

# Barriers to HIV Cure

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# HIV Reservoir Persists during ART

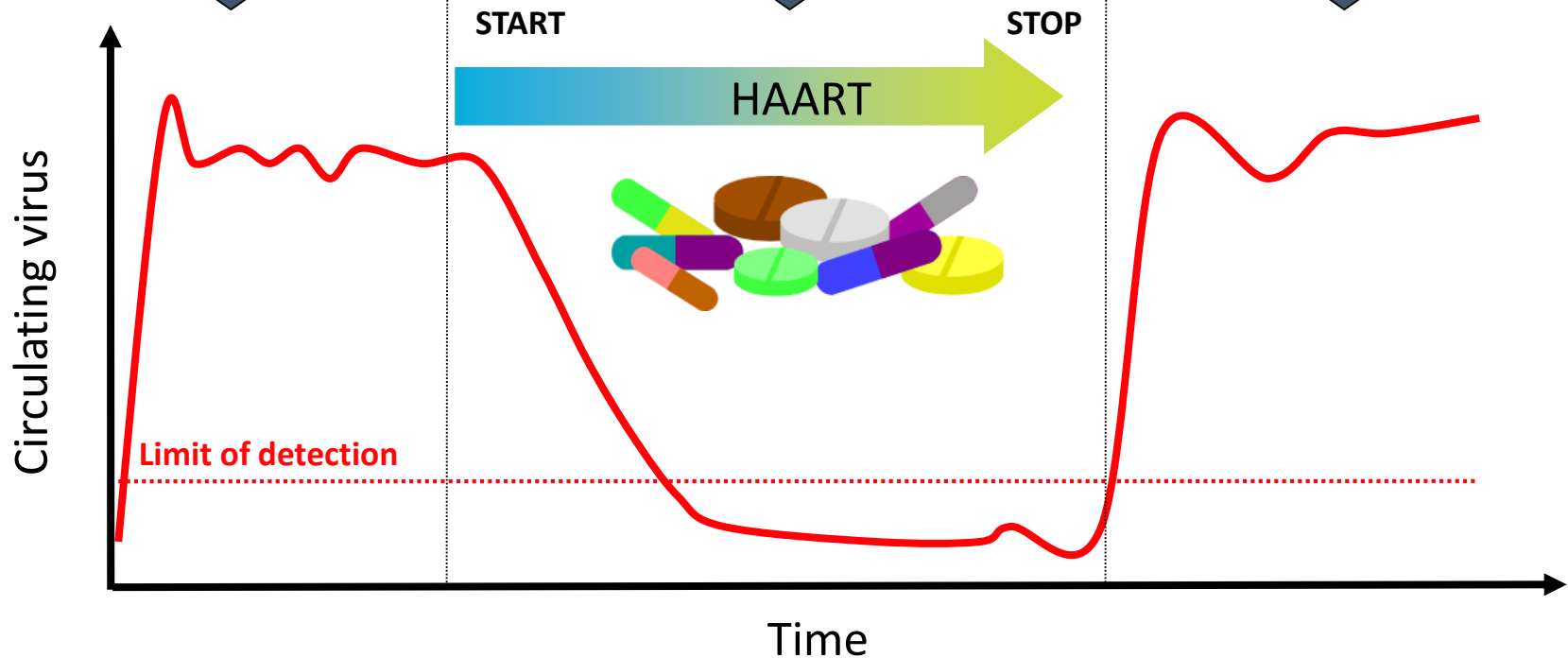
HIV infection is characterized by high levels of circulating viruses in the blood



