Factors Associated with Willingness to Participate in End-of-Life HIV Cure Research: Perspectives from People Living with HIV

1. RATIONALE

Since the discovery of HIV in the 1980s as the virus causing Acquired Immune Deficiency Syndrome (AIDS), the landscape of HIV medicine has been revolutionized by the advent of combined antiretroviral therapy (cART). People living with HIV (PLWH) now have near-normal life expectancies and most individuals pass away due to conditions similar to those in the general population[1]. The research landscape has shifted to mirror this change, and HIV cure—the ultimate achievement—has been at the center of many major research endeavours.

The presence of long-lived viral reservoirs within various anatomical sites in the body underlies the major challenge to viral eradication[2]. Approaches to eliminate the latent HIV reservoir have focused on developing either a sterilizing cure, whereby all infectious HIV particles would be eliminated from the body, or a functional cure, whereby a very low HIV viral load would be maintained at undetectable levels in the absence of cART by the host's own immune responses[2]. While simian immunodeficiency virus (SIV) infection has enabled some characterization of the latent reservoir, primate models do not completely reflect the nature of HIV within a human body. Invasive procedures such as colonoscopy to obtain colonic biopsies[3, 4], bronchoscopies to obtain bronchoalveolar lavage fluid[5] and lumbar puncture to obtain cerebrospinal fluid[6] have been performed for the purpose of characterizing the HIV reservoir[7]. However, these specimens only partially reflect what is going on within anatomical sites within the body. More invasive procedures may be harmful to the participants and hence are not done for research alone.

The US National Institute of Allergies and Infectious Diseases and the National Institute of Mental Health have set a new research priority to include terminally-ill PLWH in cure research[8, 9]. An example of such a study is the Last Gift, a study at the University of California San Diego for PLWH with a terminal illness, such as cancer or neurodegenerative disease, and prognosis under 6 months[9]. These participants donate their blood or other ante-mortem specimens (blood, genital secretions, rectal swabs) or their entire bodies as post-mortem specimens to advance HIV Cure research[9]. However, a challenge with these studies is that research autopsies must be performed within 6 hours of death. If performed later than that, virus and cells degrade and physiological processes become obscured[10, 11].

In 2016 in Canada, Medical Assistance in Death (MAID) became legal. In 2018 in Ottawa, a person living with HIV, well-known to the Ottawa Hospital clinic, had requested MAID. He had expressed a strong interest to donate his body and organs to research and consented to the autopsy for research purposes[7]. Within 12 hours, an autopsy was performed and various organs, including brain, lungs, liver, spleen, testes, the gastrointestinal tract and aorta as well as cells from the tissues were processed for future immune and virological studies[7]. Following this, investigators who are members of the Canadian Enterprise for Cure Research (CanCURE)—an HIV reservoir and cure research collaboratory—assembled to create the CanCURE HIV Autopsy Biobank. Currently under RI MUHC REB review, the hope is that PLWH will be inspired to donate their bodies for HIV cure research following their deaths.

End-of-life HIV cure research raises a number of ethical issues[12]. As examined by Dubé, to ensure that research with terminally-ill PLWH remains ethical, 5 topics emerged 1) protecting autonomy through informed consent, 2) avoiding exploitation and fostering altruism, 3) maintaining a favourable benefits/risks balance, 4) safeguarding against vulnerability thought patient-participant centeredness and 5) ensuring the acceptance of next-of-kin/loves ones and community stakeholders[10]. We will conduct a qualitative research study using in-depth interviews with PLWH to better understand their perspectives on end-of-life HIV cure research and the factors that could improve their associated experience. A better understanding of these factors could then be taken into consideration when designing patient-centred interventions to approach, include, and interact with patient participants in the CanCURE HIV Autopsy Biobank study.

2. Hypothesis

We hypothesize that designing approaches to end-of-life (EOL) HIV cure research that account for PLHIV's knowledge and factors associated with a meaningful experience for such research could increase individuals' willingness to participate in such studies and subsequent benefits.

