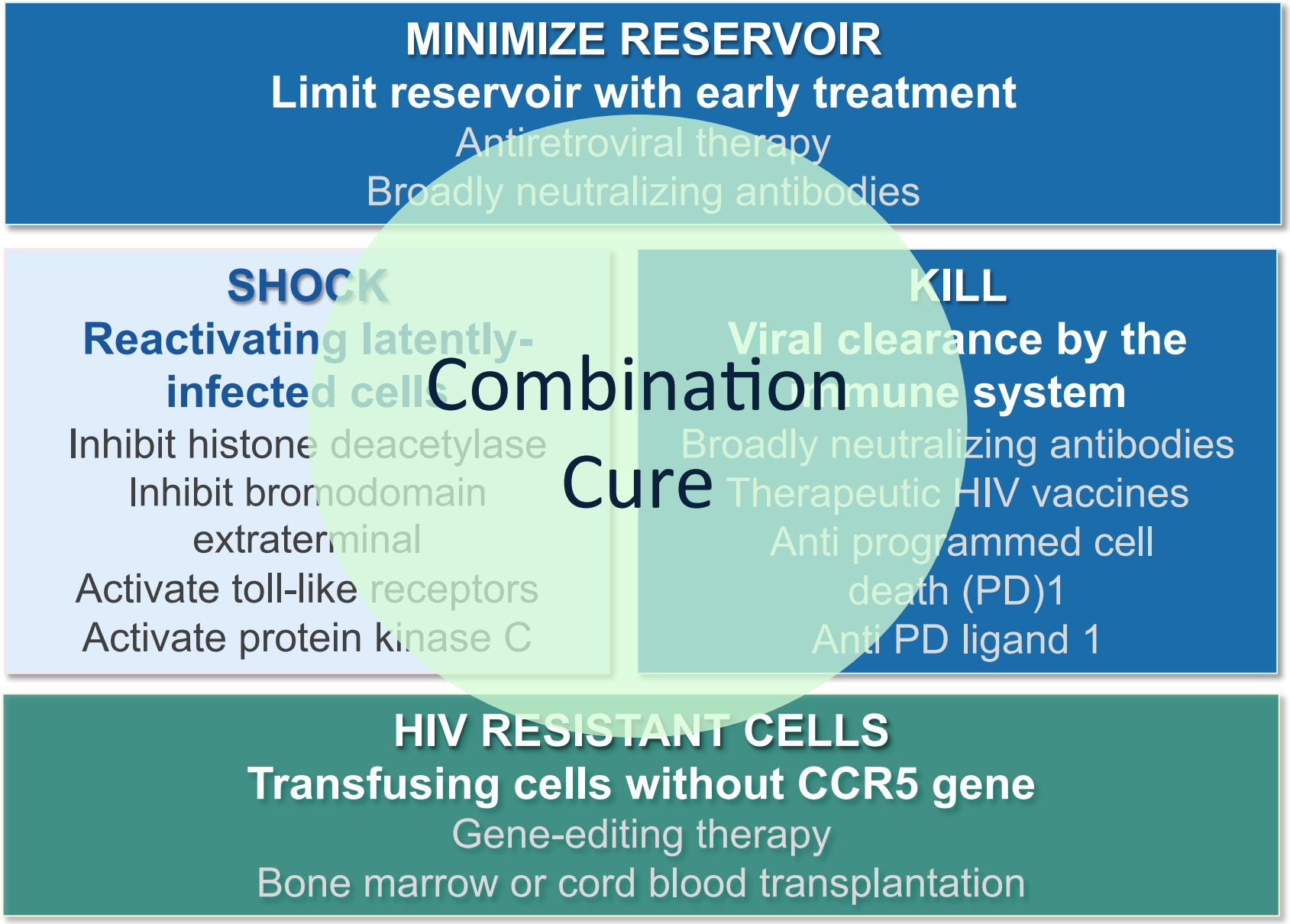
- > 30 antibodies identified
- Human studies
  - VRC01: RV397/398 in acute HIV
  - 3BNC117, 10-1074, PGT121

Gene therapy to eliminate CCR5



Tebas P, NEJM 2014

Examples of strategies currently in human studies



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HIV Cure and Cure Research: Social and Ethical Considerations

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Societal and Individual Expectation