Antiretroviral drugs are capable of suppressing HIV to undetectable levels

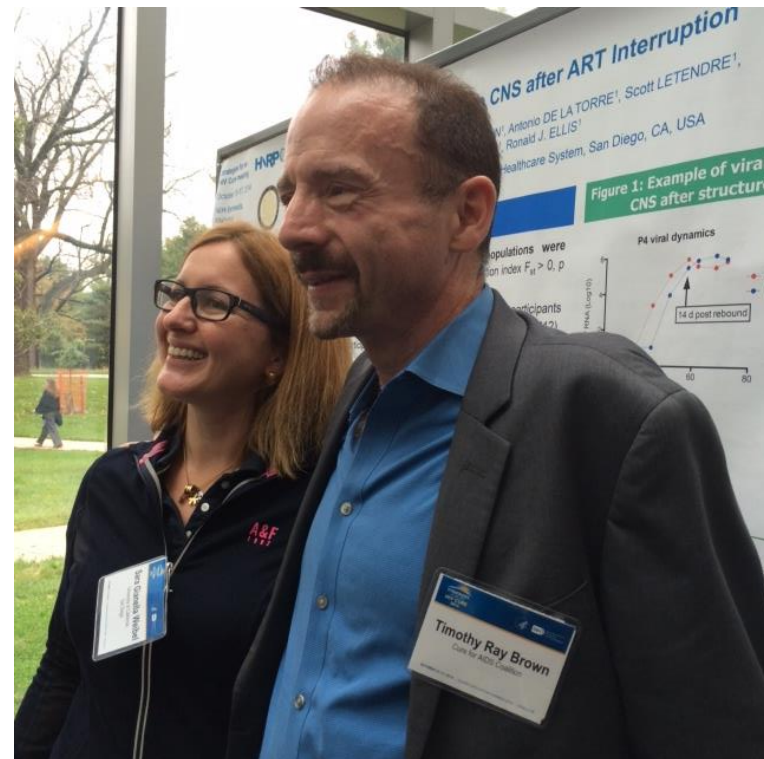


HIV rebounds after stopping therapy



# HIV Latency

- Main barrier for HIV eradication.
- Only one person has been cured from HIV so far.