3. Objectives

Primary objective: To describe PLWH's perspectives on EOL HIV cure research

Secondary objectives: a) To identify factors associated with willingness to participate in EOL HIV cure research

b) To identify ways to improve the participant experience in EOL research and make the process meaningful

c) To explore how much PLWH already know about EOL research for HIV cure and educate participants about this field of research

4. Methodology

We will use a participatory qualitative research design. Two community members, a PLWH and an important Montreal-based community organization representative, are included on this application as co-investigators and have been involved in the study design and preparation of this application. All steps of the research process, including the preparation of this application, are planned to be conducted in partnership with these community members, 1) for the research to benefit from their expertise and experiences, 2) to provide training to community members on conducting research, from setting research priorities, to developing research questions and conducting interviews, and analyzing collected data, and 3) to increase the range of knowledge dissemination.

Data collection: To document PLWH's perspectives, we will use semi-structured in-depth interviews. The interview schedule will include a series of themes to explore allowing us to achieve our secondary objectives and situate these results in the broader context of PLWH's experiences and perspectives. Thirty(30) interviews will be conducted with PLWH aged ≥65 years of age and diagnosed with HIV for at least 1 year. We will attempt to enrol participants of various socioeconomic backgrounds and approximately equal numbers of males and females. We will maintain a contact log during the study to determine the acceptance rate of participation. Demographic variables will be collected. Each interview will be done in either English or French, as preferred by the participants, will be in person and will last between 30-60 minutes. Interviews will be audio-recorded but will be anonymized. Following our participatory design, interviews will be conducted by an investigator - i.e., David Lessard, PhD, a qualitative research methodologist with significant experience performing such interviews -and a community member working in team. Key-informant interviews will enable us to solicit more detailed, textured, and frank opinions about the process aimed at improving the patient experience for this qualitative study. Results will enable us to enhance the patient experience of being approached to participate in the CanCURE HIV Autopsy Biobanking Study. Before each interview, participants will be informed of the delicate nature of the questions. We will provide a debriefing afterward, to discuss with participants any undesirable feelings which the interview has provoked, such as fear or sadness, and offer advice to calm and comfort the participant. If the interview has caused any significant anxiety or distress that persists beyond the debriefing period, we will ensure the participants have proper follow-up with a psychologist at the Chronic Viral Illness Service or one of the study doctors to address the distress. At the end of sessions, the interviewer and community member will discuss the content and execution of the interview, for research purposes and also to favour knowledge transfer and dialogue about the process.

Table 1— Themes for the semi-structured interview

Themes	Questions
Getting to know you	Tell me about yourself (education and occupation, marital status, etc.)./ When were you diagnosed with HIV? How was this experience?/ To what extent have you felt discriminated against or stigmatized due to your HIV? To which extent have you received support from family, friends, or the community in relation to HIV?

Your past health care/ research experiences	How do you feel about your current health care?/ To what extent did you participate in HIV research studies before? What type(s) of research? How was this/these experience(s)?
Your knowledge about HIV cure and end-of-life research	What is your understanding of HIV cure research? /What do you know about end-of-life research? / What would make it easier for you to participate in end-of-life research? / What would make it more difficult for you to participate in end-of life research?
Your needs for support	What does mortality mean to you? /Is there anything that we can offer you to help you feel more comfortable about your eventual mortality? /What information or message would you like to pass on to researchers involved in end-of-life HIV cure research

5. ANALYSIS AND ANTICIPATED RESULTS

Recorded interviews will be transcribed. Each participant will have a code and no personal identifiers will be included in transcripts. Investigators and community members will be involved in the analysis of the transcriptions. They will first establish an inductive coding grid for content analysis. Following Dubé et al, results will then be examined using both grounded theory and phenomenology to facilitate understanding of « the realities anchored in the view of key informants » while the latter enables « capturing the essence of a phenomenon and the lived experiences of the individuals». Results will be discussed to seek consensus between investigators and community members on their implications for the identification of factors associated with willingness to participate in EOL HIV cure research, for ways to improve patient experience, and PLWH's level and nature of knowledge of EOL research for HIV cure.

