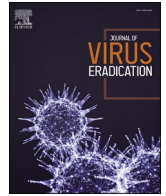




Contents lists available at ScienceDirect

## Journal of Virus Eradication

journal homepage: [www.sciencedirect.com/journal/journal-of-virus-eradication](http://www.sciencedirect.com/journal/journal-of-virus-eradication)

Original research



## Perceived risks and benefits of enrolling people with HIV at the end of life in cure research in Southern California, United States

Karine Dubé<sup>a,b,\*</sup>, Brittany Shelton<sup>c</sup>, Hursch Patel<sup>a,b</sup>, Samuel O. Ndukwe<sup>a,b</sup>,  
 Susanna Concha-Garcia<sup>d,e</sup>, Cheryl Dullano<sup>d</sup>, Stephanie Solso<sup>d</sup>, Steven Hendrickx<sup>d</sup>,  
 Andy Kaytes<sup>f</sup>, Jeff Taylor<sup>f,g</sup>, Thomas J. Villa<sup>h</sup>, Susan J. Little<sup>a,d</sup>, Patricia K. Riggs<sup>a</sup>,  
 David Lessard<sup>i,j,k</sup>, Anish K. Arora<sup>j,k,l</sup>, Cecilia T. Costiniuk<sup>i,m,n,o</sup>, Shadi Eskaf<sup>p</sup>,  
 Davey M. Smith<sup>a,d</sup>, Sara Gianella<sup>a,d</sup>

<sup>a</sup> Division of Infectious Diseases and Global Public Health, School of Medicine, University of California San Diego, CA, USA

<sup>b</sup> UNC Gillings School of Global Public Health, Chapel Hill, NC, USA

<sup>c</sup> Department of Public Health, College of Education, Health and Human Sciences, University of Tennessee Knoxville, TN, USA

<sup>d</sup> AntiViral Research Center (AVRC), University of California San Diego, San Diego, CA, USA

<sup>e</sup> HIV Neurobehavioral Research Center, University of California San Diego, San Diego, CA, USA

<sup>f</sup> AntiViral Research Center Community Advisory Board, San Diego, CA, USA

<sup>g</sup> HIV+Aging Research Project-Palm Springs (HARP-PS), Palm Springs, CA, USA

<sup>h</sup> Reversing Immune Dysfunction (RID) Martin Delaney Collaboratory for HIV Cure Research Community Advisory Board, Rockville, MD, USA

<sup>i</sup> Division of Infectious Diseases and Chronic Viral Illness Service, Department of Medicine, McGill University Health Center (MUCH), Montreal, QC, Canada

<sup>j</sup> Canadian Institutes of Health Research Strategy for Patient-Oriented Research Mentorship Chair in Innovative Clinical Trials, Montreal, QC, Canada

<sup>k</sup> Center for Outcome Research and Evaluation, Research Institute of the McGill University Health Center, Montreal, QC, Canada

<sup>l</sup> Department of Family Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

<sup>m</sup> Department of Microbiology and Immunology, McGill University, Montreal, QC, Canada

<sup>n</sup> Division of Experimental Medicine, Department of Medicine, McGill University Health Centre, Montreal, QC, Canada

<sup>o</sup> Infectious Diseases and Immunity in Global Health Program, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

<sup>p</sup> Public Health Research Consultant, Chapel Hill, NC, USA

## ARTICLE INFO

## Keywords:

HIV cure Research  
 End of life  
 Perceived risks  
 Perceived benefits  
 Last gift  
 Altruism  
 Socio-behavioral research

## ABSTRACT

**Introduction:** Although current antiretroviral therapy allows most people with HIV (PWH) to experience normal longevity with a good quality of life, an HIV cure remains elusive due to HIV reservoir formation within deep tissues. An HIV cure remains highly desirable to the community of PWH. This study reports on the perceived risks and benefits of participation in the Last Gift study, a study aimed at characterizing HIV reservoirs via post-mortem autopsy, among PWH at the end of life (EOL) and their next-of-kin (NOK)/loved ones.

**Methods:** Last Gift participants (PWH with a terminal illness and/or near the end of life) and their NOK/loved ones were surveyed for perceptions of risks, benefits, and meaning for participation in the Last Gift study.

**Results:** The average age of the 17 Last Gift participants was 66.6 years, 3 were females, 1 person identified as Hispanic, and 15 as Caucasian. The average age of the 17 NOK/loved ones was 56.7 years, and relationships to Last Gift participants included partner/spouse, sibling, friend, child, parent, grandparent, and nephew. The only perceived personal risk of the Last Gift among participants was the blood draws (3/17). NOK/loved ones perceived the following risks: blood draws (2/17), physical pain (3/17), worry that something bad will happen (2/17), and unpleasant side effects (1/17). Participants in Last Gift and NOK/loved ones indicated the study had various positive social effects. For both participants and NOK/loved ones, the most frequent perceived personal benefit of the Last Gift was the satisfaction of supporting HIV cure research.

**Discussion:** Participants perceived minimal personal and societal risks and valued the altruistic benefits of participating in the Last Gift study. Last Gift participants and NOK/loved ones were cautious about possible personal risks of EOL HIV cure research but still viewed that the emotional, psychological and societal benefits of participation outweighed potential risks.

\* Corresponding author. Division of Infectious Diseases and Global Public Health (IDGPH), School of Medicine (SOM), University of California San Diego (UCSD), 9500 Gilman Drive, MC, 0507, La Jolla, CA, 92093, USA.

E-mail address: [kdube@health.ucsd.edu](mailto:kdube@health.ucsd.edu) (K. Dubé).

<https://doi.org/10.1016/j.jve.2023.100328>

Received 4 March 2023; Accepted 30 May 2023

Available online 5 June 2023

2055-6640/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

In the last four decades, HIV has become a manageable chronic condition for many people with HIV (PWH).<sup>1</sup> Since the late 1990s, combination antiretroviral treatment (cART) has proven to be lifesaving and has significantly reduced HIV-related mortality.<sup>2</sup> Causes of HIV-associated morbidity and mortality now resemble those of the general population and include cancer, cardiovascular disease, and neurological disorders.<sup>3</sup> Once faced with a death sentence in the 1980s, many PWH now wish to give back to science and contribute to HIV cure-related research at the end-of-life (EOL).<sup>4-7</sup>

The Last Gift<sup>8</sup> is one such observational EOL HIV cure study that evaluates HIV reservoirs throughout the entire body.<sup>9-11</sup> The Last Gift was initiated in 2017 at the University of California San Diego (UCSD) and enrolls PWH who have a terminal illness and a prognosis of 6 months or less as determined by their physician.<sup>4</sup> In 2019, the Last Gift was amended to include PWH with a chronic illness and multiple co-morbidities associated with a five-year mortality of greater than 50%. This component of the study is called 'On Deck', a name provided by the UCSD AntiViral Research (AVRC) Community Advisory Board (CAB).<sup>12</sup> Last Gift study participants elect to donate their body at the time of death to contribute to HIV cure research.<sup>9-11</sup> Participants provide informed consent to undergo socio-behavioral interviews, ante-mortem blood and other biospecimen sampling, and, upon death, to undergo a rapid research autopsy (within 6 h of death) to preserve viral and tissue integrity.<sup>4</sup> To date, over 30 Last Gift participants have been enrolled with no expectation of direct clinical benefit.<sup>5,12</sup> Similar EOL translational research models have been employed in cancer research.<sup>13,14</sup>

Participants are considered partners in research towards an HIV cure, and the study also recognizes the importance of involving next-of-kin (NOK)/loved ones.<sup>15</sup> NOK/loved ones serve as caregivers and help honor the last wishes of the participants.<sup>16,17</sup> The Last Gift holds a broad definition of NOK/loved ones, recognizing that the definition of family may be different for each participant.<sup>12</sup> Last Gift participants have the option to refer a NOK/loved one to also participate in the interview part of the study, while respecting the participants' unique situations and wishes for confidentiality.<sup>12</sup> To date, most Last Gift participants have referred a NOK/loved one, although a minority of participants have elected not to.