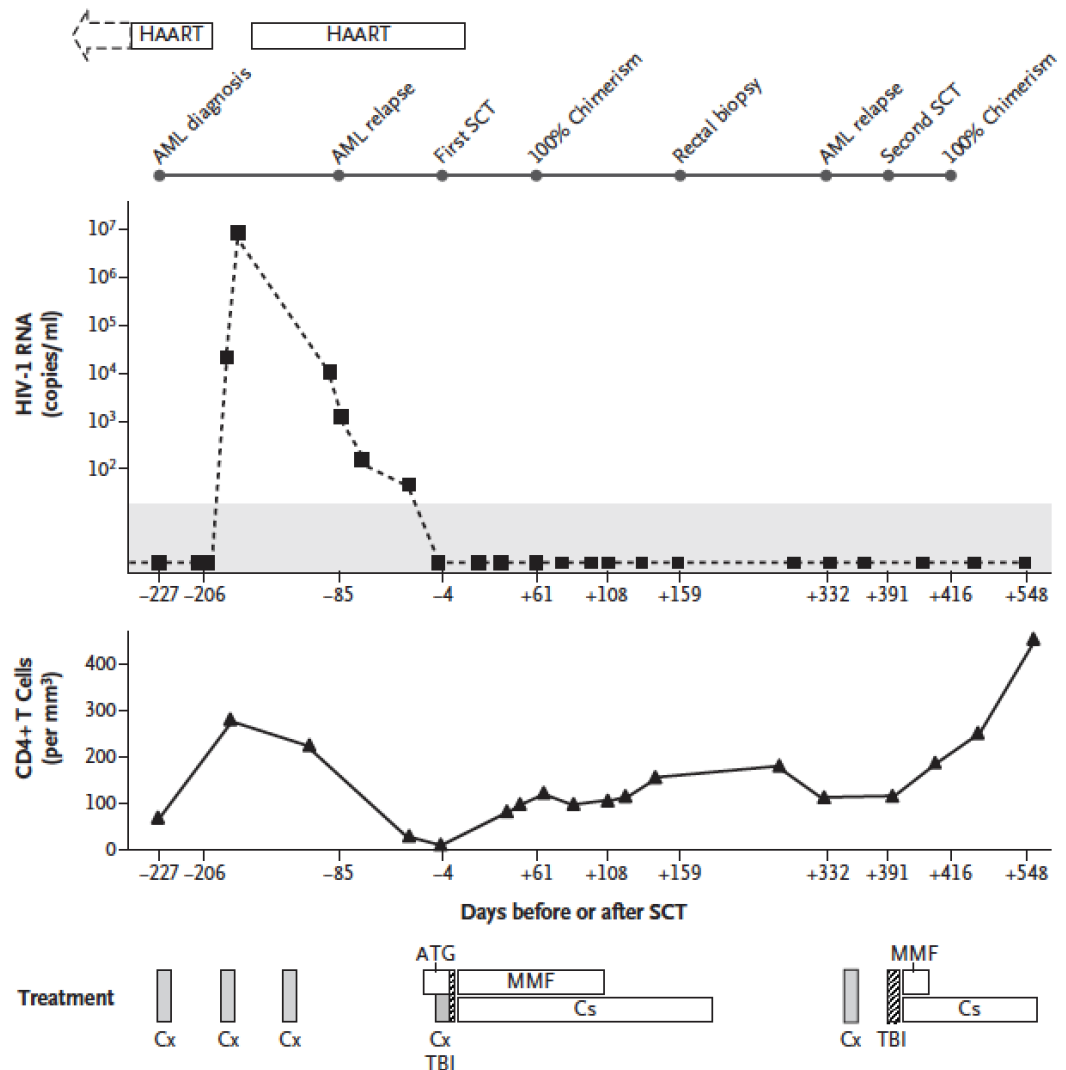


Timothy Ray Brown (The Berlin Patient)

