



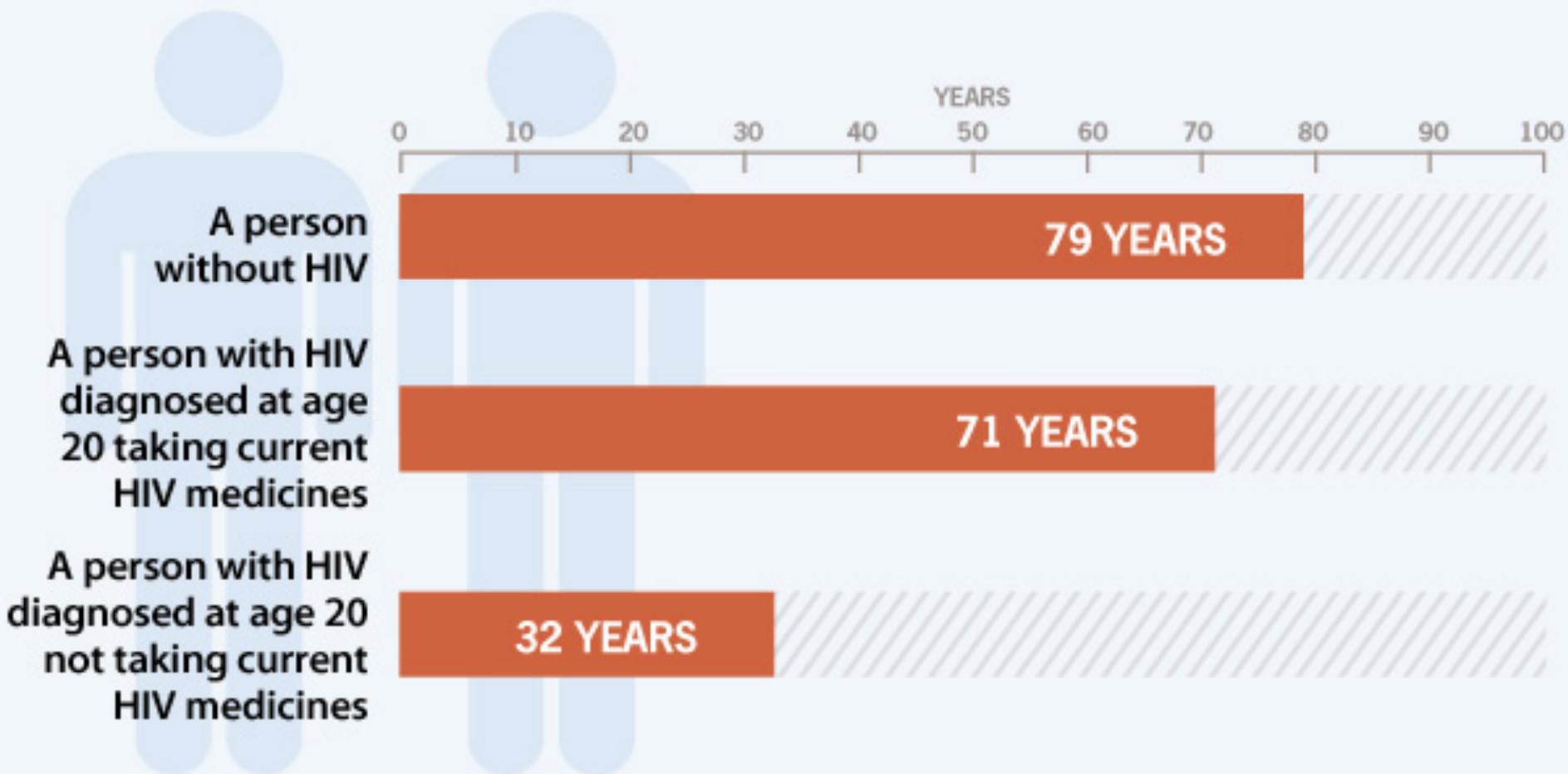
The Last Gift

End of life Research Model for HIV Cure Research

Sara Gianella, MD,

Associate Professor of Medicine
University of California San Diego

Current State of HIV



SOURCE: National Vital Statistics Reports, 2012; PLoS One, 2013; and Journal of the American Medical Association, 1993.



Vital^{CDC}signs™

U = U

UNDETECTABLE = UNTRANSMITTABLE.

**PEOPLE LIVING WITH HIV, WHO ARE TAKING
EFFECTIVE TREATMENT, CANNOT PASS
ON HIV THROUGH SEX.**

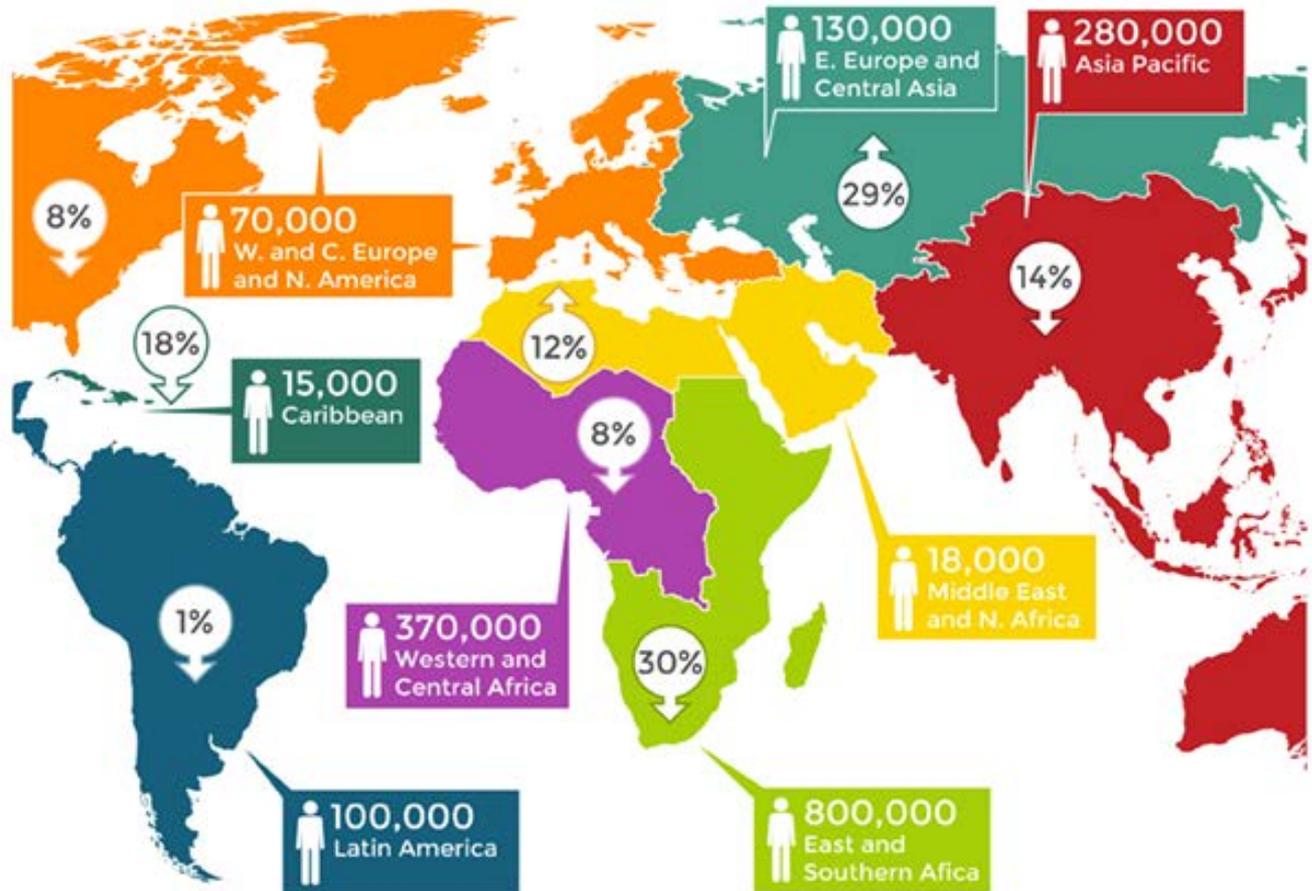


Number of new HIV infections in 2017 and change since 2010

1.8 million
people newly
infected in
2017 globally

Decrease in
number of new
infections across
the global
population each
year since 2010

18%



Source: UNAIDS Data 2018

Why do we need a cure if HIV
Treatments work so well?



