

## Quiz 6 – due in discussion Fri, Dec. 6<sup>th</sup>.

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- ▶ 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

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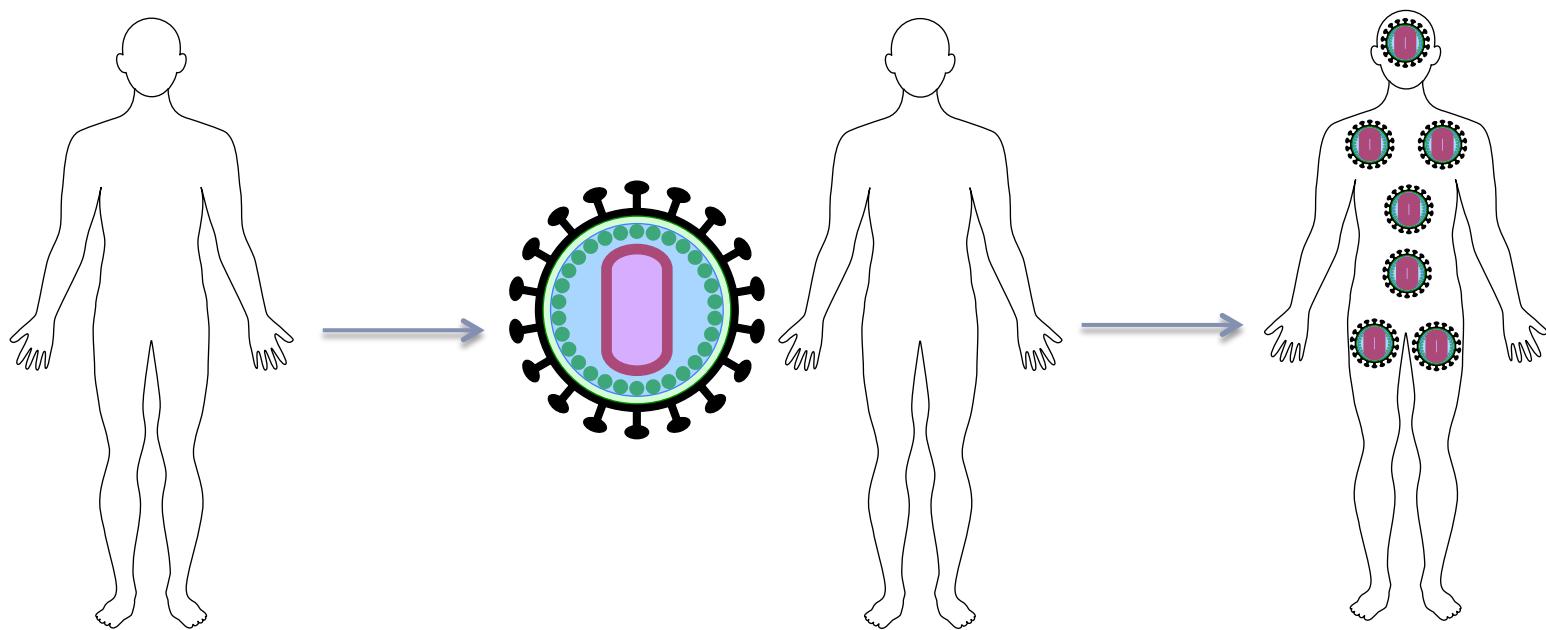
- ▶ **What does it mean to be cured of HIV?**
  - ▶ What language do we use to discuss an HIV cure?
- ▶ What are current challenges to curing HIV?
- ▶ Four cure stories and the future of cure research
- ▶ Conclusions

# What does it mean to cure someone of HIV?

# How is a cure different from a prophylactic vaccine?

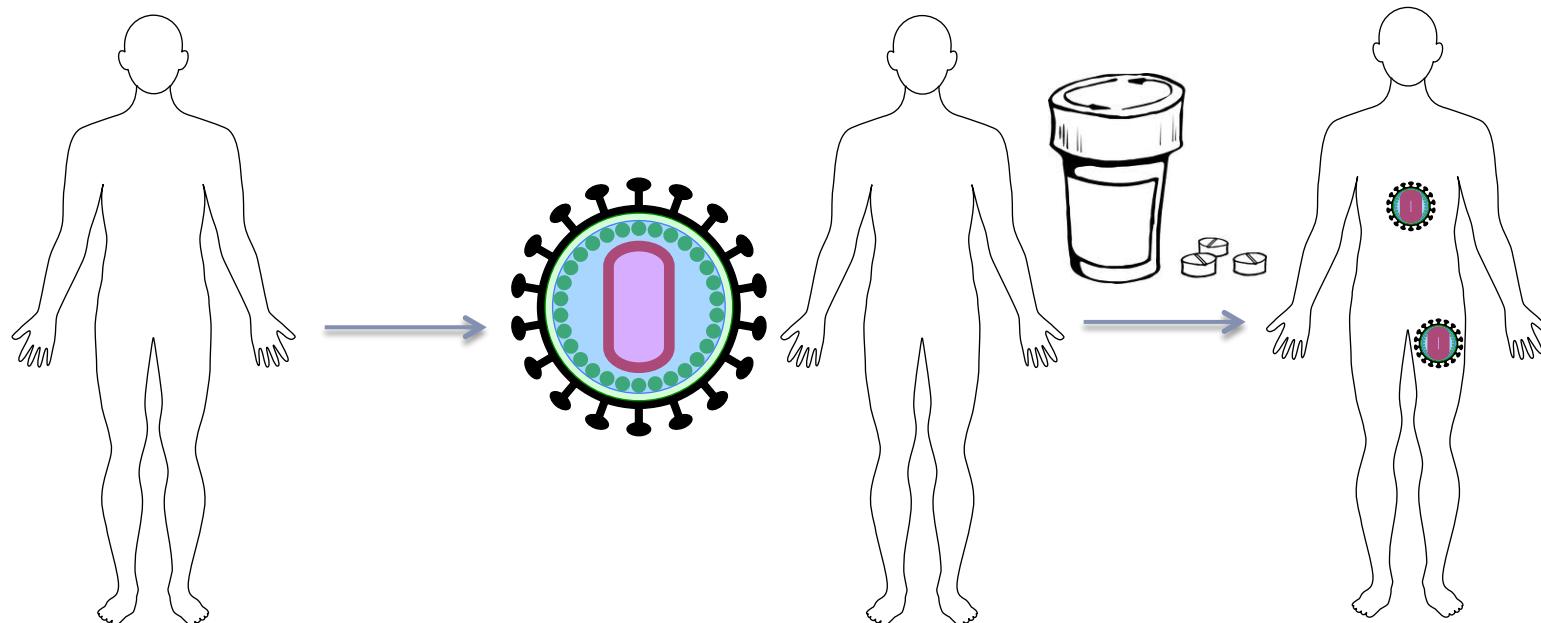
-intended to prevent disease

# Typical HIV infection



# Treatment with ART

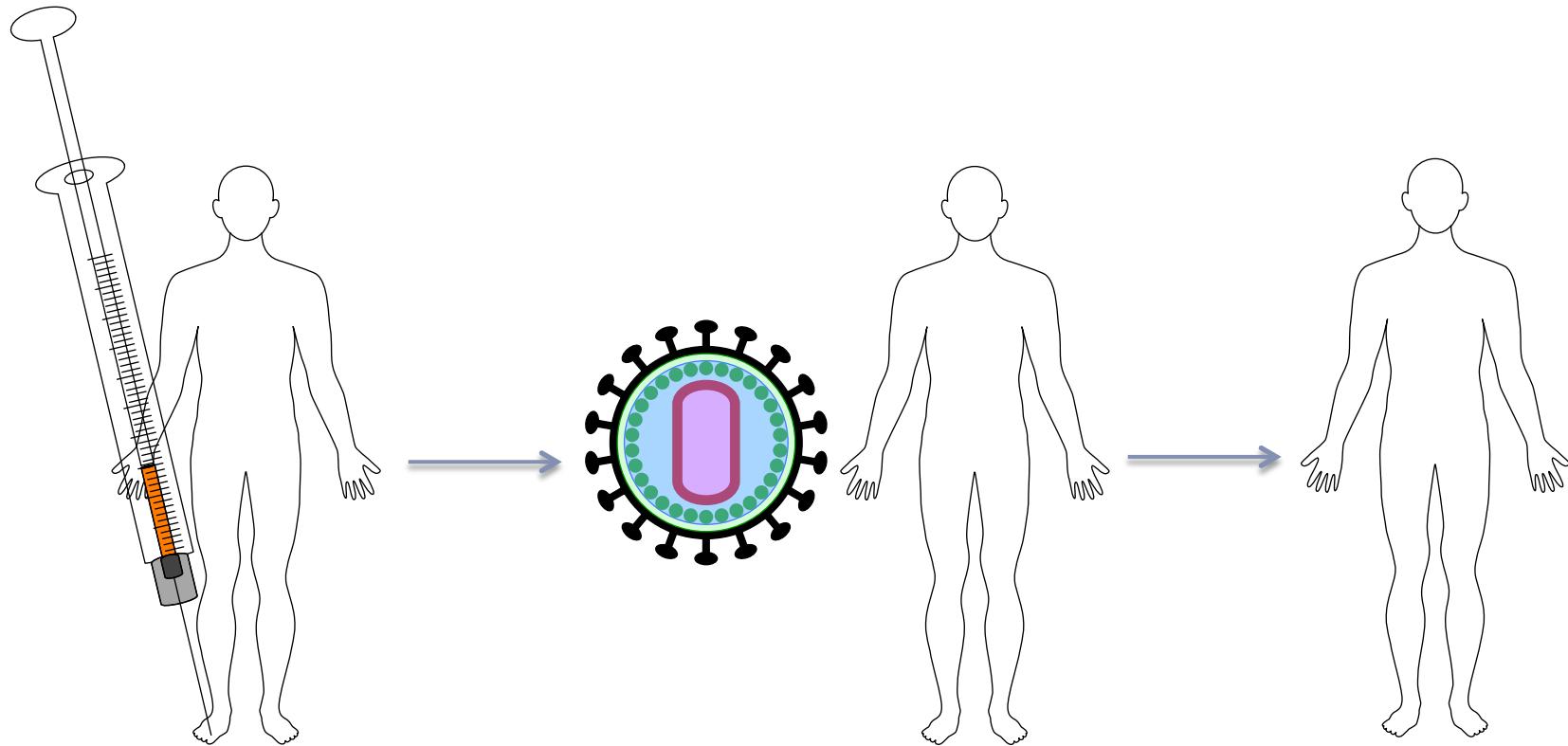
does not eliminate the virus from the body