6. KNOWLEDGE TRANSLATION

We will present our findings at the Canadian Enterprise for Cure Research annual fall meeting and the Canadian Association of HIV Research Annual Conference. The manuscript of our final results will be published in an open-access journal to ensure world-wide accessibility without barriers. We will also seek knowledge-transfer directly to the community through ACCM workshops and website, based on needs and opportunities identified with community members, and through Dr B Lebouché's CIHR Strategy for Patient-Oriented Research Mentorship Chair's online public platform.

7. TIMELINE

REB approval : June 2019/Database set-up : May-June 2019/Participant recruitment and interviews : July 2019-December 2019-01-22/Preliminary Data analysis : October 2019 (for CanCURE meeting and CAHR abstract submission)/Presentation at CanCURE and CAHR : November 2019 and April 2020, respectively Complete Data analysis : December-April 2019/Manuscript submission : April-May 2019

8. EXPERTISE

Dr C Costiniuk is a Junior Scientist at the Research Institute(RI) of the McGill University Health Centre (MUHC) and HIV physician at the Chronic Viral Illness Service (CVIS) of the MUHC and has a established a protocol for research bronchoscopy for HIV reservoir evaluation. **Dr JP Routy** is a Senior Scientist and clinic Director at the MUHC/CVIS who has established a leukapheresis platform and colonoscopy platform to pursue HIV cure research. Both members of CanCURE, Dr Costiniuk and Dr Routy are establishing the HIV Autopsy Biobank at the RI-MUHC to enable Montreal HIV cure researchers access to post-mortem tissue. **Dr B Lebouché, Md, PhD,** is a new investigator and assistant professor with McGill University's Department of Family Medicine as well as practicing physician at the CVIS. He is also the holder of a 5-year CIRH Strategy for Patient-Oriented Research (SPOR) Mentorship Chair in innovative clinical trials, which allowed him to advance innovative research projects and ground-breaking research trials in HIV focusing on patient-oriented research. **D Lessard** has a PhD in anthropology and his experience as Patient Engagement Agent in Dr Lebouché's Mentorship Chair has provided him with skills to create safe environments and trust-building relationships with PLWH, to synthesize and translate knowledge and subjective perceptions across sociodemographic contexts, levels of understanding ,and fields of research. **M Bilodeau** is an expert patient involved in Dr Lebouché's and David Lessard's projects since 2015 and actively involved in building leadership in the HIV community. **P Keeler** is a community actor involved in organizing knowledge transfer on treatment to PLWH and the broader community and a knowledge-user mentor in Dr Lebouché's Mentorship Chair.

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BUDGET ET JUSTIFICATIONS BUDGÉTAIRES

Le budget doit être réaliste, les justifications budgétaires doivent clairement indiquer l'impact de la subvention du Réseau sur la pérennité du projet. Cette section ne doit pas excéder ***1 page****.*

The majority of the funds requested will be to compensate the time of the post-doctoral fellow who will be conducting the interviews and who will be doing most of the analysis.

1. **Study Personnel :** A post-doctoral fellow (D.L.) will conduct the interviews and analyze the data. The time to conduct the interviews will be 1 hour for 30 interviews or 30 hours. At $42/hour (35 +19% benefits), this comes to $1,260 for the interviews. Data analysis will require 4 hour of work for each participant (120 hours of analysis for 30 interviews). At the same rate, this comes to an additional $5,040. We will also require compensation for our community member who will attend all meetings and provide input at each step for the process. For a 30-hour commitment at $40 per hour, this will come to $1,200. Therefore the total cost for study personnel will be $7,500.

