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# Can research at the end of life be a useful tool to advance HIV cure?

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Modern antiretroviral therapy (ART) has saved millions of years of life [1], but it cannot eradicate latently infected cells [2,3]. The replication-competent provirus that remains during ART represents the major barrier to curing HIV [4]. Most of this latent reservoir resides in solid tissues and not in circulating blood, and we have yet to fully define the sanctuary sites of HIV persistence [5]. Timothy Ray Brown (known by many as the 'Berlin Patient') may be the closest to an HIV cure after being treated with an allogeneic hematopoietic stem cell transplant from a donor who was homozygous for the CCR5Δ32 deletion [6]. Unfortunately, this remarkable success has not been reproduced, and robust viral replication resumes almost universally following treatment interruption [7–9]. Even if strategies currently in development succeed in purging HIV from circulating $CD4^+$ T cells, residual virus can remain in the central nervous system (CNS), gut-associated lymphoid tissue (GALT), genital tract, adipose tissue, and others [9–12].

Thus, cure efforts must tackle the eradication of HIV reservoirs in anatomic compartments and sanctuaries throughout the body.

The earliest stages of HIV infection are characterized by high levels of viral replication and little immune response [13,14]. This window of uncontrolled replication allows the virus to seed reservoirs throughout the body, as early as within 2 weeks of HIV infection [15], and to persist indefinitely throughout the lifespan of HIV-infected individuals [10]. These proviral reservoirs continue to expand and diversify until viral replication is successfully suppressed with ART. Despite extensive investigations, we still do not fully understand the dynamics of the total body HIV reservoir and how sub-reservoirs in various compartments relate to one another. For example, it remains unclear what factors govern the size and the activity of replication-competent HIV DNA in the CNS compared to the genital tract and blood. Most studies that have explored nonblood reservoirs among persons living with HIV infection have been limited to small samples of cerebrospinal fluid (CSF), genital secretion, gut, and shallow lymph nodes [10,16]. Studies using macaque models with simian immunodeficiency viruses (SIVs) have been enlightening for reservoirs in different tissues [17–23], but while SIV shares a high degree of structural and sequence identity to HIV, studies of SIV will not suffice to test eradication strategies for humans. For example, the Merck adenovirus type 5 (Ad5) trivalent HIV-1 vaccine trial (STEP trial) did not show efficacy in preventing HIV infection or slowing disease progression [24], despite promising results in various macaques' trials [25–27].

As the field tackles the ambitious goal of eradicating HIV from the human body, we will need to test the effectiveness of cure interventions in living persons.

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Consequently, we will need to measure changes in HIV reservoirs in circulating blood, and limited sampling in accessible compartments, like CSF, genital secretions, gut, and so on. Unfortunately, we do not know how these measures relate to reservoirs in harder-to-reach places, like the brain, spleen or prostate. Cure strategies based on reducing HIV populations in circulating blood cells may have no impact whatsoever on deeper noncirculating HIV reservoirs. Such 'hard-to-reach' reservoirs can subsequently repopulate the systemic HIV RNA pool, similar to the viral rebounds observed in persons who were thought to have been eradicated, such as 'Mississippi baby' and the 'Boston patients' [28,29].

Most of our understanding of deep HIV reservoirs in humans has come from autopsy studies, but these previous studies had variable ART intake and limited ante-mortem characterization that can be compared to post-mortem measures [12,30,31]. Also, there is typically a significant delay in time from ante-mortem visits until death: for example the average time between the last clinical assessment and death is 262.6 days (standard deviation 402.7 days) and is rarely less than 6 months in the California NeuroAIDS Tissue Network [32]. The inability to collect information during the last months of life about the use of ART and other drugs, and he lack of HIV measures in blood close to the time of death, limit our ability to interpret reservoir data in post-mortem samples. To better understand how accessible HIV reservoirs relate to deeper reservoirs, we will need evaluations that span the peri-mortem timeframe. In our 'Last Gift' model, we propose that some HIV-infected individuals with a non-AIDS-related advanced illness would be willing to participate in such research. Examples of non-AIDS-related diseases relevant for a Last Gift cohort include solid cancers, cardiovascular disease, and neurodegenerative diseases [33,34]. Participants would be eligible for the Last Gift cohort when they are certified as being terminally ill by a physician and having a prognosis of 6 months or less. From these volunteers, limited blood samples can be collected while they are alive, and some participants might be willing to also donate genital secretions, stool, CSF samples, or even limited rectal and lymph node biopsies. Importantly, participants could be extensively characterized closely prior to death in terms of ART intake and other drugs, neurocognitive and daily functioning, all illnesses, and so on, and this information could be very helpful with the interpretation of data generated on post-mortem tissue.