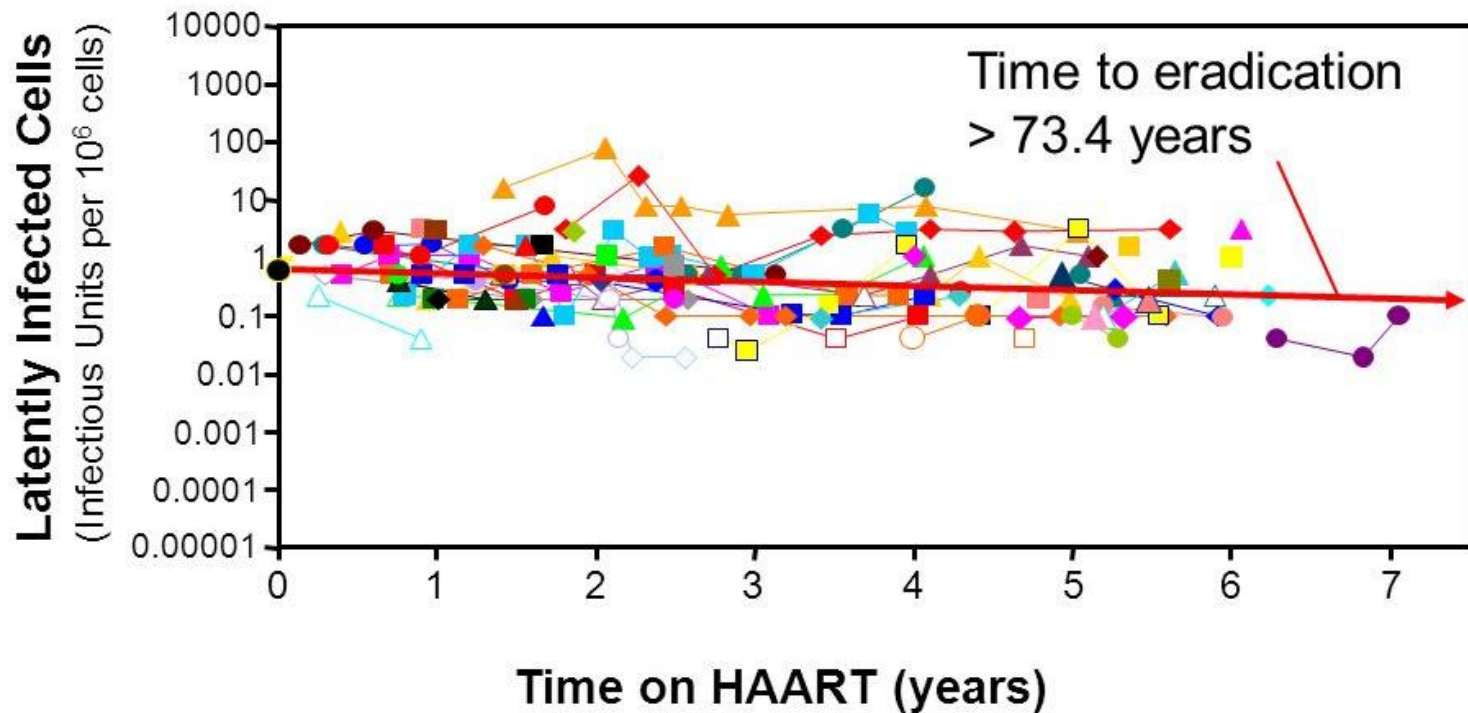
# Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

