

Quiz 6 – due in discussion Fri, Dec. 6th.

- ▶ Currently posted on Learn@UW
- ▶ You will be asked to think about the best way to address the HIV epidemic in a specific country given a limited budget.





Can HIV be cured?



Justin Greene | Monday | November 18, 2013

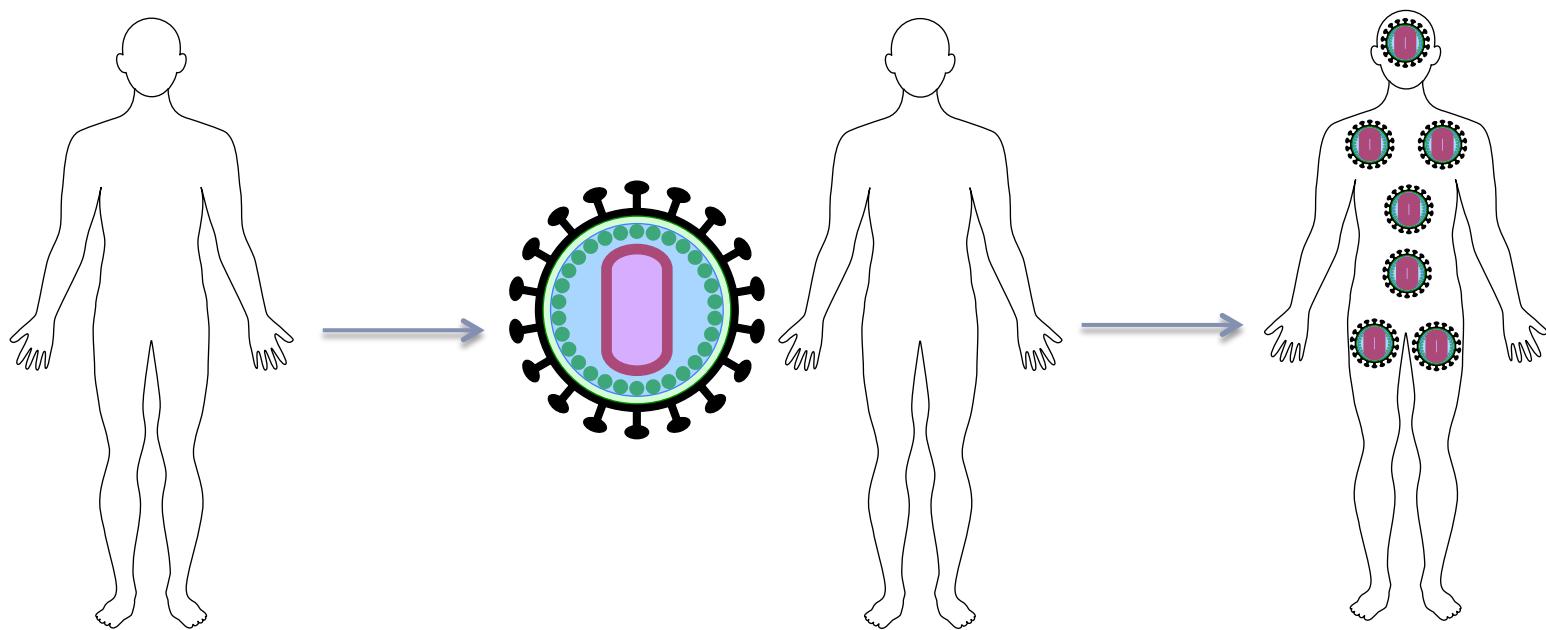
Outline

- ▶ **What does it mean to be cured of HIV?**
 - ▶ What language do we use to discuss an HIV cure?
- ▶ What are current challenges to curing HIV?
- ▶ Four cure stories and the future of cure research
- ▶ Conclusions

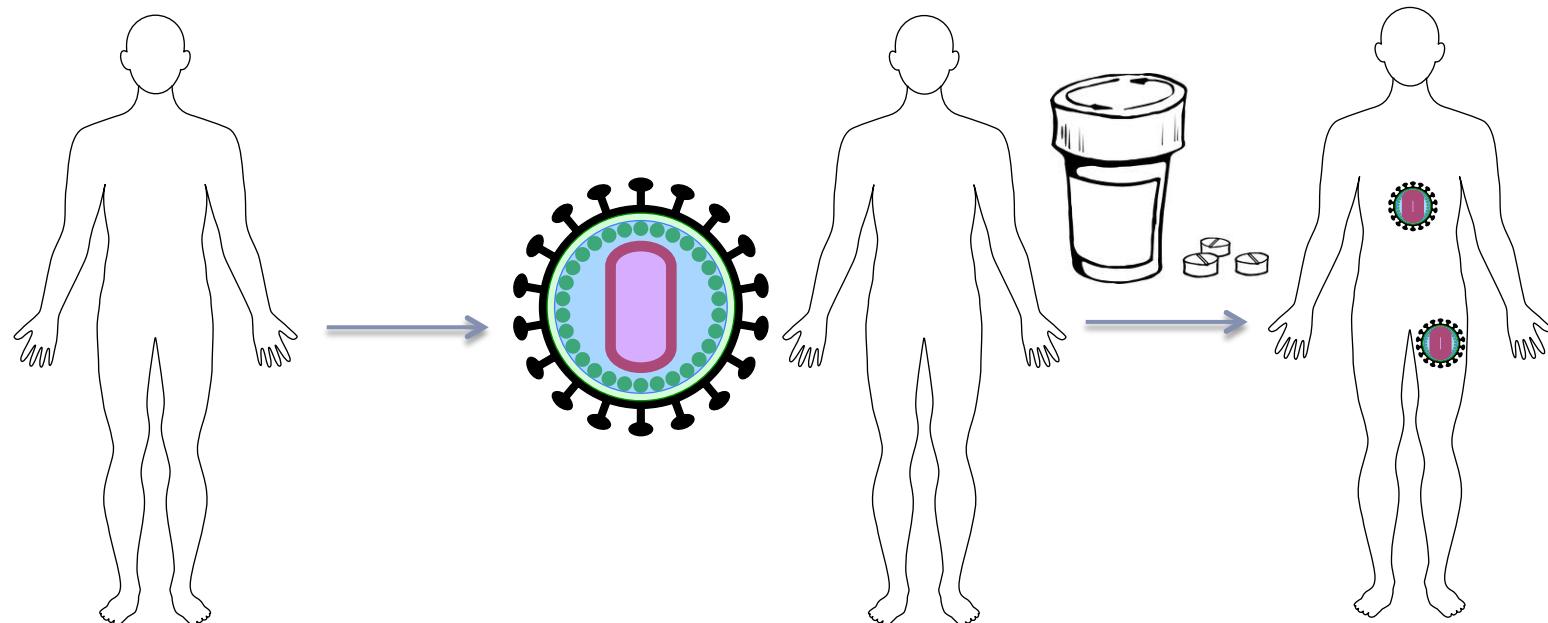
What does it mean to
cure someone of HIV?

How is a cure different
from a prophylactic
vaccine?