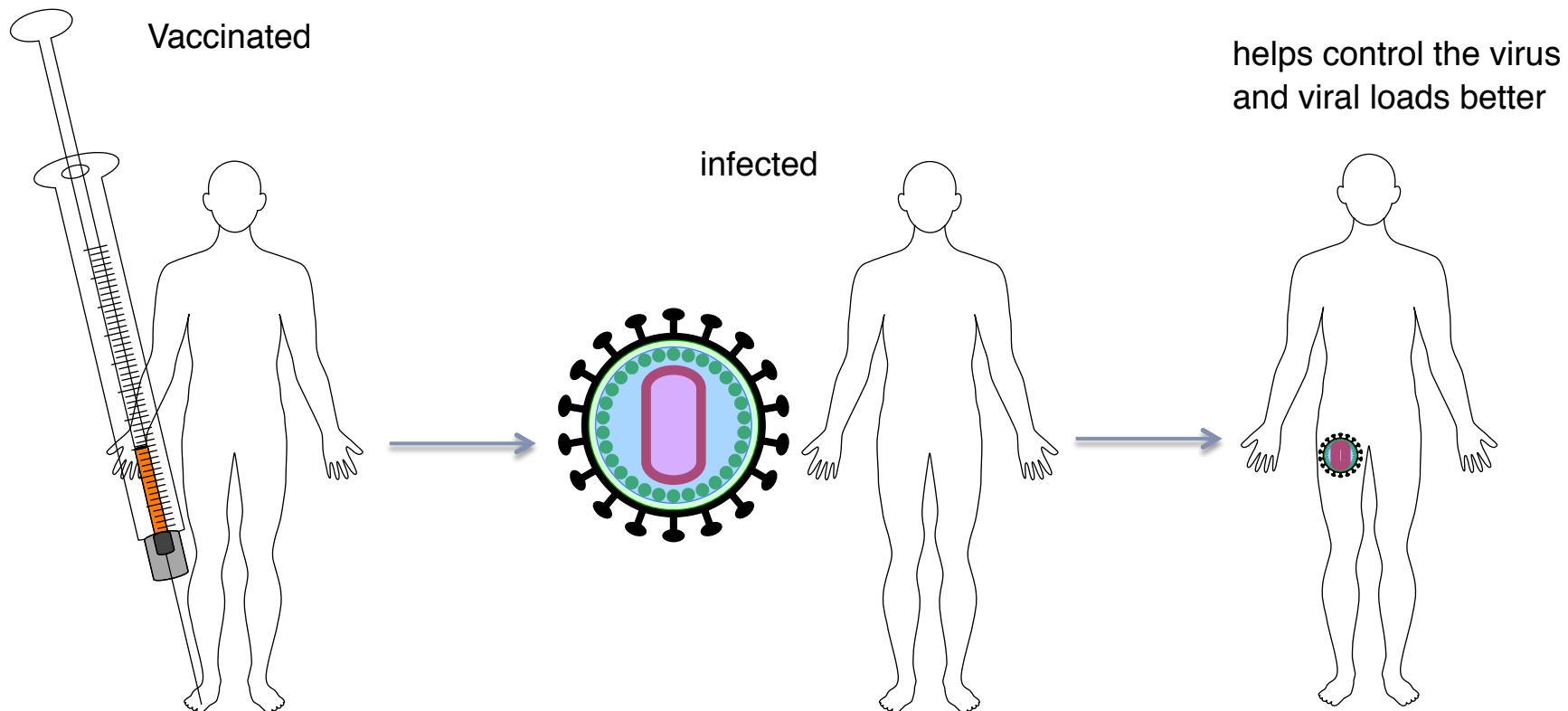
Think about why ART may not eliminate the virus

# Prophylactic Vaccine – intended to prevent disease

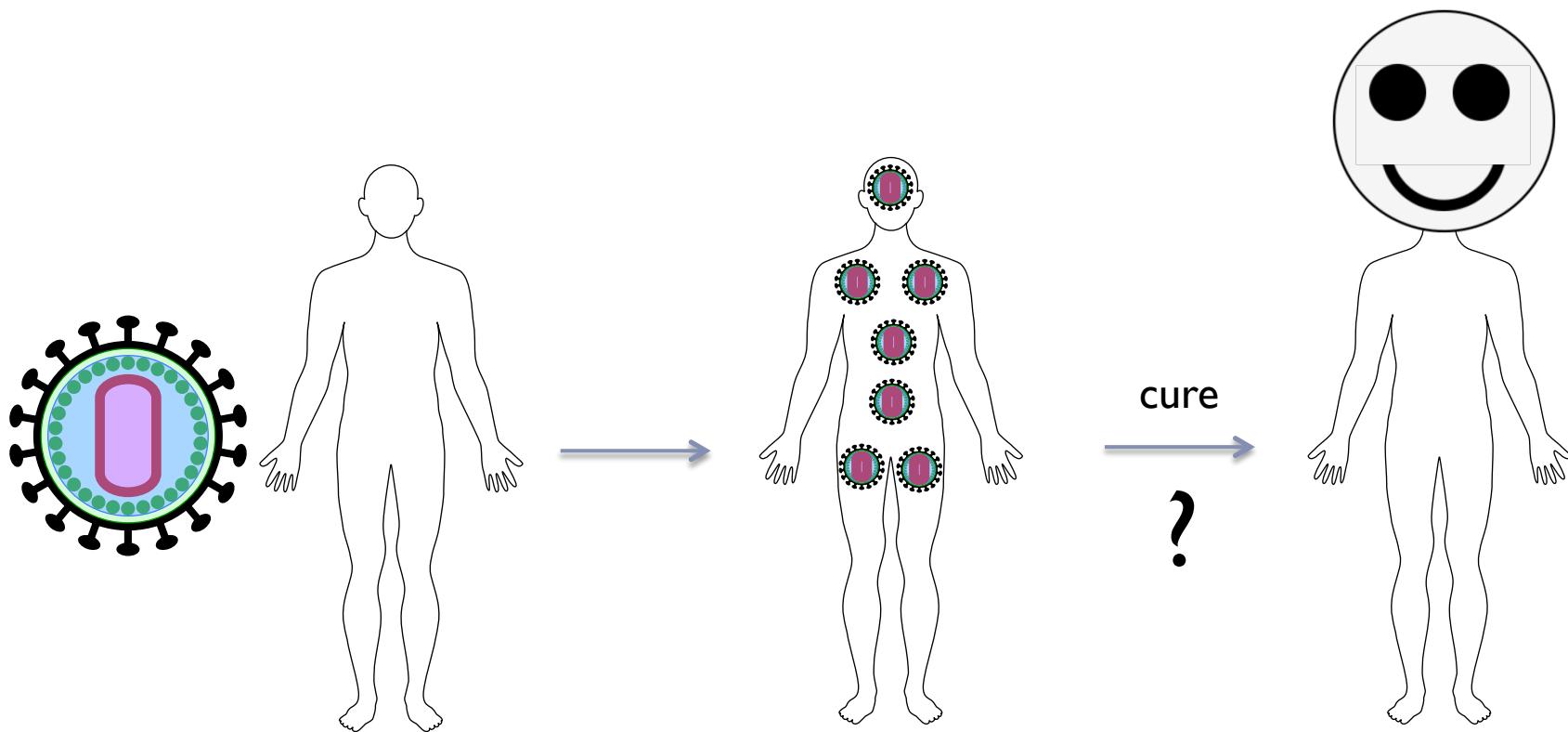
ideal HIV vaccine would completely prevent infection



# Novel Vaccine ideas



# An HIV cure



# Key Terms

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- ▶ **Prophylactic vaccine** – agent that elicits an immune response which provides protection against a pathogen in the future
  - 1 ▶ Might prevent infection
  - 2 ▶ 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

Doesn't completely get rid of the virus

may come back and could progress to AIDS

# Why is the distinction between functional cure and cure important.

## ▶ Eradication -Cure

- ▶ 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

# Outline

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- ▶ 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

# Challenges to developing a cure for HIV

#1 reason ▶ Latently infected cells that why ART doesn't cure

- ▶ 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

Brain, gut tissue, CNS

▶ Replication in tissues that are inaccessible to drugs

testes, eyes, CNS

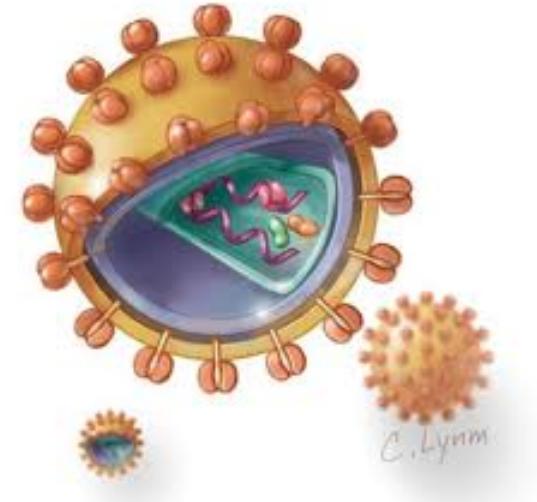
▶ Replication in immune privileged sites

You don't want huge immune response in these areas - could go blind

Neuro damage

▶ Drug resistance mutations

▶ Immune escape virus can escape from the immune response



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

# Key Terms and concepts

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- ▶ **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](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)

# Outline

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- ▶ 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

