CFAR
CENTER FOR AIDS RESEARCH
University of California San Diego

Last Gift

The Last Gift Update

(LESSONS LEARNED AND FUTURE DIRECTIONS)

Jeff Taylor

on behalf of the Last Gift Study Team

July 28, 2022

CLEARING HIV RESERVOIRS

- 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

- Studies in living people.
  - Hard to reach anatomic sites safely
  - Even harder to get enough tissue/cells
  - Cannot ask PWH to stop ART for research

- 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

Initial Ethical Considerations (2018)

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

BMC Medical Ethics

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 Little[2], Andy Kaytes[4], Jeff Taylor[4,5], Kushagra Mathur[3], Sogol Javadi[3], Anshula Nathan[1], Hursch Patel[1], Stuart Luter[1], Sean Philpott-Jones[6], Brandon Brown[7] and Davey Smith[2,3]

- Protecting autonomy through informed consent
- Avoiding exploitation and fostering altruism
- Maintaining a favorable benefits/risks balance
- Safeguarding vulnerability through patient-participant centeredness
- Ensuring acceptance of next-of-kin/loved ones and community stakeholders

Table 2 Examples of Patient-Participant Centeredness Considerations for Last Gift Study

EOL Clinical Research Conduct

- Minimize burden of study participation for terminally ill participants [54]
- Ensure research remains flexible, taking into consideration fatigue and fluctuating symptoms across disease trajectory [27, 54]
- Assist participants with completion of study procedures and questionnaires [27]

Quality of Life at the EOL

- Pay attention to quality of life at the EOL [12]. For example, location of care is an important indicator of quality of EOL care [109].
- Honor treatment preferences of terminally ill individuals, including pain management and palliative care [110]
- Respect participants' privacy and need for time with next-of-kin/loved ones
- Consider participants' food preferences and other small attentions
- Consider how substance use at the EOL affects study participation (e.g. alcohol, cannabis)

Advance Care Planning

- Assist participants with advance care planning needs [74]
- Provide proper referral and counseling for participants who desire medical aid to end life under California End of Life Option Act (EOLOA) of 2016

Mental Health, Cultural and Spiritual Issues

- Provide adequate psychosocial support to study participants. The Last Gift study team has a two psychiatrists and one licensed psychologist on staff.
- Give consideration to mental health issues of participants, including fear, suicide ideation, depression, among others [28]
- Pay attention to cultural issues, spiritual well-being and meaning as integral to the dying process [3, 28]

Financial and Legal Issues

- Pay attention to issues around the burden of cost of dying and health insurance
- Help ensure participants have support for EOL legal needs [111]

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

http://lastgift.ucsd.edu/

TONY

MAX


NEVER AGAIN
SHOULD
CHILDREN DIE
BECAUSE OF GUNS
#LEADERNOTTWEETER
No more GUNS please
CAMP KAJAR
Carry KIDS
NOT GUNS
GUNS=
Remove
EQUAT


P
TRAIN STATION
PARKING

Rapid Autopsy Team - 2018

Susanna – The heart and soul of our team

Ethics and Socio-Behavioral Component: Terminal Kindness

› AIDS Res Hum Retroviruses. 2020 May 25. doi: 10.1089/AID.2020.0020. Online 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 [1], Karine Dube [2], Susanna Concha-Garcia [3,4], Hursch Patel [5], Andy Kaytes [6], Jeff Taylor [7], Sogol Stephanie Javadi [8], Kushagra Mathur [9], Megan Lo [10], Brandon Brown [11], John Sauceda [12], David A Wohl [13], Susan J Little [3,14], Steven Hendrickx [15], Steven Rawlings [3,16], D M Smith [17], Sara Gianella [18]

› AIDS Res Hum Retroviruses. 2020 May 25. doi: 10.1089/AID.2020.0025. Online ahead of print.

