CHARACTERIZING THE HIV DNA RESERVOIRS IN WHOLE-BODY TISSUES IN THE "LAST GIFT" COHORT

Michelli F. Oliveira[1], Ben Murrell[1], Thomas Vollbrecht[1,2], Susanna Concha-Garcia[1], Venkatesh Kumar[1], Magali Porrachia[1], Brianna Scott[1], Laura Layman[1], Caroline Ignacio[1], Sara Gianella[1], Davey Smith[1,2]

[1]University of California San Diego, La Jolla, CA, USA
[2]Veterans Affairs San Diego Healthcare System, San Diego, CA, USA

Michelli Faria de Oliveira, Ph.D.
University of California San Diego
9500 Gilman Drive MC 0679
La Jolla, CA 92093-0679, USA
E-mail: mfariadeoliveira@ucsd.edu

CROI Conference on Retroviruses and Opportunistic Infections

CFAR Center for AIDS Research, University of California San Diego

Last Gift

Abstract # 0327

BACKGROUND

- HIV persistence in cellular reservoirs is the main barrier to a cure.
- The size and composition of HIV DNA populations in solid tissues during suppressive antiretroviral therapy (ART) is not well characterized.
- Tissue resources are limited by lack of precise clinical and virologic documentation at the time of death.
- Most tissue collection protocols do not include rapid autopsy procedures to preserve the quality of nucleic acids and proteins.

OBJECTIVE

To evaluate the size and genetic features of the HIV DNA reservoirs in solid tissues during documented suppressive ART.

MATERIAL AND METHODS

- The Last Gift (LG) cohort enrolls altruistic, terminally-ill persons living with HIV (PLWH), who are closely followed until the time of death and donate their "whole-body" for HIV research, and rapid autopsy within 6 h after death.
- The distribution of the HIV DNA populations was analyzed across paired post-mortem tissues from two virally suppressed study participants:
  - LG03: 72-year-old; metastatic pancreatic cancer
  - LG06: 57-year-old; metastatic oral cancer
- From each sample, total DNA was extracted and HIV DNA (*gag*) levels were quantified by droplet-digital PCR.
- The genotypic composition of the HIV DNA in tissues was evaluated in one of the participants using a high-throughput single genome amplification and the PacBio platform to deeply sequence full-length HIV envelope (FL HIV-*env*).

Acknowledgments

This work was supported by the Department of Veterans Affairs and grants from the National Institutes of Health: AI100665, AI131385, AI007384, AI106039, AI106039, MH100928, AI036214, CFAR Translational Virology Core. the James B. Pendleton Charitable Trust, CNPq-Brazil, HNRP developmental grant PST-HN39.

RESULTS

- Both LG participants had chronic HIV infection and were on ART with undetectable HIV RNA in blood plasma (confirmed up to 7 h before death).
- We included a total of 28 paired post-mortem tissues per participant: HIV DNA was detected in 24 samples from each participant, including brain, gastrointestinal, urogenital tract, lymphoid and adipose tissues (table).
- 10 tissues from LG03: 107 individual FL HIV-*env* sequences (median 11 sequences/tissue), of which 60 were unique (figure).
- We found a deep divergence, segregating the tree into two lineages by co-receptor tropism (predicted by geno2pheno).
- 100 FL HIV-*env* sequences were genetically intact, while 7 sequences appeared non-functional.
- HIV-*env* migration was extensive: many identical sequences were sampled in multiple body tissues.

Table: Levels of HIV DNA (*gag*) across two LG participants on suppressive ART*

Organ	LG03	LG06
Adipose (abdominal)	13	8
Adipose (pericardial)	874	181
Adrenal Glands	90	23
Thyroid	*n.a.*	18
Aorta	24	0.0
Occipital Cortex	3	10
Parietal Cortex	0.0	10
Frontal Cortex (motor)	0.0	2
Frontal Cortex (pre-motor)	3	2
Hippocampus	7	0.0
Basal Ganglia	11	2
Testes	46	0.0
Prostate	*n.a.*	16
Bladder	107	0.0
Rectum	90	42
Colon (left)	101	46
Colon (right)	45	64
Duodenum	59	238
Ileum	211	180
Esophagus	71	125
Pancreas	101	21
Heart	6	3
Kidney	377	54
Liver	22	46
Lung	43	39
Lymph Node (axillary)	243	689
Lymph Node (aortic)	138	123
Spleen	66	64

