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

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(See the View points by Sandstrom et al on pages 1063–7.)

Over the last decade, understanding human immunodeficiency virus' (HIV) persistence and developing strategies to cure HIV infections have emerged as key priorities for both the research community and people living with HIV (PLWH). It will be challenging to extinguish the global HIV epidemic through antiretroviral therapy (ART) alone; even among those with access to treatment, not all can sustain lifelong adherence to currently available regimens. Many of us working on strategies to reduce persistent immune activation despite ART—which may drive much of the accentuated age-related morbidity and mortality in this setting—also wonder whether these strategies can be fully effective without eradicating, controlling, or silencing the HIV reservoir. Thus, an HIV cure is an important goal. While the Berlin patient taught us that an HIV cure is possible [1], in the decade since his case was first reported, a number of obstacles to achieving this goal for the majority of PLWH have arisen.

One of those obstacles is the persistence of HIV in tissue reservoirs that may be relatively more resistant to immune-mediated clearance and/or be exposed to

lower antiretroviral drug concentrations. Indeed, the vast majority of persistently HIV-infected cells during ART reside in the gut, an immunoregulatory environment that may suppress immune-mediated clearance mechanisms, or in follicles within secondary lymphoid tissues that often exclude cytotoxic CD8⁺ T cells and natural killer cells [2]. Controversy also continues as to whether replication-competent HIV persists in myeloid-derived cells of the central nervous system during ART, which see far lower concentrations of antiretroviral drugs than plasma [3]. A major challenge to studying these important issues is the need for large amounts of tissue to fully characterize the burden and anatomic localization of infected cells, beyond what is typically feasible in biopsy procedures. Furthermore, some tissue sites, like the brain, are simply not safe to biopsy in otherwise healthy individuals. Postmortem tissues from autopsy procedures can often address these issues, but the time between death and autopsy/tissue preservation is typically too long to adequately preserve viable cells or HIV nucleic acids. Indeed, the postmortem degradation of tissues and nucleic acids begins almost immediately and impacts any scientific work conducted on posthumous tissue [4, 5], particularly the most advanced HIV RNA in situ hybridization (and sequencing with laser capture microscopy) techniques [6]. It is also often unclear whether a tissue donor interrupted ART for some period prior to death, complicating the interpretation of the presence of HIV RNA or proteins in tissues.

In this issue of *Clinical Infectious Diseases*, Sandstrom et al address these issues by describing a PLWH with a terminal illness that opted for medical assistance in death (MAiD). In the days prior to death, this incredibly generous participant elected to arrange for immediate posthumous tissue processing and donation of his remains to HIV research, so that his tissues could help address some of the barriers to tissue reservoir research described above. Tissues acquired post-MAiD (with preparation before death) theoretically provide the best opportunity to mitigate the effects of delayed tissue processing on the interpretation of downstream studies. We agree with the authors that tissues prepared as described may provide valuable insights for HIV cure research. Moreover, post-MAiD tissue donation offers a pathway for individuals with terminal illness to achieve the sense of fulfillment and purpose that can improve the patient experience at this final stage of life. Indeed, the authors rightly point out that some of the most devoted PLWH participating in research—including the participant they described—have spent decades advocating for HIV research and care. Yet, they are often excluded from participating in early HIV cure studies, that commonly seek to enroll participants who started ART at much earlier disease stages (to enrich for low HIV reservoirs) or who are younger (to increase immune responses to vaccines or immunogens). Participation in research at the end of life has been a

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taboo subject for some time but, as the authors describe, can benefit the HIV cure agenda while also, in many cases, providing gratification and fulfillment to individuals at the end of life.

Nevertheless, there are obviously many important ethical and practical issues to consider carefully in such studies. First, the availability of MAiD and, thus, the ability to control the timing of death, remains modest at best. Arguments against the use of MAiD include themes of capacity, vulnerability, stigma, potential underlying mental illness, and the role of physicians [7]. Some of these concerns are addressed by the adherence to eligibility requirements that include a prognosis of less than 6 months to live, the ability to undergo informed consent, decision-making capacity, and mental stability. However, the methods of screening for these criteria vary by jurisdiction and provider and are without requirements for formal testing. While this may be suitable for the majority of individuals choosing MAiD, the wider-scale introduction of posthumous tissue donation programs may increase concerns that a vulnerable population will be pressured into MAiD. Even a perception that this might be the case could cause harm. The decision to undergo posthumous tissue donation really needs to be completely separated from the decision to undergo MAiD, to prevent even the perception of coercion. To mitigate such concerns and to preserve the efforts of those who have worked to shape the social discourse that has created a path for individuals to access MAiD, it seems appropriate to employ formalized screening criteria for those considering posthumous tissue donation. By example, such criteria may include (1) documented capacity screenings by 2 independent clinicians (1 of whom is not directly involved in the care of the patient), (2) witnessed informed consent (ideally including loved ones identified by the patient), (3) a formal mental health screening, and (4) potentially, formal neuropsychological testing

to clarify any question of cognition. Such a rigorous and structured approach may be overly cumbersome for some donors or physicians but, in the long run, may minimize risks to research participants and encourage the social acceptance of post-MAiD tissue donation.