People living with HIV

36.9m



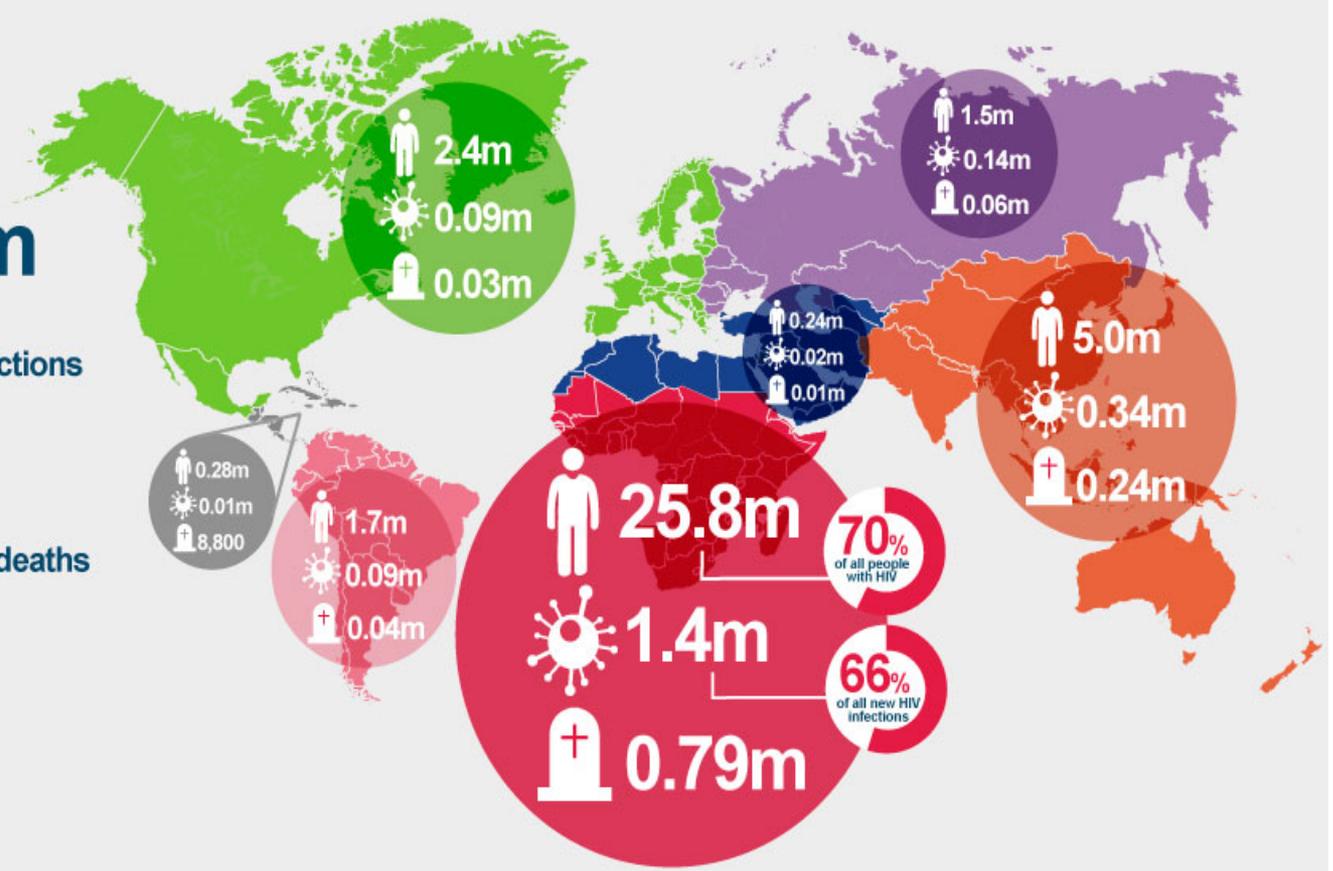
New HIV infections

2.0m



AIDS-related deaths

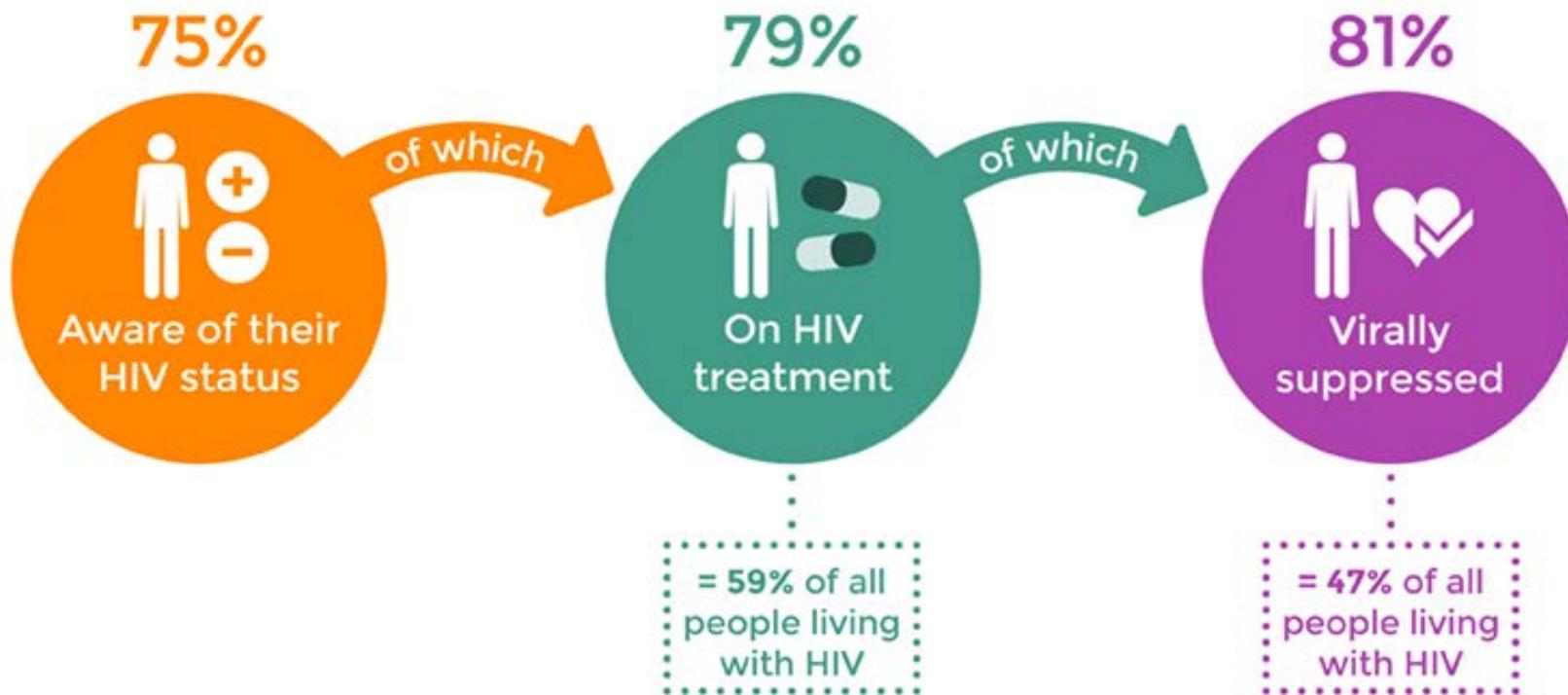
1.2m



Source: UNAIDS

Credit: Rebecca Robinson/LSHTM

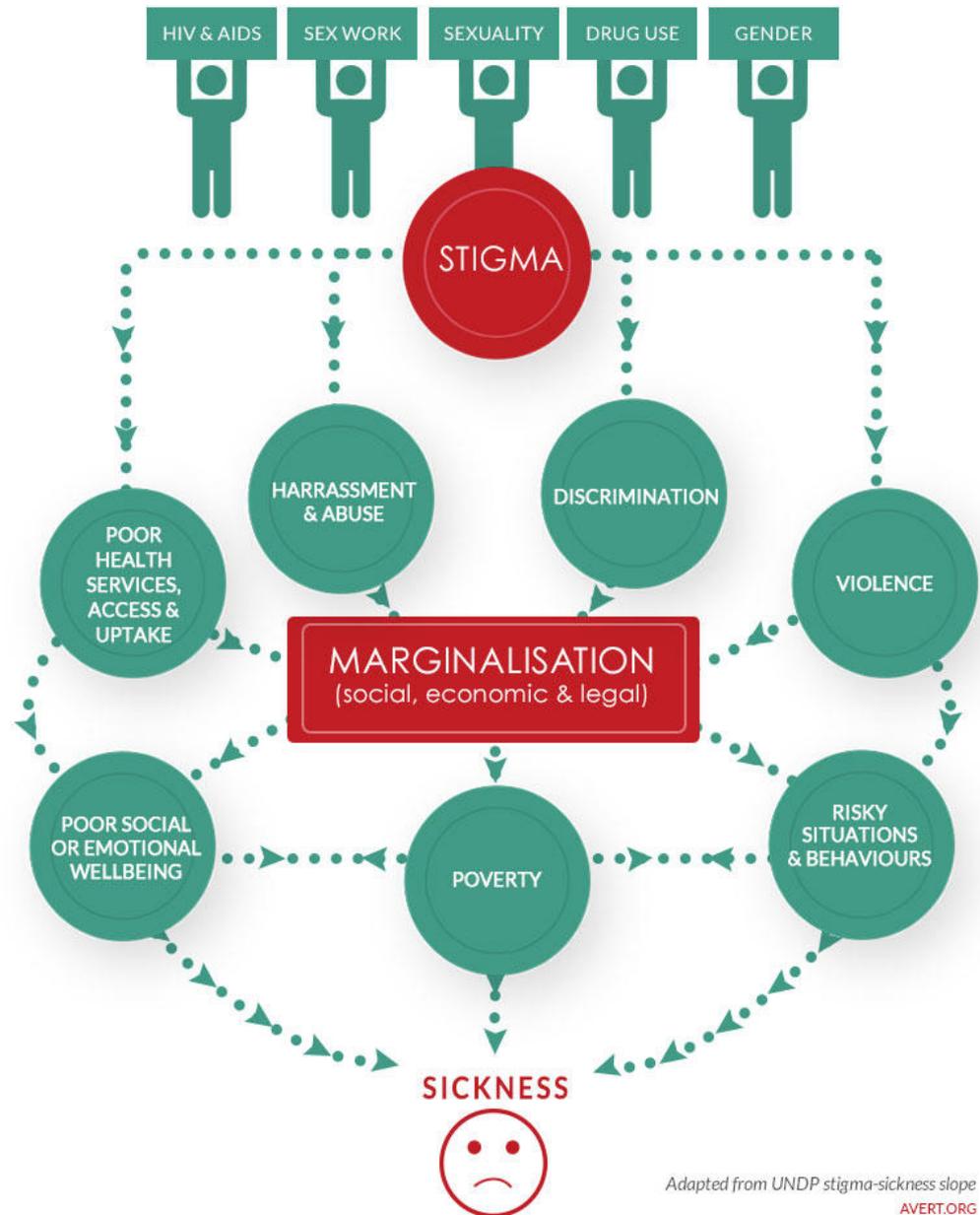
Global progress towards the 90 90 90 targets 2017 (all ages)



Source: UNAIDS Data 2018

Stigma

a mark of disgrace associated with a circumstance, quality, or person.

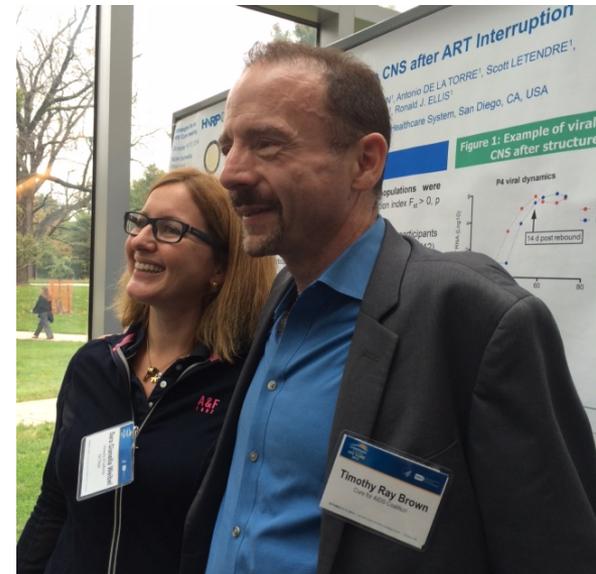


HIV Persistence

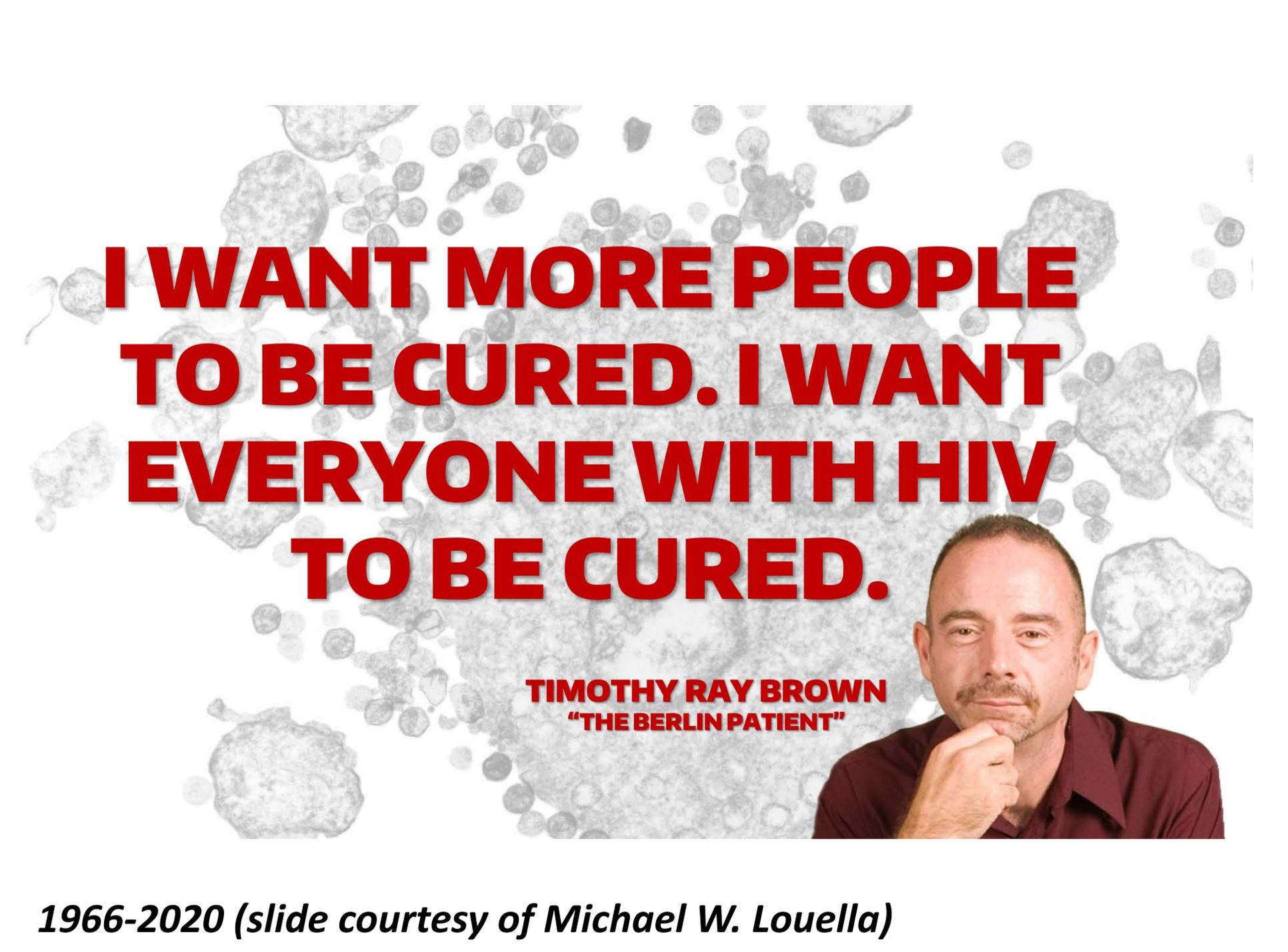
- Main barrier for HIV eradication.
- Only very few persons have been cured from HIV so far.



Adam Castillejo (The London Patient)



Timothy Ray Brown (The Berlin Patient)

The background of the slide features a grayscale microscopic image of various cells, including some with prominent nuclei and others that are more rounded and granular. In the bottom right corner, there is a portrait of Timothy Ray Brown, a man with a mustache and short hair, wearing a dark red shirt and resting his chin on his hand.

**I WANT MORE PEOPLE
TO BE CURED. I WANT
EVERYONE WITH HIV
TO BE CURED.**

**TIMOTHY RAY BROWN
"THE BERLIN PATIENT"**

1966-2020 (slide courtesy of Michael W. Louella)



CLEARING HIV RESERVOIRS IS HARD

- 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.