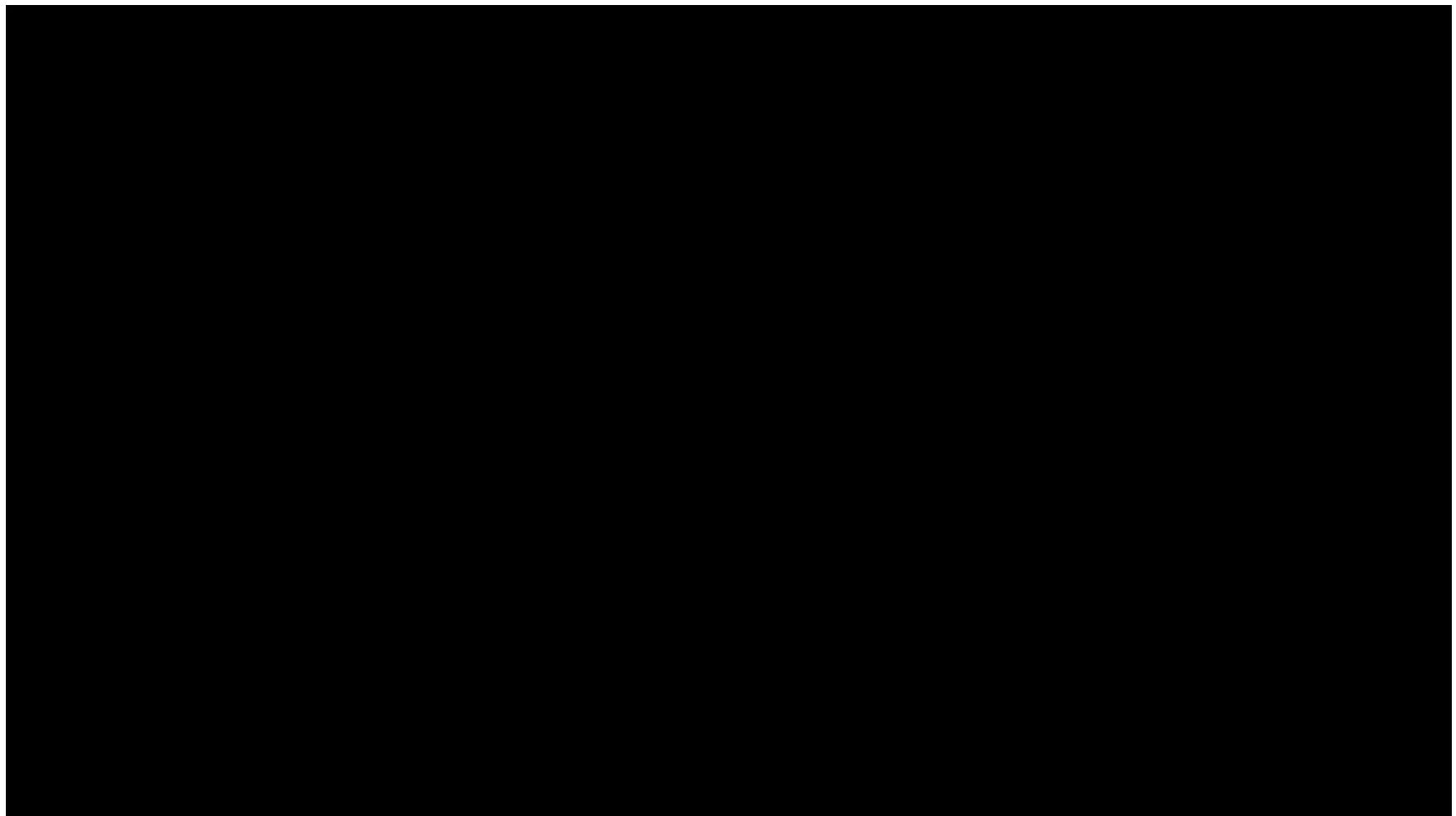
# Current Cure Stories

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- ▶ Berlin Patient
- ▶ MIT/Boston Patients
- ▶ The Mississippi baby
- ▶ The French cohort -group of people being studied that were HIV+

# 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-/](http://www.cbs.com/shows/cbs_evening_news/video/1970438971/a-functional-cure-for-hiv-/)

Timothy Ray Brown - Tested positive for HIV in 1995  
HIV completely eliminated from his body;  
functional cure - no way to check every cell in a person body; no way to know

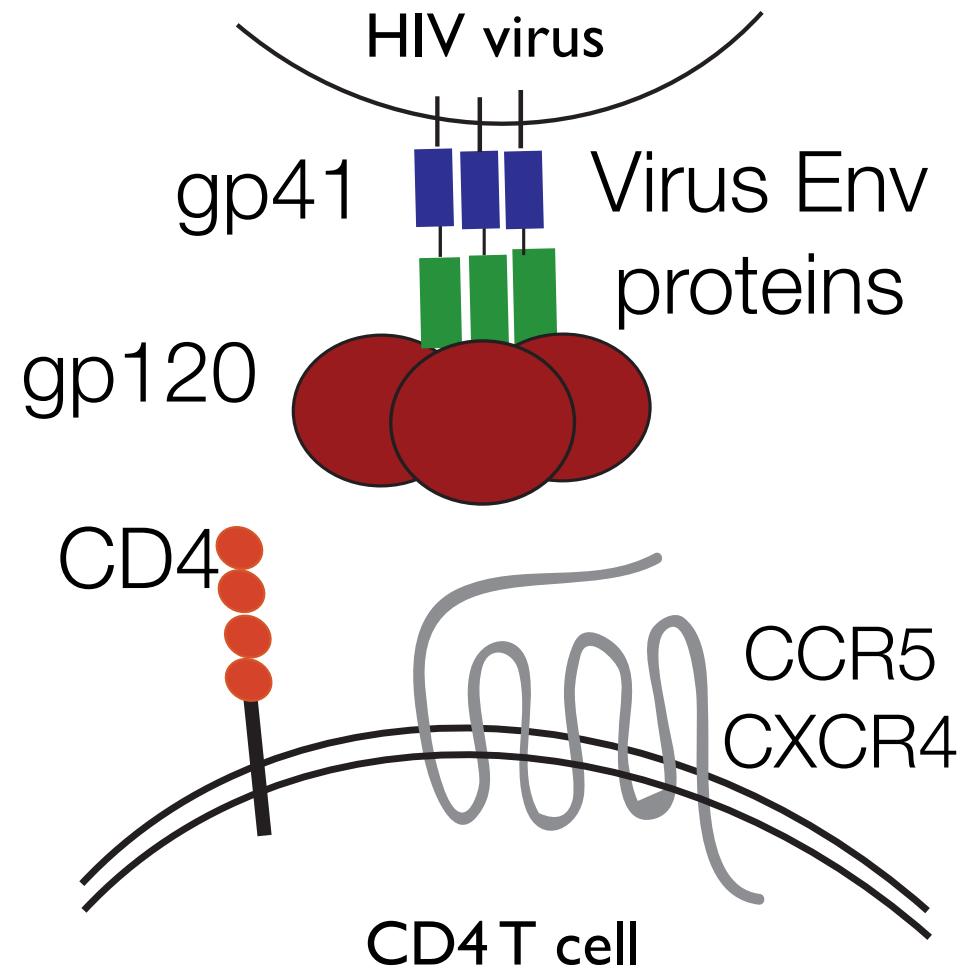
## The Berlin Patient

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- ▶ 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 -immune to HIV
- 
- ▶ 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

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# Mutant CCR5 ( $\text{CCR5} \Delta 32$ )



less CCR5 on the cell surface  
Progress to AIDS more slowly

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

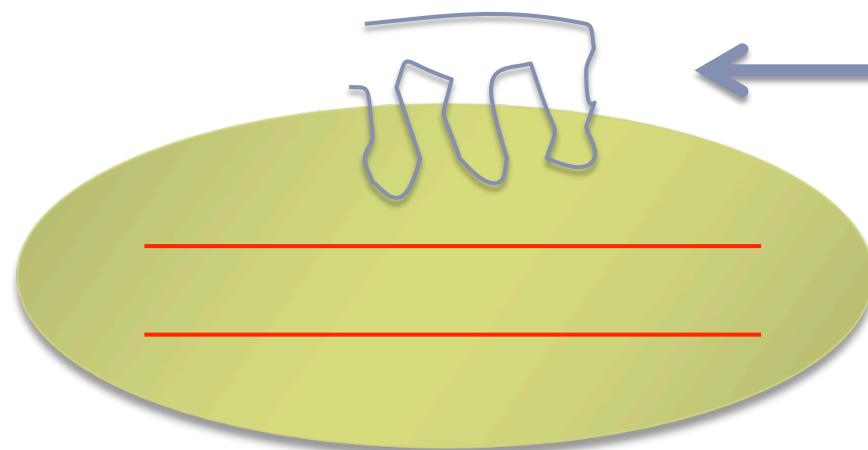


essentially have no CCR5 on the surface of their cells (CD4 T)