*HIV DNA copies/10^6 total cells; *n.a.* = not available

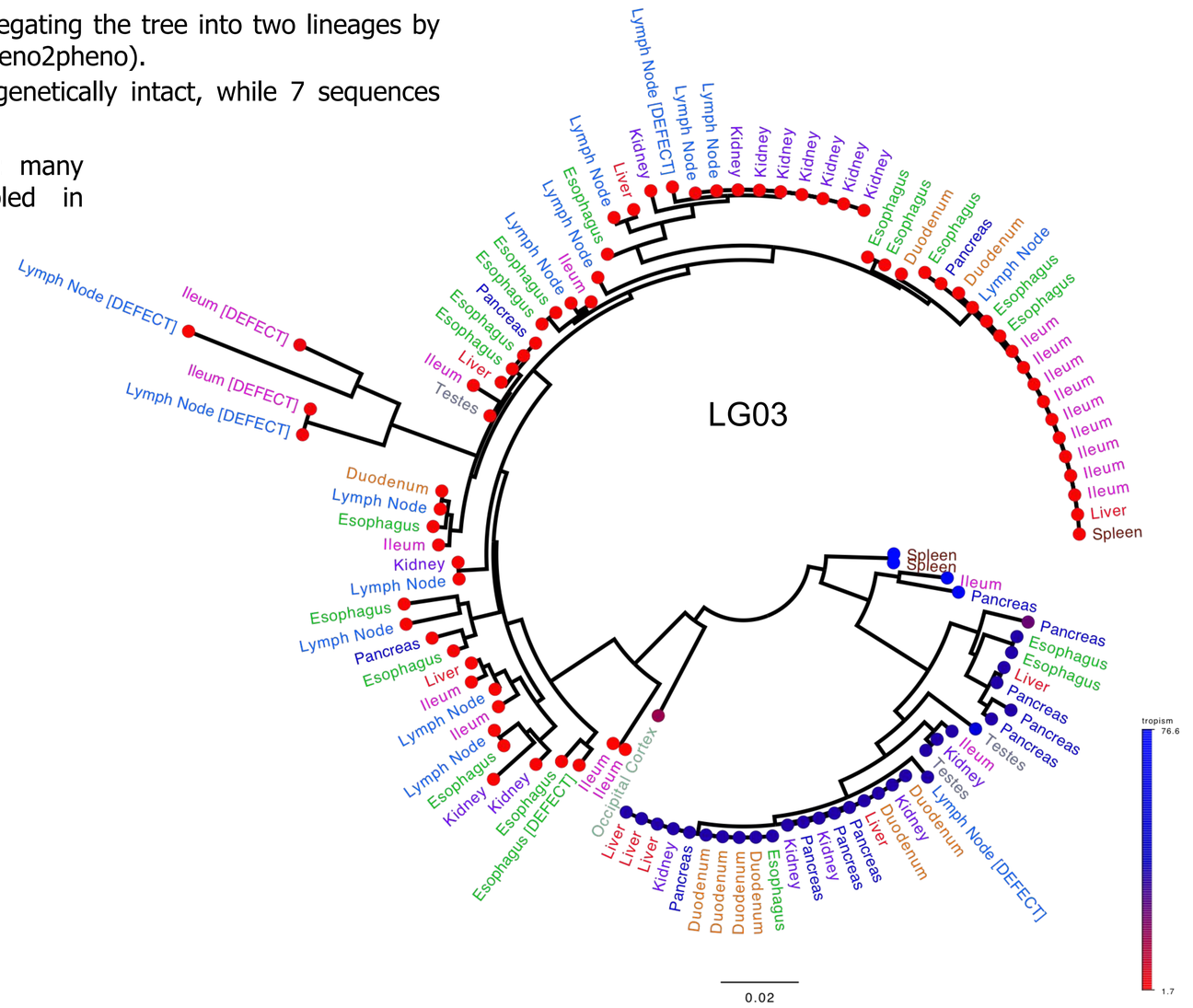


Figure Legend: Maximum likelihood phylogeny tree showing FL HIV-*env* sequences obtained from post-mortem tissues from LG03 participant. Colors represent different body tissues. Colored dots indicate in silico inferred viral tropism (red = CXCR4-tropic viruses and blue = CCR5-tropic viruses). Asterisks indicate non-intact *env* sequences containing major deletions, hyper-mutation, stop-codon mutations or frameshift mutations.

CONCLUSIONS

- **HIV DNA was detected in most body tissues despite long-term ART and despite confirmed undetectable HIV RNA in plasma at the time of death (table).**
- **The majority of FL HIV-*env* sequences appeared to be intact.**
- **The LG cohort represents a unprecedented opportunity to characterize the HIV DNA reservoirs across anatomic compartments, and can provide unique insights to the HIV cure research agenda.**