2. **Participant compensation :** We will enrol 30 PLWH. Each will be compensated $50 for their time (this figure accounts for travel costs). Therefore, participant compensation will be $50 x 30 =$1,500.

3. **Knowledge dissemination :** CanCURE is a local meeting and the only cost will involve poster printing ($60). The costs associated with travelling to CAHR and attending the meeting will be approximately $1,940. The costs to publish the article in an open-access journal will be approximately $4,000. Therefore total knowledge dissemination costs will be $6,000.

Therefore, total costs for the study are $15,000.

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POUR USAGE INTERNE

Date d'évaluation :

Acceptation ☐ **Refus :** ☐

Raisons du refus :

Signature :

1. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet.* Jul 19 2014;384(9939):241-248.
2. Eisele E, Siliciano RF. Redefining the viral reservoirs that prevent HIV-1 eradication. *Immunity.* Sep 21 2012;37(3):377-388.
3. Mehraj V, Ghali P, Ramendra R, et al. The evaluation of risk-benefit ratio for gut tissue sampling in HIV cure research. *J Virus Erad.* Oct 1 2017;3(4):212-217.
4. Planas D, Zhang Y, Monteiro P, et al. HIV-1 selectively targets gut-homing CCR6+CD4+ T cells via mTOR-dependent mechanisms. *JCI Insight.* Aug 3 2017;2(15).
5. Costiniuk CT, Salahuddin S, Farnos O, et al. HIV persistence in mucosal CD4+ T cells within the lungs of adults receiving long-term suppressive antiretroviral therapy. *AIDS.* Oct 23 2018;32(16):2279-2289.
6. Joseph SB, Kincer LP, Bowman NM, et al. HIV-1 RNA Detected in the CNS after Years of Suppressive Antiretroviral Therapy Can Originate from a Replicating CNS Reservoir or Clonally Expanded Cells. *Clin Infect Dis.* Dec 18 2018.
7. Sandstrom TS, Burke Schinkel SC, Angel JB. Medical Assistance in Death as a Unique Opportunity to Advance HIV Cure Research. *Clin Infect Dis.* Jan 31 2019.
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.* Jan 2 2017;31(1):1-4.
9. http://lastgift.ucsd.edu/
10. Dube K, Gianella S, Concha-Garcia S, et al. Ethical considerations for HIV cure-related research at the end of life. *BMC Med Ethics.* Oct 20 2018;19(1):83.
11. Alsop K, Thorne H, Sandhu S, et al. A community-based model of rapid autopsy in end-stage cancer patients. *Nat Biotechnol.* Oct 2016;34(10):1010-1014.
12. Dube K, Taylor J, Sylla L, 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.

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CRITÈRES DE SÉLECTION

	Impact potentiel	Intervalle	Mérite scientifique
Subventionnable	Extrêmement important	4,5 – 4,9	Exceptionnel
	Très important	4,0 – 4,4	Excellent
	Important	3,5 – 3,9	Excellent, mais peut nécessiter une révision
Non subventionnable	Modéré	3,0 – 3,4	Très bien, mais nécessite une révision pour être subventionnable
	Limité	2,5 – 2,9	Révision importante nécessaire
	Négligeable	0,0 – 2,4	Laisse beaucoup à désirer

Il est proposé aux évaluateurs d'accorder une note (0,0 à 4,9) pour chacun des critères, en vue de les additionner et de les diviser par