The last few years have witnessed an expansion of the ethics literature on EOL HIV cure research.<sup>12,15</sup> Our team has involved community members to establish basic ethical criteria for EOL HIV cure research. These include: 1) protection of autonomy through robust informed consent, 2) avoidance of exploitation and fostering altruism, 3) maintenance of acceptable benefits/risks, 4) reducing vulnerability and ensuring participant-centered focus<sup>18</sup> and 5) preserving acceptance of NOK/loved ones and the community.<sup>15</sup> Our team also prospectively documents ethical lessons learned.<sup>12</sup> The socio-behavioral research component of the Last Gift helps ensure EOL HIV cure research remains acceptable to Last Gift participants,<sup>5</sup> NOK/loved ones,<sup>16,17</sup> research staff,<sup>19</sup> and the community.

Our interdisciplinary team was interested to determine if Last Gift participants and their NOK/loved ones had a clear understanding of possible risks and benefits associated with being in the Last Gift. Here, we report results from the closed-ended interview questions related to the perceived risks and benefits from their perspectives. This data can inform how we design, conduct, and communicate about EOL HIV cure research.

## 2. Methods

### 2.1. Participants and setting

All participants who met eligibility criteria had the option to be interviewed to discuss their perceptions of the study, including risks and benefits. They were also given the option to refer a NOK/loved one.

### 2.2. Data collection

We developed interview guides in collaboration with the UCSD AVRC CAB. Prior to implementation, we have pilot-tested study guides with community members and revised them iteratively prior to data collection. From 2017 to 2022, two study team members conducted interviews (including closed-ended questions) with Last Gift participants and NOK/loved ones. Given the EOL status of participants, we elected to conduct interviews (including closed-ended questions) for feasibility reasons, instead of asking participants to complete surveys directly. Last Gift participants had the option to realize the interview over multiple visits given the constraints posed by conducting EOL research.<sup>3,20</sup> Upon interview completion, Last Gift participants and NOK/loved ones received \$20 in compensation.

**Perceived Risks:** Participants and NOK/loved ones were asked to indicate whether the Last Gift was associated with risks (Yes/Agreement or No/Disagreement). Perceived personal risks to participants were framed in terms of possible worries (e.g., worry about large blood draws needed, about physical pain, and/or worry of unpleasant side effects). Perceived social risks to participants were also framed in terms of possible worries (e.g., worry about being recognized as someone living with HIV, and worry about being treated poorly by study staff).

**Perceived Benefits:** Participants and NOK/loved ones were asked to indicate whether the Last Gift was associated with personal benefits (Yes/Agreement or No/Disagreement). Perceived personal benefits to Last Gift participants included items such as feeling good about contributing to HIV cure research, regular access to medical doctors/researchers, meaning given to the remainder of participants' lives, and coverage of cremation costs. Perceived societal benefits to participants included items such as contributing one last gift to society, helping other PWH, an opportunity to give back, and receiving support from family, loved ones and friends.

**Perceived Sense of Meaning:** Participants indicated their support (Yes/Agreement or No/Disagreement) for various statements related to the perceived sense of meaning provided by their participation in the Last Gift. For example, they indicated whether they joined the study to give back while not expecting anything in return, to benefit a greater cause, and whether they believed the study would benefit science and society.

**Perceived Benefits of an Eventual Cure for HIV:** Participants and NOK/loved ones were asked whether they agreed or not (Yes/Agreement or No/Disagreement) with various statements related to perceived benefits of an eventual cure for HIV. For example, they indicated whether a cure for HIV would allow others to stop thinking about having HIV, stop taking HIV medications, have improvements in day-to-day health, and experience a better quality of life.

### 2.3. Data management and analysis

Last Gift participants and NOK/loved ones completed closed-ended surveys in-person with a trained research associate. After each interview (including closed-ended questions), two study team members uploaded audio files to a secure database (RedCap, Vanderbilt University, TN and/or UCSD One Drive). Two study team members transcribed interviews to Microsoft Word and removed all personal identifiers. The same team members alternated roles to review transcripts for quality control and fidelity to the interview data. Once checked for quality, study team members entered closed-ended data into a pre-programmed study database in Qualtrics™ (Provo, UT). Qualtrics™ provided a platform for gathering and analyzing closed-ended data. After completing transcription, quality control and data entry, original audio files were deleted, as per the Institutional Review Board (IRB)-approved informed consent form.

2.4. Descriptive analyses

We conducted simple descriptive analyses to summarize the closed-ended results. For each question, we report the number of Last Gift participants and NOK/loved ones who reported ‘Yes/Agreement’. The small sample size of the Last Gift study precluded more complex bivariate and multivariate analyses.

2.5. Ethical considerations

The UCSD IRB approved the Last Gift study with the socio-behavioral research component (Project #160563). All participants provided written informed consent to be interviewed.

3. Results

3.1. Demographics

3.1.1. Last Gift study participants

Between 2017 and 2022, 17 Last Gift participants completed the socio-behavioral interviews. Of these, 3 were females, 1 identified as Hispanic, and 15 as Caucasian. Mean age of participants was 66.6 years. Most (15/17) had some college education. Last Gift participants’ terminal/chronic illness(es) included solid organ cancer, other types of cancer (e.g., brain, oral, rectal, lung, acute myeloid leukemia), cardiovascular disease, neurodegenerative disease (e.g., amyotrophic lateral sclerosis), and other condition(s). Most participants reported a disability at the EOL (Table 1).

3.1.2. NOK/loved ones

A total of 17 Last Gift participants referred a NOK/loved one, of which all 17 agreed to participate in this study (10 male and 7 female). Mean age of NOK/loved ones was 56.5 years. Relationships to the Last Gift participants included partner/spouse, sibling, friend, child, parent, grandparent, and nephew (Table 2).

3.1.3. Perceived personal risks

Last Gift participants and NOK/loved ones indicated some perceived personal risks associated with participation in the Last Gift study. The only perceived personal risk from the perspective of the Last Gift participants was the large blood draws (3/17). NOK/loved ones perceived the following personal risks for Last Gift participants: worry about large blood draws (2/17), worry that participants would have physical pain (3/17), worry that something bad will happen (2/17), and unpleasant side effects (1/17). No participant or NOK/loved one worried about the impact of the study on health insurance, possible permanent or irreversible side effects, not being cured (of HIV or terminal illness), or quality of life decreasing. Further, no NOK/loved one worried about confidentiality being violated or having their quality of life decreased (Fig. 1).