FINDING RESERVOIRS IS HARD

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



PROPOSED SOLUTION

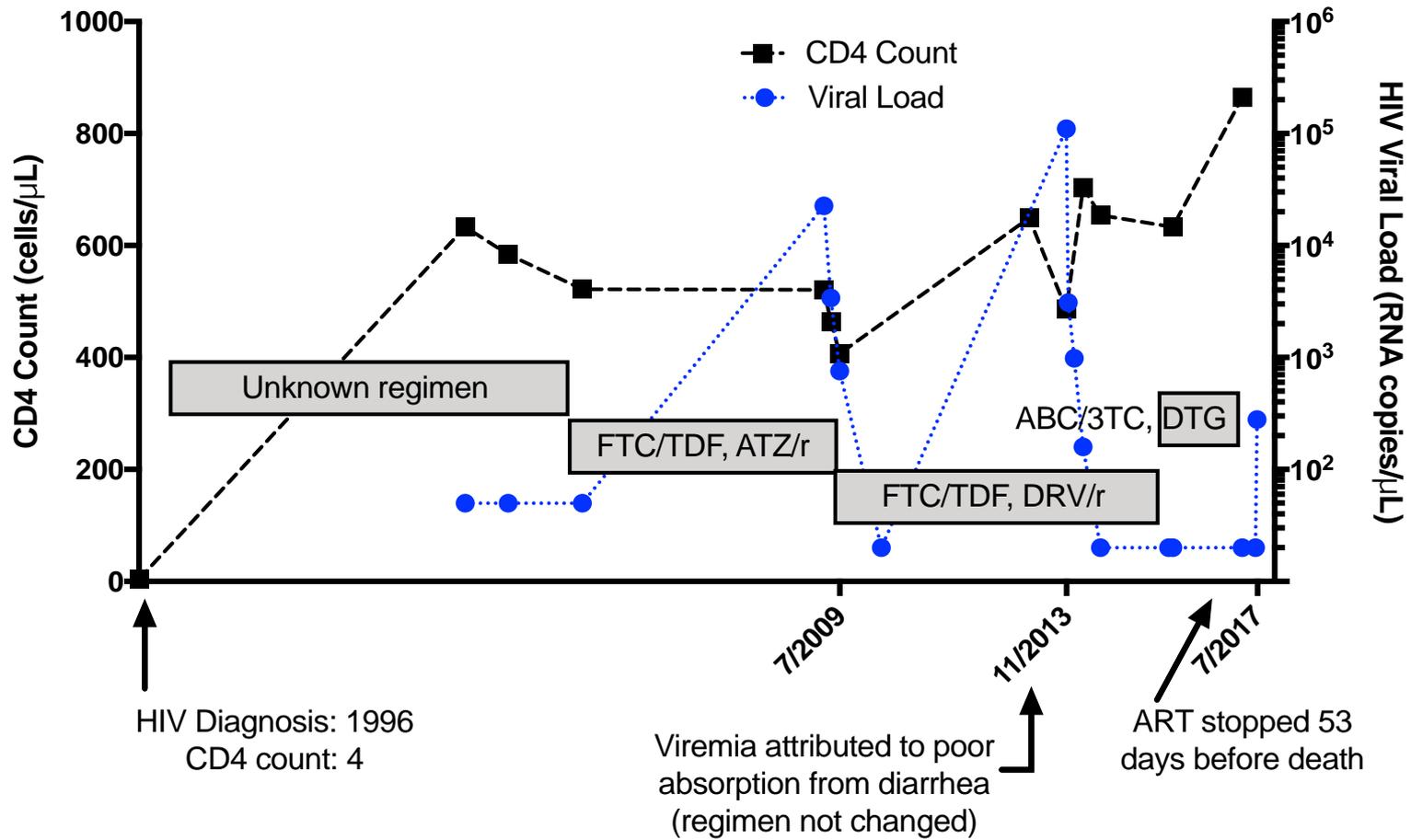
- Altruistic PWH with a terminal illness.
 - E.g. cancer, cardiovascular disease, ALS
- Follow them to collect clinical data and blood.
- Perform a Rapid Autopsy.
 - Similar to Cancer Research
 - Within 6 hours from death
 - Preserve quality of RNA and proteins



THE LAST GIFT STUDY

- Started in July 2017 (PI: Davey Smith)
- Goal:
 - 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

LG01 Clinical Data



ID	Age	Gender	Diagnosis	Stopped ART?	Last ART Regimen	Last CD4 count	Deceased
01	58	M	ALS	Yes	ABC/3TC+DTG	864 (time of death)	July 2017
02	50	M	Brain Tumor	Yes	FTC/TAF/BIC	141 (12/20/18)	November 2020
03	72	M	Pancreatic Tumor	No	FTC/TAF+DTG	330 (time of death)	May 2018
04	69	M	AML	Yes	FTC/TAF+DTG	497 (time of death)	March 2018
05	57	M	ALS	No	TAF/FTC/RPV+DTG	347 (time of death)	March 2019
06	57	M	Oral Cancer	No	FTC/TAF+DTG	174 (time of death)	May 2018
07	45	M	Brain tumor	No	ABC/3TC/DTG	91 (6/7/18)	Currently enrolled
08	52	M	Rectal cancer	No	DRV/c+DTG	224 (time of death)	Dec 2018
09	80	M	Lung cancer	No	FTC/TAF+DTG	656 (time of death)	Nov 2018
10	74	M	Liver Cirrhosis				
11	89	F	Heart Failure	No	FTC/TDF+RAL	220 (12/22/18)	Currently enrolled
12	71	F	Breast cancer	No	ABC/3TC/DTG	347 (11/15/19)	Dec 2019
13	55	M	Metastatic Melanoma	No	FTC/TAF/BIC	398 (10/30/19)	Currently enrolled
14	59	M	SCC of Tongue	No	FTC/TAF+DTG	102 (11/21/19)	April 2020
15	88	M	Co-morbidities	Yes	3TC+DTG	214 (6/10/19)	May 2020
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Legend: ALS: amyotrophic lateral sclerosis; AML: Acute Myeloid Leukemia. PJP: Pneumocystis jiroveci Pneumonia; RCC: Renal cell carcinoma
ABC: abacavir, 3TC: lamivudine, DTG: dolutegravir, DRV/c: darunavir and cobicistat, FTC: emtricitabine, TAF: tenofovir alafenamide, RPV: rilpivirine.



Team



Cutters



Tissue Homogenizers



Flash Frozen



Tubes



May 7 2018 LG03 Rapid Autopsy



LAST GIFT 1





LAST GIFT 5





SOCIO BEHAVIORAL STUDIES

Dubé et al. *BMC Medical Ethics* (2018) 19:83
<https://doi.org/10.1186/s12910-018-0321-2>

BMC Medical Ethics

AIDS Research and Human Retroviruses, Ahead of Print |

DEBATE

Open Access

Ethical considerations for HIV cure-related research at the end of life

Karine Dubé^{1*}, Sara Gianella^{2,3}, Susan Concha-Garcia^{2,3}, Susan J Little², Andy Kaytes⁴, Jeff Taylor^{4,5}, Kushagra Mathur³, Sogol Javadi³, Anshula Nathan¹, Hursch Patel¹, Stuart Luter¹, Sean Philpott-Jones⁶, Brandon Brown⁷ and Davey Smith^{2,3}



Perceptions of Next-of-Kin/Loved Ones About Last Gift Rapid Research Autopsy Study Enrolling People with HIV/AIDS at the End of Life: A Qualitative Interview Study

Karine Dubé, Hursch Patel, Susan Concha-Garcia, Kelly E. Perry, Kushagra Mathur, Sogol Stephanie Javadi, Jeff Taylor, Andy Kaytes, Brandon Brown, John A. Saucedo, Susan Little, Steven Hendrickx, Stephen A. Rawlings, Davey M. Smith, and Sara Gianella

Published Online: 25 Jun 2020 | <https://doi.org/10.1089/aid.2020.0025>

AIDS Research and Human Retroviruses, Ahead of Print |

“My Death Will Not [Be] in Vain”: Testimonials from Last Gift Rapid Research Autopsy Study Participants Living with HIV at the End of Life

Kelly E. Perry, Karine Dubé, Susanna Concha-Garcia, Hursch Patel, Andy Kaytes, Jeff Taylor, Sogol Stephanie Javadi, Kushagra Mathur, Megan Lo, Brandon Brown, John A. Saucedo, David A. Wohl, Susan Little, Steven Hendrickx, Stephen A. Rawlings, Davey M. Smith, and Sara Gianella

Published Online: 24 Jun 2020 | <https://doi.org/10.1089/aid.2020.0020>

RESEARCH ARTICLE

“[It] is now my responsibility to fulfill that wish:” Clinical and rapid autopsy staff members’ experiences and perceptions of HIV reservoir research at the end of life