## The Berlin Patient

- **1995:** Diagnosed with HIV
- **2006:** Started ART
- Diagnosed with acute myeloid leukemia
- **2007/2008:** Received two allogeneic hematopoietic stem cell transplant from a donor **homozygous for CCR5  $\Delta$ 32**
- Stopped taking ART
- No evidence of HIV in any body fluid or sampled tissue



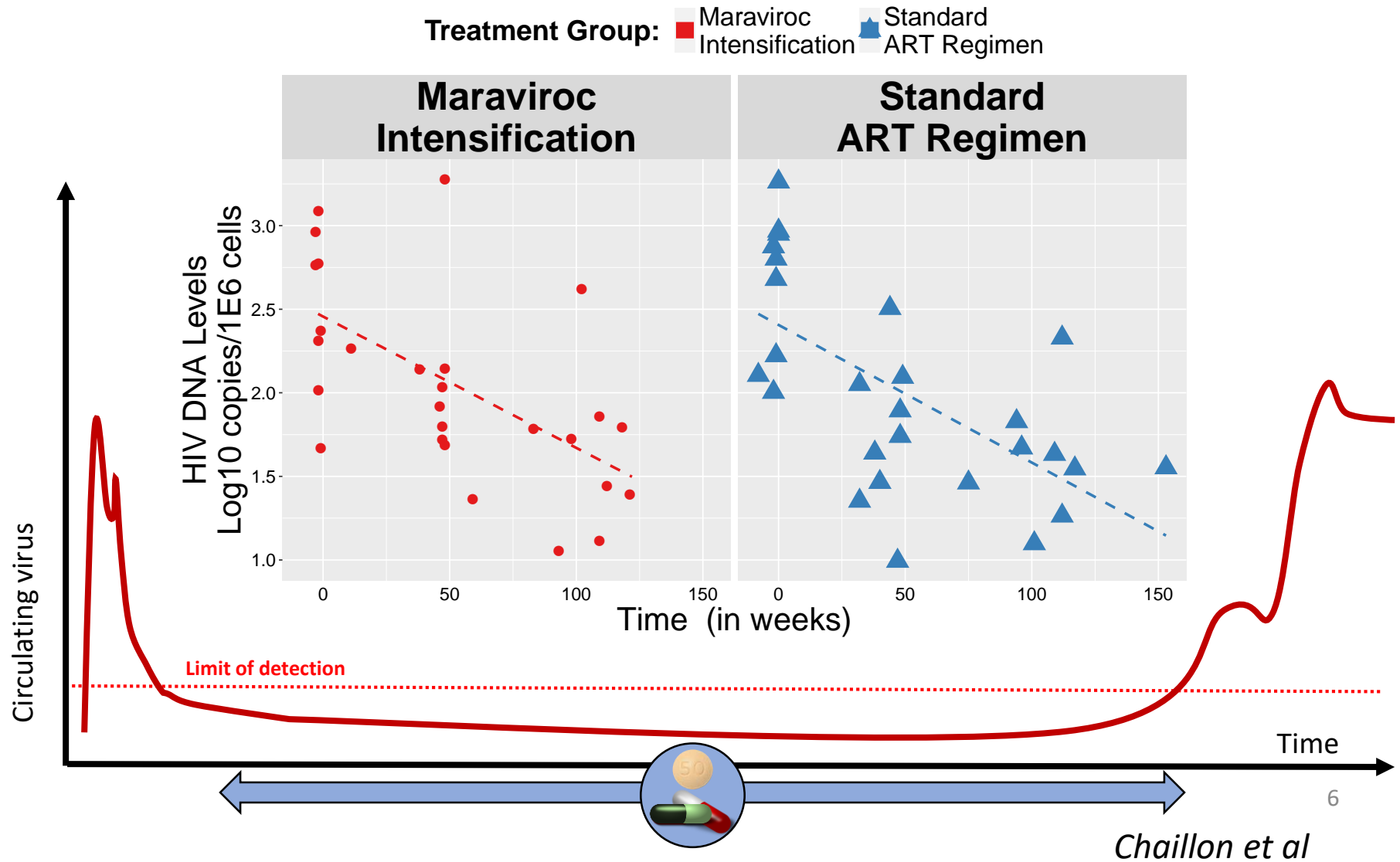
# Stability of HIV Reservoir



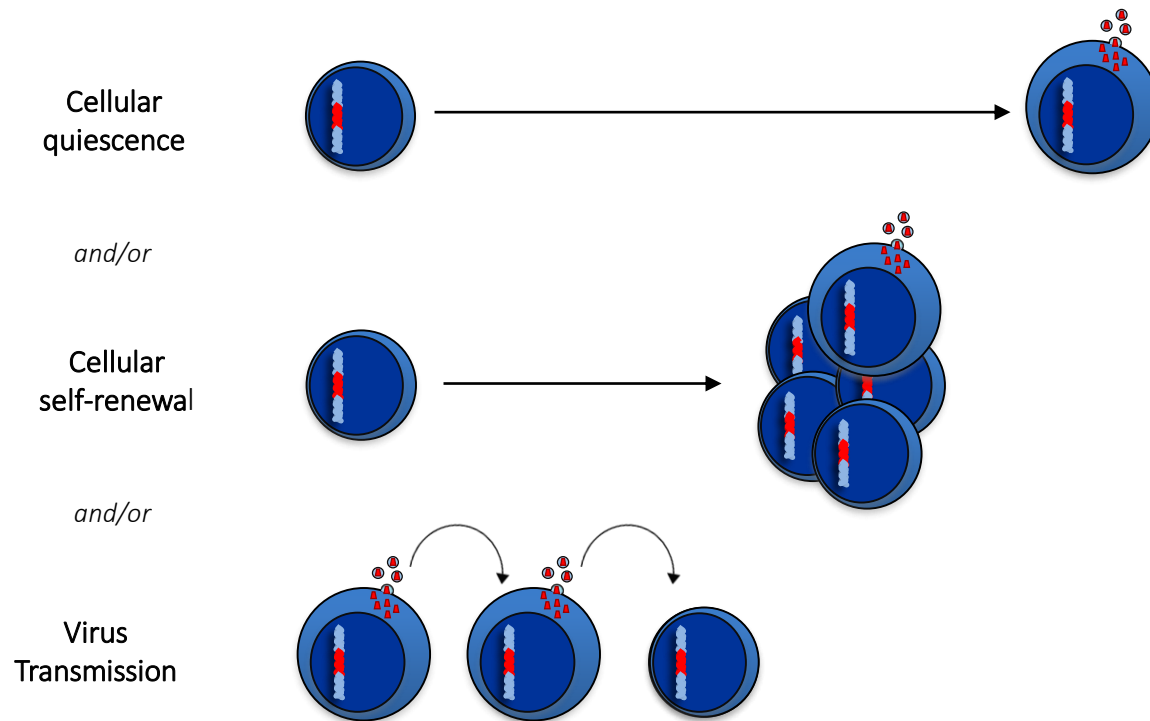