Typical HIV infection

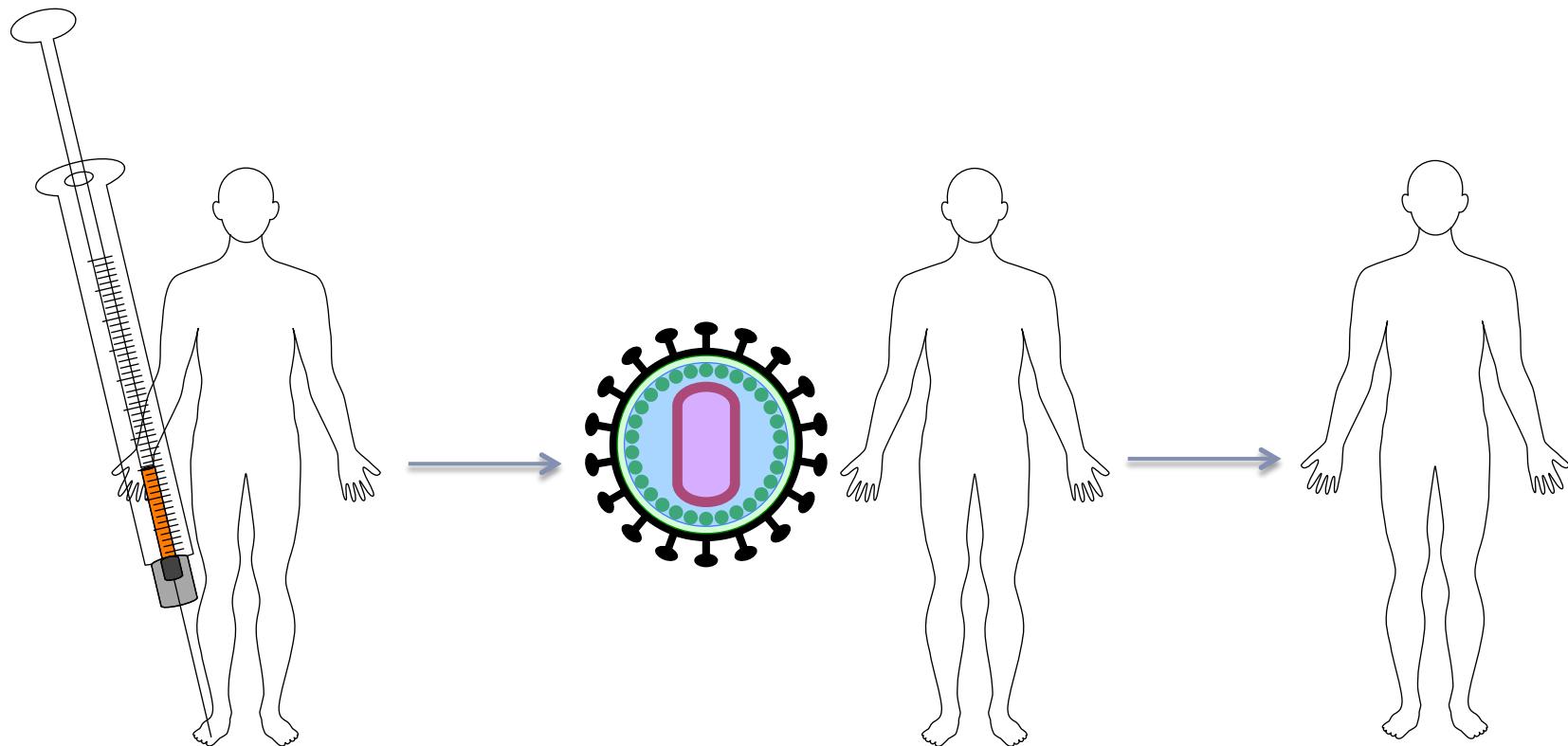


Treatment with ART

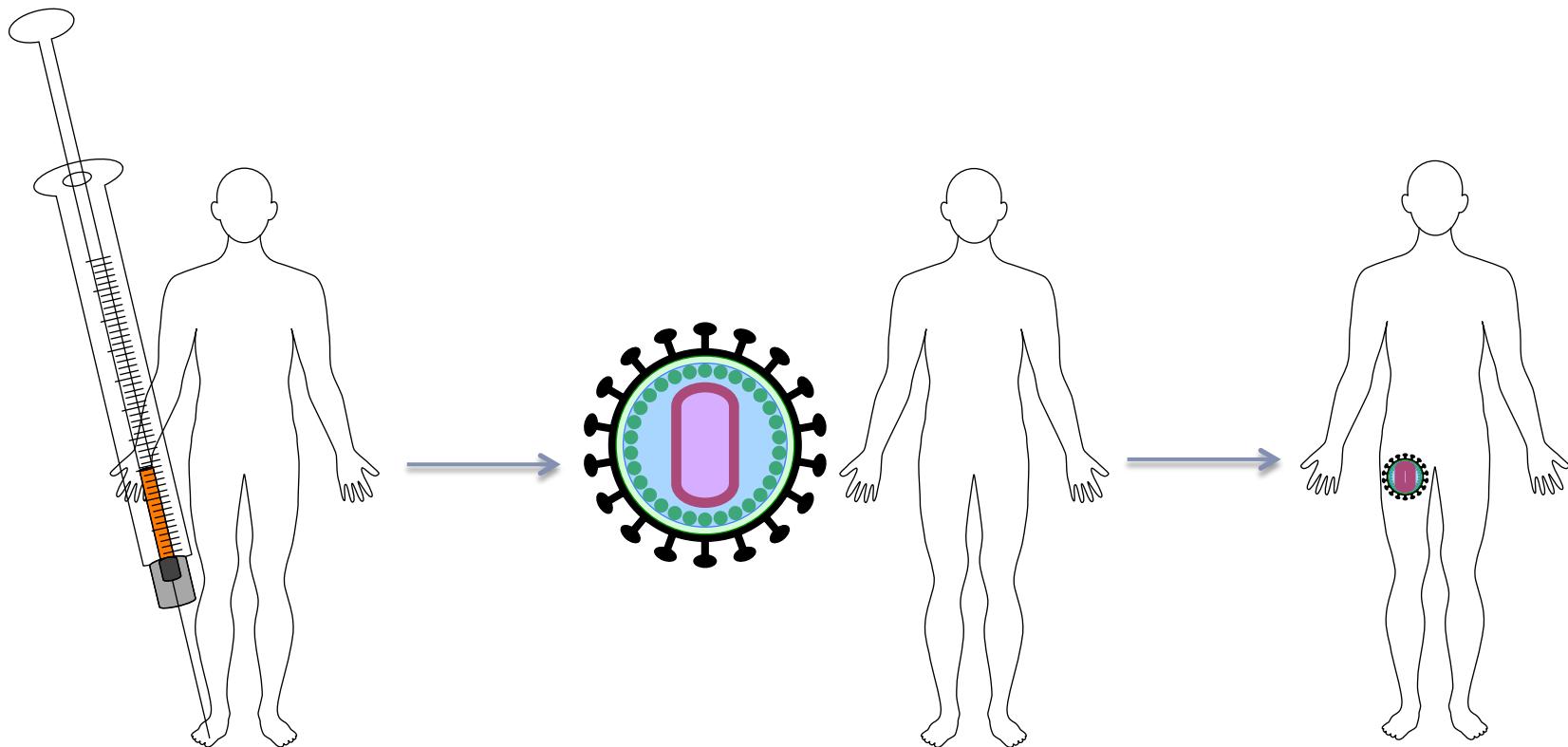


Think about why ART may not eliminate the virus

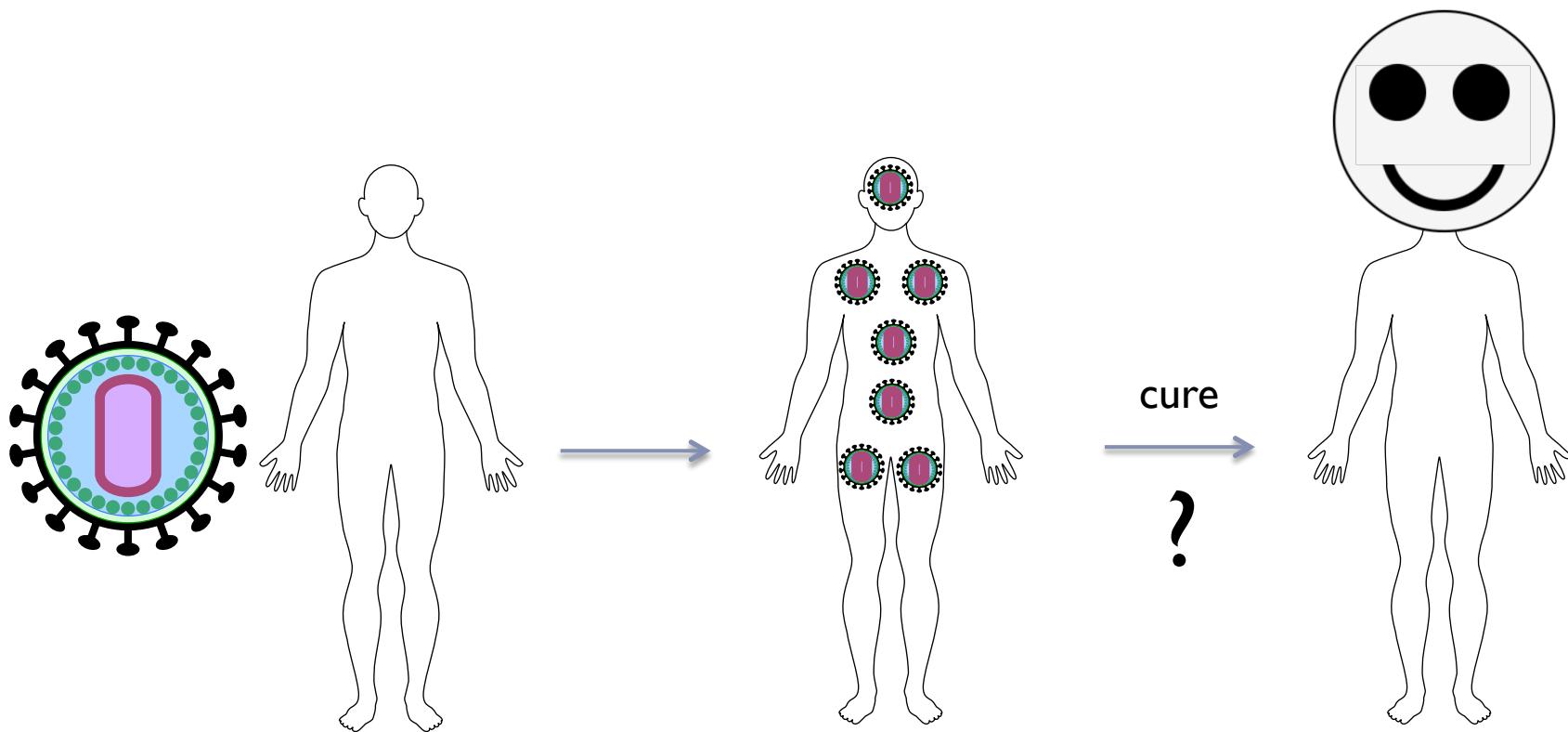
Prophylactic Vaccine – intended to prevent disease



Novel Vaccine ideas



An HIV cure



Key Terms

- ▶ Prophylactic vaccine – agent that elicits an immune response which provides protection against a pathogen in the future
 - ▶ Might prevent infection
 - ▶ Might lead to reduced viral loads and delayed disease progression
- ▶ Cure – an agent or therapy that eliminates HIV from an individual already infected with the virus
- ▶ Functional cure – agent or therapy that leads to control of virus and eliminates need for additional treatment
 - ▶ Remission – period of time in which disease symptoms have subsided

Why is the distinction between functional cure and cure important.

- ▶ Eradication
 - ▶ Less stigma
 - ▶ No chance to pass virus on to another person
 - ▶ An end to the disease
- ▶ Functional Cure/Remission – implies that the disease is gone but that this may be temporary
 - ▶ Virus may not be completely cleared
 - ▶ Virus could potentially be transmitted to others
 - ▶ The disease may come back

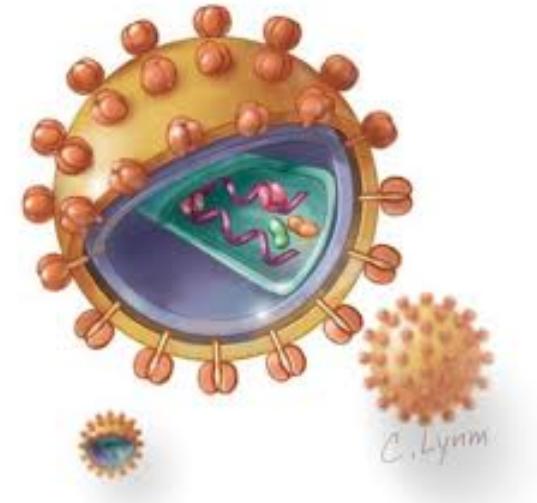


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Challenges to developing a cure for HIV

- ▶ Latently infected cells
 - ▶ No gene expression means there are no proteins/peptides for the immune system to recognize
 - ▶ Without replication and gene expression ART cannot act on the virus
- ▶ Replication in tissues that are inaccessible to drugs
- ▶ Replication in immune privileged sites
- ▶ Drug resistance mutations
- ▶ Immune escape



- ▶ 13 <http://newsatjama.jama.com/2013/10/24/latent-hiv-reservoir-may-be-larger-than-previous-estimates/>

Key Terms and concepts

- ▶ Reservoir – sites in which the virus persists despite the immune response and/or drug treatment
- ▶ Immune privileged – anatomical locations where antigens do not elicit an inflammatory immune response
- ▶ HIV RNA – a measure of active viral replication
- ▶ HIV DNA – a measure of the latent virus reservoir
 - ▶ HIV DNA integrates into the host genome
- ▶ 14 http://www.annualreviews.org/doi/full/10.1146/annurev.immunol.18.1.665?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