A potentially more feasible and accessible approach to enabling posthumous tissue donation for HIV cure research is already being piloted by a group at the University of California San Diego: the “Last Gift” project [8]. This program has already enrolled 9 PLWH with terminal illnesses, most of whom did not elect to undergo MAiD. Rather, the team arranges for sample collection prior to death and also the availability of a rapid autopsy (within 6 hours) following a naturally occurring death (or after MAiD, if this was the participant’s prior choice). Readers are encouraged to review the Last Gift website and testimonials from participants (<http://lastgift.ucsd.edu> and [9]), to truly appreciate the sense of respect, partnership, and trust that has developed between the researchers, the participants, and their loved ones. We also acknowledge the great responsibility the research team feels for honoring the heartfelt altruism of the participants, not overselling the impact tissue donation can have on a research agenda, while at the same time making sure the donated tissues are utilized for the highest-impact science. This program also requires an impressive degree of coordination and a well-resourced team. As groundbreaking programs like this gain acceptance, it will be important to broaden outreach to communities that might not always seek out posthumous tissue donation. Indeed, well-educated White men tend to be much more likely than other demographic groups to seek out whole-body tissue donation, indicating that other groups may have less access or more difficulties in finding paths to donation [10]. While cultural beliefs and perceptions of donation may play a role in who participates in donation, a global

meta-analysis found that attitudes in favor of donation, including a sense of altruism and solidarity with a broader community, were found across all cultures and demographics studied [11]. Perhaps the topic of posthumous tissue donation is not as delicate or controversial as we perceive. Thus, studies evaluating the impact of cultural, logistical, and system-wide barriers to donation and rapid tissue processing are needed.

Logistical barriers to posthumous donation may include: (1) a lack of understanding of local or federal laws by potential donors and physicians (eg, who can consent to donate and under what conditions), (2) a lack of or prohibitive institutional guidelines on donation and posthumous tissue processing (<https://newoldage.blogs.nytimes.com/2014/09/18/donating-the-body/>), (3) difficulty in locating accepting organizations, as many organizations exclude individuals who are not in hospice or those with HIV and other chronic diseases, who may have spent their lives advocating for their respective disease, (4) differing desires of the loved ones associated with the individual and the decedent, resulting in the cancellation or delay of donation, and (5) the logistics of how a body is handled, as significant delays in tissue processing, whether occurring within or outside of the hospital, make precious donations less useful to researchers. In the intensive care unit, for example, physician-driven discussions on death and dying rarely include questions about tissue donation. The subject is usually only broached after death, when families are faced with the question of an autopsy. Comments like “my loved one would want science to benefit from their death” are common but, unfortunately, these sentiments probably come too late for effective tissue donation. Perhaps the most common feelings from grieving loved ones lead to comments like “no, we are just too sad to think about this now.” Beginning discussions with both patients and loved ones earlier in the course of illness, as exemplified by the Last Gift

project, will be key, as will locating networks to handle posthumous logistics and educating medical institutions and first responders on these issues.

Finally, it should be noted that networks undertaking the rapid processing of posthumous tissues require a significant investment of funds that may be limited in time and scope. Therefore, without some mechanism for sustainability, such temporary networks are unlikely to significantly contribute to the cultural shift needed to make posthumous tissue donation more widely available to potential donors and to science. Examples like the post-MAiD tissue donation described by Sandstrom et al and the Last Gift project demonstrate that posthumous donation programs can be developed with high ethical standards that bring a sense of fulfillment to individuals at the end of life, while also helping to advance science. The incredible scientific progress since the beginning of the

HIV epidemic has always benefited from a close partnership between PLWH and the research community. These examples teach us that those partnerships can endure and be fulfilling even as people approach the end of life.

Notes

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References

1. Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* **2009**; 360:692–8.
2. Estes JD, Kityo C, Ssali F, et al. Defining total-body AIDS-virus burden with implications for curative strategies. *Nat Med* **2017**; 23:1271–6.
3. Bednar MM, Sturdevant CB, Tompkins LA, et al. Compartmentalization, viral evolution, and viral

latency of HIV in the CNS. *Curr HIV/AIDS Rep* **2015**; 12:262–71.

4. Sampaio-Silva F, Magalhães T, Carvalho F, Dinis-Oliveira RJ, Silvestre R. Profiling of RNA degradation for estimation of post mortem [corrected] interval. *PLOS One* **2013**; 8:e56507.
5. Sidova M, Tomankova S, Abaffy P, Kubista M, Sindelka R. Effects of post-mortem and physical degradation on RNA integrity and quality. *Biomol Detect Quantif* **2015**; 5:3–9.
6. Vasquez JJ, Hussien R, Aguilar-Rodriguez B, et al. Elucidating the burden of HIV in tissues using multiplexed immunofluorescence and in situ hybridization: methods for the single-cell phenotypic characterization of cells harboring HIV in situ. *J Histochem Cytochem* **2018**; 66(6):427–46.
7. Dembo J, Schuklenk U, Reggler J. “For their own good”: a response to popular arguments against permitting medical assistance in dying (MAiD) where mental illness is the sole underlying condition. *Can J Psychiatry* **2018**; 63:451–6.
8. Gianella S, Taylor J, Brown TR, et al. Can research at the end of life be a useful tool to advance HIV cure? *AIDS* **2017**; 31:1–4.
9. Danielson MM, Dubé K. Michael’s testimonial. *Ann Intern Med* **2018**; 169:349.
10. Asad AL, Anteby M, Garip F. Who donates their bodies to science? The combined role of gender and migration status among California whole-body donors. *Soc Sci Med* **2014**; 106:53–8.
11. Newton JD. How does the general public view posthumous organ donation? A meta-synthesis of the qualitative literature. *BMC Public Health* **2011**; 11:791. Available at: <https://bmcpublichealth.biomedcentral.com/track/pdf/10.1186/1471-2458-11-791>.