3.1.4. Perceived social risks

No Last Gift participants reported perceived social risks from being in the study. NOK/loved ones worried about Last Gift participants being recognized as someone living with HIV (3/17), an eventual cure for HIV not being available to those who need it (3/17), and Last Gift participants being treated poorly by research staff (1/17) (Fig. 2).

3.1.5. Perceived personal benefits

The most common personal benefit identified by both participants and NOK was feeling good about contributing to HIV cure research at the EOL (13/17 and 17/17, respectively). Last Gift participants valued coverage of cremation costs (13/17), receiving updated information about HIV (11/17), and having regular access to medical doctors/researchers (11/17). Similarly, NOK/loved ones felt the following were the most salient personal benefits for the Last Gift participants: coverage

Table 1

Demographic characteristics of the Last Gift/On Deck participants (San Diego, CA, 2017–2022).

	Last Gift/On Deck Participants N = 17
Age in years, mean (std. dev.)	66.6 (9.9)
Assigned male sex at birth	14 (82.4)
Assigned female sex at birth	3 (17.6)
Gender identity: man	14 (82.4)
Current identity: woman	3 (17.6)
Non-Hispanic or Latino ethnicity	16 (94.1)
Hispanic or Latino ethnicity	1 (5.9)
Caucasian race	15 (88.2)
African American/Black	1 (5.9)
Multiracial	1 (5.9)
<b>Education</b>	
Less than high school	1 (5.9)
High school or G.E.D.	1 (5.9)
Some college (less than 2 years)	2 (11.8)
Associate degree or > 2 years of college	4 (23.5)
Undergraduate degree or equivalent	4 (23.5)
Professional degree	2 (11.8)
Doctorate degree or equivalent terminal degree	3 (17.6)
<b>Marital status</b>	
Single, never married	9 (52.9)
Registered domestic partners	1 (5.9)
Married	2 (11.8)
Divorced	1 (5.9)
Widowed	4 (23.5)
<b>Health Characteristics</b>	
Terminal/Chronic Illness	
Solid tumor malignancy	3 (17.6)
Hematologic malignancy	10 (58.8)
Cardiovascular disease	2 (11.8)
Neurodegenerative disease	1 (5.9)
<b>Reported disability</b>	10 (58.8)

Table 2

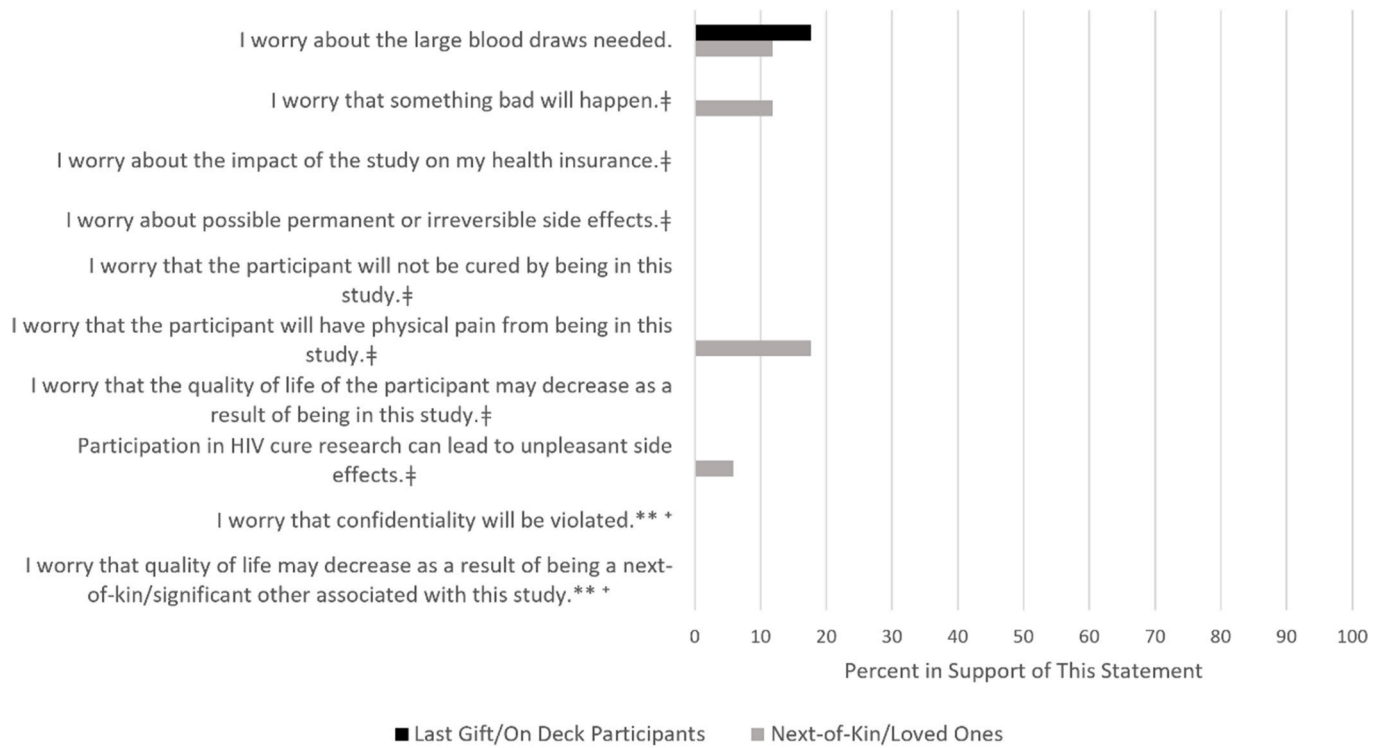
Demographic characteristics of next-of-kin/loved ones (San Diego, CA, 2017–2022).

	Next-of-Kin/Loved Ones N = 17 (%)
Age in years, mean (std. dev.)	56.5 (13.1)
Gender identity: men	10 (58.8)
Gender identity: women	7 (41.2)
<b>Relationship to Last Gift and On Deck Participants</b>	
Partner/Spouse	5 (29.4)
Sibling	4 (23.5)
Friend	3 (17.6)
Child	2 (11.8)
Parent	1 (5.9)
Grandparent	1 (5.9)
Nephew	1 (5.9)

of cremation cost (16/17), added meaning to the remainder of their lives (16/17), receiving updated information about HIV (14/17), and having regular access to doctors and researchers (10/17) (Fig. 3).