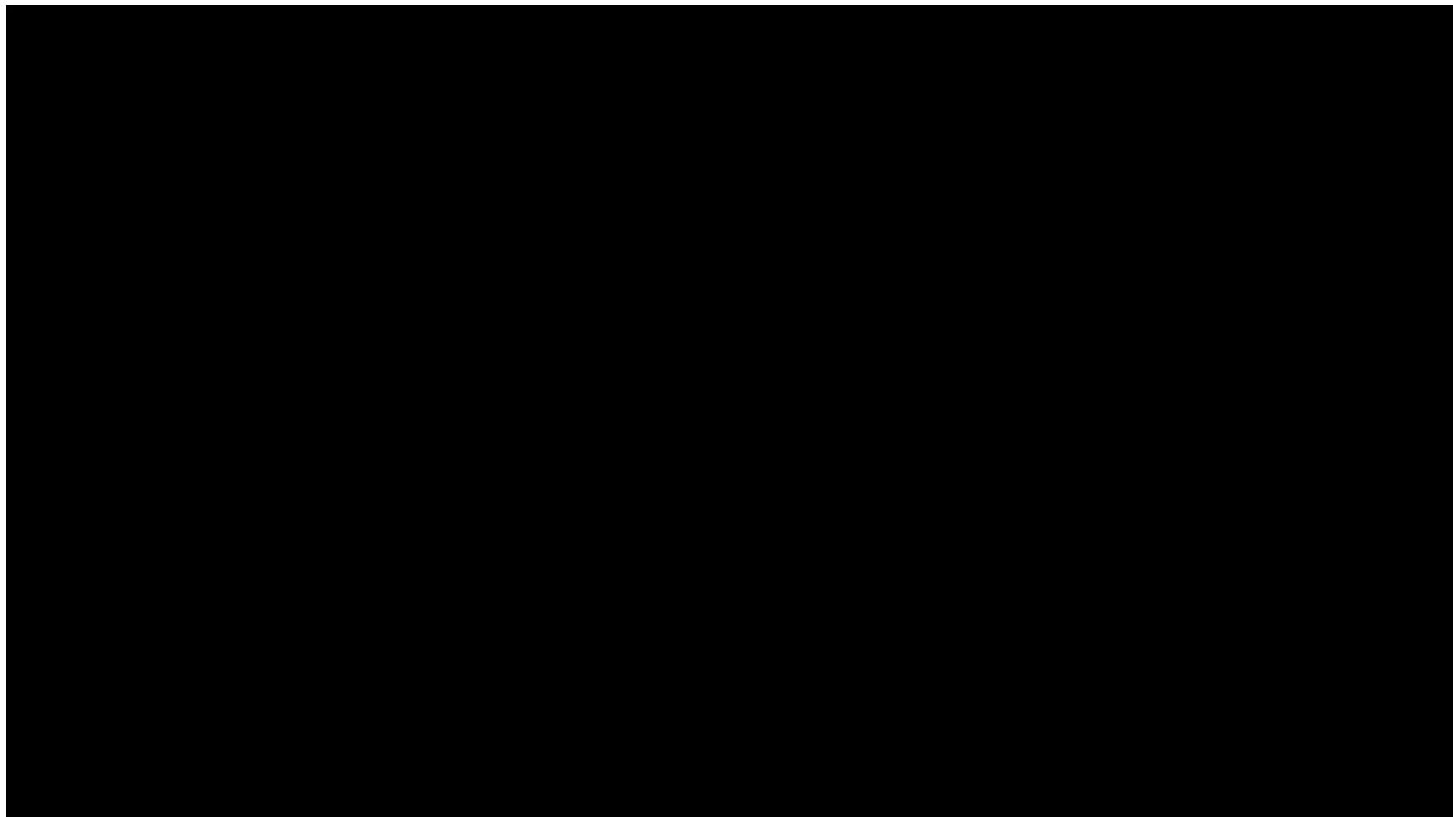
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Current Cure Stories

- ▶ Berlin Patient
- ▶ MIT/Boston Patients
- ▶ The Mississippi baby
- ▶ The French cohort

Who is the Berlin Patient and how was he cured?



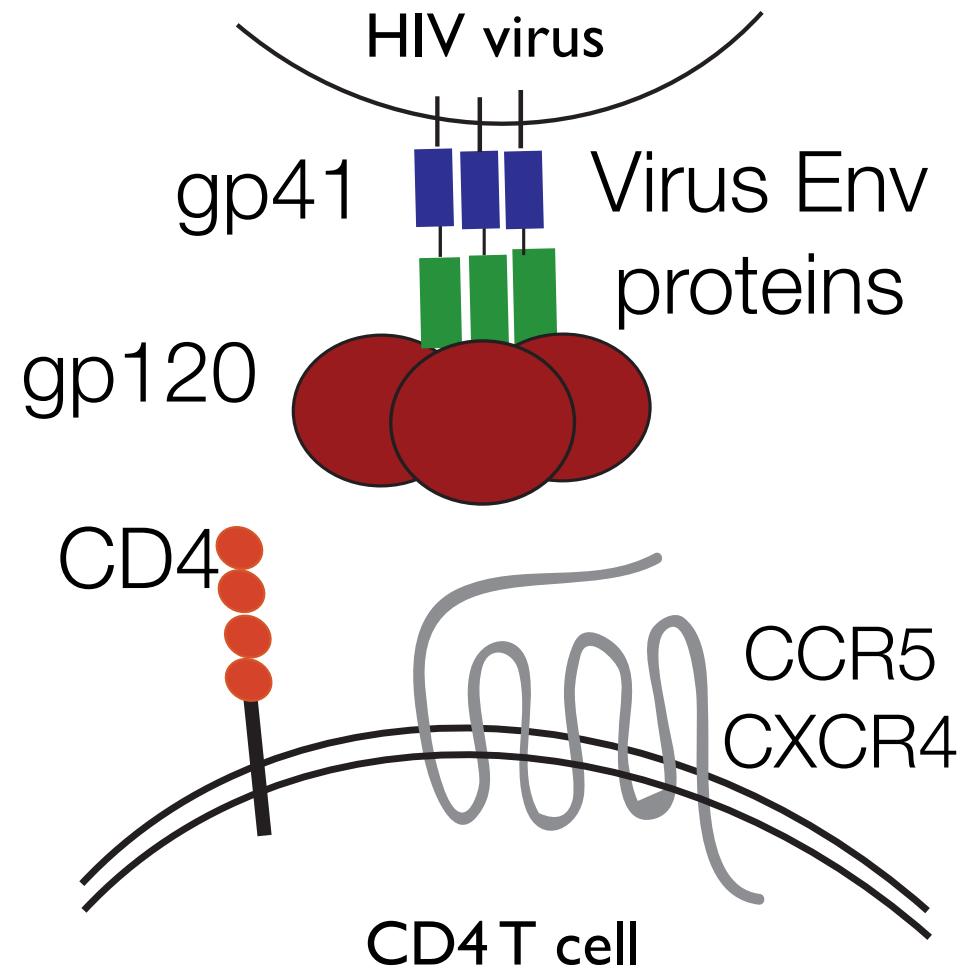
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- ▶ 17 http://www.cbs.com/shows/cbs_evening_news/video/1970438971/a-functional-cure-for-hiv-/

The Berlin Patient

- ▶ 40 year old male with HIV for 10 years
 - ▶ Effectively treated with HAART for 4 years
 - ▶ Presented with acute myeloid leukemia (AML)
 - ▶ AML - Cancer in the bone marrow that leads to overproduction of white blood cells (immune cells)
 - ▶ Treatment is to clear the immune system and perform a bone marrow stem cell transplant
 - ▶ Stem cell transplant with cells from a donor with the CCR5 Δ 32 mutation
-
- ▶ 18 {Hutter et al., 2009, #16085}

HIV uses CD4 and the coreceptor CCR5 to enter CD4 T cells

- ▶ HIV binds to CD4 and a co-receptor (CCR5 or CXCR4)
- ▶ Virus envelope fuses with membrane
- ▶ Viral RNA genome uncoats



Normal CCR5



Mutant CCR5 ($CCR5\Delta 32$)

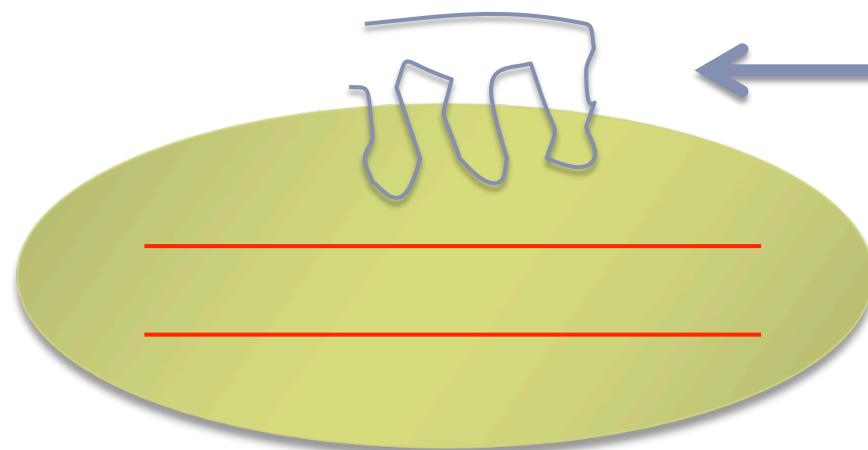


10% of Northern Europeans are heterozygous (one copy of the mutant CCR5)



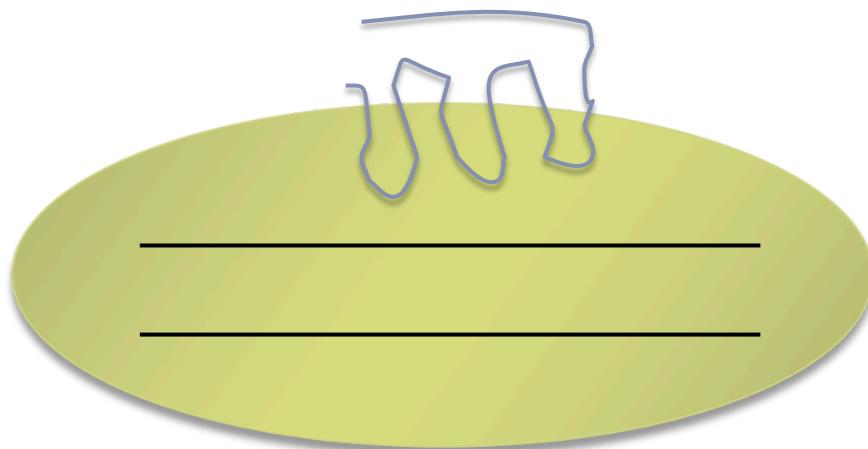
1% of Northern Europeans are homozygous (two copies of the mutant CCR5)