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 Dube [1], Hursch Patel [2], Susanna Concha-Garcia [3,4], Kelly E Perry [5], Kushagra Mathur [6], Sogol Stephanie Javadi [7], Jeff Taylor [8], Andy Kaytes [9], Brandon Brown [10], John Sauceda [11], Susan J Little [12], Steven Hendrickx [13], Steven Rawlings [3,14], D M Smith [15], Sara Gianella [16]

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 Patel[1], Sogol Stephanie Javadi[4], Kushagra Mathur[4], Andy Kaytes[2], Susanna Concha-Garcia[4,5], Susan Little[4,6], Davey Smith[4,6], Sara Gianella[4,6], Karine Dubé[1]

ELSEVIER

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.viruseradication.com

Review

Altruism: Scoping review of the literature and future directions for HIV cure-related research

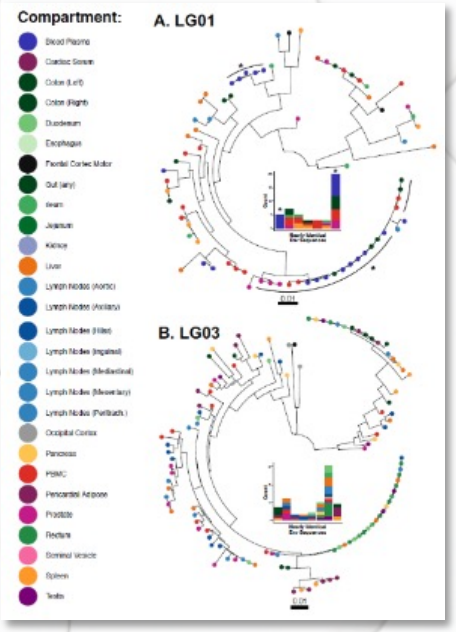
Karine Dubé [a,*], Kelly E. Perry [a], Kushagra Mathur [b], Megan Lo [b], Sogol S. Javadi [b], Hursch Patel [a], Susanna Concha-Garcia [c,d], Jeff Taylor [e,f,g], Andy Kaytes [e], Lynda Dee [f,h,i], Danielle Campbell [i,j], John Kanazawa [a], David Smith [c,k], Sara Gianella [c,k], Judith D. Auerbach [l], Parya Saberi [m], John A. Sauceda [m]

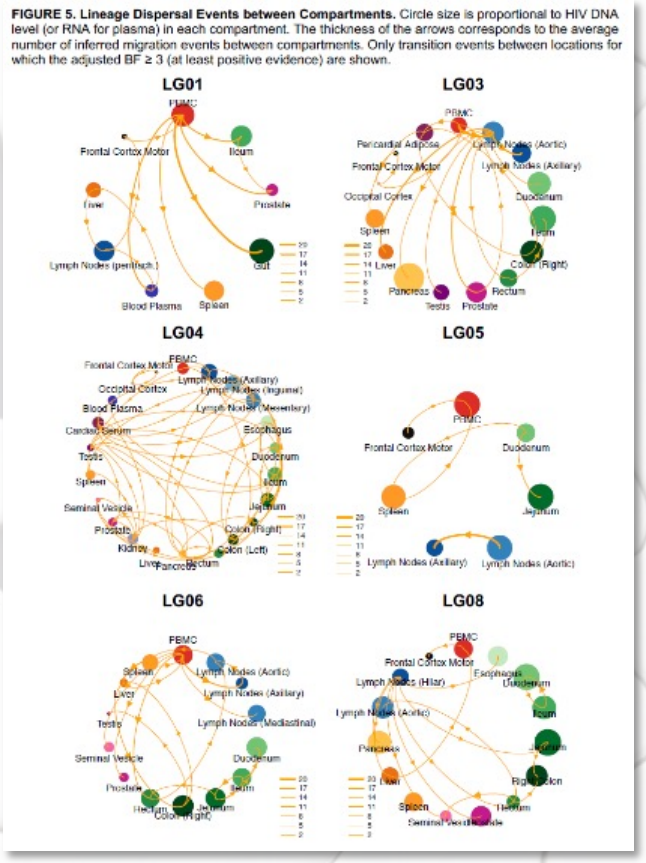
OUR FIRST PAPER ADDRESSING THE PRIMARY AIMS

JCI The Journal of Clinical Investigation

HIV persists throughout deep tissues with repopulation from multiple anatomical sources