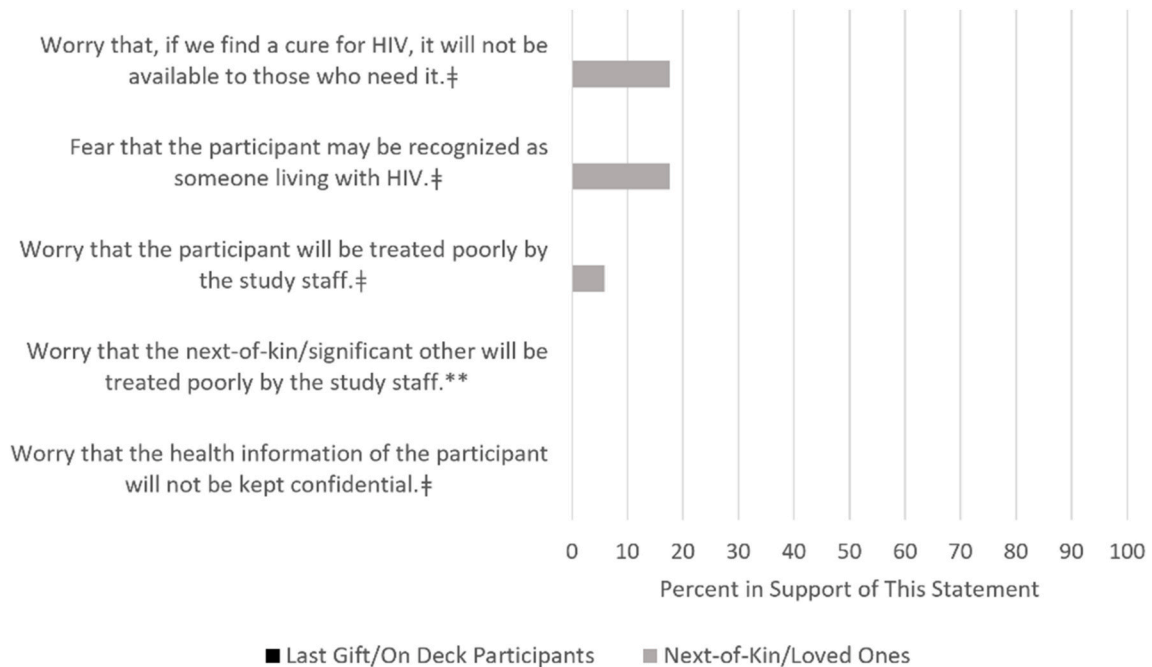
3.1.6. Perceived social benefits

Last Gift participants and NOK/loved ones perceived several societal benefits from the Last Gift. These included contribution to research at the EOL (16/17 and 17/17, respectively), giving one last gift to society (16/17 and 15/17), helping other people with HIV (15/17 and 17/17), giving back to the HIV community (15/17 and 17/17), helping advance biomedical science (15/17 for both groups), and receiving support from family, loved ones and friends (14/17 and 17/17). NOK/loved ones also viewed EOL research as moving us closer to finding a cure for HIV (16/17) (Fig. 4).



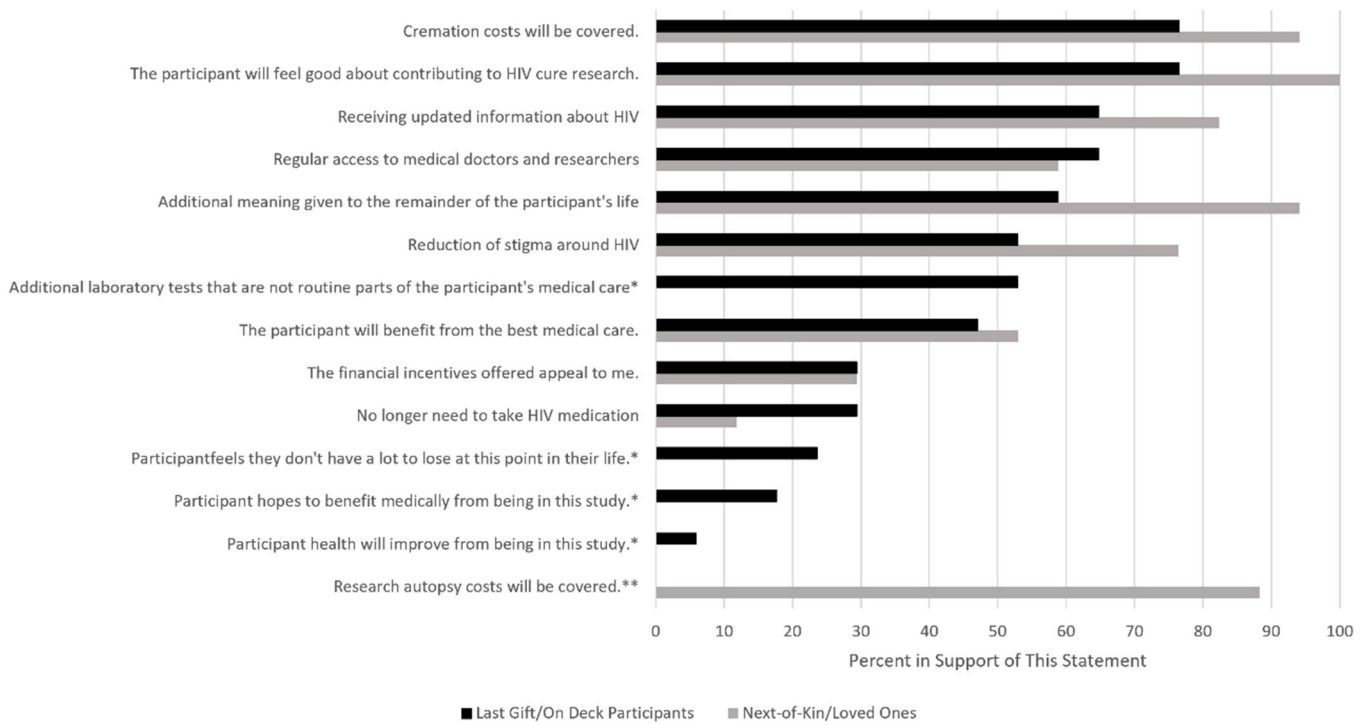
‡ indicates that no Last Gift/On Deck Participants reported this concern  
 \*\* Question only asked of Next-of-Kin/Loved Ones  
 † indicates no Next-of-Kin/Loved Ones reported this concern

Fig. 1. Perceived personal risks associated with participation in the Last Gift study (San Diego, CA, 2017–2022).



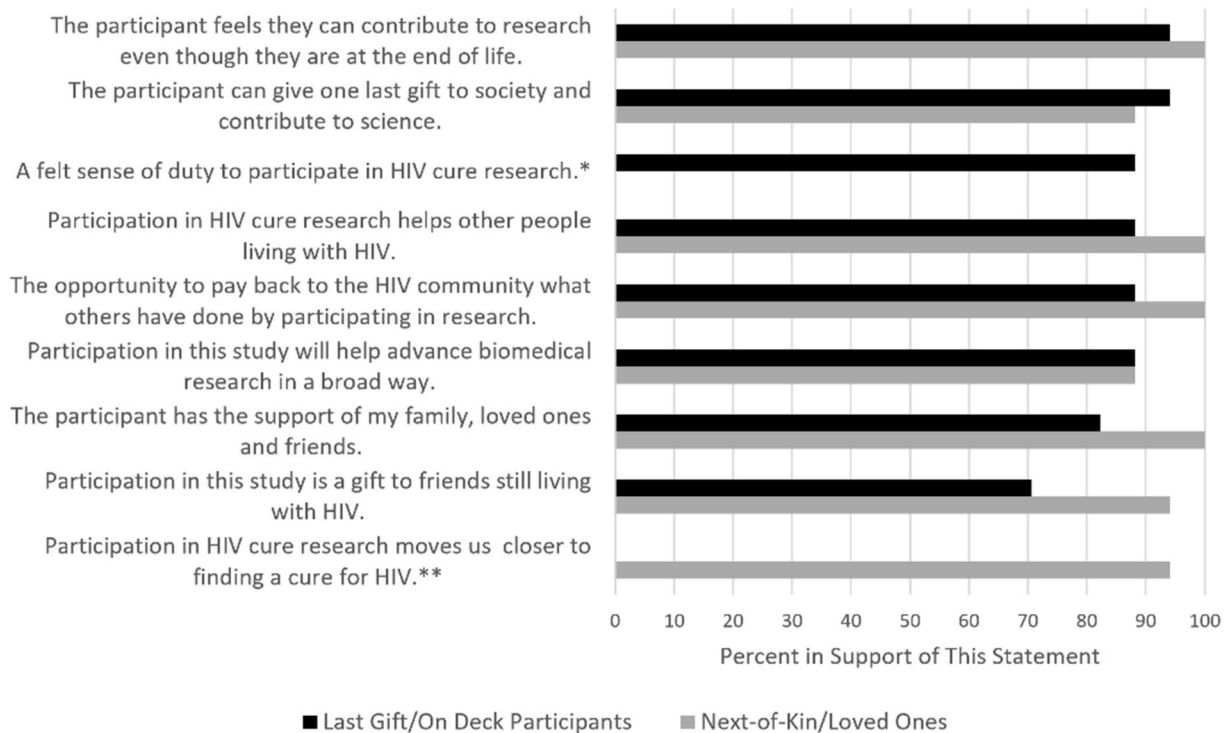
‡ indicates that no Last Gift/On Deck Participants reported this concern  
 \*\* Question only asked of Next-of-Kin/Loved Ones