In fact, we hypothesize that some individuals would welcome the opportunity to 'give back' to their community, even if it will provide them no tangible benefit whatsoever. This is analogous to the early days of HIV where hundreds and thousands of gay men and other affected communities enrolled into research at enormous self-sacrifice, with many knowing they personally were unlikely to benefit [35]. We propose that such innate human altruism can be tapped with open and honest discussions with very sick HIV-infected persons about research participation at the end of their lives.

Ultimately, an HIV cure will need to be at least as safe and well tolerated as current ART [36]. However, the first generation of cure interventions will likely come with significant toxicities and other burdens. Also, like the first generations of ART, their effectiveness will likely be suboptimal. Thus, first-generation cure efforts will require significant sacrifice and risk for research participants. We understand that HIV cure efforts are important for the whole HIV community and many altruistic individuals will be motivated to participate if provided opportunities to advance the cure field. We propose that HIV-infected people at the end of their lives may be willing to accept greater risks for research participation. For example, volunteers may be more willing to participate in trials of potentially toxic immunomodulatory agents, neutralizing antibodies or highly experimental 'kick-and-kill' strategies, thus offering a unique opportunity to evaluate the mechanisms of clinical cure interventions and their effect across various tissues, which are not accessible in living participants.

The proposed research model has been useful for cancer research [33]. In particular, cancer research has greatly benefited from rapid autopsy programs by allowing a better understanding of cancer disease mechanisms and how various therapies have impacted these mechanisms [33,37]. Characterization of these mechanisms has involved samples collected from rapid autopsies and state-of-the-art laboratory techniques like proteomics, genomics, metabolomics, and so on. Similarly, HIV cure research can benefit from this peri-mortem research model by allowing deep tissue to be sampled quickly after death (ideally within 6 h), thus allowing lab-based techniques to clarify how HIV can persist in deep tissues during ART. The End of Life Option law that went into effect in California from 9 June 2016 might be a way to optimize timing for autopsy and organ specimen collection in a way that could maximize their usefulness to HIV cure research. This could be comforting or gratifying to those able to make this research contribution and their families. Of course, this raises several ethical concerns, which would need to be addressed further.

Interestingly, one recent study found that HIV-infected people who perceive themselves as 'not very healthy/not at all healthy' were significantly more likely to participate to HIV cure research compared to otherwise healthy chronically HIV-infected individuals [38]. In this study, a prominent recurring theme that emerged, especially from long-term survivors approaching end of life, was the frustration that they had been excluded from most HIV research, especially cure research, because of accumulated ART drug resistance and HIV comorbidities. Similarly, we interviewed 12 HIV-infected individuals receiving

hospice services, who were referred by their primary providers at the University of California San Diego primary HIV care clinic (i.e. the Owen Clinic) or the San Diego Veterans Affairs HIV care clinic. These individuals were receiving palliative care services for a variety of illnesses (heart failure, pancreatic, liver, or lung cancer, etc.). During an unstructured interview, all of these individuals expressed a desire to be able to 'give back' in some way, especially at this time near the end of his or her life. Each of these 12 individuals expressed a strong interest in participating in research aimed at curing HIV, often citing such participation as a 'gift' to their friends still living with HIV. A few important quotes include: "I feel like these last few weeks are wasted." "I hate my cancer but I hate HIV more." "I wish I could do something else to help." "At least I could be doing something." An important theme expressed by these individuals was that they did not like the idea that they would be excluded from research "just because I am dying" (see Fig. 1). The proposed 'Last Gift' study represents an opportunity for these individuals to be involved in HIV cure research. In particular, older HIV-infected individuals are typically excluded from most cure research because of their age, length of chronic infection, or possibly confounding comorbidities, and many could appreciate the opportunity to still make a contribution to cure research, especially at the end of life. To specifically address HIV cure research questions, it might be most helpful to study volunteers who remain on ART and die with suppressed HIV RNA. These individuals are now more prevalent than a few decades ago, when most HIV-infected patients were dying from HIV-related conditions and had underlying uncontrolled infection. Such willing participants could be identified through oncology or cardiovascular hospice services, rather than AIDS-specific hospices.


**Fig. 1. A Word Cloud summarizing the most representative words and expressions used by 12 terminally sick HIV-infected individuals during our semi-structured interview.** Each of these individuals expressed a strong interest in participating in research aimed at curing HIV, often citing such participation as a 'gift' to their friends still living with HIV.

This type of research will likely encounter various barriers, which can be actively addressed by understanding the desires and needs of this special population. These achievements will require considerable participatory research efforts including engagement to educate community members, but more importantly to listen to the community members and to allow time for two-way discussion and contemplation. We believe that providing individuals who suffer from advanced diseases the opportunity to participate in clinical research could revolutionize translational HIV research by offering a large supply of well informed, eager, and appropriately consented human volunteers. The samples collected and stored, and the procedures developed for the appropriate engagement and enrollment of altruistic individuals into peri-mortem studies, will lay the groundwork for future studies that can tackle a wide variety of open questions concerning how HIV populates tissues throughout the body.