Siliciano Nat Med 2003

The Size of the HIV Reservoir is Stable During Long Term ART

# ART Intensification has no Effect on HIV Reservoir

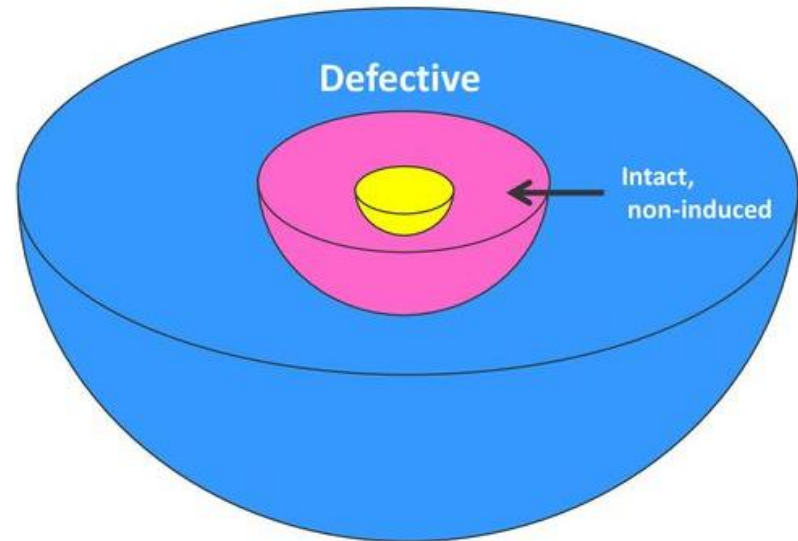
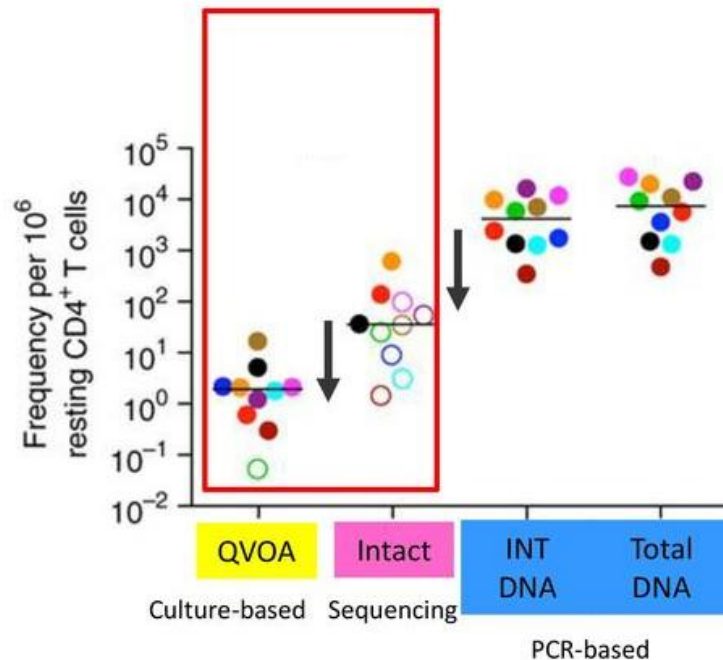


# Mechanisms of Persistence



# HIV Reservoir is hard to Measure

Ho *et al.*, Cell 2013  
 Bruner *et al.*, Nature Med 2016  
 Hosmane *et al.*, JEM., 2017