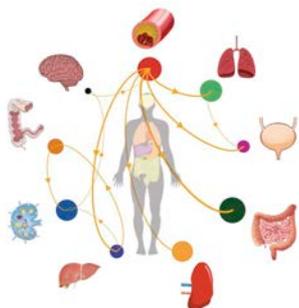
Kelly E. Perry^{1*}, Jeff Taylor^{2,3}, Hursch Patel¹, Sogol Stephanie Javadi⁴, Kushagra Mathur⁴, Andy Kaytes², Susanna Concha-Garcia^{4,5}, Susan Little^{4,6}, Davey Smith^{4,6}, Sara Gianella^{4,6}, Karine Dubé¹

1 UNC Gillings School of Global Public Health, Chapel Hill, NC, United States of America, 2 AntiViral Research Center Community Advisory Board, San Diego, CA, United States of America, 3 HIV + Aging Research Project—Palm Springs (HARP-PS), Palm Springs, CA, United States of America, 4 AntiViral Research Center (AVRC), University of California San Diego, San Diego, CA, United States of America, 5 HIV Neurobehavioral Research Center, University of California San Diego, San Diego, CA, United States of America, 6 Division of Infectious Diseases and Global Public Health, University of California San Diego, San Diego, CA, United States of America



HIV persists throughout deep tissues with repopulation from multiple anatomical sources

Antoine Chaillon, Sara Gianella, Simon Dellicour, Stephen A. Rawlings, Timothy E. Schlub, Michelli Faria De Oliveira, Caroline Ignacio, Magali Porrachia, Bram Vrancken, and Davey M. Smith



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STUDY FRAMEWORK



N=6 LAST GIFT
Participants



Virally suppressed in
blood on ART until death

Stopped ART 53-70
days before death

1. Sampling Pre and Postmortem (rapid autopsy)

2. HIV RNA/DNA Extraction and Quantification
(digital droplet PCR)

3. Limited Dilution (single genome) and
Sequencing

4. Full Length (FL) *env* Reconstruction

Non-Intact FL *env* Proviruses

Intact FL *env* Proviruses

5. Characterization of HIV Populations

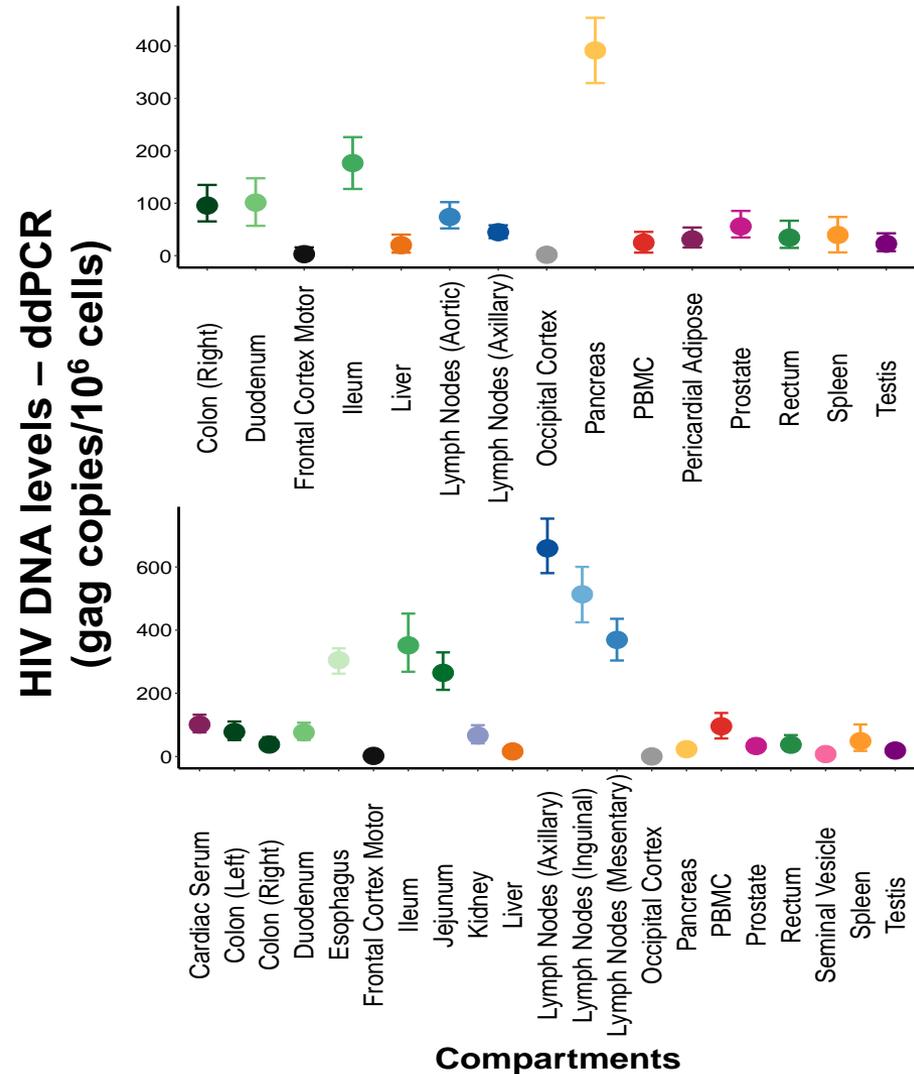
6. Viral Dispersal and Re-population

7. Predictors of Viral Dispersal



TISSUES HAVE VARIABLE PROVIRAL RESERVOIRS

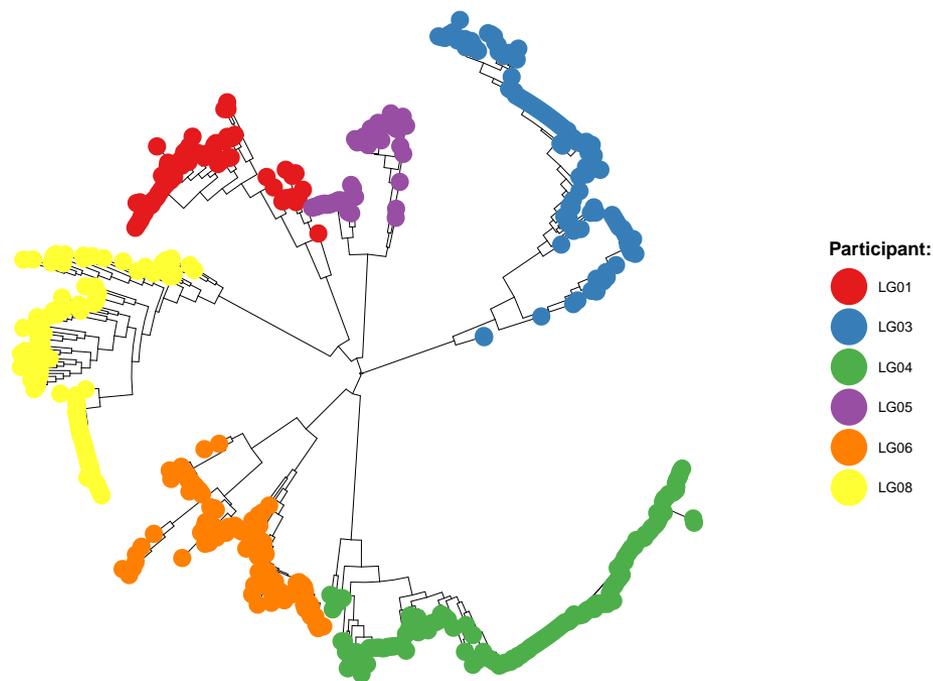
- HIV DNA levels varied in sampled blood and tissues from **~0 to 659 gag copies/10⁶ cells** (median=56, IQR:23-126)
- Lowest in CNS samples (0-34 copies/10⁶ cells)





CHARACTERIZING THE RESERVOIRS

- We recovered **605 intact FL *env* sequences**.
- Mean of 7 seq/compartiment [IQR 5-10].
- No defective sequences recovered from blood plasma.
- CNS tissue proviruses (frontal and/or occipital lobes, basal ganglia, spinal cord) recovered in 5/6 participants.