Antoine Chaillon, … , Bram Vrancken, Davey M. Smith



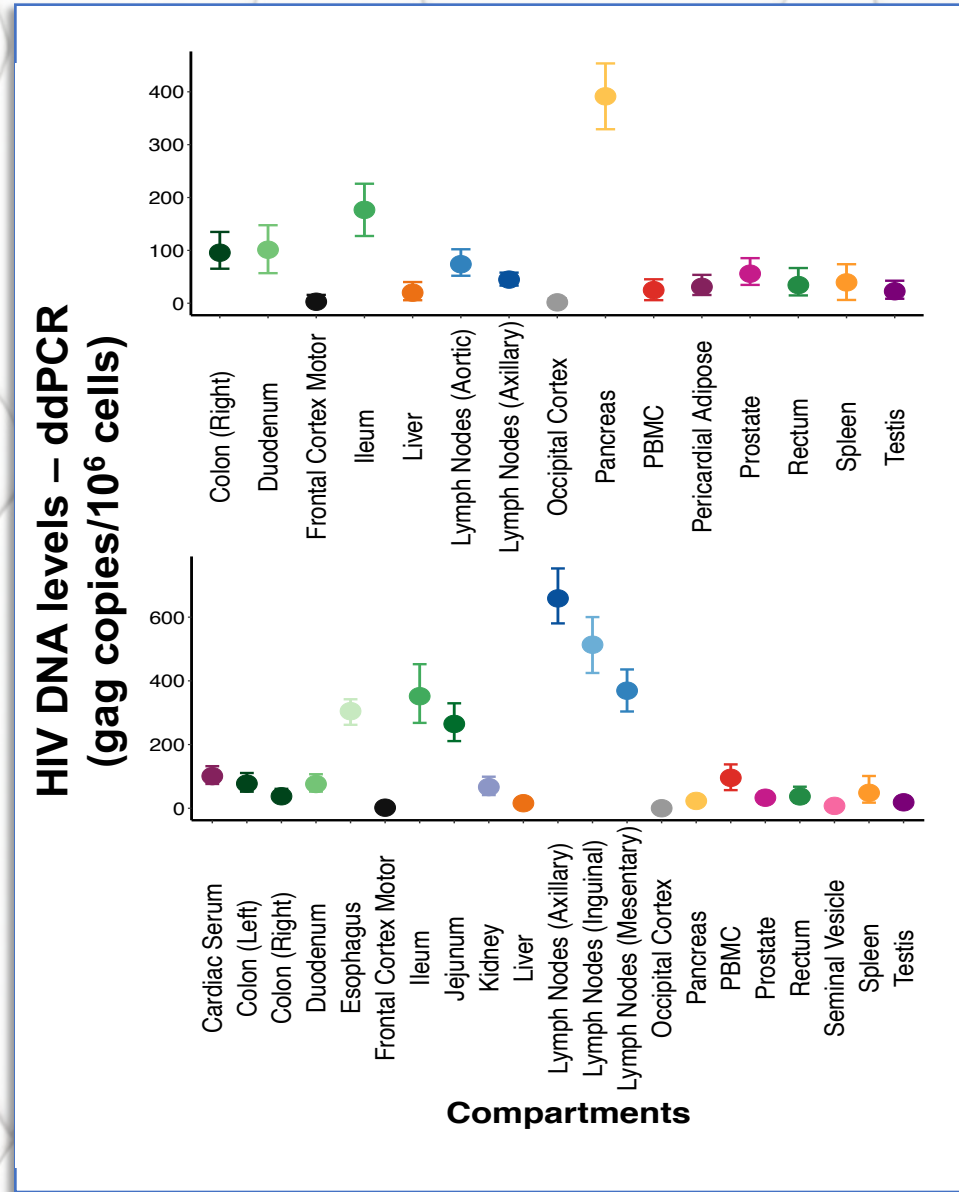


Last Gift Lessons Learned	Next Steps
Heterogeneous distribution of HIV proviral DNA with infected cells in different cortical regions	1) Cell sorting, single-cell, and spatial omics analyses to determine cellular characteristics of the different reservoirs and immunologic microenvironments 2) Compare more CNS sites (multiple cortical areas, brain stem, spinal cord, and CSF)
CNS compartmentalization and differential bNAb susceptibility in brain tissue	1) Expand analysis with larger sample size and more CNS sites 2) Measure ART concentrations, resistance mutations 3) Tropism assays
Migration within brain and bidirectionally across BBB by HIV DNA sequence analysis and statistical modeling	1) Using single-cell techniques and spatial omics analyses to identify which cell types are migrating 2) Tropism
CNS has provirus with intact full length envelope gene, supportive of potential for viral rebound from CNS reservoirs	1) Adapted quantitative viral outgrowth assays, full-length HIV genome sequencing, and insertion site analysis to better characterize replication competence and clonality 2) Tropism of replication-competent virus