Fig. 2. Perceived social risks associated with participation in the Last Gift study (San Diego, CA, 2017–2022).



\* Question was only asked of Last Gift/On Deck Participants  
 \*\* Question was only asked of Next-of-Kin/Loved Ones

Fig. 3. Perceived personal benefits associated with participation in the Last Gift study (San Diego, CA, 2017–2022).



\* Question was only asked of Last Gift/On Deck Participants  
 \*\* Question was only asked of Next-of-Kin/Loved Ones

Fig. 4. Perceived societal benefits associated with participation in the Last Gift study (San Diego, CA, 2017–2022).

3.1.7. Perceived Sense of Meaning

Last Gift participants indicated whether the study provided a sense of meaning at the EOL. Most participants (14/17) indicated that they joined the study because they wanted to give back and were not expecting anything in return, their participation would benefit a greater cause, and would benefit science and society. The majority (11/17) also indicated that the Last Gift study would benefit biomedical research (Fig. 5).

3.1.8. Perceived benefits of an eventual cure for HIV

Last Gift participants and NOK/loved ones indicated their support for perceived benefits of an eventual cure for HIV. Last Gift participants rated the following most favorably: not having to think about having the virus (15/17), having HIV eliminated from the body (15/17), permanently discontinuing HIV medications (15/17), having an improvement in day-to-day health (14/17), not worrying about the future (14/17) and being able to plan for and be hopeful about the future (14/17). NOK/loved ones rated the following most favorably: permanently discontinuing HIV medications (17/17), not being able to transmit HIV to sex partner(s) (17/17), not having to think about having the virus (16/17), having HIV completely eliminated from the body (16/17), having an improvement in day-to-day health (16/17), being able to plan for and be hopeful about the future (16/17), having no risk of disease or condition associated with or exacerbated by HIV (16/17), having closer or improved relationships with romantic and sexual partners (16/17), not having to disclose HIV with new romantic or sexual partners (16/17), and experiencing fewer concerns about the effect of HIV on work or relationships with co-workers (16/17) (Fig. 6).

4. Discussion

We report perceived risks and benefits of participation in EOL HIV cure research from the perspective of PWH at the EOL and their NOK/loved ones. Last Gift participants perceived minimal personal and societal risks of being part of the study. NOK/loved ones seemed slightly more cautious about possible personal risks of EOL HIV cure research. Both Last Gift participants and NOK/loved ones valued the altruistic benefits of the study. This paper extends the socio-behavioral literature of EOL HIV cure research by empirically exploring perceived risks and benefits from the perspectives of participants and NOK/loved ones. Findings augment qualitative reports on how Last Gift participants and

NOK/loved ones perceive and experience EOL HIV cure research<sup>5,16,17</sup> and moves us beyond hypothetical research.<sup>6,21</sup>

The only perceived personal risk from the perspective of Last Gift participants was the blood draws. The Last Gift collects 30–40 mL (approximately two tablespoons) of blood during study visits, which is no different than the volume of blood drawn during routine clinical care. Participants also have the option to refuse blood draws, particularly as they reach the EOL. The overall finding of minimal perceived personal risks for Last Gift participants is interesting, given that the EOL context may carry additional risks and burdens, such as a progressive decrease in quality of life.<sup>3,15</sup> During the informed consent, Last Gift participants are informed that “The study will involve some added risks and discomforts. Also, since this is an investigational study, there may be other unknown risks that are unforeseen or at this time cannot be predicted. You will be told of any significant risks.” The limited perceived personal risks of Last Gift participants may reflect the fact that most participants have a history of research participation at our center but also the fact that the current Last Gift study is observational in nature. As such, the Last Gift represents the culmination of a personal journey of investment in HIV research. Analogously, the worry about study procedures, such as blood draws, was also reflected in qualitative interviews with Last Gift participants.<sup>5</sup> NOK/loved ones were concerned with the invasiveness of study procedures.<sup>17</sup> In the current study, NOK/loved ones appeared numerically more cautious about possible personal risks of the Last Gift, and a minority were concerned about physical pain and unpleasant side effects. The Last Gift team is aware of the potential risks and burdens related to research procedures at the EOL, and takes care to avoid undue pain, prevalent in PWH at the EOL.<sup>3</sup> The research team also takes the physical state of participants into account before any study procedure<sup>15</sup> and follows process consent to ensure participants continue to agree to procedures as they near the EOL.<sup>15</sup> We also ensure good communication with NOK/loved ones throughout the study to help alleviate any concern about study procedures.<sup>16,17</sup>

We were encouraged that no Last Gift participants or NOK/loved ones worried about the study not leading to a cure. This finding is ethically relevant, because it indicates a lack of curative misconception for participants involved in this specific EOL HIV cure research study. This theme was also reflected in qualitative interviews.<sup>5,16</sup> However, previous focus group discussions with NOK/loved ones had revealed a potential for therapeutic misconception, or the belief that the Last Gift team also serves as the participants’ care team.<sup>17</sup> In addition to