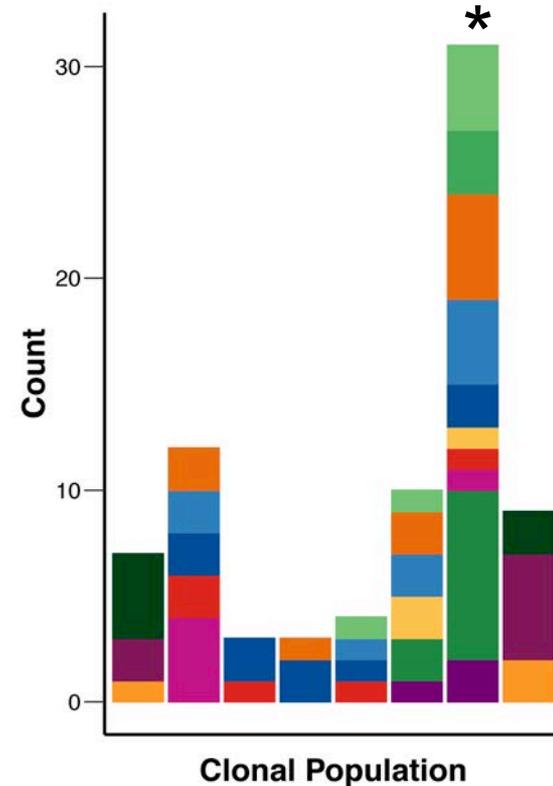
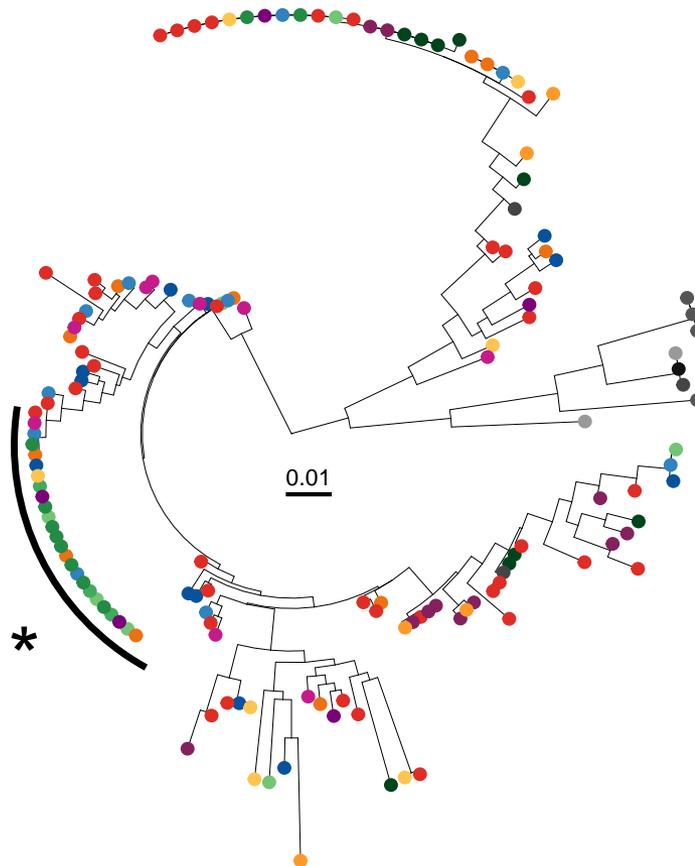




Individual virally suppressed

Compartment:

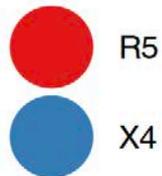
- Blood Plasma
- Cardiac Serum
- Colon (Left)
- Colon (Right)
- Duodenum
- Esophagus
- Frontal Cortex Motor
- Gut (any)
- Ileum
- Jejunum
- Kidney
- Liver
- Lymph Nodes (Aortic)
- Lymph Nodes (Axillary)
- Lymph Nodes (Hilar)
- Lymph Nodes (Inguinal)
- Lymph Nodes (Mediastinal)
- Lymph Nodes (Mesentary)
- Lymph Nodes (Peritrach.)
- Occipital Cortex
- Pancreas
- PBMC
- Pericardial Adipose
- Prostate
- Rectum
- Seminal Vesicle
- Spleen
- Testis



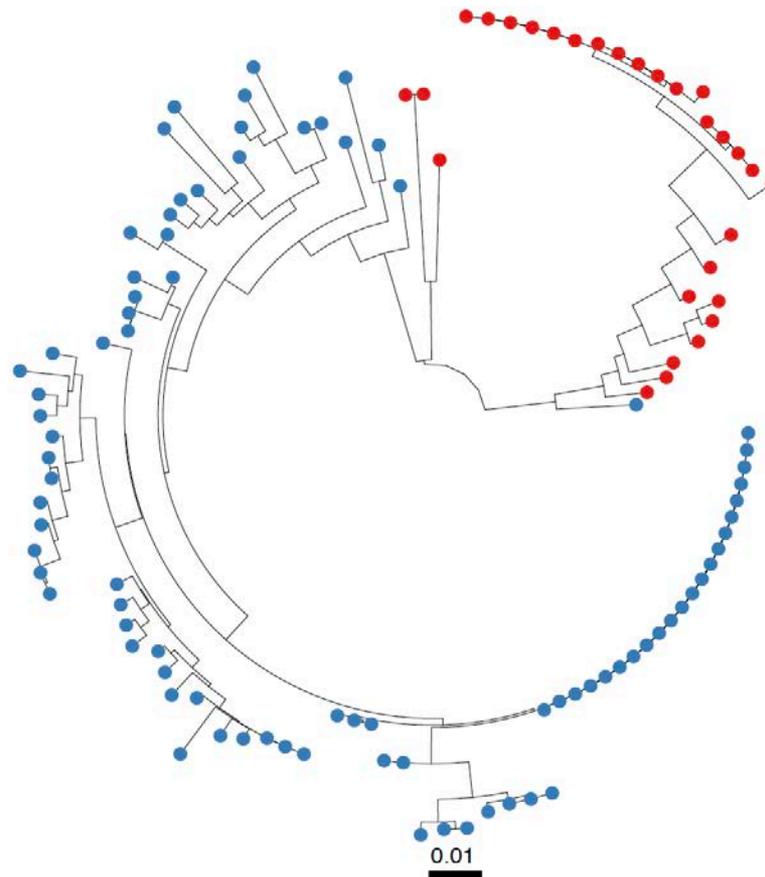


Individual virally suppressed

Genotropism:



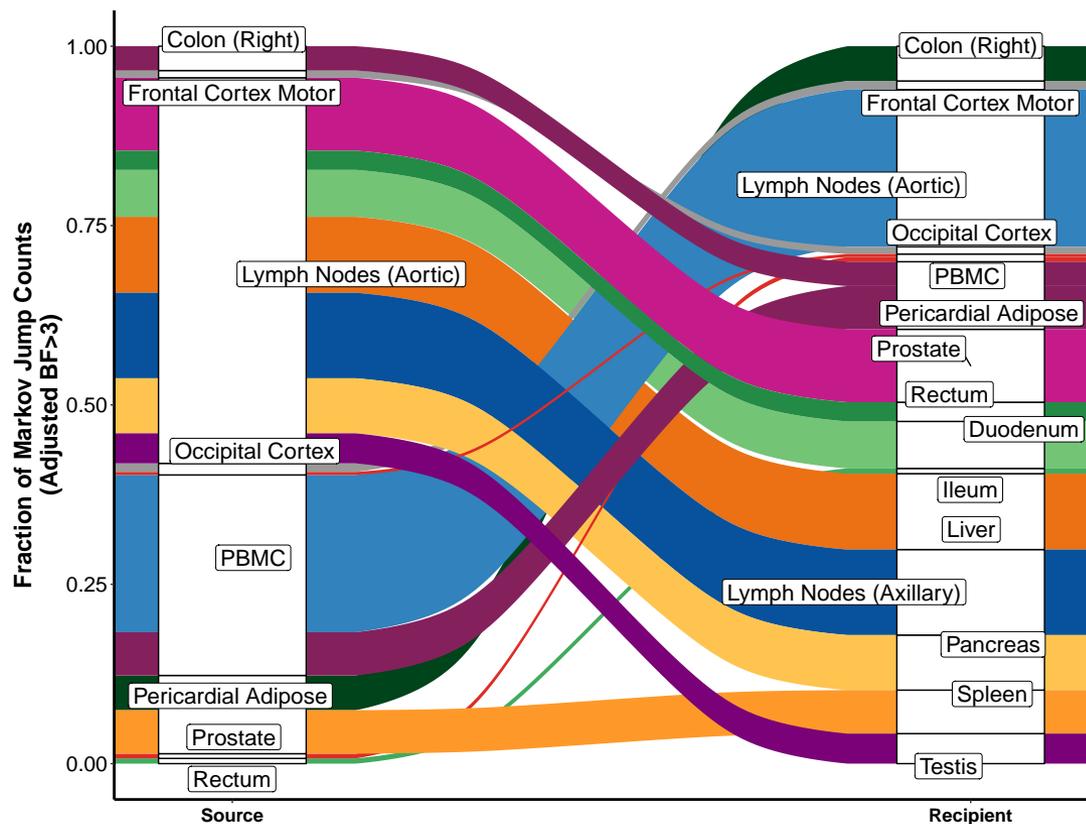
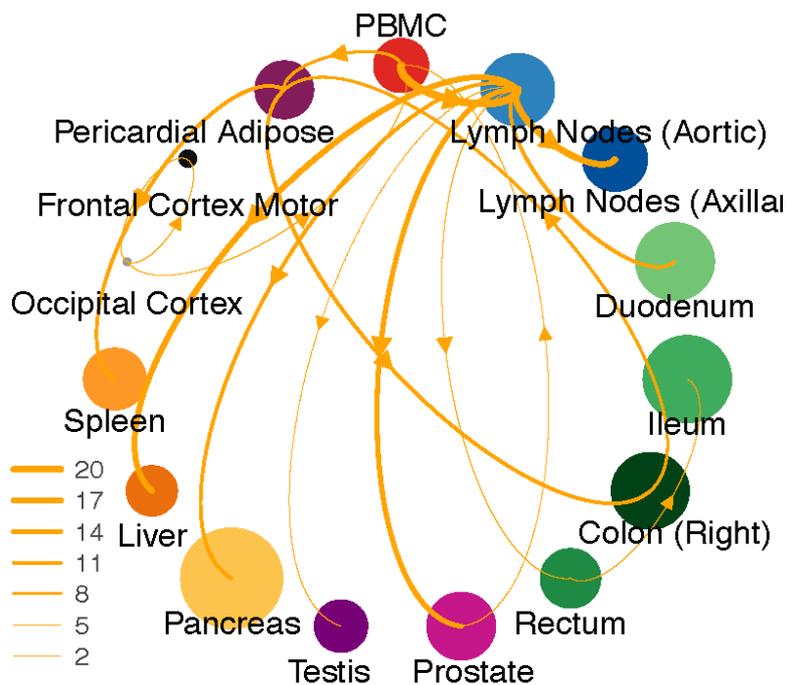
LG03