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

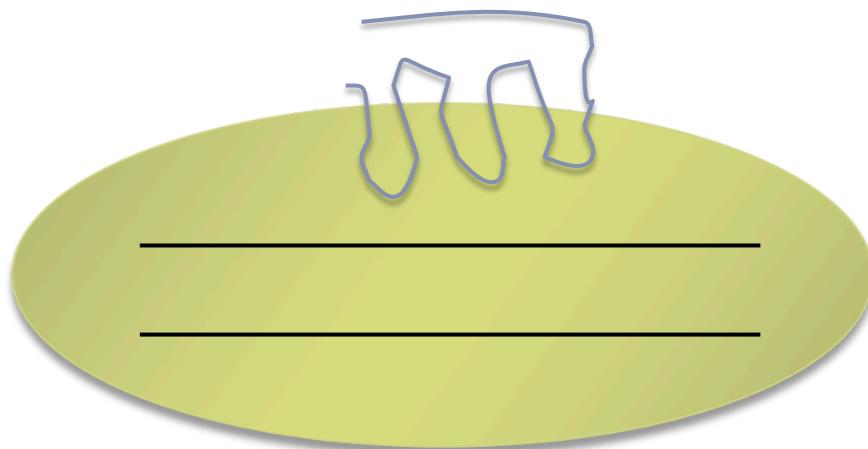
Cannot get infected by HIV

## At the cellular level



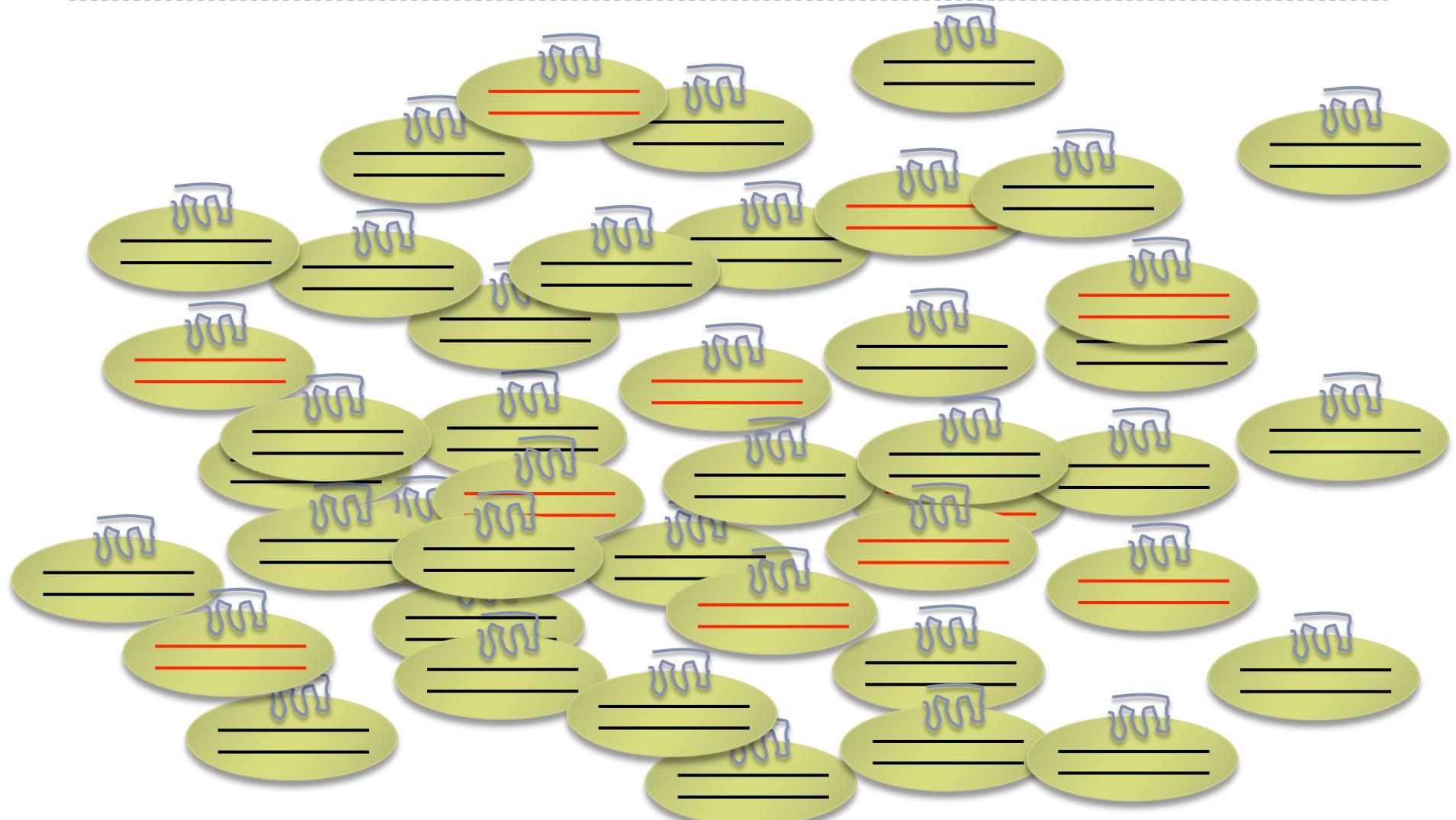
CCR5

Latently infected cell

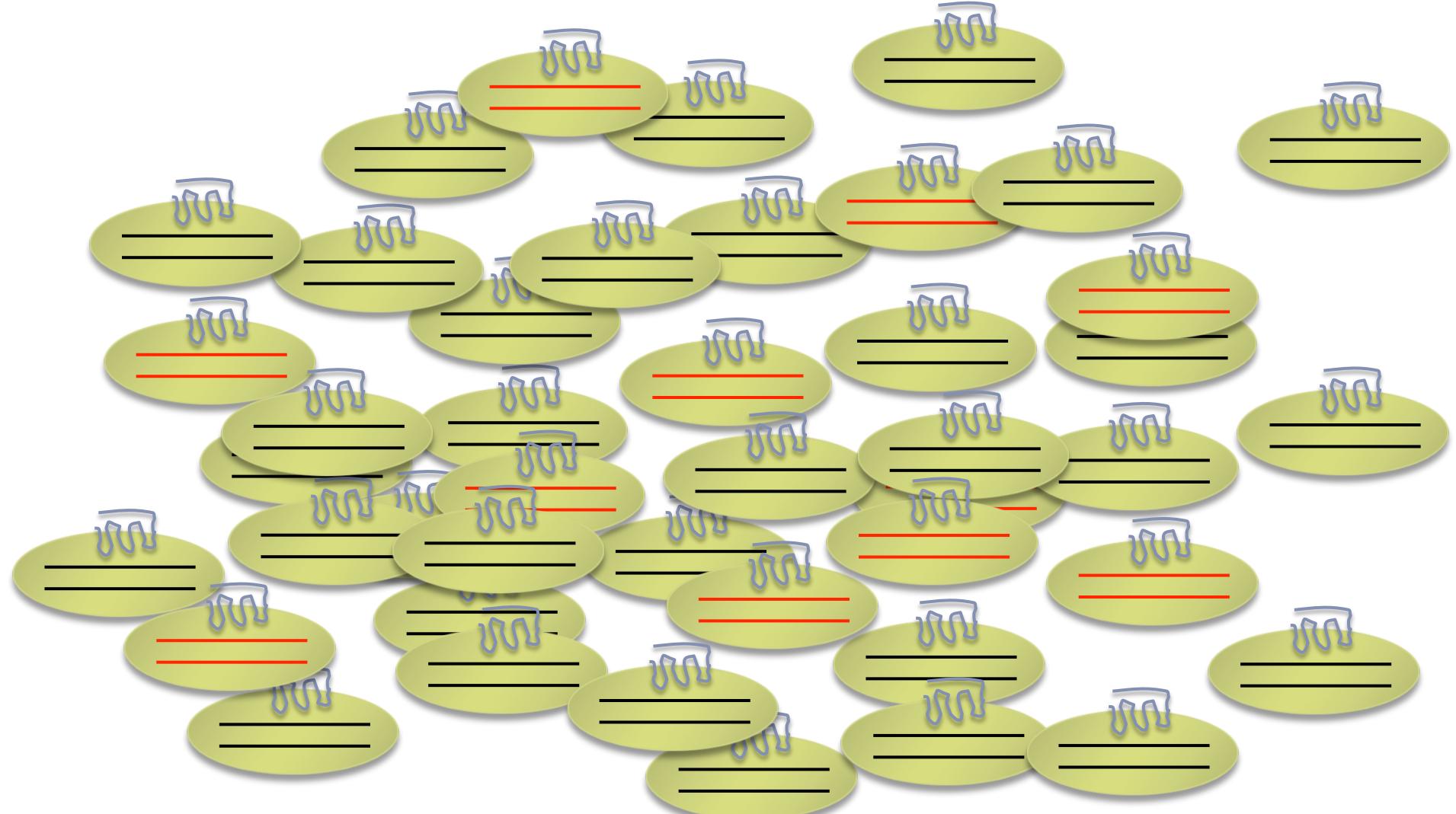


Uninfected cell

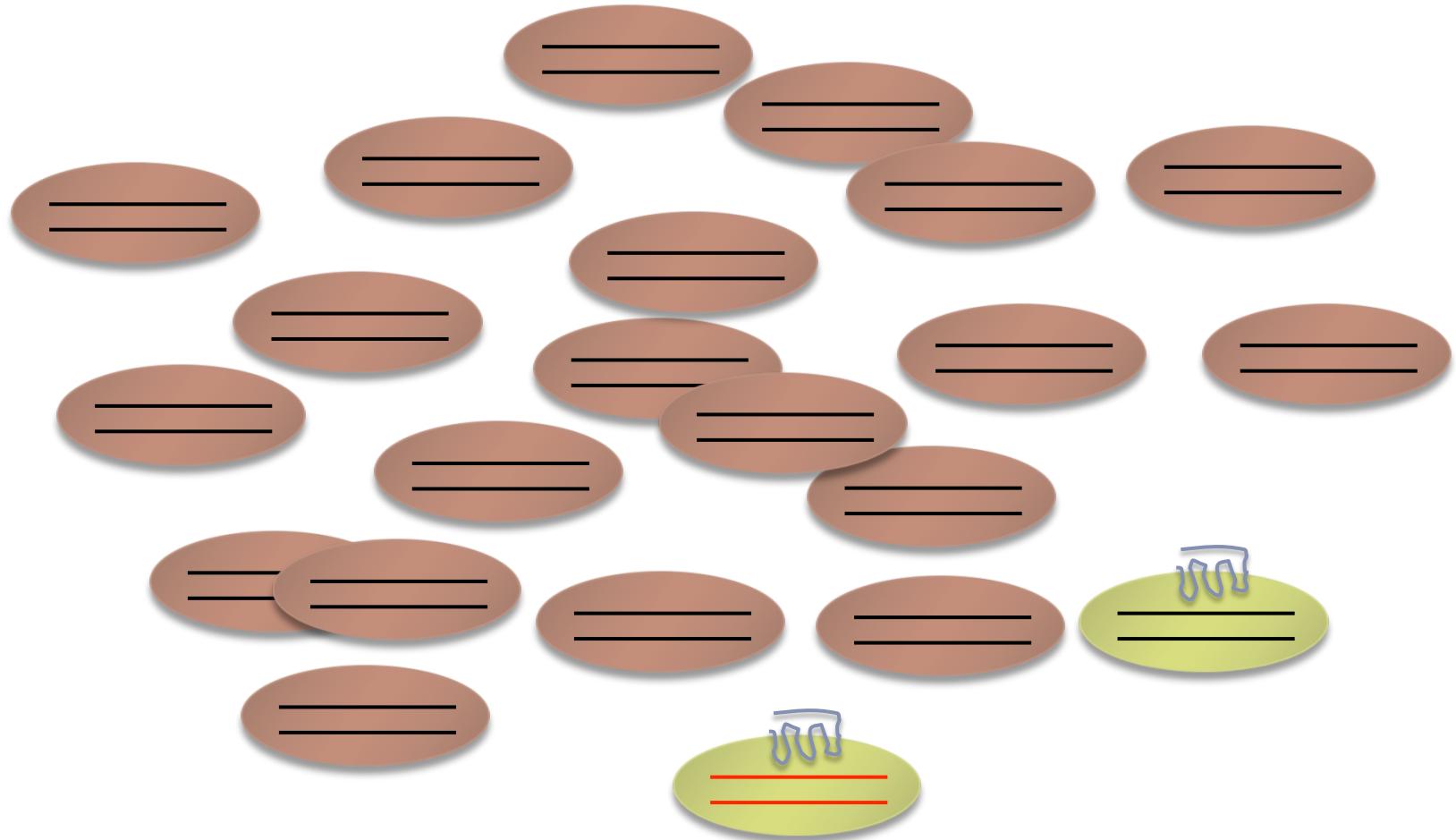
# Recipient immune system before irradiation – contains latently infected cells