At the cellular level



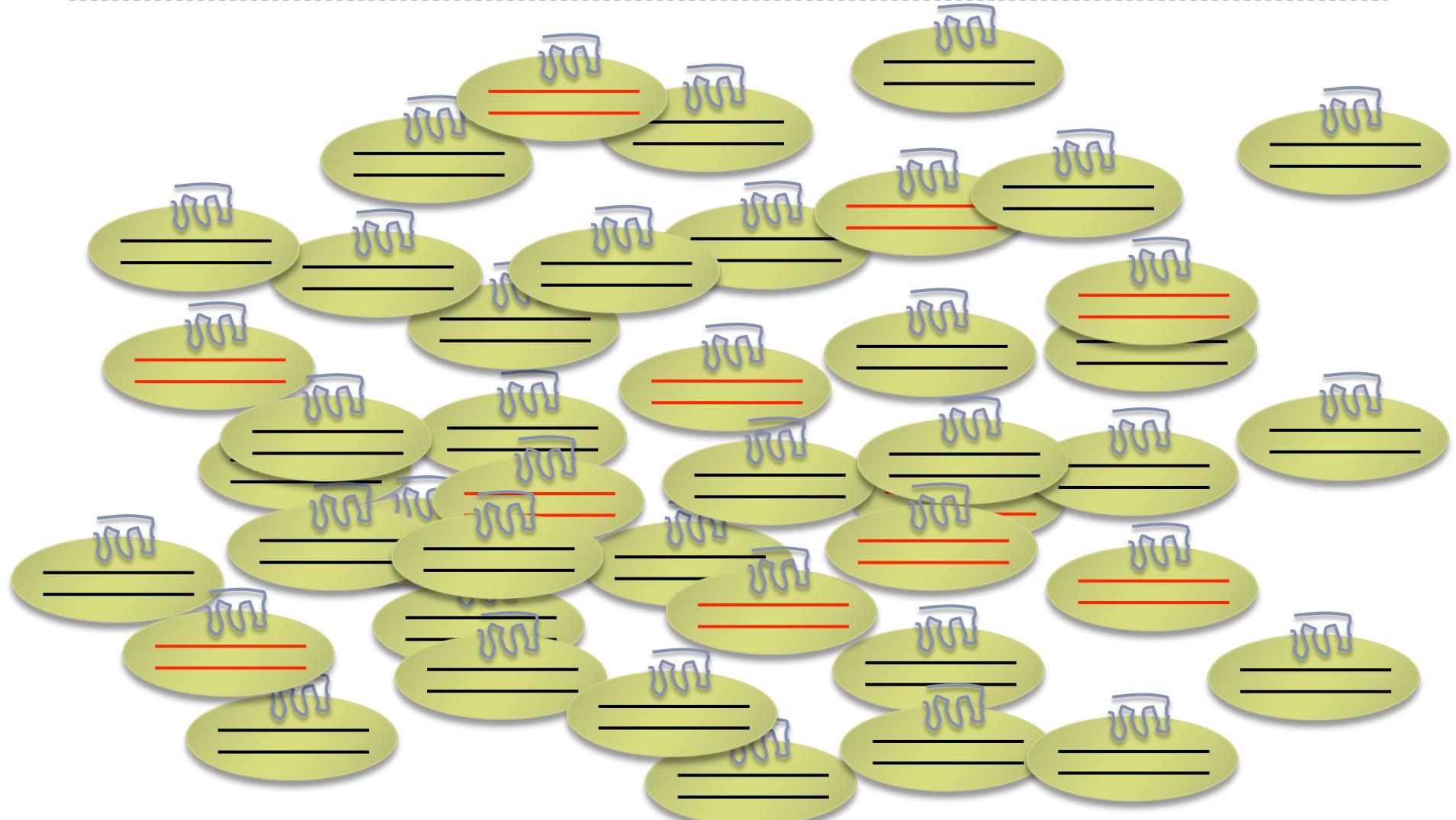
CCR5

Latently infected cell

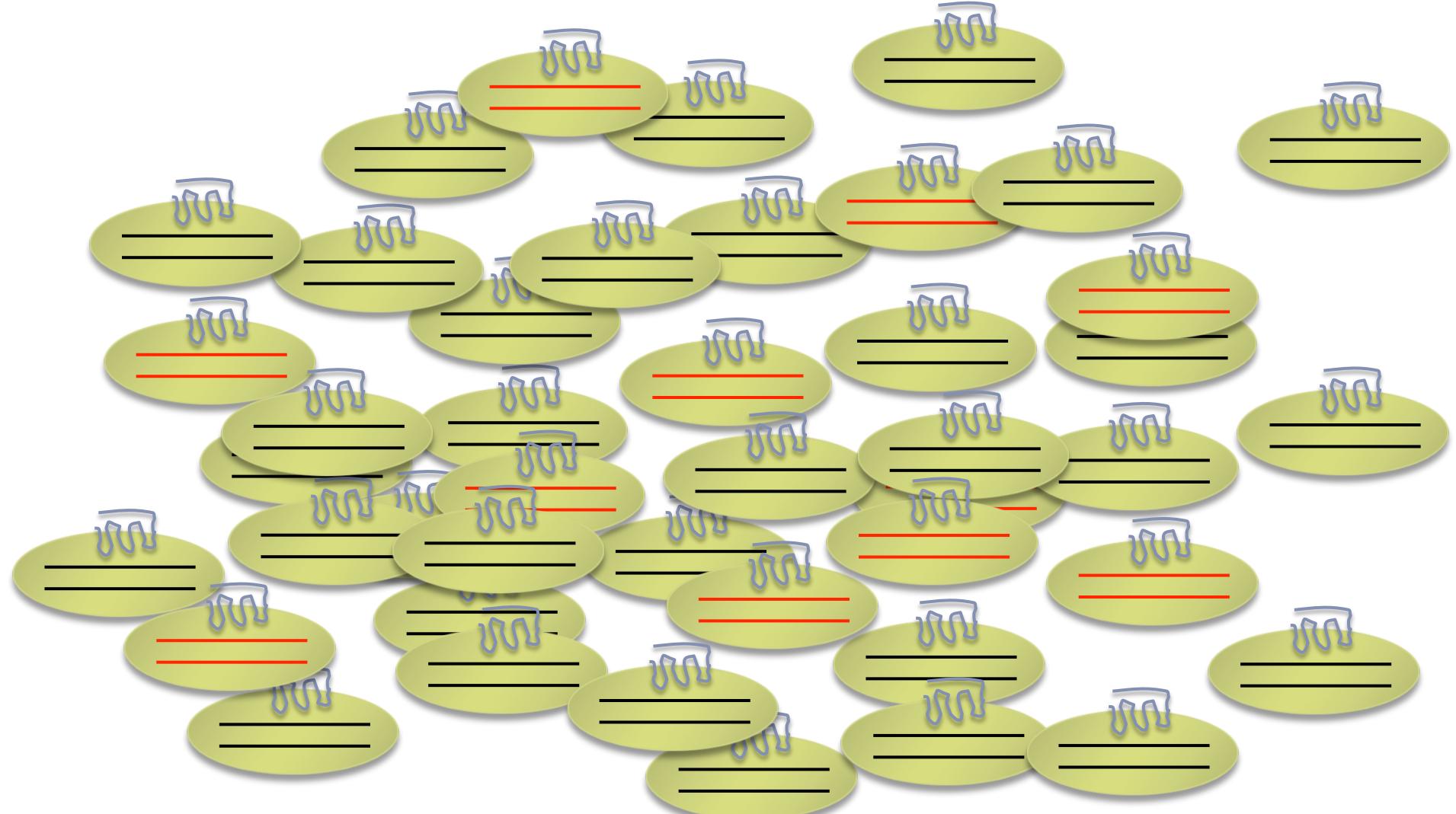


Uninfected cell

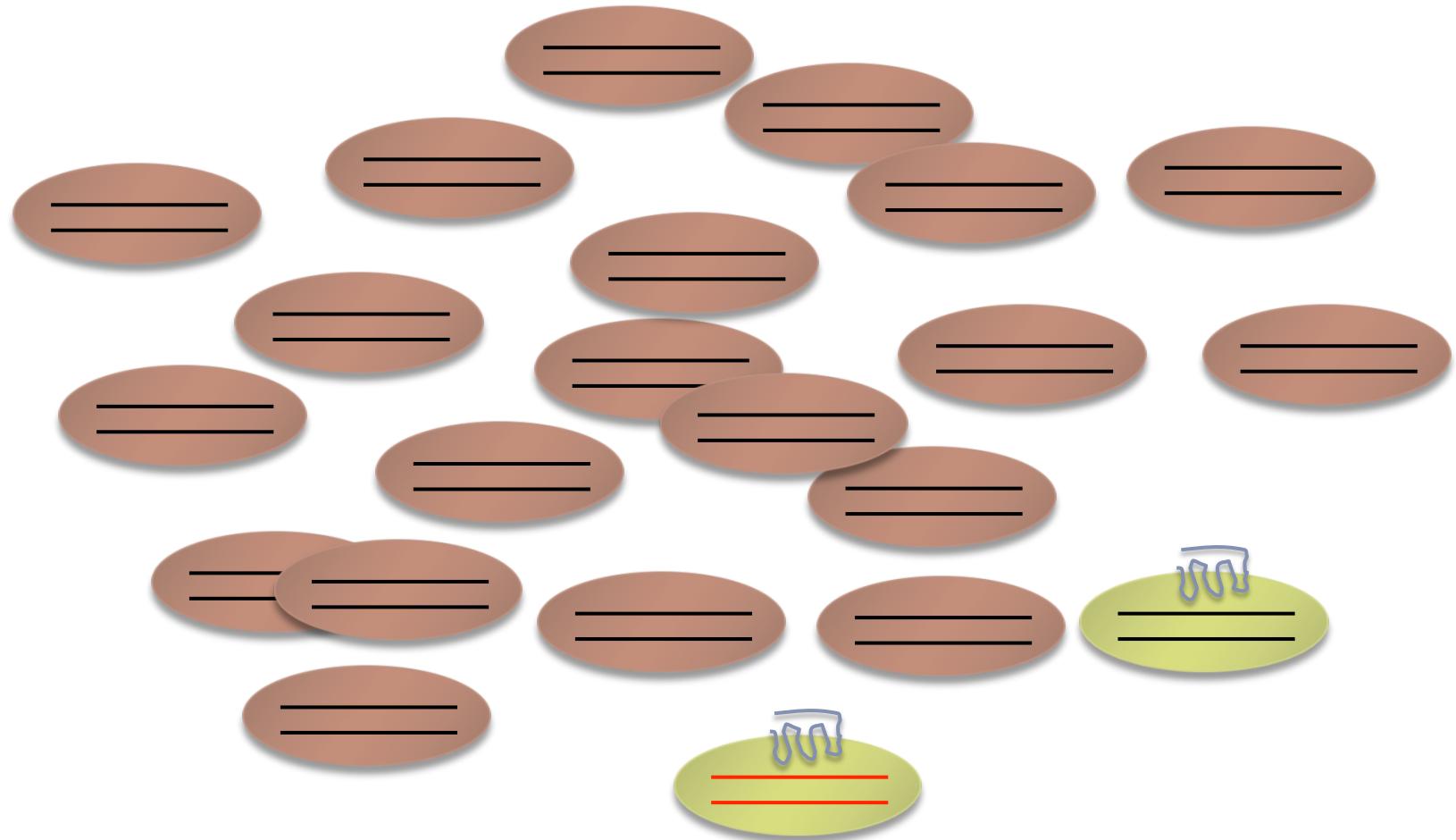
Recipient immune system before irradiation – contains latently infected cells