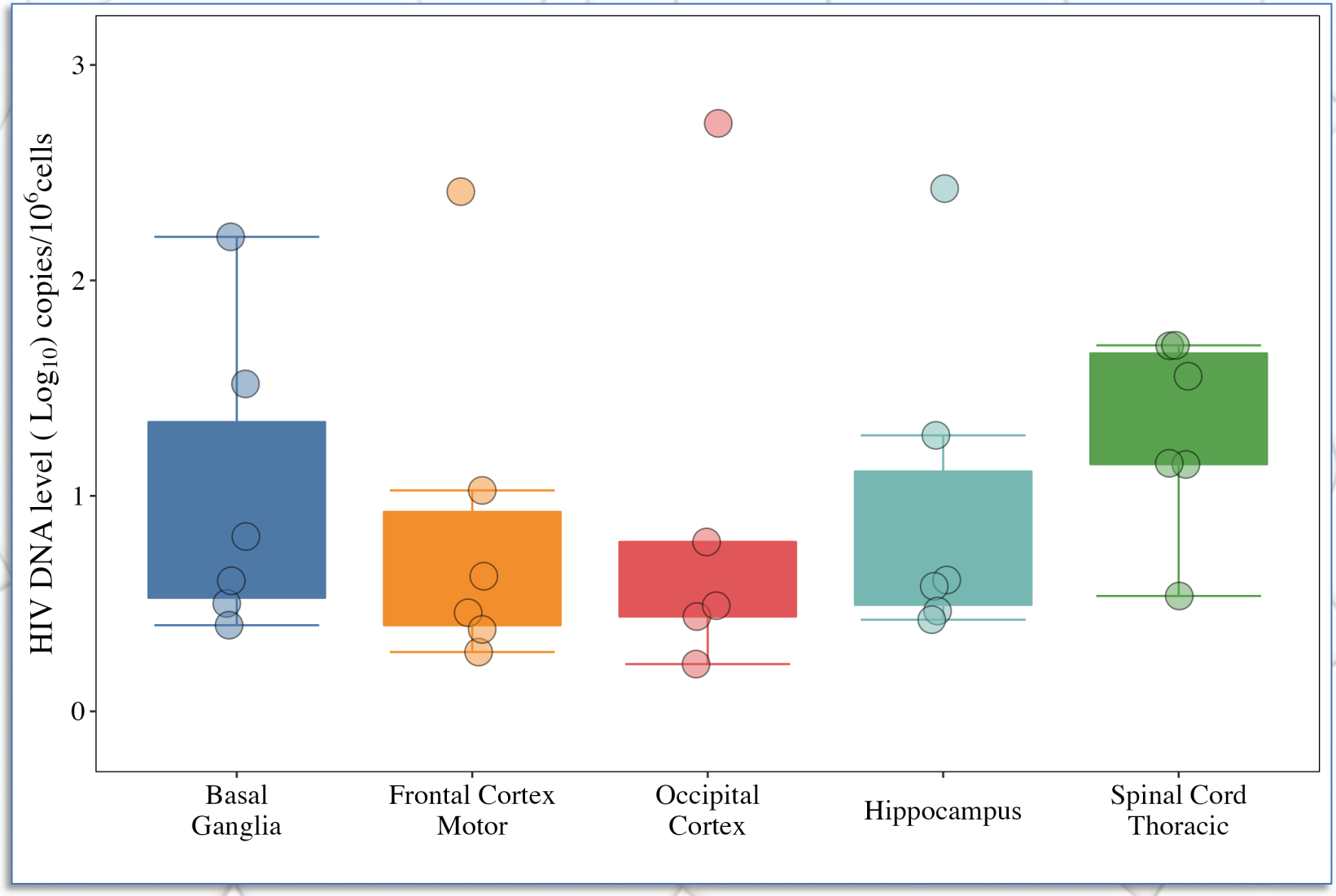
TISSUES HAVE VARIABLE PROVIRAL RESERVOIRS

- HIV DNA levels varied in sampled blood and tissues from **~0 to 659 gag copies/10^6 cells** (median=56, IQR:23-126)

- Lowest in CNS samples (0-34 copies/10^6 cells)