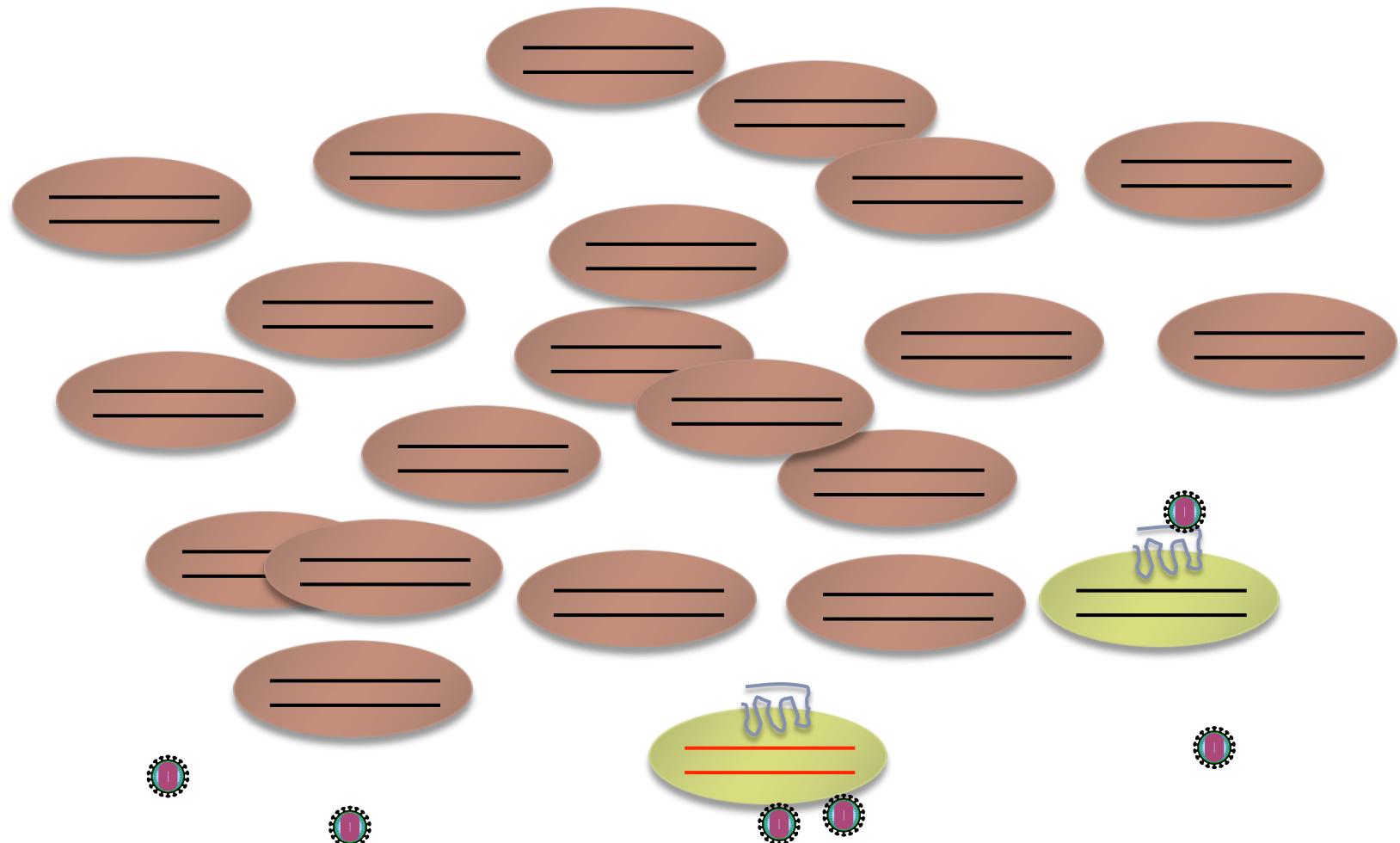
# Irradiate the recipient immune system



Add CCR5 $\Delta$ 32 donor bone marrow to replace the lost immune cells

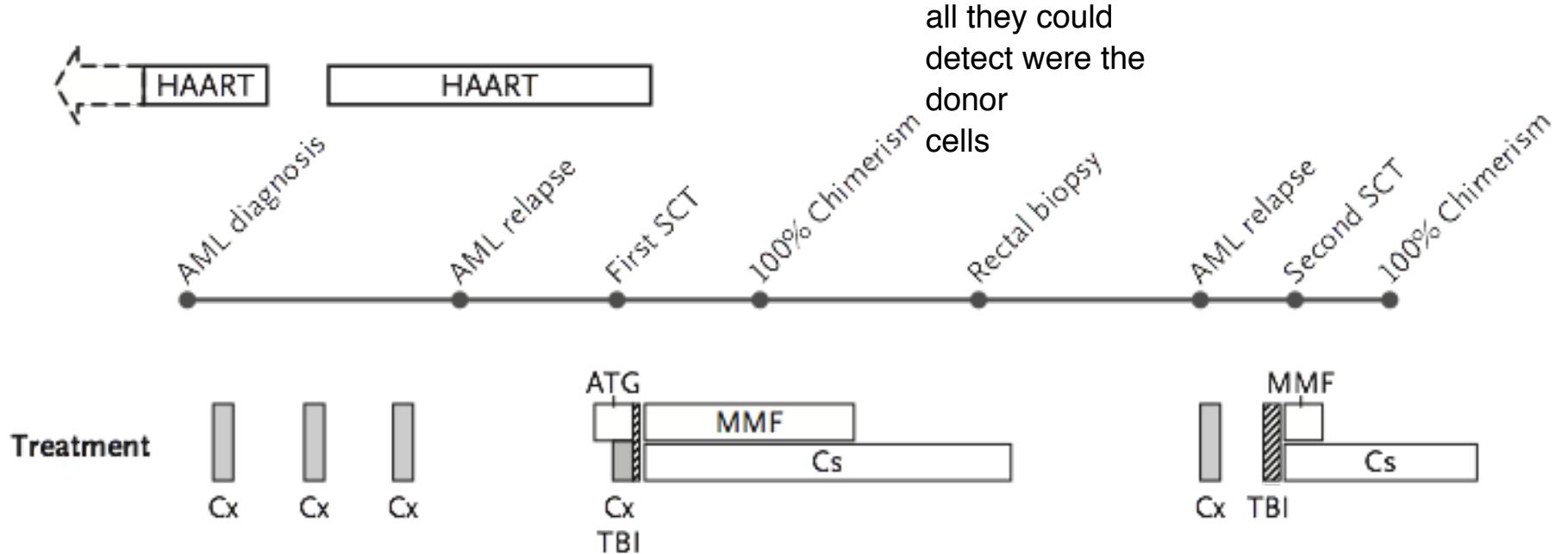


If HIV remains in the host, it is unlikely to infect new donor cells

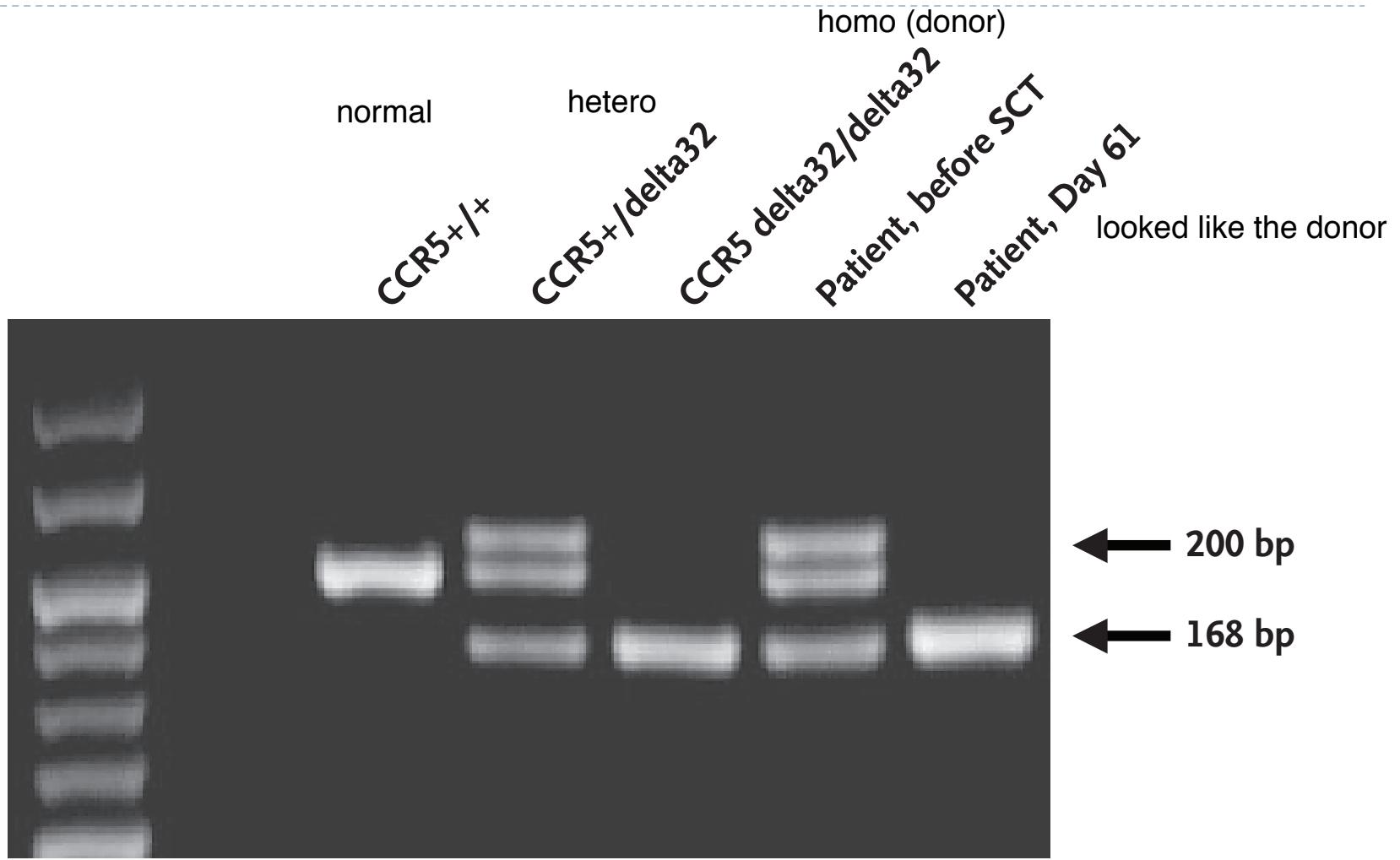


# Patient History

SCT: stem cell transplant

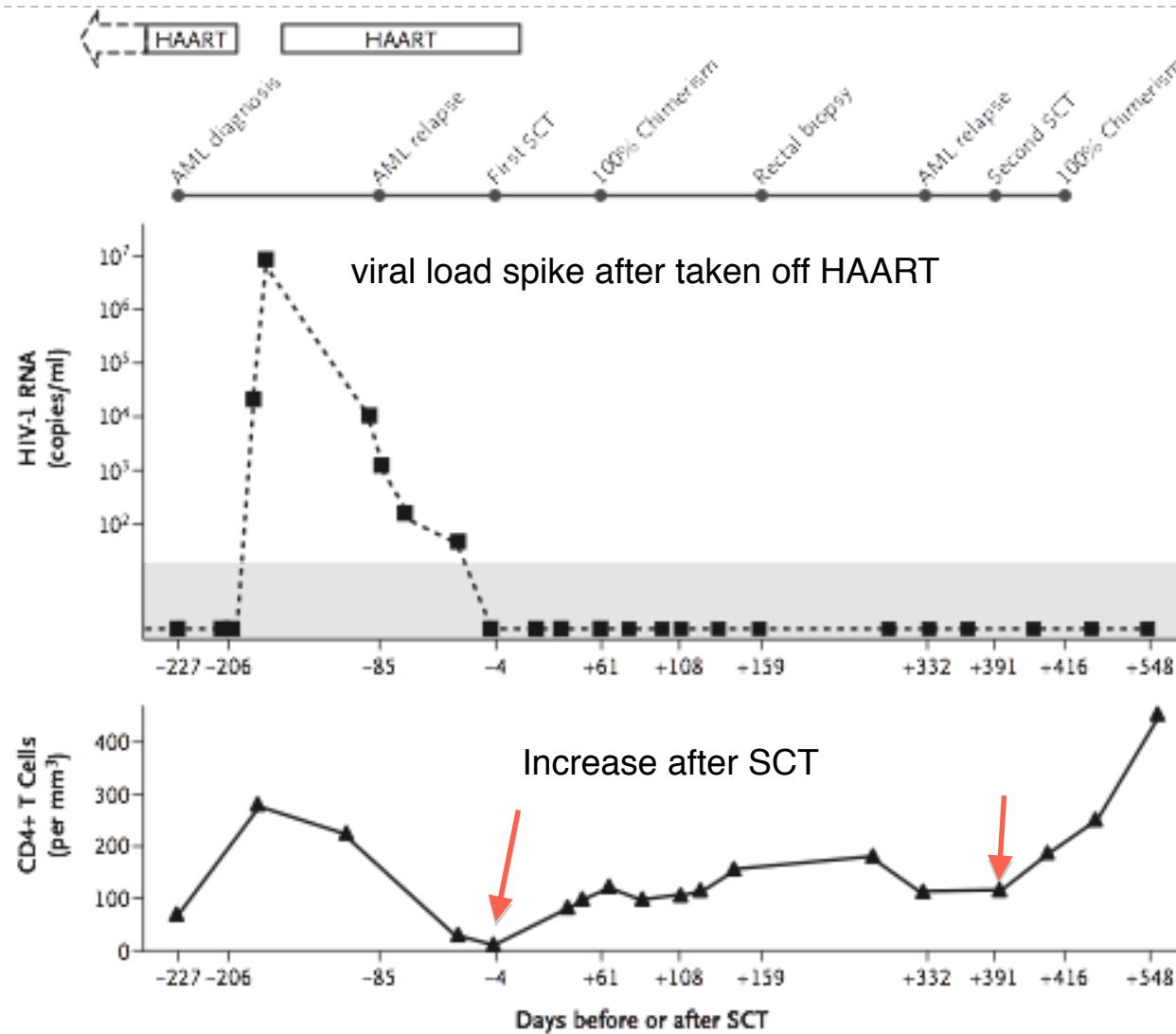


# Testing whether the donor cells persisted in the recipient



immunosuppressants for the rest of their because immune cells attack non-self cells to prevent Graft-versus-host disease (GVHD)

## Transplant success



**Table 4.** Summary of virologic measures.

<b>Sample</b>	<b>Measure</b>	<b># Labs that tested samples</b>	<b># Labs with + Test</b>	<b>Consensus</b>
Plasma	HIV RNA	4	2 labs (3 samples)	?Intermittent positive, ?<1 copy/ml
PBMC	HIV DNA	4	0	Negative ( $\leq 1$ in $10^{6-7}$ )