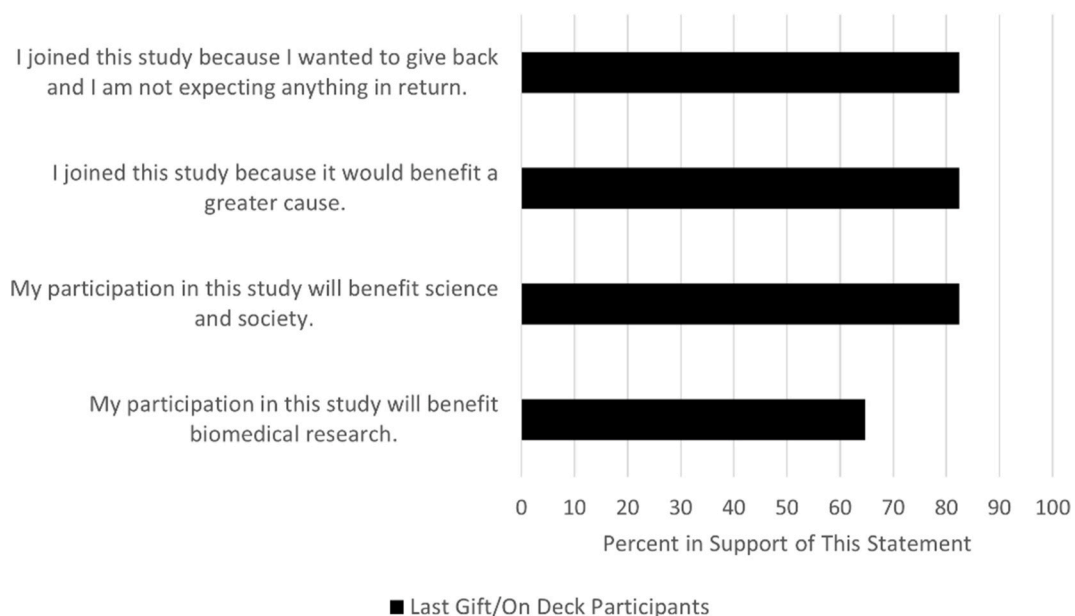


Fig. 5. Perceived sense of meaning provided by participation in the Last Gift study (San Diego, CA, 2017–2022).

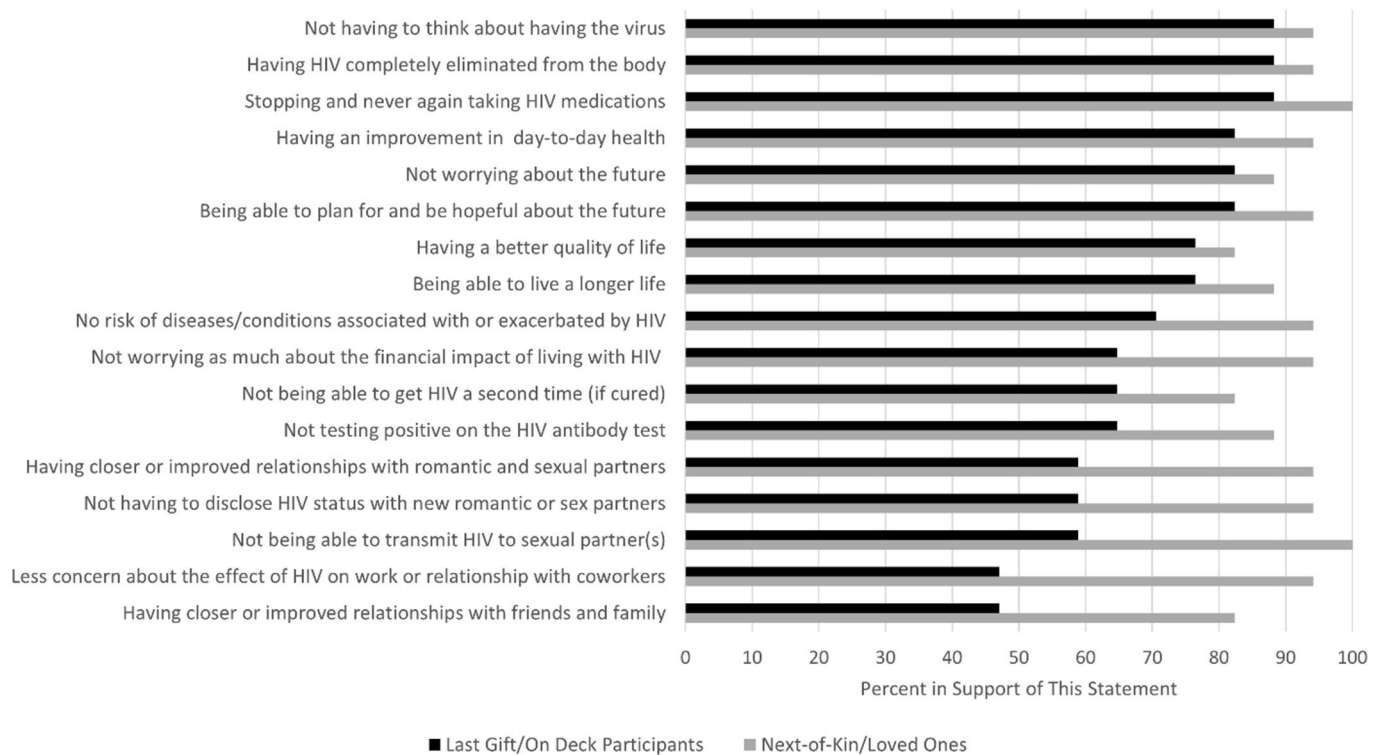


Fig. 6. Perceived benefits of an eventual cure for HIV (San Diego, CA, 2017–2022).

therapeutic misconception, the research team must safeguard against psychological distress when conducting research with terminally ill individuals<sup>22</sup> and remain careful not to infringe on precious time between participants and NOK/loved ones at or near the EOL.<sup>22</sup> While no Last Gift participants reported social risks from being in the study, NOK/loved ones again appeared more cautious, expressing concerns around participants being recognized as PWH. These worries were also reflected in our prior focus group discussions with NOK/loved ones, who expressed concerns about HIV-related stigma.<sup>17</sup> Only one individual expressed concern of being treated poorly by study staff. On this note, we believe it takes a dedicated team to conduct EOL HIV cure research.<sup>19</sup>

The most common perceived personal benefits of the Last Gift study by both participants and NOK/loved ones related to feeling good about contributing to HIV cure research. These findings are reminiscent of our qualitative data, wherein Last Gift and NOK/loved ones alike reported deep emotional and psychological benefits from the study.<sup>5,16,17</sup> Further, the Last Gift study informed consent form states: “You will not receive direct benefits from being in this study. However, what is learned from this study may help other people with HIV by improving our knowledge about HIV persistence within anatomic compartments.” The apparent contradiction between what Last Gift participants and NOK/loved ones report as benefits and the mention of the lack of direct personal benefits in the informed consent form has been noted elsewhere,<sup>23–27</sup> and prompted some scholars to advocate for inclusion of psychosocial benefits as part of the consent process.<sup>28,29</sup> The Last Gift experience has taught us that we should not discount psychosocial benefits of participation in meaningful research for PWH at the EOL.

