The Last Gift Update

(LESSONS LEARNED AND FUTURE DIRECTIONS)

Jeff Taylor
on behalf of the Last Gift Study Team
July 28, 2022
• 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)

- 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
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/
Susanna – The heart and soul of our team
Ethics and Socio-Behavioral Component: Terminal Kindness

"My Death Will Not [Be] in Vain": Testimonials From Last Gift Rapid Research Autopsy Study Participants Living With HIV at the End of Life

Kellie E. Perry 1, 2, Karine Dube 2, 3, Susanna Concha-Garcia 3, 4, Hirsch 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 14, Steven Hendrickx 15, Steven Rawlings 8, 16, D.M. Smith 17, Sara Gianella 18

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 2, 3, Hirsch Patel 5, Susanna Concha-Garcia 3, 4, Kellie E. Perry 5, Kushagra Mathur 9, Sogol Stephanie Javadi 8, Jeff Taylor 7, Andy Kaytes 6, Brandon Brown 10, John Sauceda 12, Susan J. Little 14, Steven Hendrickx 15, Steven Rawlings 8, 16, D.M. Smith 17, Sara Gianella 18

"[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, 2, Jeff Taylor 2, 3, Hirsch Patel 5, Sogol Stephanie Javadi 8, Kushagra Mathur 9, Andy Kaytes 6, Susanna Concha-Garcia 3, 4, Susan Little 1, 4, 5, Davey Smith 8, 16, Sara Gianella 18, Karine Dube 2, 3
OUR FIRST PAPER ADDRESSING THE PRIMARY AIMS

HIV persists throughout deep tissues with repopulation from multiple anatomical sources

Antoine Chaillon, ... , Bram Vrancken, Davey M. Smith
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| 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 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
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SUSCEPTIBILITY TO bNAbS ALSO VARIES BY SITE – ESP BRAIN
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HIV DNA MIGRATION EVENTS

A. Fraction of migration events (BF adj. ≥ 3)

Source

Recipient

B. Fraction of migration events (BF adj. ≥ 3)

Source

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

1 David Lessard1,2, Karine Dubé13,18, Martin Bilodeau7, Patrick Keeler4, Shari Margolese5, Ron Rosenes6, Liliya Sinyavskaya6, Madeleine Durand6,7, Erika Benko8, Colin Kovacs8, Charlotte Guerlotté11,9, Wangari Thara5,10, Keresa Arnold5,11, Renée Masching5,12, Darien Taylor5, José Sousa5, Mario Ostrowski13, Jeff Taylor14, Andy Kayte14, Davey Smith14, Sara Gianella14, Nicolas Chomont15, Jonathan B. Angel16, Jean-Pierre Routh1, Éric Cohen17,18, Bertrand Lebouché12,20, Cecilia Costiniuk12,21

Clinical Infectious Diseases

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

Tetsin S. Sandstrom,1 Stephanie C. Berke Schinkel,1 and Jonathan B. Angel1,2

Ottawa Hospital Research Institute, 1Department of Bacteriology, Microbiology & Immunology, University of Ottawa, and 2Division of Infectious Diseases, Ottawa Hospital General Campus, Canada

Clinical Infectious Diseases

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

Joshua J. Viquez and Peter W. Rent

Department of Medicine, University of California San Francisco
THANK YOU