PBMC	HIV RNA	3	0	Negative ( $\leq 1$ 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 ( $\leq 1$ 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
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Ileum (biopsy or cells)	HIV DNA	1	0	Negative ( $\leq 1$ 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



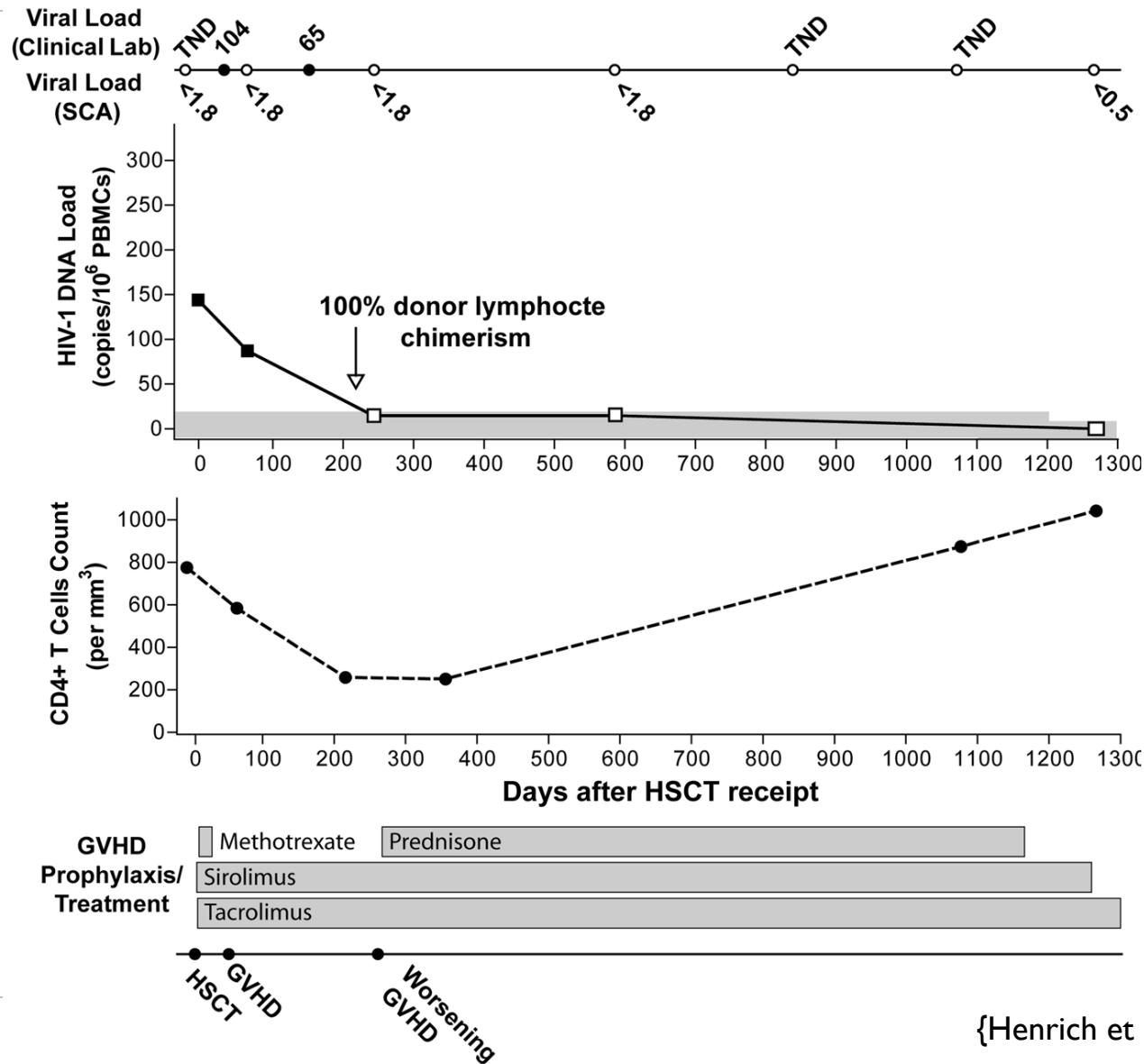
- ▶ 32 <http://www.nytimes.com/2013/07/04/health/post-transplant-and-off-drugs-hiv-patients-are-apparently-virus-free.html>

# MIT/Boston Patients

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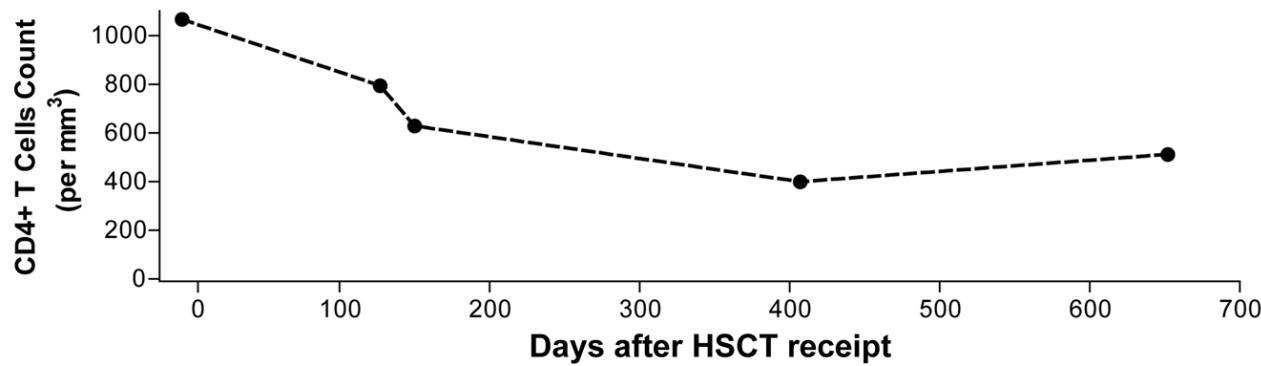
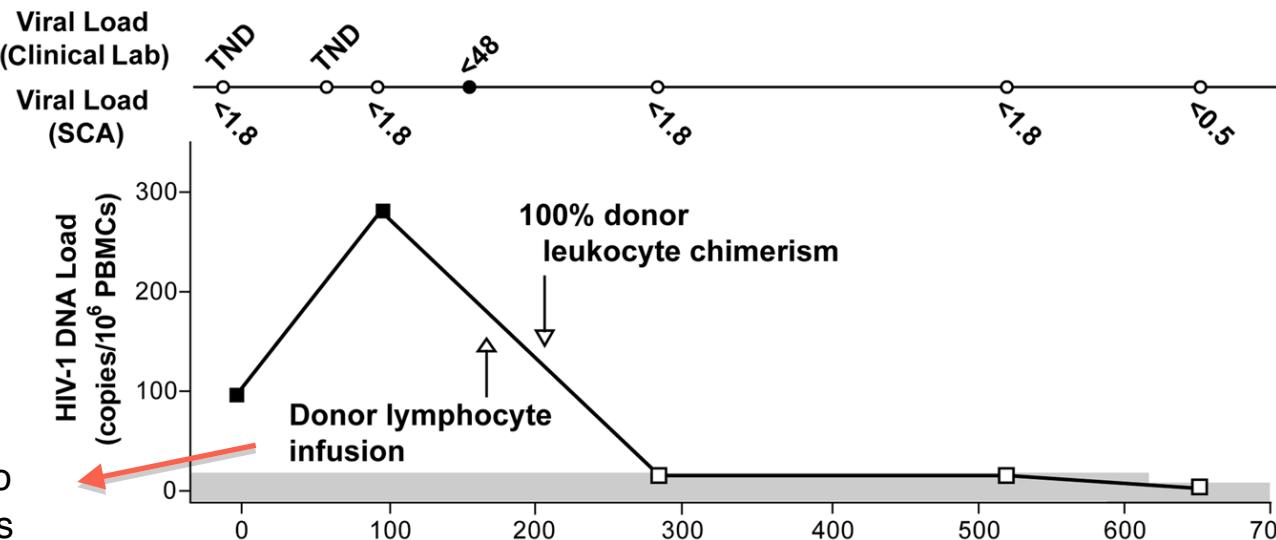
- ▶ Patient A
  - ▶ Hodgkins lymphoma Immune cells growing out of control
  - ▶ Reduced-intensity conditioning stem cell transplant
- ▶ Patient B
  - ▶ B cell lymphoma
  - ▶ Reduced-intensity conditioning stem cell transplant
- ▶ Patients remained on ART after transplant
- ▶ Both patients experienced graft vs. host disease
  - new immune cells started attacking the body