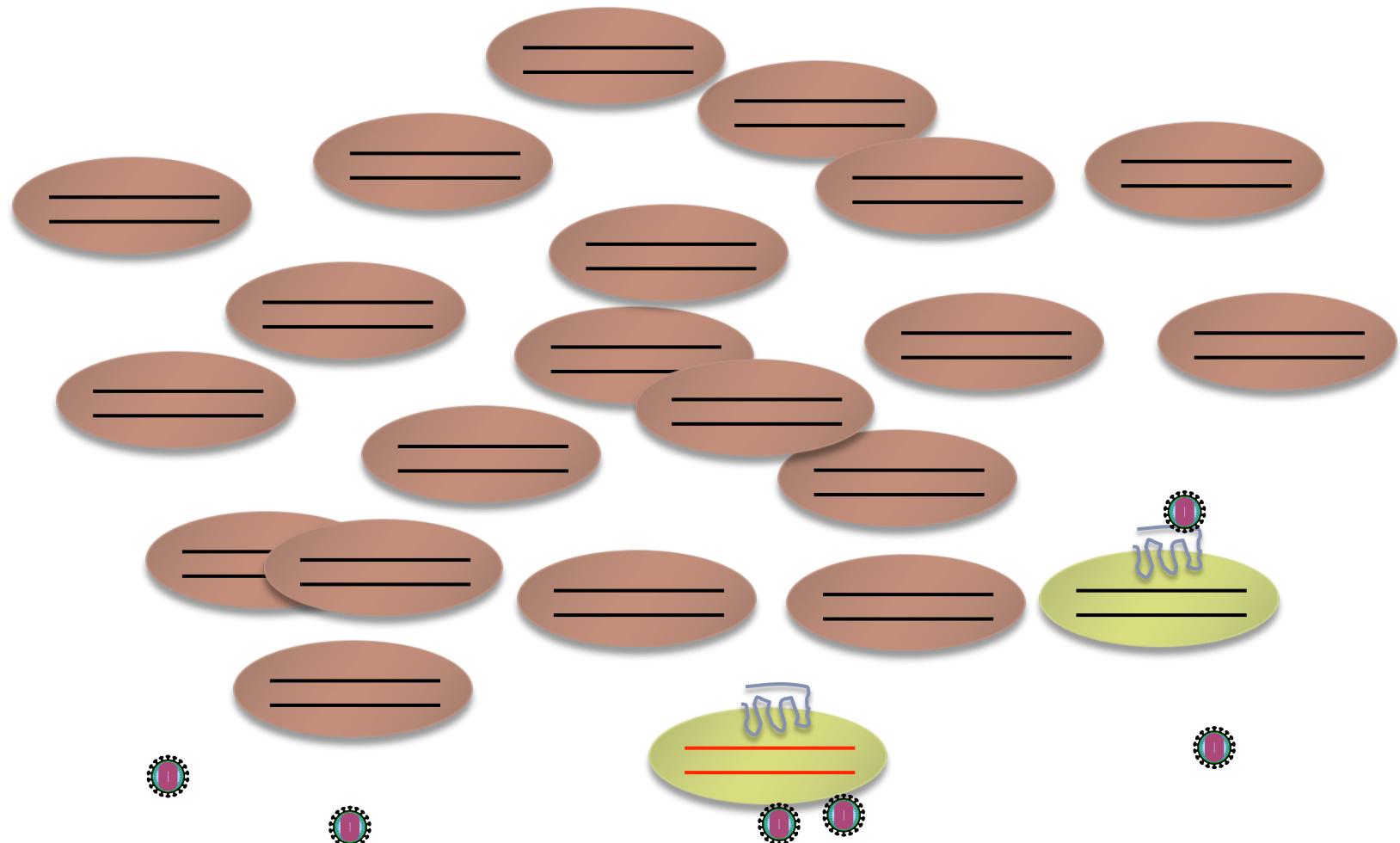
Irradiate the recipient immune system



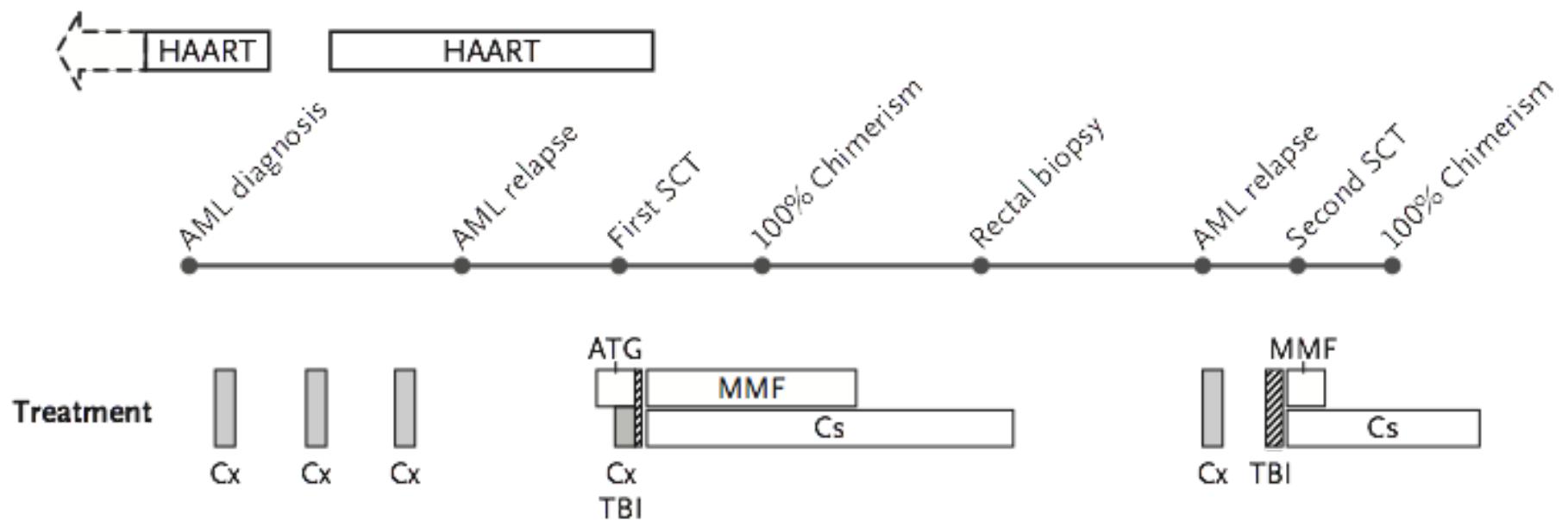
Add CCR5 Δ 32 donor bone marrow to replace the lost immune cells



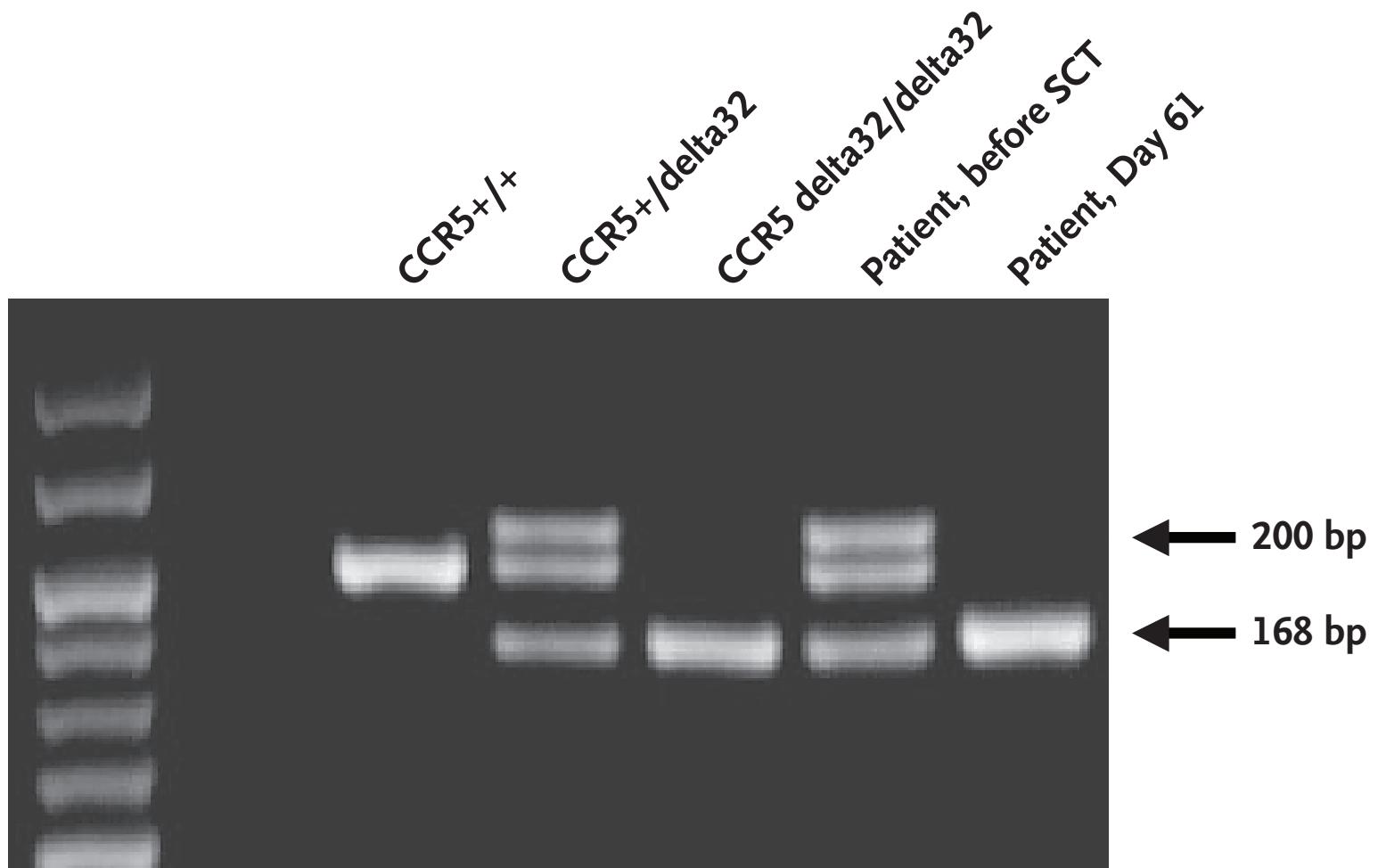
If HIV remains in the host, it is unlikely to infect new donor cells