Currently, there are few opportunities for terminally ill individuals to participate in HIV research, likely due to various cultural taboos and ethical concerns, such as exploitation, vulnerability, and coercion. While unreasonable expectations related to cure research outcomes might create greater vulnerability in this population, with appropriate education and ethical review, we feel that it would be unethical to withhold cure research opportunities from those who have the capability to provide informed consent. The proposed model should be developed following the strictest ethical guidelines and in complete accordance with the Declaration of Helsinki. Individuals with advanced disease that qualifies them for hospice support are routinely ineligible for HIV research trials, yet such an opportunity may offer considerable meaning to the individual, his or her community, and the world.

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## Conflicts of interest

The authors do not have any commercial or other associations that might pose a conflict of interest.

## References


1. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, *et al*. **Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study.** *J Acquir Immune Defic Syndr* 2006; **43**:27–34.
2. Wong JK, Hezareh M, Gunthard HF, Havlir DV, Ignacio CC, Spina CA, *et al*. **Recovery of replication-competent HIV despite prolonged suppression of plasma viremia.** *Science* 1997; **278**:1291–1295.
3. Deeks SG, Lewin SR, Ross AL, Ananworanich J, Benkirane M, Cannon P, *et al*. **International AIDS Society global scientific strategy: towards an HIV cure 2016.** *Nat Med* 2016; **22**:839–850.
4. Ho YC, Shan L, Hosmane NN, Wang J, Laskey SB, Rosenbloom DI, *et al*. **Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure.** *Cell* 2013; **155**:540–551.
5. Svicher V, Ceccherini-Silberstein F, Antinori A, Aquaro S, Perno CF. **Understanding HIV compartments and reservoirs.** *Curr HIV/AIDS Rep* 2014; **11**:186–194.
6. Hutter G, Nowak D, Mossner M, Ganepola S, Mussig A, Allers K, *et al*. **Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation.** *N Engl J Med* 2009; **360**:692–698.
7. Li JZ, Smith DM, Mellors JW. **The critical roles of treatment interruption studies and biomarker identification in the search for an HIV cure.** *AIDS* 2015.
8. Hoen B, Fournier I, Lacabaratz C, Burgard M, Charreau I, Chaix ML, *et al*. **Structured treatment interruptions in primary HIV-1 infection: the ANRS 100 PRIMSTOP trial.** *J Acquir Immune Defic Syndr* 2005; **40**:307–316.
9. Gianella S, Kosakovsky Pond SL, Oliveira MF, Scheffler K, Strain M, Delatorre A, *et al*. **Compartmentalized HIV rebound in the central nervous system after interruption of antiretroviral therapy.** *Virus Evol* 2016:2.
10. Richman DD, Margolis DM, Delaney M, Greene WC, Hazuda D, Pomerantz RJ. **The challenge of finding a cure for HIV infection.** *Science* 2009; **323**:1304–1307.
11. Lorenzo-Redondo R, Fryer HR, Bedford T, Kim EY, Archer J, Kosakovsky Pond SL, *et al*. **Persistent HIV-1 replication maintains the tissue reservoir during therapy.** *Nature* 2016.
12. Lamers SL, Rose R, Maidji E, Agsalda-Garcia M, Nolan DJ, Fogel GB, *et al*. **HIV DNA is frequently present within pathologic tissues evaluated at autopsy from cART-treated patients with undetectable viral load.** *J Virol* 2016.
13. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, *et al*. **Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection.** *AIDS* 2003; **17**:1871–1879.
14. Perrin L. **Primary HIV infection.** *Antivir Ther* 1999; **4 (Suppl 3)**: 13–18.
15. Ananworanich J, Chomont N, Eller LA, Kroon E, Tovanabutra S, Bose M, *et al*. **HIV DNA set point is rapidly established in acute HIV infection and dramatically reduced by early ART.** *EBio Med* 2016.
16. Margolis DM. **How might we cure HIV?** *Curr Infect Dis Rep* 2014; **16**:392.
17. Carryl H, Swang M, Lawrence J, Curtis K, Kamboj H, Van Rompay KK, *et al*. **Of mice and monkeys: can animal models be utilized to study neurological consequences of pediatric HIV-1 infection?** *ACS Chem Neurosci* 2015.
18. Mavigner M, Watkins B, Lawson B, Lee ST, Chahroudi A, Kean L, *et al*. **Persistence of virus reservoirs in ART-treated SHIV-infected rhesus macaques after autologous hematopoietic stem cell transplant.** *PLoS Pathog* 2014; **10**:e1004406.