# Patient A

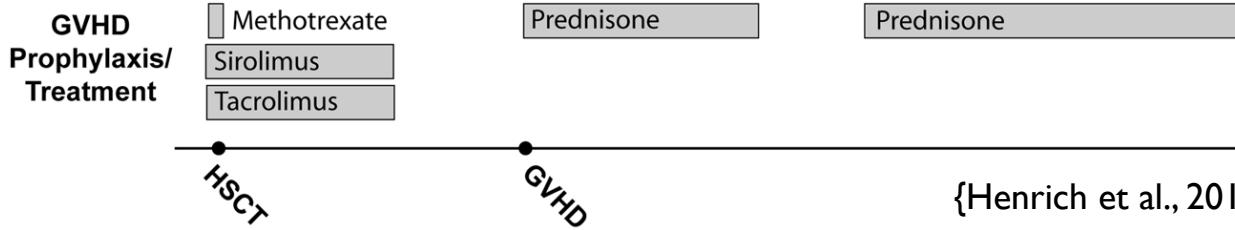


# Patient B

had a problem: had to re-infusion donor cells



also latent reservoir was gone, could not detect HIV DNA



# MIT/Boston Patients – announced but unpublished data

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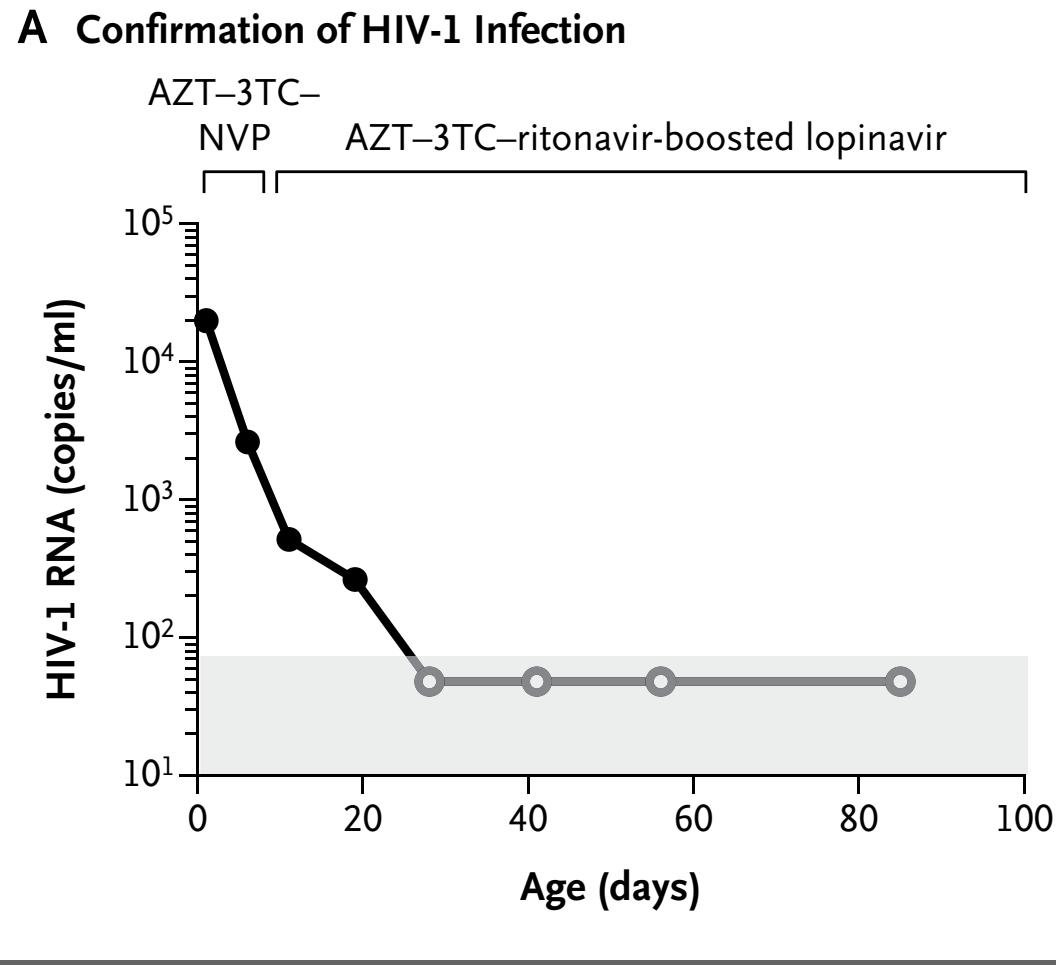
- ▶ The researchers decided to interrupt treatment
    - Stop the treatment on both patients
  - ▶ HIV DNA and HIV RNA remained undetectable after treatment interruption
  - ▶ The researchers believe that graft vs. host disease may **incidentally** have helped clear latently infected cells
  - ▶ This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

# The Mississippi baby

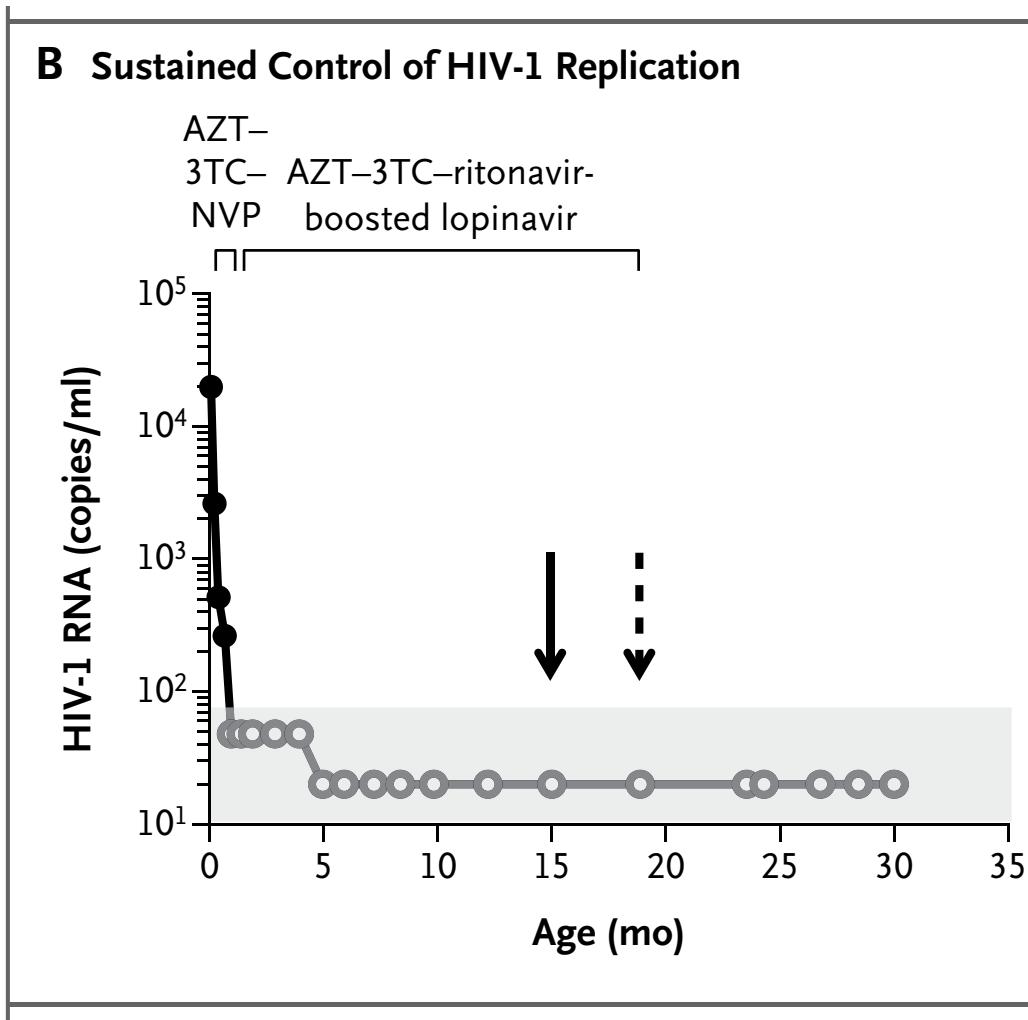
- ▶ Infant born to HIV+ mother who received no prenatal care Avg. is 30,000
  - ▶ Mother had viral loads of approximately 2000vRNA copies/ml
- ▶ ART was started at 30 hours of age
- ▶ HIV RNA was detected in the plasma at 30 hours (~20,000 vRNA copies/ml plasma) and until 19 days of age 