The finding that both Last Gift participants and NOK/loved ones highly rated the coverage of cremation costs as a personal benefit also merits attention. For ethical reasons, the UCSD IRB historically has been hesitant to include cremation costs as benefits to avoid undue influence. The AVRC CAB advocated that cremation costs be covered as part of the study as a necessity, given the nature of the research, and for fair compensation.<sup>12</sup> Nevertheless, it remains possible that participants still view these as benefits.<sup>5,16</sup> It is also possible that NOK/loved ones

appreciate being freed of the responsibility of organizing the logistics of cremation and can use the time for mourning or reflection. Further, the rapid research autopsy does not preclude an open-casket funeral if desired.<sup>12</sup> In our focus groups, NOK/loved ones were adamant that the team should observe seamless procedures with the cremation process (“My concern was the cremation seemed to take forever and I just wanted to get him home”).<sup>17</sup> The Last Gift team acknowledges that preparing for death and funeral services in a respectful manner is important for both participants and NOK/loved ones.<sup>30</sup>

Last Gift participants and NOK/loved ones indicated several perceived societal benefits from the Last Gift study, including helping other people with HIV and advancing biomedical science. These findings were also reflected in qualitative data, where altruistic benefits were embedded within the context of community and moral obligations.<sup>5,16</sup> In evaluating willingness to participate in EOL HIV research, scholars have postulated that altruism may be heightened near the EOL.<sup>21,31</sup> Scientific altruism also emerged prominently in the socio-behavioral research assessing motivations for joining early-phase HIV cure trials focused on acute HIV, where participants viewed their bodies as uniquely suited for clinical research.<sup>25</sup> In the cancer field, Quinn and colleagues proposed a typology for categorizing different types of altruism in the context of post-mortem donations: 1) gifting relationship, 2) reciprocal altruism (e.g., expecting psychosocial support), and 3) empathy-induced altruism (e.g., deepening sense of community).<sup>32</sup> Similar altruism *in extremis* was observed among organ donors.<sup>33</sup> The Last Gift study appeared to provide a sense of meaning to participants. This meaning was described in terms of fulfillment, hope, legacy, self-actualization, and existentialism<sup>5,16</sup> and is also reflected in the EOL cancer literature.<sup>13</sup> However, in a hypothetical study of willingness to participate in EOL HIV cure research in Canada, PWH rated perceived meaning as low because they already considered their lives meaningful.<sup>6</sup> Thus, we should remain realistic in setting expectations about what observational EOL HIV cure research can accomplish.

Moreover, respondents noted the perceived benefits of an eventual cure for others, including having HIV eliminated from the body and not

having to take medications, corroborating results from prior similar studies.<sup>23,34,35</sup> Numerically, NOK/loved ones appeared slightly more optimistic about the perceived benefits of an eventual cure for HIV, compared to Last Gift participants.

Findings from this paper are relevant to the scholarly debate attempting to resolve the benefit/risk ratio challenge in HIV cure research.<sup>36–38</sup> In any clinical research, risks – whether clinical, social, psychosocial, or financial – must be minimized (non-maleficence), while benefits maximized (beneficence).<sup>39,40</sup> However, there is no objective metric with which to assess these potential benefits and risks.<sup>41</sup> In HIV cure research, participants face risks, while benefits oftentimes accrue to science and society.<sup>41</sup> Last Gift participants are not joining the study with the hope of curing disease or prolonging their lives.<sup>15</sup> Weijer and Miller instead proposed the use of a ‘risk-knowledge calculus’ to determine whether clinical studies could be justified based on asymmetric risks and benefits.<sup>42</sup> Based on these and prior findings,<sup>5,16,17</sup> we believe that the Last Gift study maintains a favorable benefit/risk profile. Our findings also strengthen the argument that a thorough examination of how participants, and additionally in this case, NOK/loved ones, perceive benefits and risks, has ethical significance. However, a true appreciation of benefits and risks would also require an evaluation in the context of individual circumstances, particularly at the EOL. What represents acceptable benefits and risks may vary for each participant, and personal values should be considered.<sup>43</sup>

#### 4.1. Limitations

Given the EOL condition of Last Gift participants, not all were able to complete an interview; therefore, there is missing data. This phenomenon has been coined ‘functional attribution’ and is common in EOL research.<sup>20</sup> We used Yes/Agreement and No/Disagreement questions to reduce cognitive burden at the EOL. It is possible that Likert scales would have yielded more nuanced data. The small sample size precluded complex bivariate and multivariate analyses and data disaggregation by sex and/or gender. Because the Last Gift and NOK/loved one’s questionnaires were developed separately, there are asymmetries in the questions asked. We also suspect a social desirability bias. The design was cross-sectional, and we recognize that perceived risks and benefits may change over time. The Last Gift study is occurring at one research center in California, and data is not generalizable to all PWH. Analysis of open-ended interview data is ongoing, will be reported separately and likely lead to additional emergent perceived risks and benefits of the Last Gift study.

#### Conclusions

We attempted to quantify perceived benefits and risks from the perspectives of the Last Gift participants and their NOK/loved ones. The next scientific frontier would be to introduce interventions at the EOL.<sup>44</sup> We foresee that perceived benefits and risks would be different in the setting of interventional EOL HIV cure research. Knowing how participants and affected parties perceive HIV cure research is critical to the design of ethical and well-informed studies.

#### Funding statement

This work was supported by R21MH118120 to K.D. (including an Ethics Supplement) We also acknowledge the support received from P01 AI131385 (Smith – Revealing Reservoirs during Rebound (R3) Last Gift, Early Treatment Interruption) and P01 AI169609 (Smith – Leaving, Coming and Staying HIV Obligate Microenvironments (HOME). PKR is supported by T32 AI007384.

We would also like to acknowledge the support received from UM1AI126620 and UM1AI164570 (BEAT-HIV Collaboratory) which is co-supported by the National Institute of Allergies and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH), the

National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Drug Abuse (NIDA), and the Robert I. Jacobs Fund of The Philadelphia Foundation.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Data availability

The authors do not have permission to share data.

#### Acknowledgements

The authors are deeply indebted to the Last Gift study participants and their next-of-kin/loved ones. We are grateful to the UCSD AntiViral Research Center Community Advisory Board, the HIV and Aging Research Project–Palm Springs (HARP-PS) and the Palm Springs Positive Life Program. We also give thanks to the California NeuroAIDS Tissue Network (U.S. National Institute of Mental Health, National Institutes of Health (NIMH/NIH Award Number U24MH100928)).

We would like to thank the Brocher Foundation. The Brocher Foundation’s mission is to encourage research on the ethical, legal, and social implications of new medical technologies.