19. Garrido C, Margolis DM. **Translational challenges in targeting latent HIV infection and the CNS reservoir problem.** *J Neurovirol* 2015; **21**:222–226.
20. Ling B, Piatak M Jr, Rogers L, Johnson AM, Russell-Lodrigue K, Hazuda DJ, *et al*. **Effects of treatment with suppressive combination antiretroviral drug therapy and the histone deacetylase inhibitor suberoylanilide hydroxamic acid; (SAHA) on SIV-infected Chinese rhesus macaques.** *PLoS One* 2014; **9**:e102795.
21. Kline C, Ndjomou J, Franks T, Kiser R, Coalter V, Smedley J, *et al*. **Persistence of viral reservoirs in multiple tissues after antiretroviral therapy suppression in a macaque RT-SHIV model.** *PLoS One* 2013; **8**:e84275.
22. Hansen SG, Piatak M Jr, Ventura AB, Hughes CM, Gilbride RM, Ford JC, *et al*. **Immune clearance of highly pathogenic SIV infection.** *Nature* 2013; **502**:100–104.
23. North TW, Higgins J, Deere JD, Hayes TL, Villalobos A, Adamson L, *et al*. **Viral sanctuaries during highly active antiretroviral therapy in a nonhuman primate model for AIDS.** *J Virol* 2010; **84**:2913–2922.
24. Fitzgerald DW, Janes H, Robertson M, Coombs R, Frank I, Gilbert P, *et al*. **An Ad5-vectored HIV-1 vaccine elicits cell-mediated immunity but does not affect disease progression in HIV-1-infected male subjects: results from a randomized placebo-controlled trial (the Step study).** *J Infect Dis* 2011; **203**:765–772.
25. Amara RR, Villinger F, Altman JD, Lydy SL, O'Neil SP, Staprans SI, *et al*. **Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine.** *Science* 2001; **292**:69–74.
26. Barouch DH, Santra S, Schmitz JE, Kuroda MJ, Fu TM, Wagner W, *et al*. **Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination.** *Science* 2000; **290**:486–492.
27. Shiver JW, Fu TM, Chen L, Casimiro DR, Davies ME, Evans RK, *et al*. **Replication-incompetent adenoviral vaccine vector elicits effective antiimmunodeficiency-virus immunity.** *Nature* 2002; **415**:331–335.
28. Persaud D, Gay H, Ziemniak C, Hui Chen Y, Piatak M Jr, Chun TW, *et al*. **Absence of detectible HIV-1 viremia following treatment cessation in an infant.** *N Engl J Med* 2013(in press).
29. Henrich TJ, Hu Z, Li JZ, Sciaranghella G, Busch MP, Keating SM, *et al*. **Long-term reduction in peripheral blood HIV type 1 reservoirs following reduced-intensity conditioning allogeneic stem cell transplantation.** *J Infect Dis* 2013; **207**:1694–1702.
30. Desplats P, Dumaop W, Cronin P, Gianella S, Woods S, Letendre S, *et al*. **Epigenetic alterations in the brain associated with HIV-1 infection and methamphetamine dependence.** *PLoS One* 2014; **9**:e102555.
31. Wong JK, Ignacio CC, Torriani F, Havlir D, Fitch NJ, Richman DD. **In vivo compartmentalization of human immunodeficiency virus: evidence from the examination of pol sequences from autopsy tissues.** *J Virol* 1997; **71**:2059–2071.
32. Bumpus N, Ma Q, Best B, Moore DJ, Ellis R, Crescini M, *et al*. **Antiretroviral Drug Concentrations in Human Brain Tissue Are Similar to or Exceed Historical Concentrations in CSF.** *22th Conference on Retroviruses and opportunistic infections (CROI)* 23–26 February 2015. [Abstract 436].
33. Quinn GP, Murphy D, Pratt C, Munoz-Antonia T, Guerra L, Schabath MB, *et al*. **Altruism in terminal cancer patients and rapid tissue donation program: does the theory apply?** *Med Healthcare Philos* 2013; **16**:857–864.
34. Walker DG, Whetzel AM, Serrano G, Sue LI, Lue LF, Beach TG. **Characterization of RNA isolated from eighteen different human tissues: results from a rapid human autopsy program.** *Cell Tissue Bank* 2016; **17**:361–375.
35. Shilts R. *And the band played on: politics, people and the AIDS epidemic.* New York: St Martins Press; 1987.
36. Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel.** *J Am Med Assoc* 2016; **316**:191–210.
37. Alsop K, Thorne H, Sandhu S, Hamilton A, Mintoff C, Christie E, *et al*. **A community-based model of rapid autopsy in end-stage cancer patients.** *Nat Biotechnol* 2016.
38. Dubé K. **Factors affecting participation in HIV cure-related research in the United States: implications for effective and ethical implementation.** *2016 Towards an HIV Cure Symposium* 2016; Durban, 16–17 July 2016.