Higher than mother, active viral replication in the infant

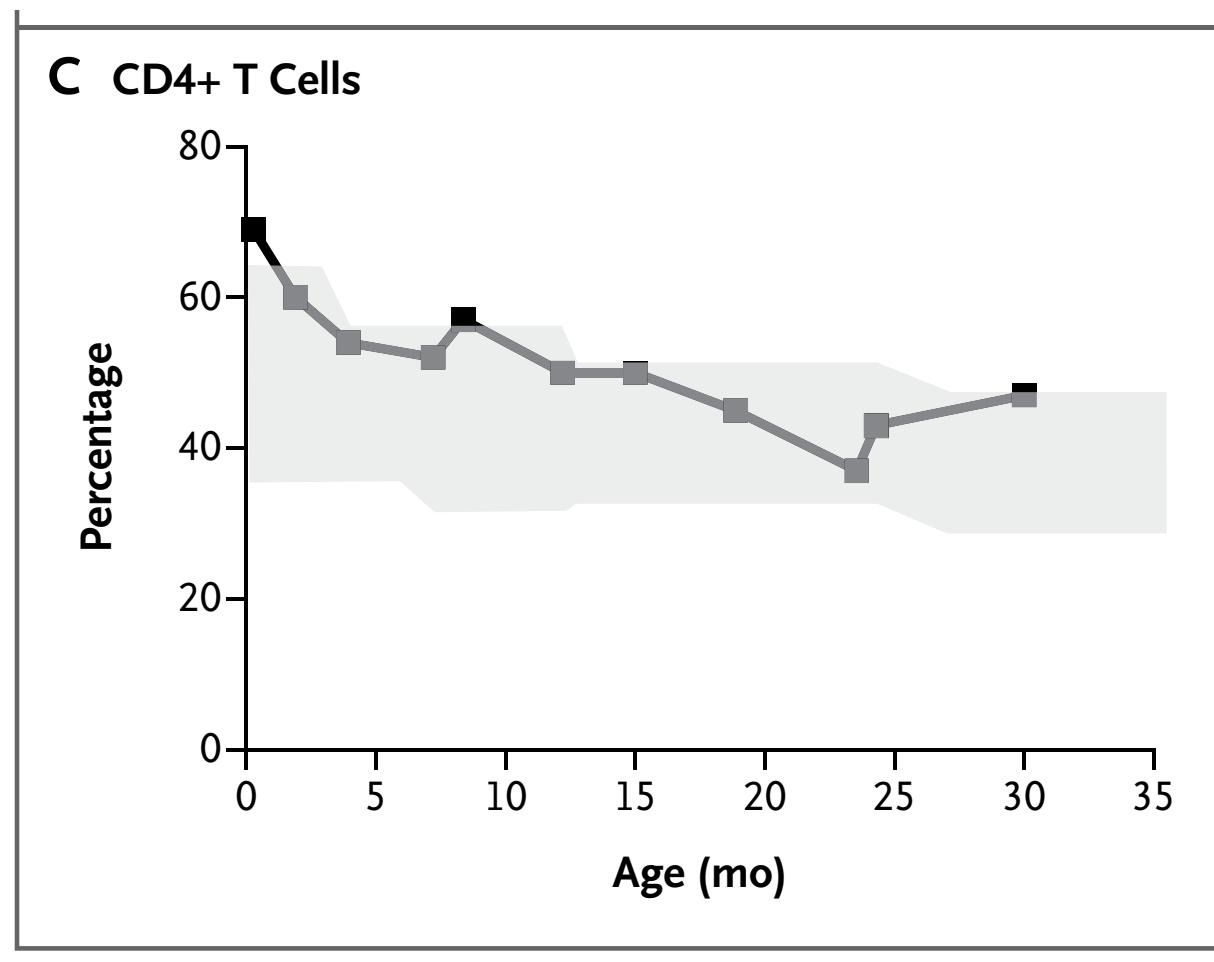
# The infant appears to have been HIV+



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

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- ▶ 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
    - should have never happened in the first place
    - PMTCT
- 
- ▶ 41 {Persaud et al., 2013, #39396}

# French Cohort

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- ▶ 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
  - then stopped treatment
- ▶ While these patients still have detectable HIV in their bodies, they are controlling viral replication and no longer require ART.
  - w/o drugs

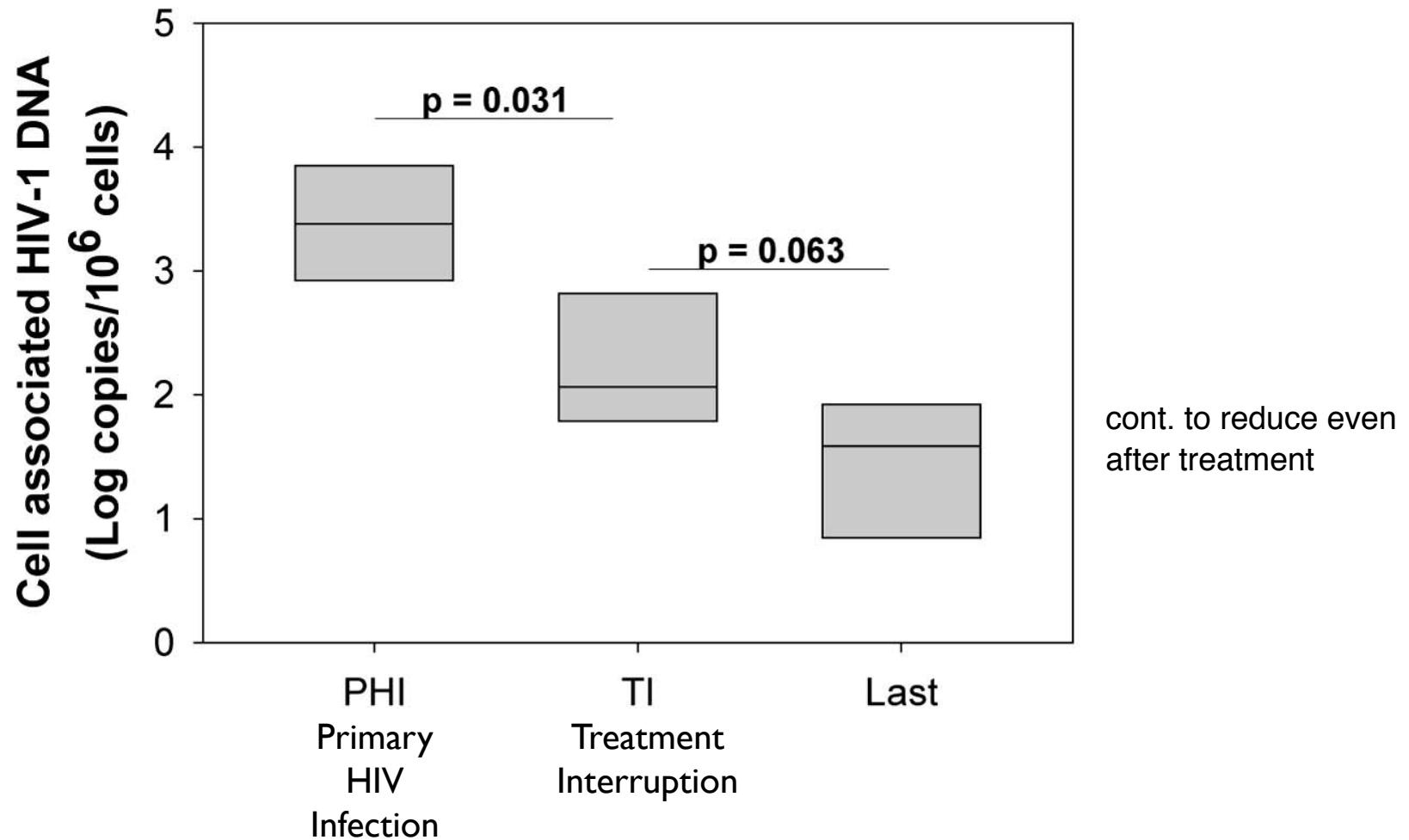
## Multiple questions were addressed

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- ▶ Do these individuals have unique genetics that allow them to control?  
They do not have unique genes like CCR5 delta 32
- ▶ 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

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- ▶ 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”

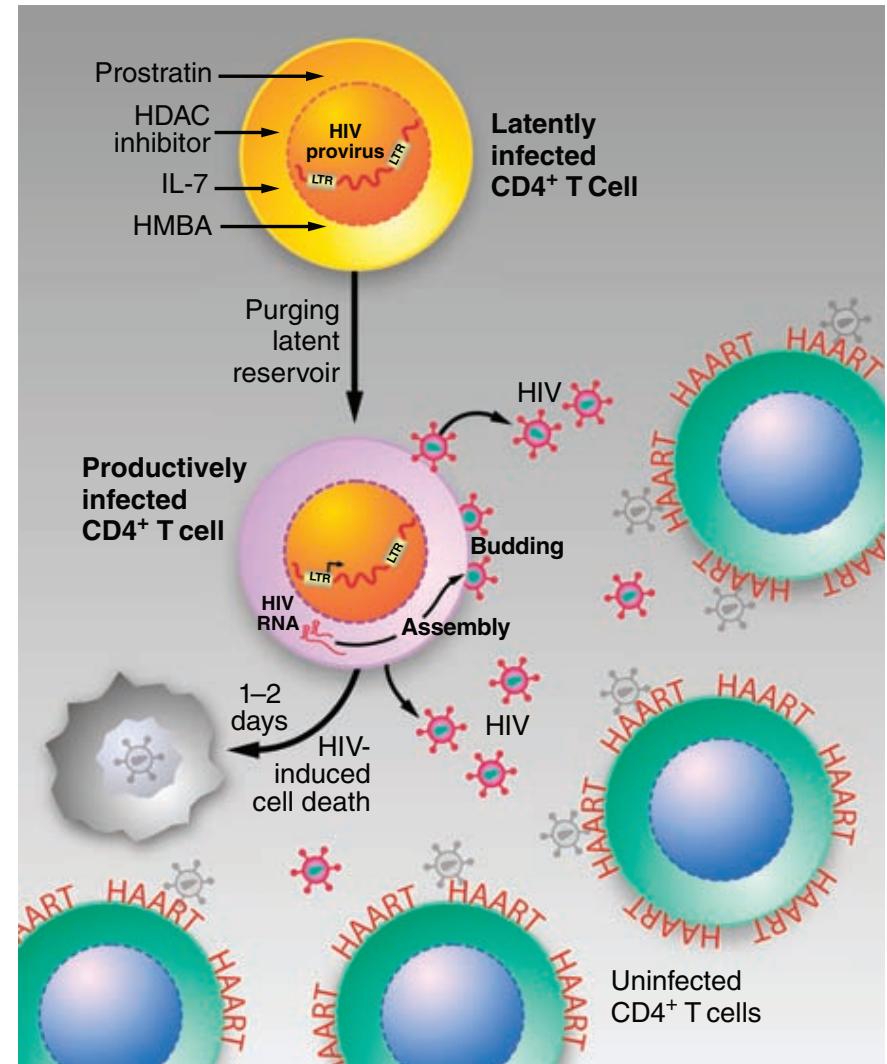
# Successful cure strategies

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- ▶ 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?

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- ▶ 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?