Patient History



Testing whether the donor cells persisted in the recipient



Transplant success

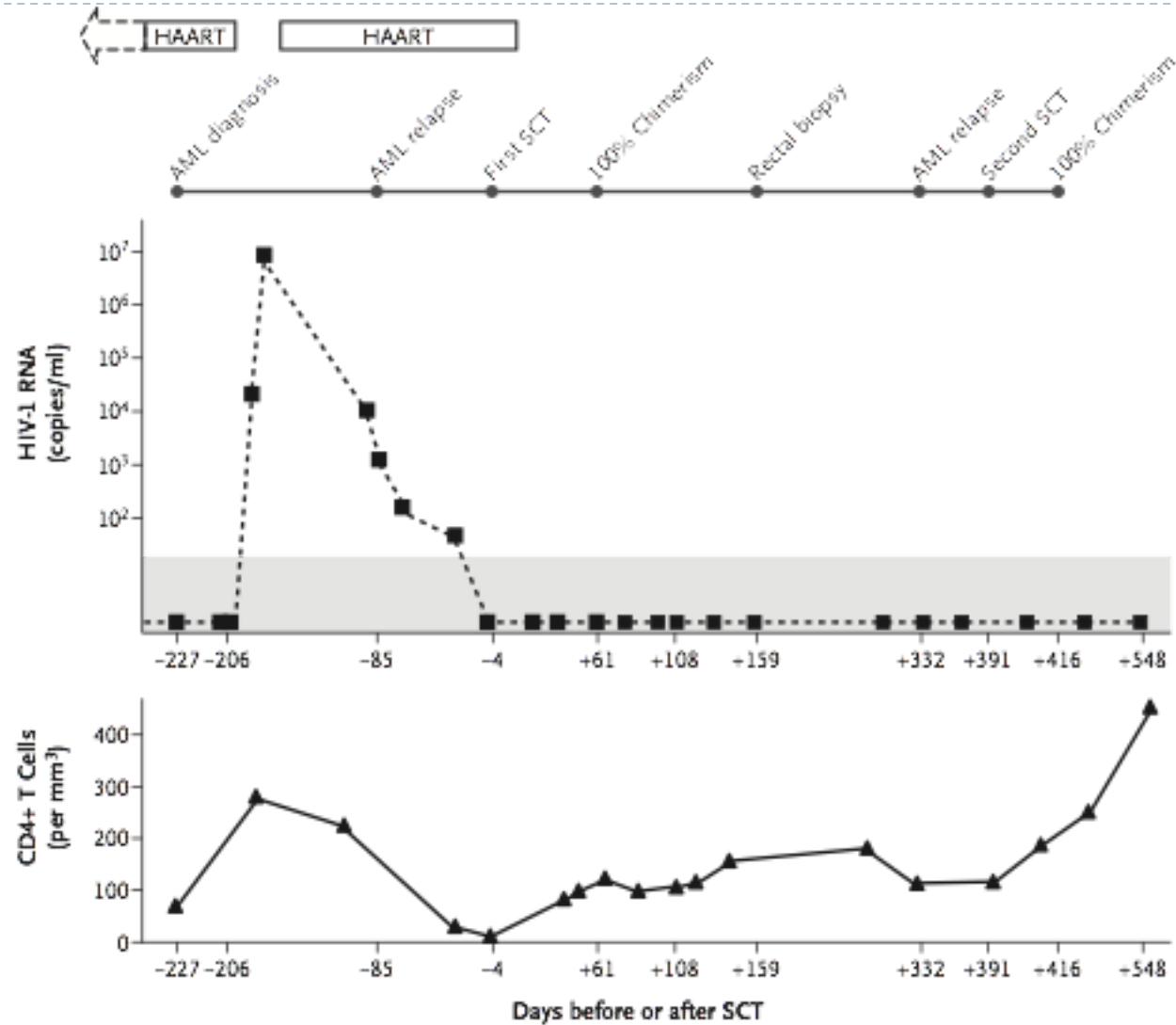


Table 4. Summary of virologic measures.

Sample	Measure	# Labs that tested samples	# Labs with + Test	Consensus
Plasma	HIV RNA	4	2 labs (3 samples)	?Intermittent positive, ?<1 copy/ml
PBMC	HIV DNA	4	0	Negative (≤ 1 in 10^{6-7})
PBMC	HIV RNA	3	0	Negative (≤ 1 in 10^{6-7})
Sorted cells from blood	HIV DNA	1	0	Negative
Sorted cells from blood	HIV RNA	1	0	Negative
Peripheral CD4+T	IUPM	2	0	Negative (≤ 1 IU/ 10^{7-9} cells)
CSF	HIV RNA	2	0	Negative
CSF cells	HIV DNA	1	0	Negative
Lymph node	HIV DNA	1	0	Negative
Lymph Node	HIV RNA	1	0	Negative
Rectum (biopsy or cells)	HIV DNA	2	1	?Intermittent positive, <1 in 10^6 cells
Rectum (biopsy or cells)	HIV RNA	3	0	Negative (<1 in 10^{6-7})
Ileum (biopsy or cells)	HIV DNA	1	0	Negative (≤ 1 in 10^6)
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Berlin Patient Summary

- ▶ Received a treatment for AML that also cured his HIV
 - ▶ Treatment related mortality is ~40% depending on age
- ▶ Researchers have been unable to reproducibly detect HIV in his blood or tissues
- ▶ The Berlin patient no longer requires drugs to treat his HIV infection

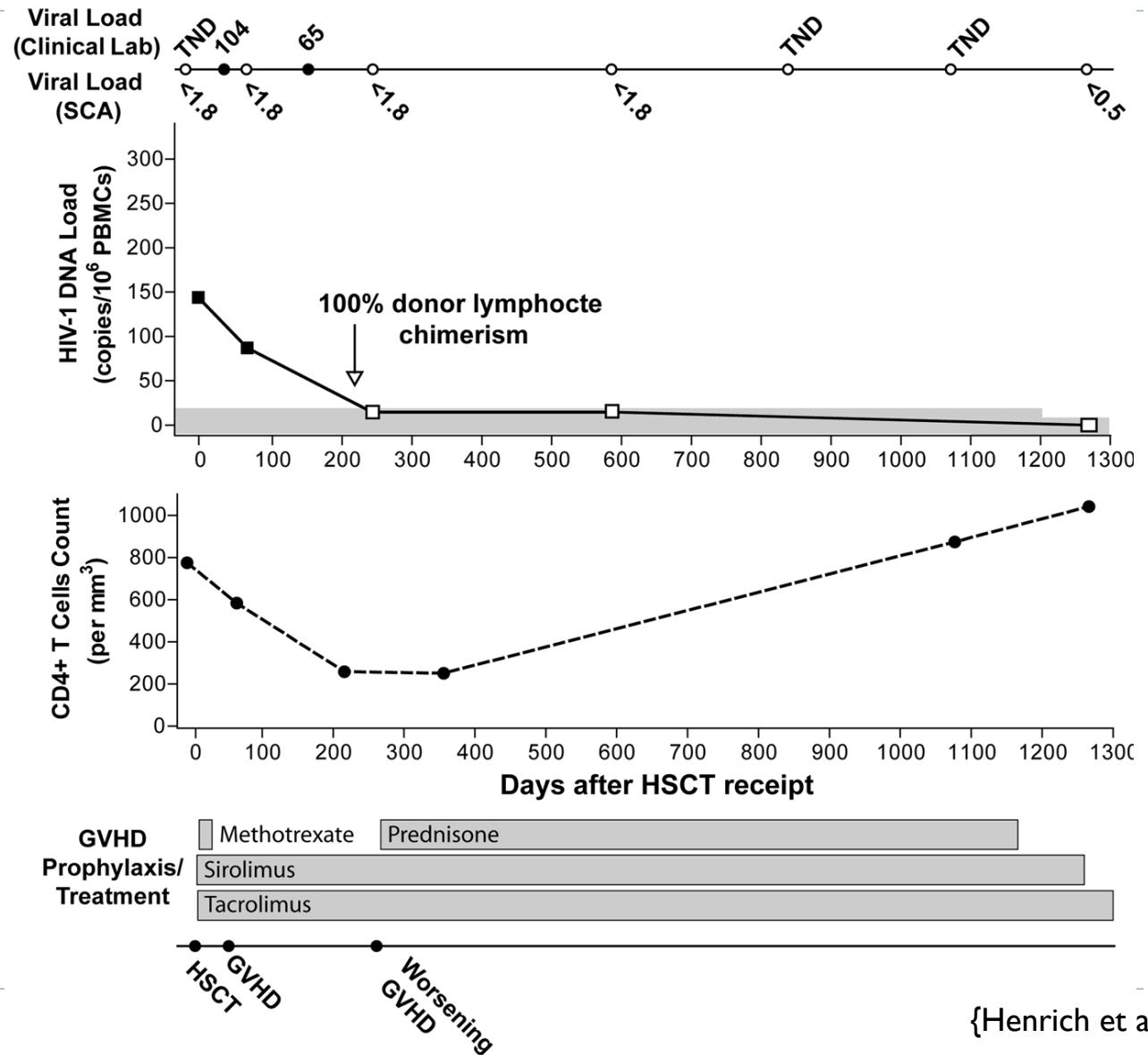


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- ▶ 32 <http://www.nytimes.com/2013/07/04/health/post-transplant-and-off-drugs-hiv-patients-are-apparently-virus-free.html>