Individual virally suppressed

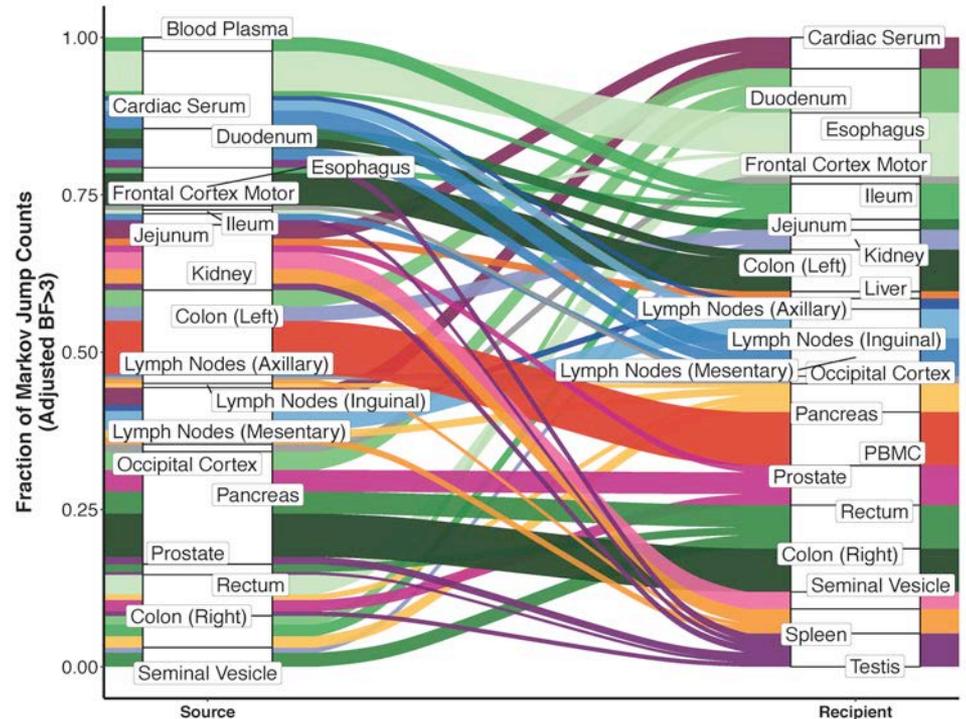
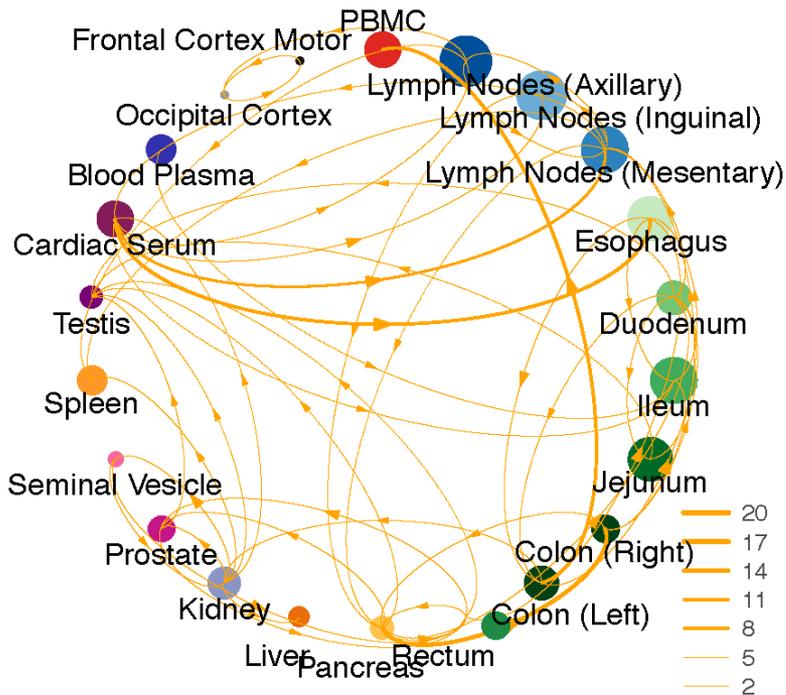
Migration pathways with positive support (BF ≥ 3)





Individual who stopped therapy

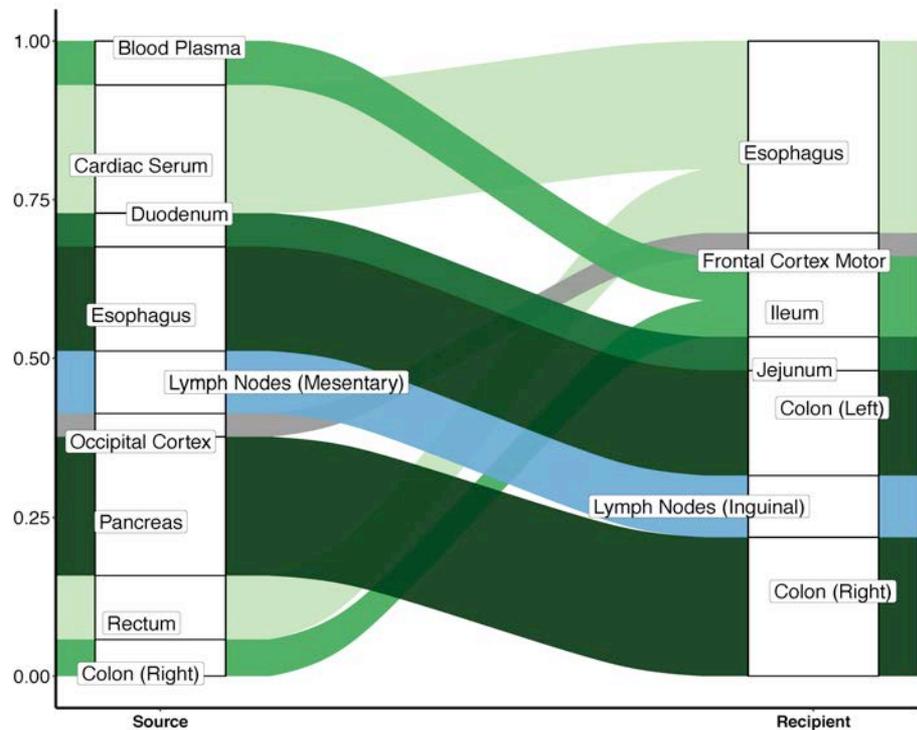
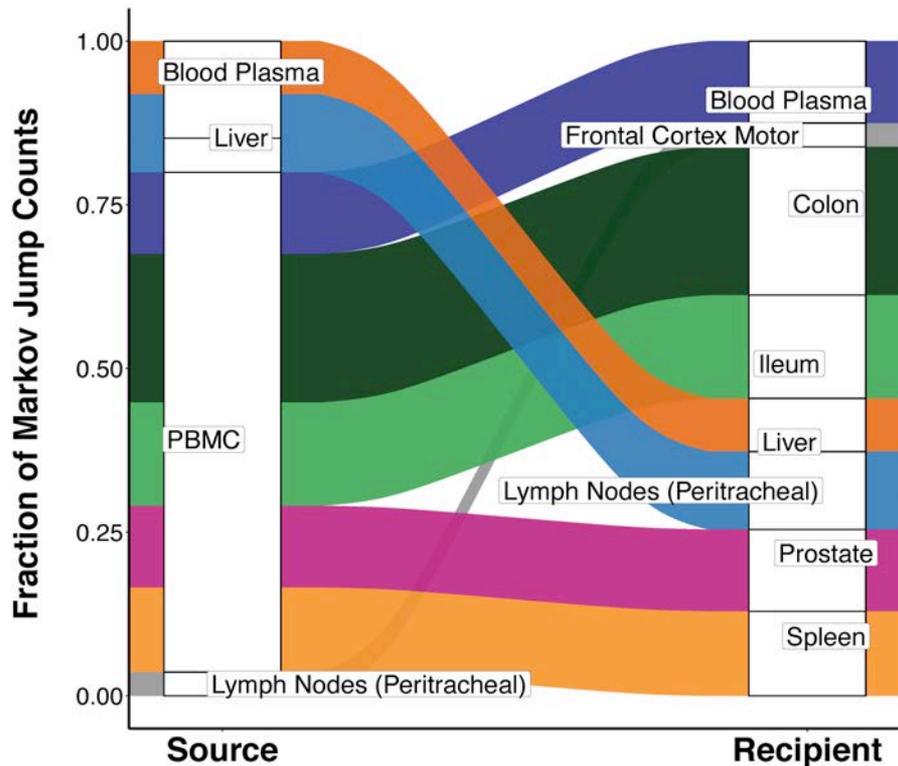
Migration pathways with positive support ($BF \geq 3$)