1. RATIONNEL *(Mise en contexte et importance de l'étude proposée)*	4.8
2. HYPOTHÈSE *(Veuillez énoncer clairement l'hypothèse principale du projet et les hypothèses secondaires, le cas échéant).*	4.5
3. OBJECTIFS *(Veuillez spécifier les objectifs principaux, et les objectifs secondaires, le cas échéant).*	4.7
4. MÉTHODOLOGIE *(Si des outils ou des méthodologies innovantes seront utilisées pour ce projet, veuillez les spécifier ici. Veuillez préciser la faisabilité, les difficultés potentielles et les mesures d'atténuation, lorsque pertinent)*	4.8
5. ANALYSES ET RÉSULTATS ANTICIPÉS *(Veuillez préciser les méthodes statistiques qui seront utilisées et énoncer les résultats attendus).*	4.8
6. ÉCHÉANCIER *(Veuillez identifier les étapes à suivre pour l'atteinte des objectifs.)*	4.8
INSCRIRE LE CODE RS DU PARTICIPANT : RS-012	**TOTAL** = 4.7

FORCES : PROJET TRÈS ORIGINAL ET TRÈS PERTINENT AVEC TRÈS PEU D'ÉTUDES SUR CE SUJET. MÉTHODOLOGIE ET CADRE ÉTHIQUE DE LA RECHERCHE BIEN DÉCRITS. APPORTERA DE NOUVEAUX RÉSULTATS DANS LE DOMAINE

FAIBLESSES : AUCUNE

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	Impact potentiel	Intervalle	Mérite scientifique
Subventionnable	Extrêmement important	4,5 – 4,9	Exceptionnel
	Très important	4,0 – 4,4	Excellent
	Important	3,5 – 3,9	Excellent, mais peut nécessiter une révision
Non subventionnable	Modéré	3,0 – 3,4	Très bien, mais nécessite une révision pour être subventionnable
	Limité	2,5 – 2,9	Révision importante nécessaire
	Négligeable	0,0 – 2,4	Laisse beaucoup à désirer

Il est proposé aux évaluateurs d'accorder une note (0,0 à 4,9) pour chacun des critères, en vue de les additionner et de les diviser par

1. RATIONNEL *(Mise en contexte et importance de l'étude proposée)*	4,6
2. HYPOTHÈSE *(Veuillez énoncer clairement l'hypothèse principale du projet et les hypothèses secondaires, le cas échéant).*	4,9
3. OBJECTIFS *(Veuillez spécifier les objectifs principaux, et les objectifs secondaires, le cas échéant).*	4,9
4. MÉTHODOLOGIE *(Si des outils ou des méthodologies innovantes seront utilisées pour ce projet, veuillez les spécifier ici. Veuillez préciser la faisabilité, les difficultés potentielles et les mesures d'atténuation, lorsque pertinent)*	4,9
5. ANALYSES ET RÉSULTATS ANTICIPÉS *(Veuillez préciser les méthodes statistiques qui seront utilisées et énoncer les résultats attendus).*	4,9
6. ÉCHÉANCIER *(Veuillez identifier les étapes à suivre pour l'atteinte des objectifs.)*	4,6
INSCRIRE LE CODE RS DU PARTICIPANT : RS 012	**TOTAL = 28,8 / 6 = 4,8**

FORCES :

L'argumentaire situe avec justesse un projet aux enjeux multiples, éthiques, médicaux, sociaux, et de recherche. L'approche de ce sujet délicat est présentée avec beaucoup d'humanité. **L'hypothèse** qui en découle est à la fois raisonnable et pertinente.

Les objectifs sont clairement exposés et intelligemment limités.

La méthode paraît tout à fait adaptée (approche qualitative, compréhensive), avec une participation communautaire et une attention soutenue aux éventuels effets des entretiens sur les participant-e-s (offre de soutien post-entretien).

La participation d'un anthropologue est appréciée.

Le plan d'analyse est classique et anticipe les communications/publications, avec une attention bienvenue à l'accessibilité des résultats obtenus.

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FAIBLESSES :

Les faiblesses sont très secondaires et relatives en regard de l'intérêt du projet.

1) Existe-t-il dans la littérature des démarches comparables dans le contexte d'autres pathologies graves, en situation de fin de vie ?

2) Le calendrier de la recherche serait éventuellement à clarifier un peu (tableau, par exemple).