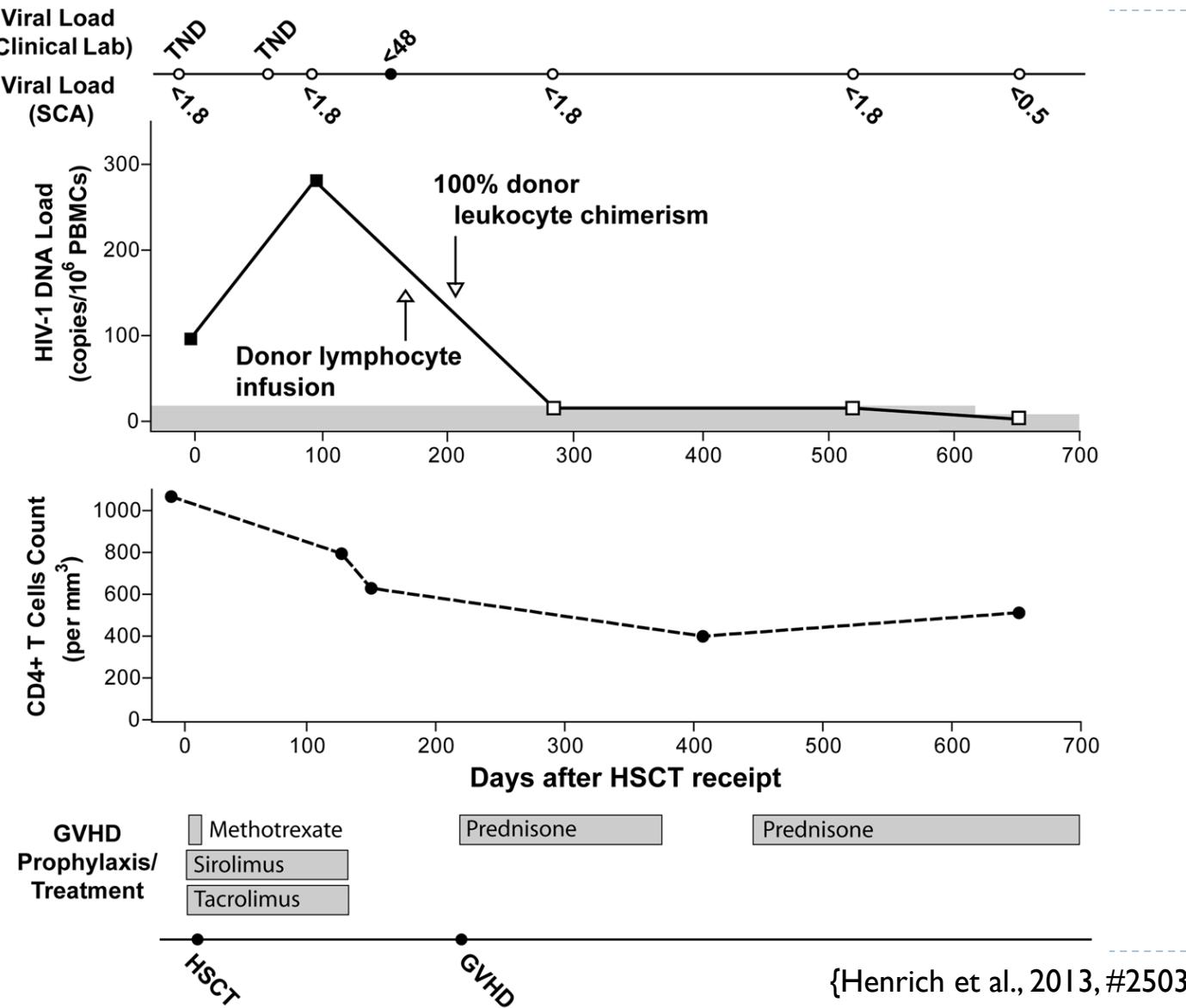
MIT/Boston Patients

- ▶ Patient A
 - ▶ Hodgkins lymphoma
 - ▶ Reduced-intensity conditioning stem cell transplant
- ▶ Patient B
 - ▶ B cell lymphoma
 - ▶ Reduced-intensity conditioning stem cell transplant
- ▶ Patients remained on ART after transplant
- ▶ Both patients experienced graft vs. host disease

Patient A



Patient B



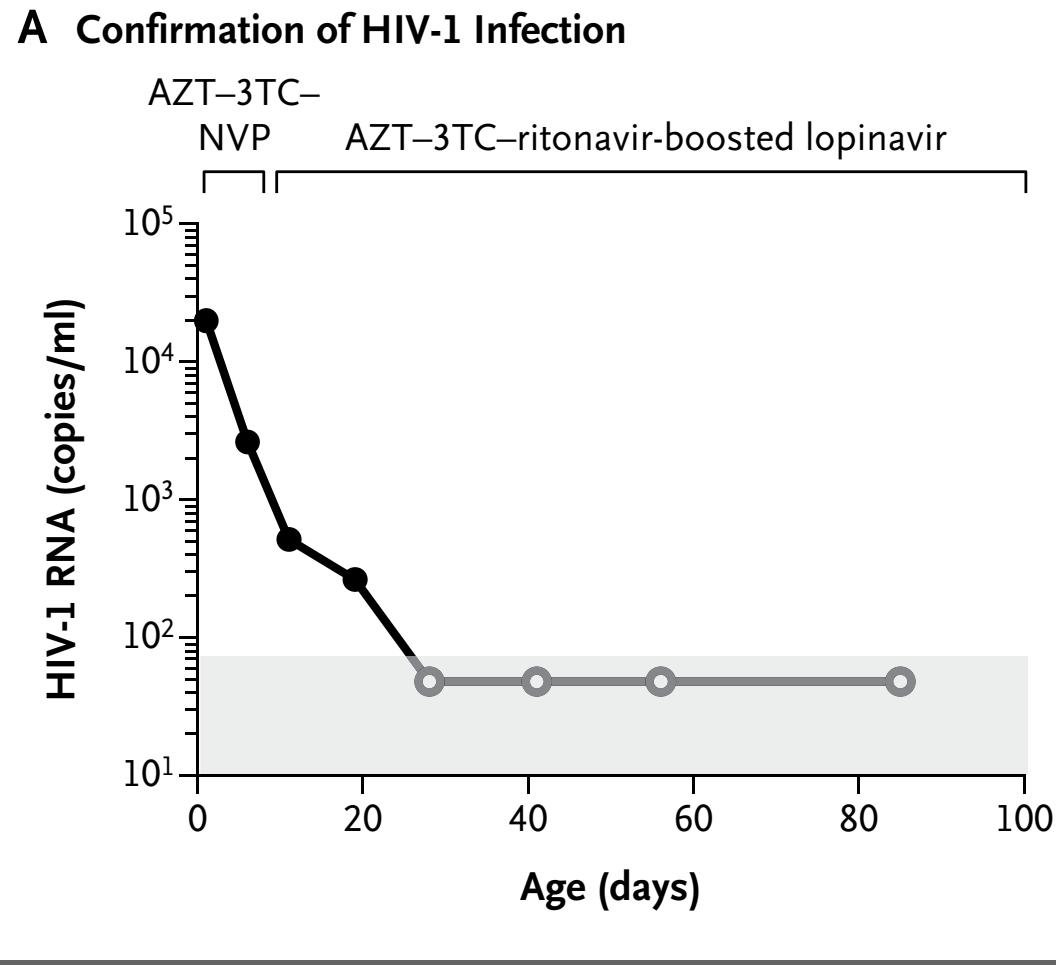
MIT/Boston Patients – announced but unpublished data

- ▶ The researchers decided to interrupt treatment
 - ▶ HIV DNA and HIV RNA remained undetectable after treatment interruption
 - ▶ The researchers believe that graft vs. host disease may **incidentally** have helped clear latently infected cells
 - ▶ This procedure has treatment related mortality of ~15-20%
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- ▶ 36 <http://www.nytimes.com/2013/07/04/health/post-transplant-and-off-drugs-hiv-patients-are-apparently-virus-free.html>

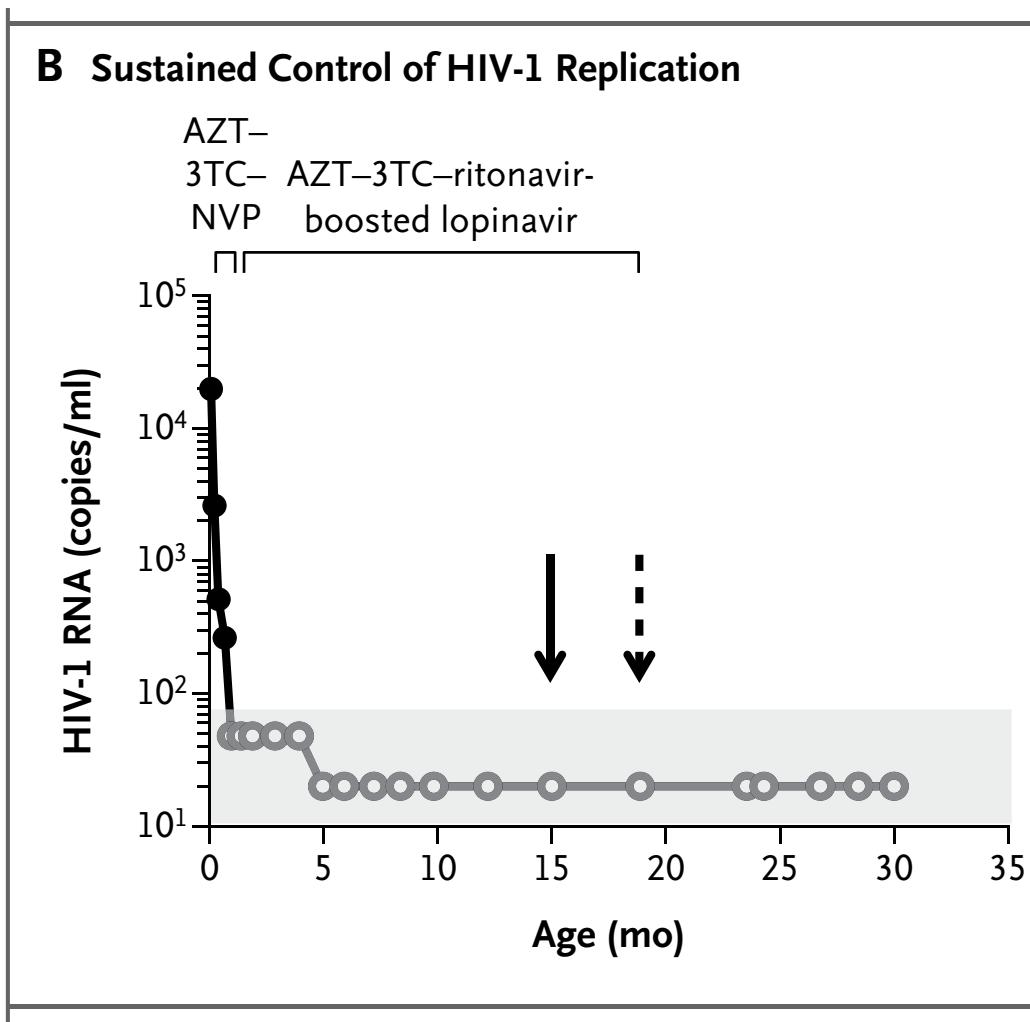
The Mississippi baby

- ▶ Infant born to HIV+ mother who received no prenatal care
 - ▶ Mother had viral loads of approximately 2000vRNA copies/ml
- ▶ ART was started at 30 hours of age
- ▶ HIV RNA was detected in the plasma at 30 hours (~20,000 vRNA copies/ml plasma) and until 19 days of age