## Total DNA

Total frequency of HIV infected cells containing **HIV DNA**

## Integrated DNA

Total frequency of HIV infected cells measured by *Alu* PCR assessing **Integrated HIV DNA**

## Intact

Total frequency of HIV infected cells containing **full intact HIV provirus**

## QVOA

Total frequency of HIV infected cells containing **inducible replication competent virus** as assessed by quantitative viral outgrowth assay



# Lack of Biomarkers of HIV Persistence



# Sites of Persistence

- Established during primary HIV infection.
  - In peripheral blood cells
  - In anatomic sites and solid tissues
- HIV plays “hide and seek” with the immune system and ART.
- Source of viral rebound when ART is stopped.

# Current Limitations

- Studies in living people.
  - Hard to reach anatomic sites safely
- Autopsy studies.
  - Often poor ante mortem characterization
  - Autopsies rarely performed quick enough

# Our Proposed Solution

- Altruistic PLWH with a terminal illness.
  - E.g. cancer, cardiovascular disease, ALS
- Follow them to collect clinical data and blood.
- Perform a Rapid Autopsy.
  - Similar to Cancer Research
  - Within 6 hours from death
  - Preserve quality of RNA and proteins

# Why Terminally-ill Volunteers?

- The possibility for donating their full body for a rapid research autopsy.
- Absence of expectation of direct clinical benefits.
- Manifest desire to 'give back' to the HIV research field.
- Limited opportunities for terminally ill PLWH to participate in HIV clinical research.
- The opportunity to create a new translational research model to advance HIV cure science.



# The Last Gift

- Started in July 2017 (PI: Davey Smith)
- Goal: Use deep sequencing and phylodynamic analyses
  - To characterize the HIV reservoirs in blood and in various anatomic tissues
  - To determine the dynamics of HIV rebounding variants after ART interruption
- Enroll 5 participants/year

# Summary Study Participants



- **LG01** → Neuro-degenerative disease (ALS) → Rapid autopsy July 2017.
- **LG02** → Multiple brain lesions.
- **LG03** → Pancreatic cancer → Rapid autopsy May 2018.
- **LG04** → Acute Leukemia → Rapid autopsy March 2018.
- **LG05** → ALS.
- **LG06** → Oral Cancer → Rapid autopsy June 2018.
- **LG07** → Progressive multifocal leukoencephalopathy.
- **LG08** → Rectal Cancer. → Rapid autopsy December 2018.
- **LG09** → Lung Cancer. → Rapid autopsy November 2018.