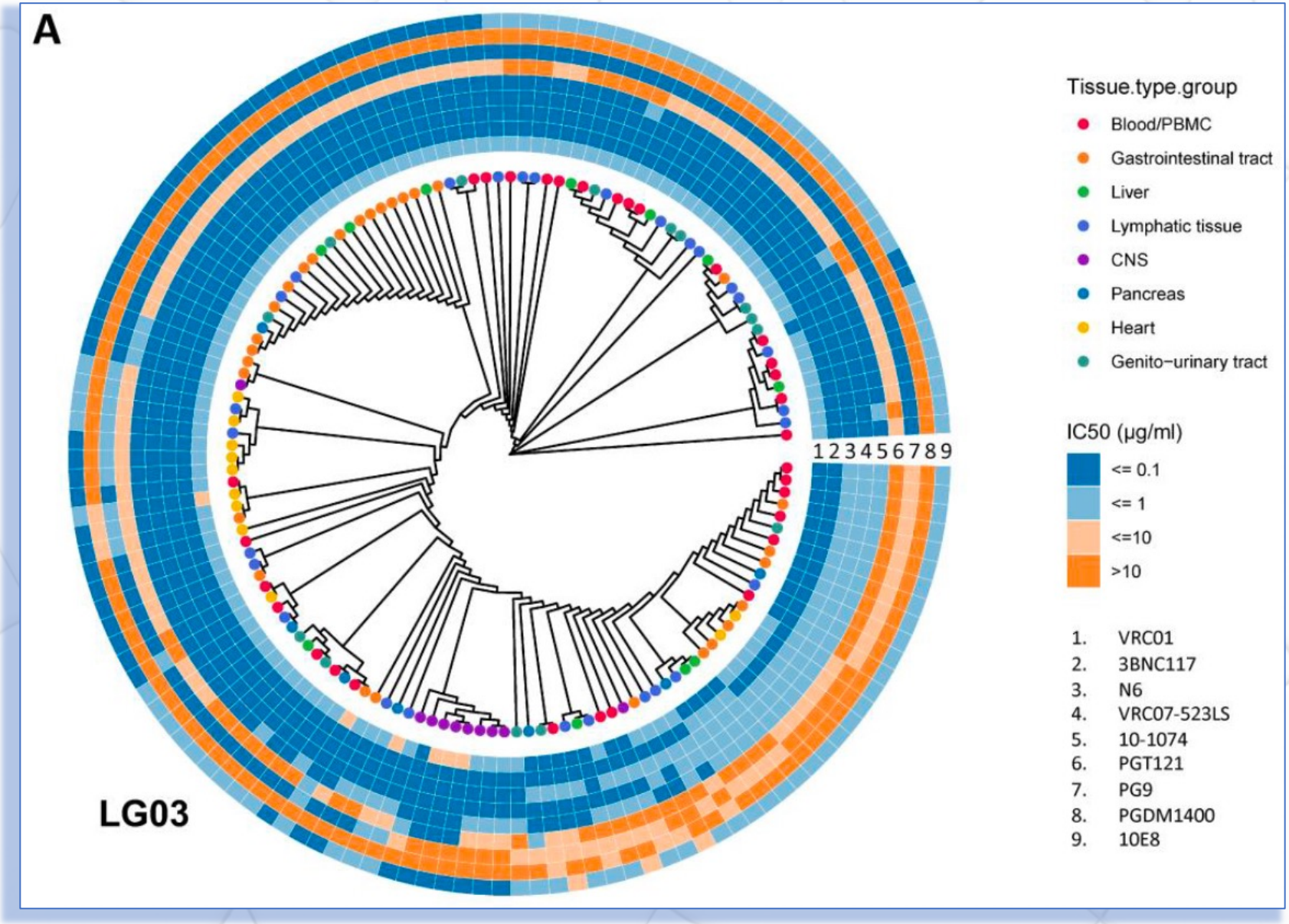


CNS REGIONS HAVE VARIABLE PROVIRAL RESERVOIRS



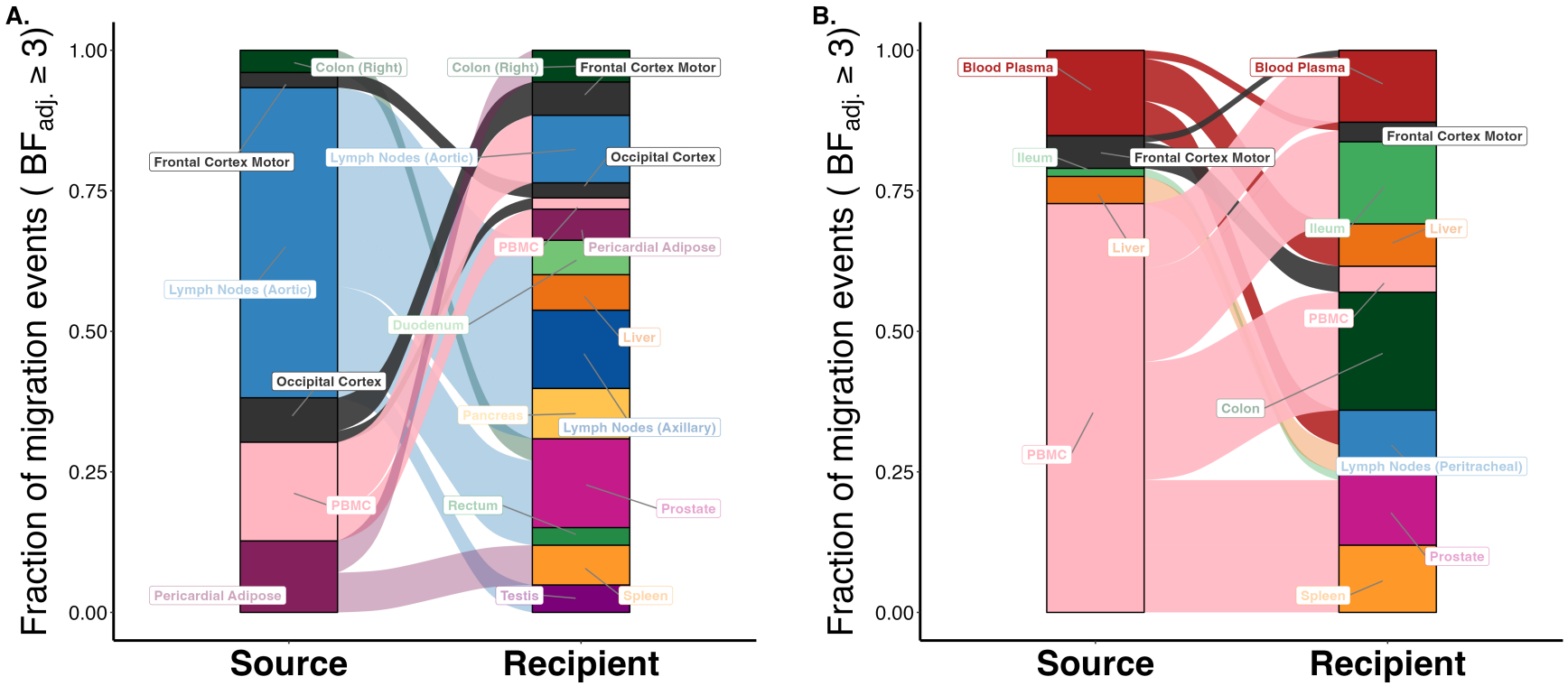
Last Gift Lessons Learned	Next Steps
Heterogeneous distribution of HIV proviral DNA with infected cells in different cortical regions	1) Cell sorting, single-cell, and spatial omics analyses to determine cellular characteristics of the different reservoirs and immunologic microenvironments 2) Compare more CNS sites (multiple cortical areas, brain stem, spinal cord, and CSF)
CNS compartmentalization and differential bNAb susceptibility in brain tissue	1) Expand analysis with larger sample size and more CNS sites 2) Measure ART concentrations, resistance mutations 3) Tropism assays
Migration within brain and bidirectionally across BBB by HIV DNA sequence analysis and statistical modeling	1) Using single-cell techniques and spatial omics analyses to identify which cell types are migrating 2) Tropism
CNS has provirus with intact full length envelope gene, supportive of potential for viral rebound from CNS reservoirs	1) Adapted quantitative viral outgrowth assays, full-length HIV genome sequencing, and insertion site analysis to better characterize replication competence and clonality 2) Tropism of replication-competent virus