- Eradicated = normal or free of disease or healed
- Long-term adverse consequences of HIV
  - New normal
- Long-term monitoring of viral load
- Stigma and discrimination
- When to call someone "cured"?[1]
  - Best measure of reservoir is not known
  - HIV remission
    - $VS_{LLD}OT_{time}$ = Viral Suppression Off ART

[1]Forum Cure Project (V. Miller)

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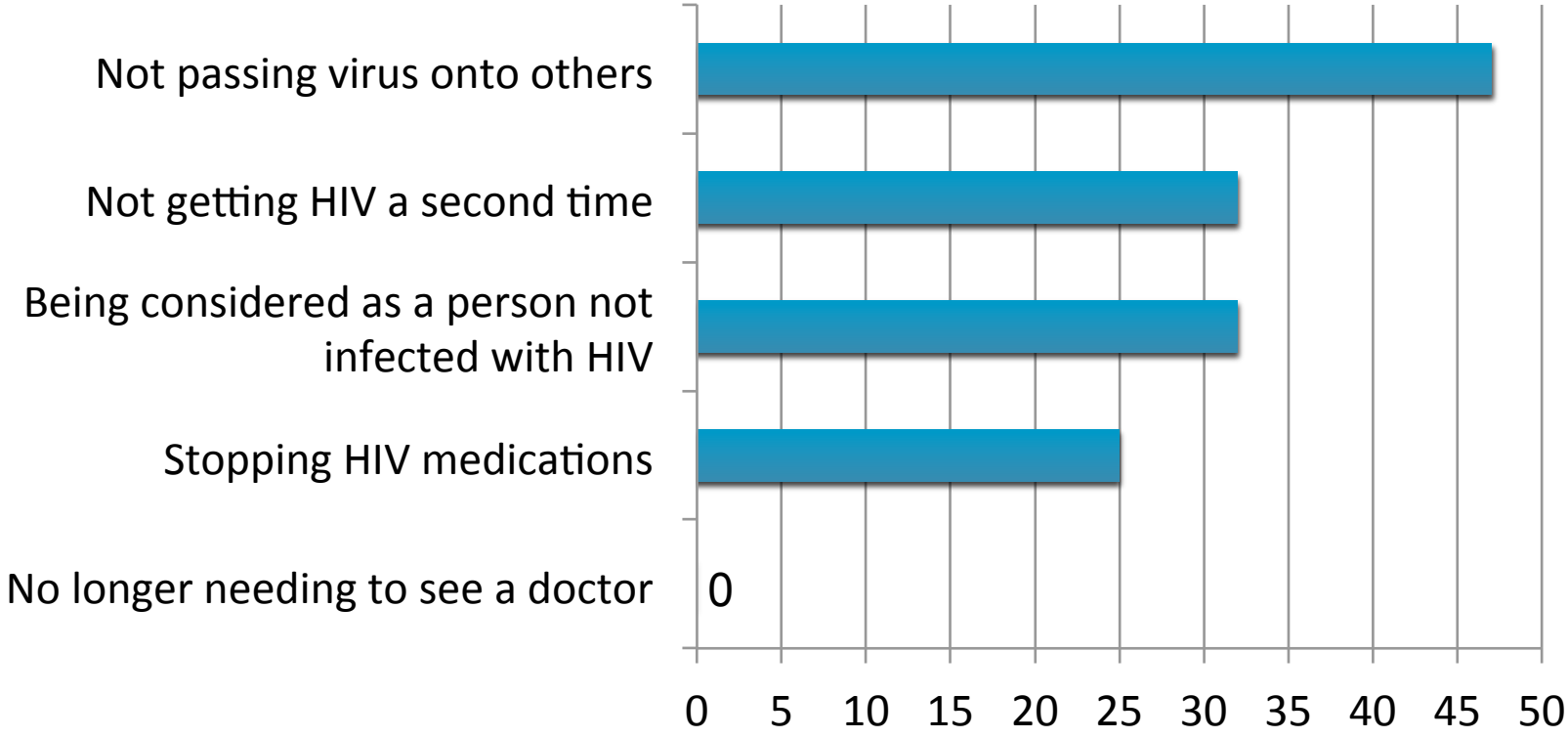
Australian Participants' Priorities on Outcomes of Cure Research