# Rapid Autopsy





# Preliminary Data

# Characterizing the HIV DNA Reservoirs in Whole-Body Tissues in the “Last Gift” Cohort

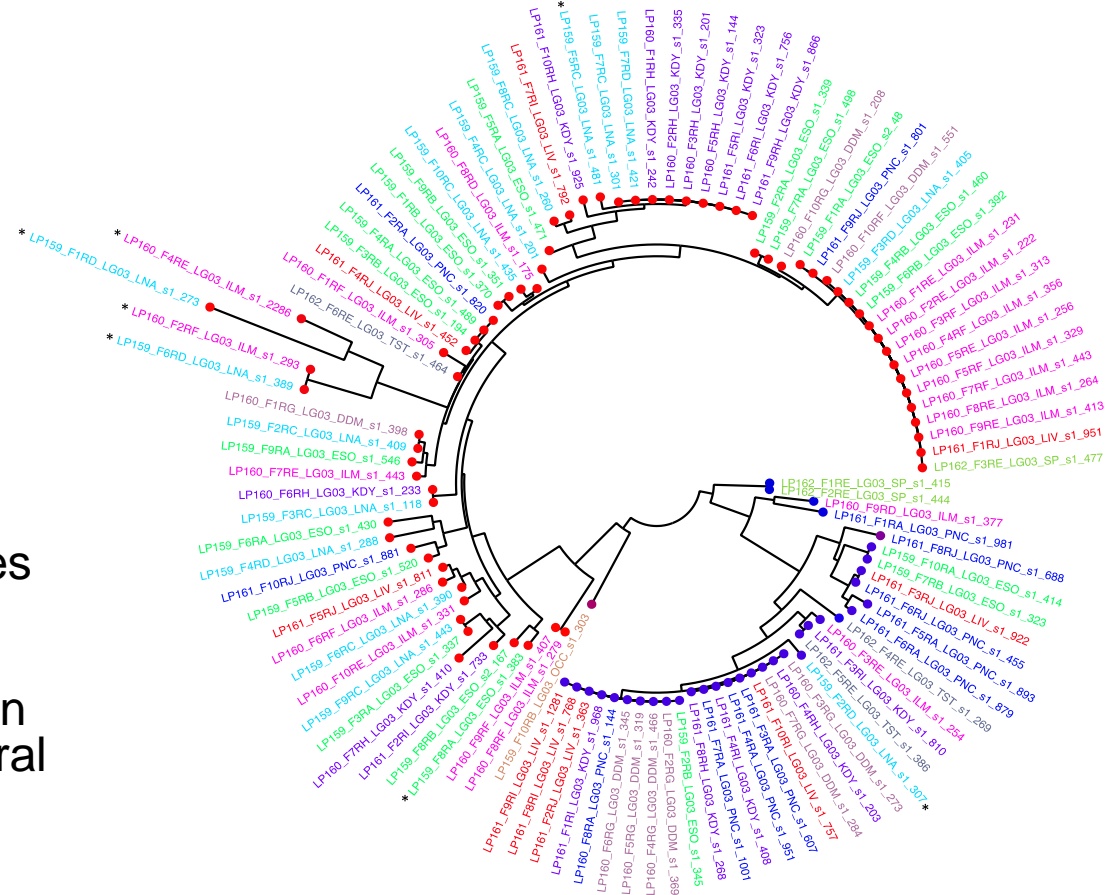
- 72-year-old man and metastatic pancreatic cancer
- On ART and undetectable HIV RNA in blood plasma, up to 7h prior death (<20 copies/ml)
- Levels of HIV DNA by droplet digital PCR
- FL HIV *env* sequences (SGA and PacBio)

Organ	HIV DNA cp/10 <sup>6</sup> cells
Adipose (pericardial)	874
Lymph Node (axillary)	417
Kidney	377
Lymph Node (axillary)	243
Ileum	211
Lymph Node (aortic)	138
Adipose (abdominal)	13
Bladder	107
Colon (left)	101
Pancreas	101
Rectum	90
Adrenal Glands	90

Organ	HIV DNA cp/10 <sup>6</sup> cells
Esophagus	71
Spleen	66
Duodenum	59
Colon (right)	45
Testes	46
Lung	43
Aorta	24
Liver	22
Heart	6
Basal Ganglia	11
Occipital Cortex	3
Parietal Cortex	0
Frontal Cortex (motor)	0
Frontal Cortex (pre-motor)	3
Hippocampus	7

# Full Length HIV *env* Sequences

- 107 FL HIV *env* sequences (across 10 tissues), 60 were unique
- 100 sequences were intact, 7 were obviously non-functional
- many identical sequences sampled in multiple body tissues
- deep divergence and separation of two lineages with different viral tropisms (as predicted by geno2pheno)



# Limitations

- Potentially confounding effect of the underlying terminal illness and therapies
- Limited sample size
- Possible blood contamination

# Summary: Barriers to HIV Cure

- Latency
- Stability
- Sites of persistence
- Lack of biomarkers
- “ [...] virologists who can’t measure replication competent virus without exsanguinating my patients!!”

(Mike Lederman, Immunologist)

# THANK YOU

All the Last Gift study participants and loved ones

**Jeff Taylor** and **Andy Kaytes**

Our wonderful HIV community  
AVRC Community Advisory Board  
Palm Springs HIV and Aging Research Project

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