Individual who stopped therapy

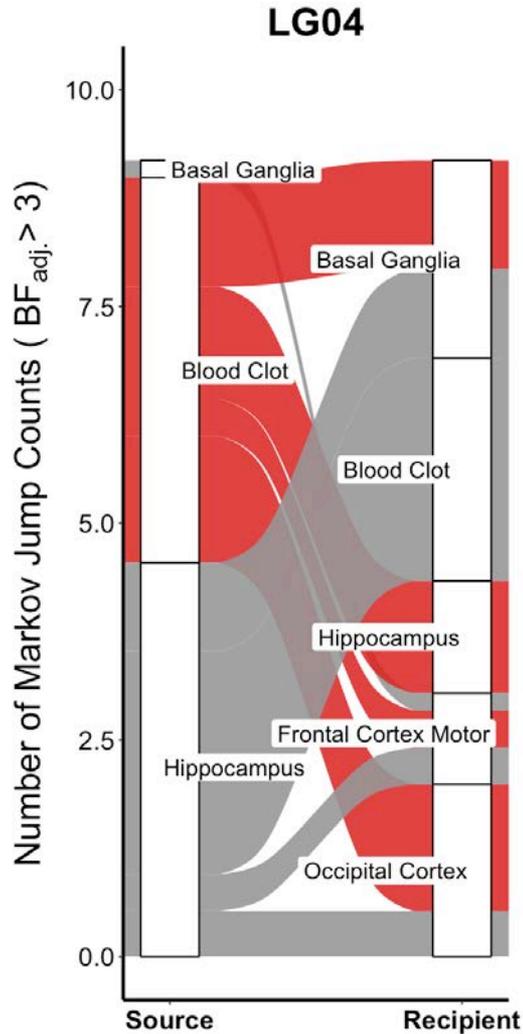
- Migration from and toward blood plasma
- Migration within the CNS and across the BBB



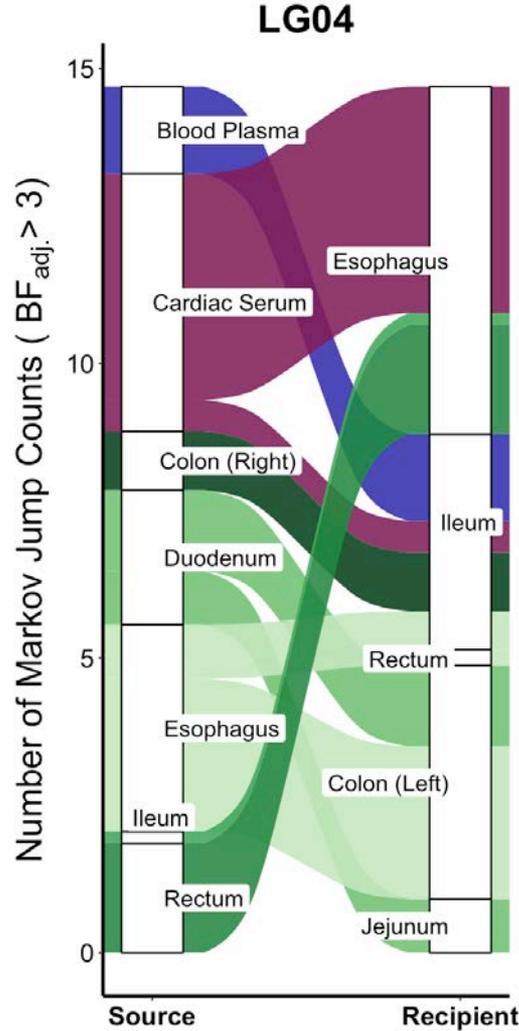


RESULTS

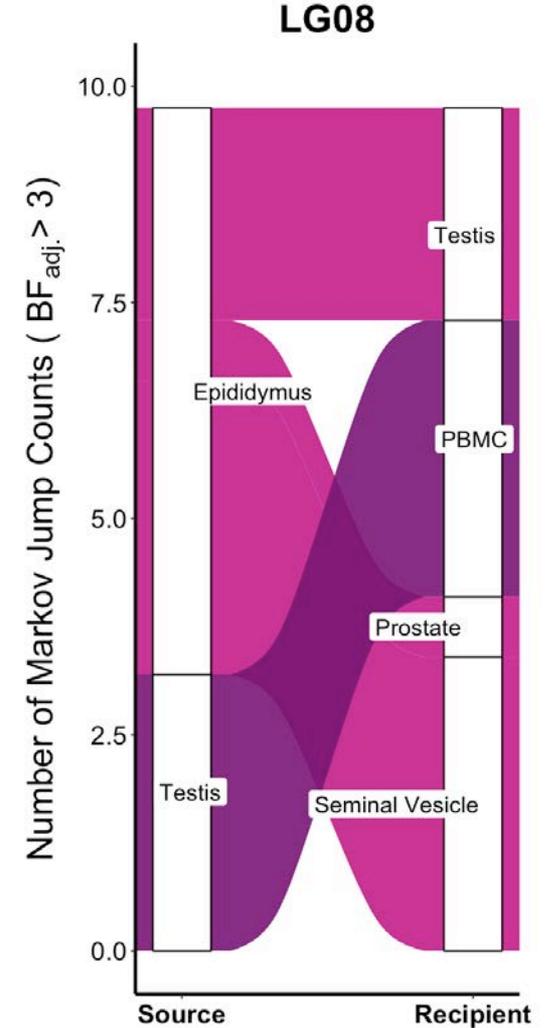
Blood Brain Barrier



Blood Gut Barrier



Genital Tract Barrier





CONCLUSIONS

- Emergence of large, clonal, intact HIV RNA populations after stopping ART, which **repopulated tissues** throughout the body.
- Multiple sites can act as **hubs for dissemination** of HIV within host, predominately blood, gut and lymph nodes.
- Viral exchanges occur within brain areas and across the **blood brain barrier**.
- Viral dynamics are associated with low HIV divergence between sites and high HIV diversity at the recipient site.



- Focus on CNS, GUT and Genital Tract Barriers
- TCR and Integration Site analysis (Clonality)
- Antigen specificity of more abundant TCR clones across tissues
- Micro-environment (Immunologic, pharmacologic)
 - scRNASeq, CyTOF
 - Drug/ART levels
 - Microbiome
 - Viral levels (CMV, EBV, other HHV)



ACKNOWLEDGEMENTS

- **LG participants**
- **Community Advisors**
 - Andy Kaytes
 - Jeff Taylor
- **LG Team**
 - Davey Smith
 - Antoine Chaillon
 - Susanna Concha-Garcia
 - Stephanie Solso
 - Steven Hendrickx
 - Stephen Rawlings
 - Karine Dubé
 - Sarah LaMere
 - Karole Ignacio
 - Magali Porrachia
 - Laura Layman
 - Bree Smith
 - Susan Little
 - Deedee Pacheco
- Gemma Caballero
- Brendon Woodworth
- Craig Gibson
- **KU Leuven**
 - Bram Vrancken
 - Simon Dellicour

Last
Gift



KU LEUVEN