SUSCEPTIBILITY TO bNAbs ALSO VARIES BY SITE – ESP BRAIN



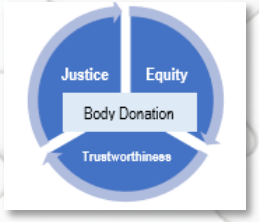
Last Gift Lessons Learned	Next Steps
Heterogeneous distribution of HIV proviral DNA with infected cells in different cortical regions	1) Cell sorting, single-cell, and spatial omics analyses to determine cellular characteristics of the different reservoirs and immunologic microenvironments 2) Compare more CNS sites (multiple cortical areas, brain stem, spinal cord, and CSF)
CNS compartmentalization and differential bNAb susceptibility in brain tissue	1) Expand analysis with larger sample size and more CNS sites 2) Measure ART concentrations, resistance mutations 3) Tropism assays
Migration within brain and bidirectionally across BBB by HIV DNA sequence analysis and statistical modeling	1) Using single-cell techniques and spatial omics analyses to identify which cell types are migrating 2) Tropism
CNS has provirus with intact full length envelope gene, supportive of potential for viral rebound from CNS reservoirs	1) Adapted quantitative viral outgrowth assays, full-length HIV genome sequencing, and insertion site analysis to better characterize replication competence and clonality 2) Tropism of replication-competent virus

HIV DNA MIGRATION EVENTS



More Lessons Learned
Research at EOL has provided our participants with autonomy and ability to leave a meaningful scientific legacy
Community engagement and patient/participant-centered focus is particularly critical in EOL research throughout the entire study
Multi-disciplinary teams are key and should include paid positions for socio-behavioral scientists and members of the HIV community
Decisions regarding goals of care, hospice, and medical aid in dying (MAiD)* must be done completely outside the scope of the study

Possible Next Steps for Last Gift v2.0 → Discussion



1. Continue assessing perceptions of Last Gift participants (e.g., informed consent) and NOK/loved ones
2. Explore motivators and deterrents of participating in EOL HIV cure research with increased focus on justice, equity and trustworthiness
3. Examine motivators and deterrents of participating in EOL HIV cure research among diverse PLWH in the entire U.S.
4. Continue to derive and document ethical and practical recommendations for engaging diverse PWH in EOL HIV cure research
5. Possibly incorporate elements of 3-Wishes Project into Last Gift (e.g., 1 Wish?)

→ Increased community, patient and stakeholder engagement (diverse settings; perspectives for website)

- Suggestion from Susanna (November 2021): More emphasis on cultural and spiritual considerations
- Possible collaborations with CANCure
- Possible collaborations with IAVI (South Africa, India)
- Possible collaborations with Ici-Stem (Europe)

Submitted Jan 2022 (Canada willingness paper)

Older people with HIV's willingness to participate in end-of-life HIV cure research in Canada: A mixed-method study

David Lessard[1,2], Karine Dubé[13,18], Martin Bilodeau[3], Patrick Keeler[4], Shari Margolese[5], Ron Rosenes[5], Liliya Sinyavskaya[6], Madeleine Durand[6,7], Erika Benko[8], Colin Kovacs[8], Charlotte Guerlotté[5,9], Wangari Tharao[5,10], Keresa Arnold[5,11], Renée Masching[5,12], Darien Taylor[5], José Sousa[5], Mario Ostrowski[13], Jeff Taylor[14], Andy Kaytes[14], Davey Smith[14], Sara Gianella[14], Nicolas Chomont[15], Jonathan B. Angel[16], Jean-Pierre Routy[1], Éric Cohen[17,18], Bertrand Lebouché[1,2,20], Cecilia Costiniuk[1,21]

Clinical Infectious Diseases

VIEWPOINTS

Medical Assistance in Death as a Unique Opportunity to Advance Human Immunodeficiency Virus Cure Research

Teslin S. Sandstrom,[1,2] Stephanie C. Burke Schinkel,[1] and Jonathan B. Angel[1,2,3]

[1]Ottawa Hospital Research Institute, [2]Department of Biochemistry, Microbiology & Immunology, University of Ottawa, and [3]Division of Infectious Diseases, Ottawa Hospital-General Campus, Canada

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Participating in Human Immunodeficiency Virus Cure Research at the End of Life

Joshua J. Vásquez and Peter W. Hunt

Department of Medicine, University of California San Francisco


THANK YOU