#### References

- Deeks S, Lewin S, Havlir D. The end of AIDS: HIV infection as a chronic disease. *Lancet*. 2013;382(9903):1525–1533.
- Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency infection. *N Engl J Med*. 1998;338(13):853–860.
- Goodkin K, Kompella S, Kendell SF. End-of-Life care and bereavement issues in human immunodeficiency virus - AIDS [Internet]. *Nurs Clin*. 2018;53(1):123–135. <https://doi.org/10.1016/j.cnur.2017.10.010>. Available from:
- 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.
- Perry KE, Dubé K, Concha-Garcia S, et al. "My death will not [Be] in vain: testimonials from last gift rapid research study participants living with HIV at the end of life. *AIDS Res Hum Retrovir*. 2020;36(12):1071–1082.
- Lessard D, Dubé K, Bilodeau M, et al. Willingness of older Canadians with HIV to participate in HIV cure research near and after the end of life: a mixed-method study. *AIDS Res Hum Retrovir*. 2022 Aug 1;38(8):670–682.
- Sandstrom TS, Schinkel SCB, Angel JB. Medical assistance in death as a unique opportunity to advance human immunodeficiency virus cure research. *Clin Infect Dis*. 2019;69(6):1063–1067.
- UCSD. *Last Gift. A University of California San Diego Study* [Internet]; 2021. Available from: <http://lastgift.ucsd.edu/>.
- Rawlings S, Layman L, Smith D, et al. Performing rapid autopsy for the interrogation of HIV reservoirs. *AIDS*. 2020; 34(7):1089–1092.
- Chaillon A, Gianella S, Dellicour S, et al. HIV persists throughout deep tissues with repopulation from multiple anatomical sources. *J Clin Invest*. 2020;130(4):1699–1712.
- Riggs PK, Chaillon A, Jiang G, et al. Lessons for understanding central nervous system HIV reservoirs from the last gift program. In: *Current HIV/AIDS Reports*. vol. 19. Springer; 2022:566–579.
- Kanazawa J, Rawlings S, Hendrickx S, et al. Lessons learned from the last gift study: ethical and practical challenges faced while conducting HIV cure-related research at the end-of-life. *J Med Ethics*. 2023;49:305–310.
- Alsop K, Thorne H, Sanshu S, et al. A community-based model of rapid autopsy in end-stage cancer patients. *Nat Biotechnol*. 2016;34(10):1010–1014.
- Pentz RD, Cohen CB, Wicclair M, et al. Ethics guidelines for research with the recently dead. *Nat Med*. 2005;11(11):1145–1149.
- Dubé K, Gianella S, Concha-Garcia S, et al. Ethical considerations for HIV cure-related research at the end of life. *BMC Med Ethics*. 2018;19(83):1–16.
- Dubé K, Patel H, Concha-Garcia S, et al. 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. *AIDS Res Hum Retrovir*. 2020;36(12):1033–1046.
- Javadi SS, Mathur K, Concha-Garcia S, et al. Attitudes and perceptions of next-of-kin/loved ones toward end-of-life HIV cure-related research: a qualitative focus group study in southern California. *PLoS One*. 2021;16(5), e0250882.
- Dubé K, Barr L, Palm D, Brown B, Taylor J. Putting participants at the centre of HIV cure research. *Lancet HIV*. 2019;3018(19):18–19.



- 19 Perry KE, Taylor J, Patel H, et al. “[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 (EOL). *PLoS One*. 2020;15(11), e0242420.
- 20 George LK. Research design in end-of-life research: state of science. *Gerontol*. 2018; 42(11):86–98.
- 21 Prakash K, Gianella S, Dubé K, Taylor J, Lee G, Smith D. Willingness to participate in HIV research at the end of life (EOL). *PLoS One*. 2018;13(7), e0199670.
- 22 Henry B, Scales D. Ethical challenges in conducting research on dying patients and those at risk of dying. *Account Res*. 2012;19:1–12.
- 23 Dubé K, Hosey L, Starr K, et al. Participant perspectives in an HIV cure-related trial conducted exclusively in women in the United States: results from AIDS clinical trials group (ACTG) 5366. *AIDS Res Hum Retrovir*. 2020;36(4):268–282.
- 24 Dubé K, Eskaf S, Barr L, et al. Participant perspectives and experiences following an intensively monitored antiretroviral pause in the United States: results from the AIDS clinical trials group A5345 biomarker study. *AIDS Res Hum Retrovir*. 2022;38(6): 510–517.
- 25 Henderson GE, Peay HL, Kroon E, et al. Ethics of treatment interruption trials in HIV cure research: addressing the conundrum of risk/benefit assessment. *J Med Ethics*. 2018;44(4):270–276.
- 26 Henderson GE, Waltz M, Meagher K, et al. Going off antiretroviral treatment in a closely monitored HIV “cure” trial: longitudinal assessments of acutely diagnosed trial participants and decliners. *J Int*. 2019;22, e25260.
- 27 Gilbertson A, Kelly EP, Rennie S, Henderson G, Kuruc J, Tucker JD. Indirect benefits in HIV cure clinical research: a qualitative analysis. *AIDS Res Hum Retrovir*. 2019;35 (1):100–107.
- 28 Lantos J. The “inclusion benefit” in clinical trials. *J Pediatr*. 1999;(134):130–131.
- 29 Rennie S, Day S, Mathews A, et al. The role of inclusion benefits in ethics committee assessment of research studies. *Ethics Human Res*. 2019;41(3):13–22.
- 30 Steinhäuser K, Christakis N, Clipp E, McIntyre L. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA*. 2000;284 (19):2476–2482.
- 31 Dubé K, Perry K, Mathur K, et al. Altruism: scoping review of the literature and future directions for HIV cure-related research. *J Virus Erad*. 2020;6(4), 100008.
- 32 Quinn GP, Murphy D, Pratt C, Mun T, Leon ME, Haura E. Altruism in terminal cancer patients and rapid tissue donation program: does the theory apply? *Med Health Care Philos*. 2013;16:857–864.
- 33 Rosenbaum L. Altruism in extremis - the evolving ethics of organ donation. *N Engl J Med*. 2020;382(6):493–496.
- 34 Dubé K, Eskaf S, Evans D, et al. The dose response: perceptions of people living with HIV in the United States on alternatives to oral daily antiretroviral therapy. *AIDS Res Hum Retrovir*. 2020, 36(4):324–348.
- 35 Sylla L, Evans D, Taylor J, et al. If we build it, will they come? Perceptions of HIV cure-related research by people living with HIV in four U.S. Cities: a qualitative focus group study [Internet] *AIDS Res Hum Retrovir*. 2018;34(1):56–66. Available from: <http://online.liebertpub.com/doi/10.1089/aid.2017.0178>.
- 36 Buchak L. Why high-risk, non-expected utility maximising gambles can be rational and beneficial: the case of HIV cure studies [Internet] *J Med Ethics*. 2017 Feb;43(2): 90–95. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27364537>. Available from:.
- 37 Dresser R. First-in-Human HIV-remission studies: reducing and justifying risk [Internet] *J Med Ethics*. 2017 Feb;43(2):78–81. . Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27143494>. . Available from:.
- 38 Kumar R. Contractualist reasoning, HIV cure clinical trials, and the moral (Ir) relevance of the risk/benefit ratio [Internet] *J Med Ethics*. 2017 Feb 43;43(2): 124–127. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27590492>. Available from:.
- 39 Beauchamp T, Childress J. *Principles of Biomedical Ethics*. Third. Oxford: Oxford University Press; 1989:470.
- 40 Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research [Internet] *Kennedy Inst Ethics J*. 2011 Jun;21(2):141–179. Available from: [http://mu.se.jhu.edu/content/crossref/journals/kennedy\\_institute\\_of\\_ethics\\_journal/v021/21.2.rid.html](http://mu.se.jhu.edu/content/crossref/journals/kennedy_institute_of_ethics_journal/v021/21.2.rid.html). Available from:.
- 41 Dubé K, Taylor J, Sylla L, Evans D, Dee L, Burton A, et al. ‘Well, it’s the risk of the unknown ... right?’: a qualitative study of perceived risks and benefits of HIV cure research in the United States. *PLoS One*. 2017;12(1), e0170112.
- 42 Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? *Nat Med*. 2004;10(6):570–573.
- 43 Evans D. An activist’s argument that participant values should guide risk–benefit ratio calculations in HIV cure research [Internet] *J Med Ethics*. 2017;43(2):100–103. Available from: <http://jme.bmj.com/lookup/doi/10.1136/medethics-2015-103120>.
- 44 Kanazawa JT, Gianella S, Concha-Garcia S, et al. Ethical and practical considerations for interventional HIV cure-related research at the end of life: a qualitative study of key stakeholders in the United States. *PLoS One*. 2021;16(7), e0254148.