20 participants with chronic HIV infection in vorinostat (HDACi) trial



McMahon J, Elliott J and Lewin S, 2013 IAS

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Ethics of HIV cure

- Ideal candidates are persons who are well with viral suppression
- Potentially toxic interventions
- ART interruption
- Cost and accessibility

Shah SK, Lancet ID 2014; Lo B and Grady C, Curr Opin HIV AIDS 2013

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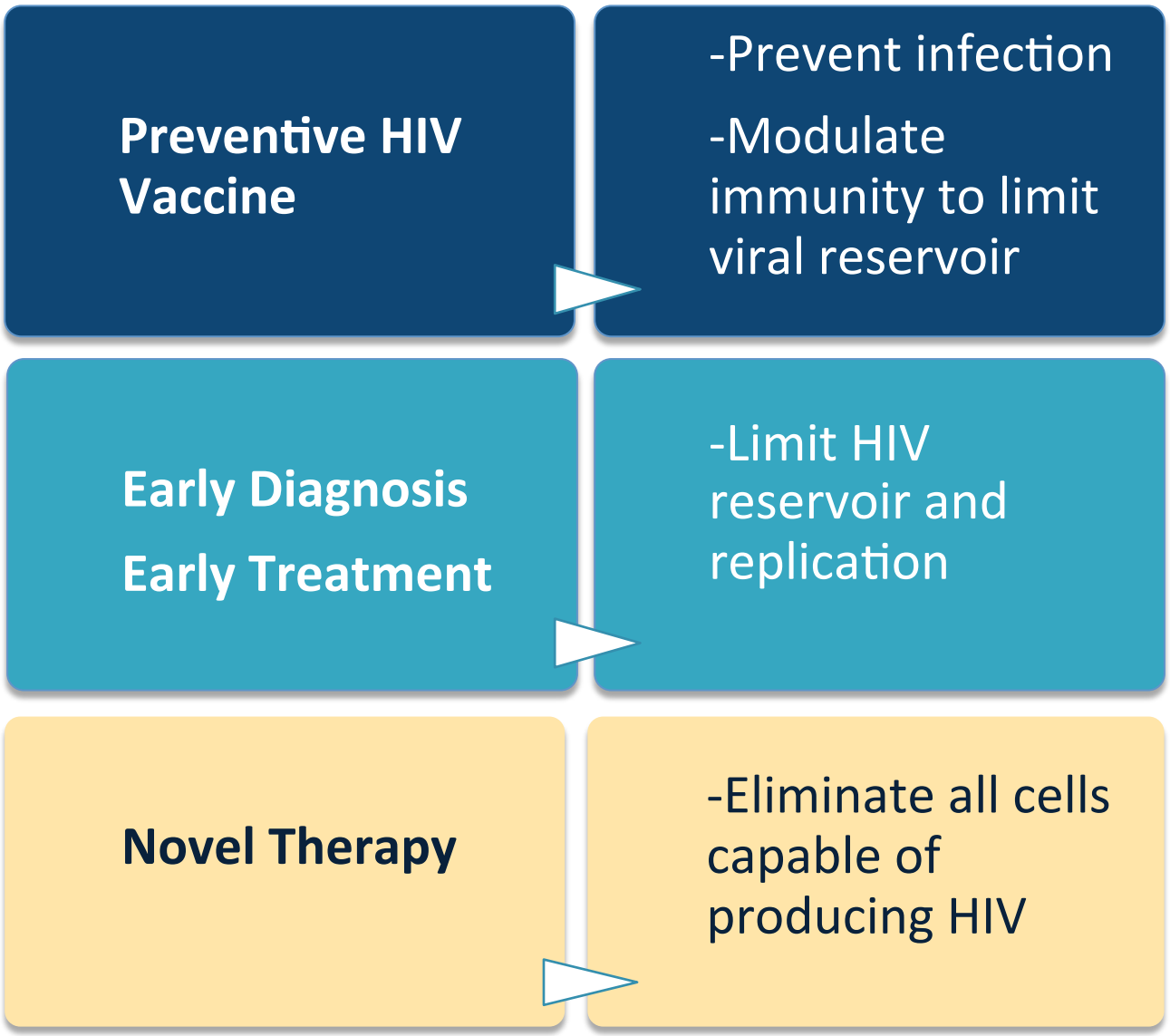
What might the future look like?



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