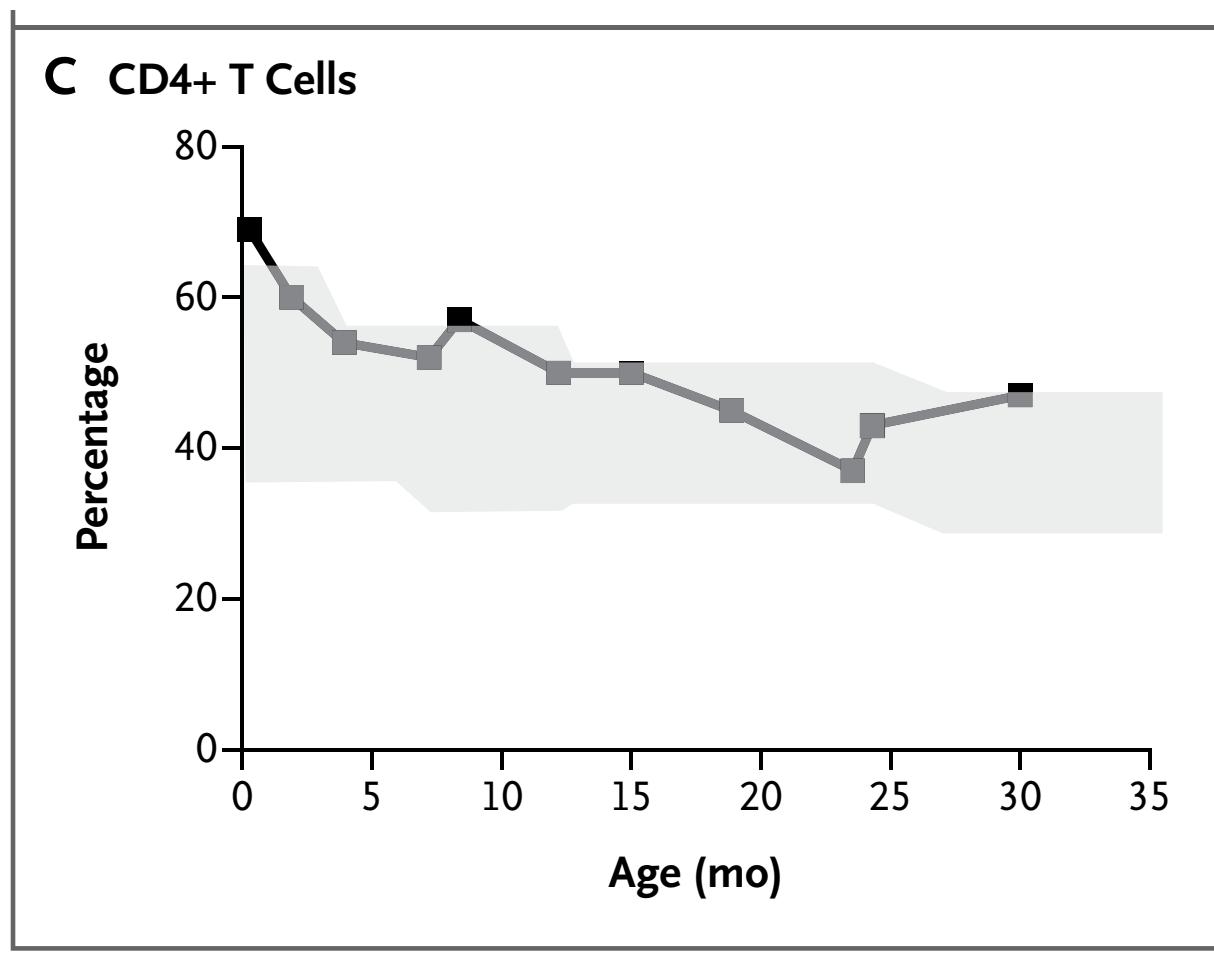
The infant appears to have been HIV+



Treatment was interrupted at 18 months and HIV DNA and RNA was undetectable



CD4 T cells remained relatively stable after birth



Summary of Mississippi baby

- ▶ The infant was likely infected in utero and began treatment by 30 hours of age
- ▶ HIV RNA and DNA is undetectable in the infant after 26 months.
- ▶ They currently say that the infant's HIV is in remission
- ▶ Ideally, in the US, we should be able to prevent infection of an infant

French Cohort

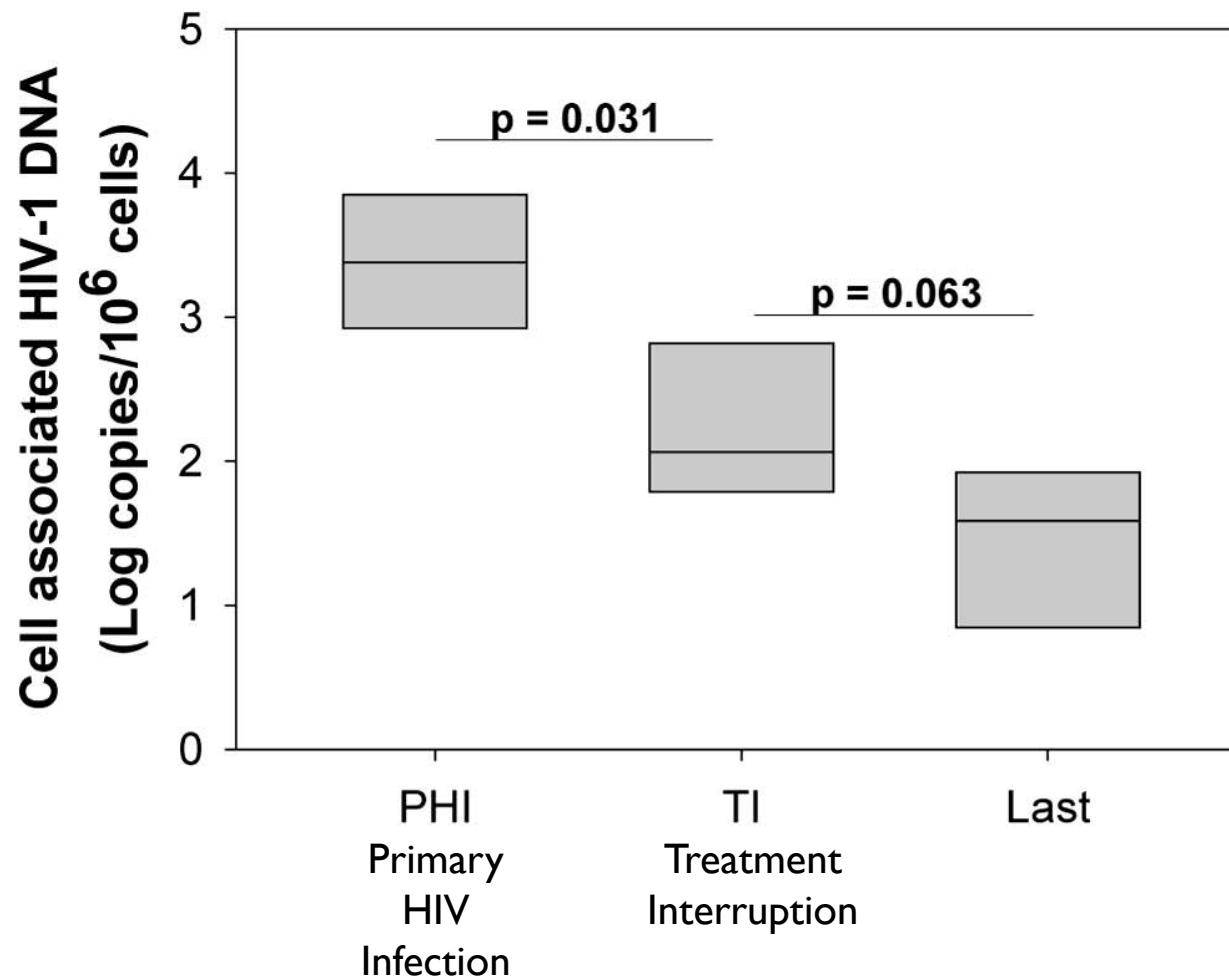
- ▶ Main Question – can early treatment of HIV (in the first 10 weeks of infection) lead to control of viral replication after interruption of ART.
- ▶ 14 patients who were treated during primary HIV infection underwent supervised treatment interruption
- ▶ While these patients still have detectable HIV in their bodies, they are controlling viral replication and no longer require ART.

Multiple questions were addressed

- ▶ Do these individuals have unique genetics that allow them to control?
- ▶ Do these patients still have a large reservoir of latently infected cells?

The reservoir continued to decline in size after treatment interruption

A



French Cohort Summary

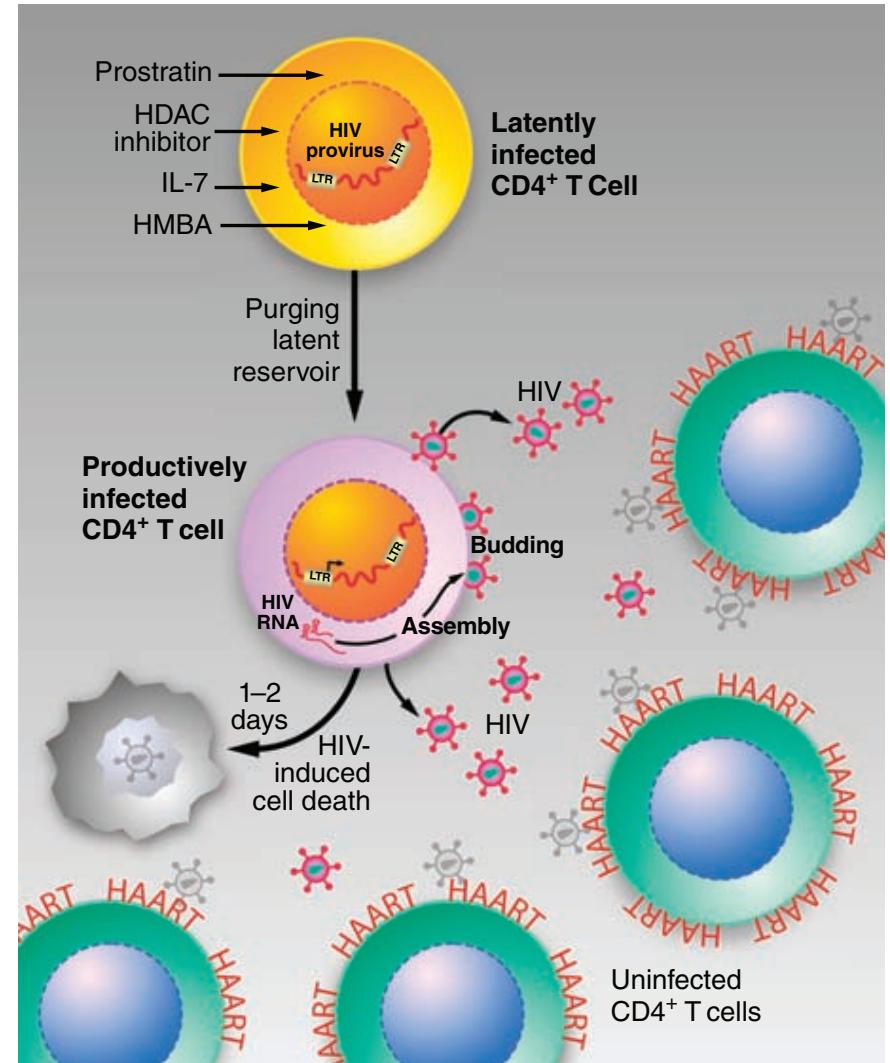
- ▶ Early treatment with ART allowed patients to interrupt treatment and maintain control of viral replication
- ▶ These patients still have measureable HIV RNA and HIV DNA
- ▶ These researchers predict that 15% of people similarly treated early could also be “cured”

Successful cure strategies

- ▶ Replace the viral reservoir with HIV-resistant cells
 - ▶ Berlin Patient
- ▶ Eliminate the viral reservoir and treat with ART while transfusing non-resistant cells
 - ▶ MIT/Boston Patients
- ▶ Treat very early after HIV infection
 - ▶ Mississippi Baby and the French Cohort

Untested ideas for an HIV cure

- ▶ Activating cells that are latently infected while treating patients with ART
- ▶ Taking a person's cells, modifying them to be HIV-resistant, returning the cells
- ▶ Keeping latent cells latent



Have we cured HIV?

- ▶ Does it matter if HIV is totally eradicated from someone's body?
- ▶ How is trying to cure HIV similar to trying to cure cancer?
- ▶ Is it economically feasible to scale up these HIV cures?
- ▶ With effective ART available, how much should we be investing in HIV cure research?
 - ▶ What are the advantages of an HIV cure compared to HIV treatment?