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Participation in HIV cure-related research: a scoping review of the proxy literature and implications for future research

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Abstract

Objective: To identify the main types of HIV cure-related strategies and examine possible risks (and benefits) associated with participating in HIV cure-related research studies.

Methods: We undertook a scoping review to first map out the landscape of HIV cure-related research and then examined the risks and potential benefits associated with participating in HIV cure research. Given the early stage of many HIV cure-related studies, we used proxy literatures from non-cure HIV research and cancer research in order to anticipate possible motivators and deterrents of participation in HIV cure-related studies.

Results: We discussed four main categories of HIV cure-related research: (1) early antiretroviral treatment (ART); (2) latency-reversing agents (LRAs); (3) therapeutic vaccinations and immune-based therapies (IBT); and (4) stem-cell transplantation and gene therapy. At this juncture, these categories of HIV cure-related research have substantial individual risks and negligible individual and clinical benefits. Non-cure HIV research (including HIV prevention and treatment) and cancer research have empirical similarities (and differences) to HIV cure research and may provide an opportunity to anticipate ethical and logistical challenges associated with HIV cure-related research participation and decision-making. Learning from the cancer field, a strong foundation of patient-participant and clinician-researcher trust will need to be established to facilitate recruitment of participants into HIV cure-related studies.

Conclusion: Further empirical social science and ethics research will be necessary to inform clinical HIV cure-related research. The study of participation in HIV cure-related research can gain insights from proxy fields by incorporating study elements to clearly explain motivators and deterrents to participation and to inform the implementation of HIV cure-related studies. Study-specific contexts from the reviewed literature further demonstrate the importance of various types of research to assess factors affecting participation in HIV cure-related research, including adequate formative and ethics research.

Keywords: HIV cure-related research, willingness to participate, social sciences

Introduction

The long-term viral suppression of Timothy Brown challenged the assumption that HIV/AIDS was incurable [1]. While Timothy Brown inspired cautious optimism that it may be possible to cure HIV infection, other examples of viral rebound, such as the Mississippi child [2] and the Boston patients [3] raised new questions and challenges for the field, particularly with regards to participation in HIV cure-related research.

There are now more than 100 ongoing HIV cure-related clinical studies worldwide [4], covering a wide range of strategies from early antiretroviral treatment during early infection, latency-reversing agents, therapeutic vaccines, gene editing, stem cell transplantation and combination modalities. Since people living with HIV have access to safe and highly effective treatment, it remains unclear what would motivate or deter them from participating in high-risk/low-benefit HIV cure-related studies, some of which requiring analytical treatment interruption. As several HIV cure-related studies are in the planning or recruitment stage, we hope to learn lessons from related (or proxy) fields to examine possible factors that would either facilitate or deter participation in such clinical research.

Previous studies that examined willingness to participate in HIV prevention studies, HIV treatment and oncology studies have identified determinants of participation (motivators and barriers to participation) [5], explored participation in trials through actual or revealed preferences [6] and examined factors associated with refusal to participate [7]. While HIV cure research differs fundamentally from HIV prevention, HIV treatment and cancer research, we believe that we can learn appreciably from these proxy fields and draw useful empirical comparisons that could help propel the social sciences on HIV cure-related research forward. While we are not equating early-phase HIV cure studies with HIV prevention, HIV treatment or cancer studies, we believe that we can learn lessons from these domains and even anticipate possible challenges to plan recruitment for HIV cure-related studies more effectively.

HIV cure-related research is both similar and different to the proxy fields examined therein and warrants exploration in a comparative context. HIV cure-related research is similar to HIV prevention and treatment research because it is part of the infection and disease progression spectrum (from seeding of the viral reservoir to attempting to purge the latent reservoir). Both HIV treatment and HIV cure-related research recruit people living with HIV. Some individuals have advocated for the use of the expression 'HIV remission' research similarly to the cancer model [8]. Analogous to HIV cure, cancer research may involve high-risk/low-benefit studies. We should also acknowledge the differences with regards to research goals between HIV cure-related studies and the proxy fields. HIV prevention trials enrol HIV-negative participants and seek to find effective methods of preventing HIV acquisition. HIV treatment research seeks the effective suppression of HIV and the augmentation of the immune system. Cancer studies are varied in term of patient-participant involvement since they have a longer tradition – from early-phase (safety) and later-phase (efficacy) studies; however, several HIV cure-research modalities are inspired

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from the cancer field. HIV cure-related studies tend to enrol fewer individuals, on average, since they remain in the early experimental stage [9].

A scoping review is a process of mapping the existing literature and evidence base to gather background information to guide possible future research and/or implementation of studies [10]. The scoping exercise provides a reference map of the existing literature without requiring systematic data synthesis [10]. This scoping review seeks to inform the topic of participation in HIV cure-related research by identifying the main types of HIV cure-related strategies and examining possible risks and potential benefits from HIV cure-related studies. We also examine the literature from HIV-related interventions as well as the cancer literature to derive themes and methodologies that may be helpful in understanding participation in HIV cure-related studies.

Methods

The present scoping review develops a picture of the broad existing evidence base related to participation in research to guide the field of HIV cure-related research. Three aims are pursued: (1) understand the types of HIV cure-related research; (2) explore the extent to which the current 'willingness to participate' literature in HIV (such as prevention or treatment) can inform HIV cure-related research; and (3) determine whether proxy literatures, such as cancer research, can inform the field of HIV cure-related research.

We based the scoping review on a search of articles from the English-language, peer-reviewed literature on PubMed exclusively. We included articles from the clinical research literature from the last 5 years (2010–2015) as well as social sciences articles related to HIV cure from the last year (2015). The HIV prevention and HIV treatment research articles spanned from 2004 to 2011. Oncology-related articles were less recent (1996–2003) due to the older tradition. In total, we included 38 articles with robust designs and internal validity, including systematic reviews and original research articles. We purposely selected journal articles based on apparent salience, relevance and applicability to inform participation in HIV cure research. We used search terms such as 'willingness AND participate', 'HIV AND prevention', 'participation AND HIV AND treatment AND trials', 'participation AND HIV AND drug AND trials', 'participation AND cancer AND clinical AND trials'. We also pursued references of references. Since this is not a systematic review, but a scoping review, we did not employ strict inclusion/exclusion criteria for the selected articles.

For each category of literature, we extracted salient themes and assessed the transferability to participation in HIV cure-related research. We appraised each journal article individually and employed data abstraction spreadsheets in Excel to organise the information. We used narrative synthesis to integrate findings into descriptive summaries. We focused on the characteristics that may affect the willingness of people living with HIV to enter these studies. We further identified important correlates of study participation and practical considerations that may inform the planning and implementation of HIV cure-related studies.

Results

HIV cure-related research

The 22 selected HIV cure-related research articles extracted some of the reported risks and benefits (as opposed to hypothetical risks and benefits occasionally found in informed consent forms) of HIV cure-related studies. We predicated that these risk and benefit considerations could affect participation in research. The selected original research articles chronicled clinical endpoints, but none explicitly addressed participants' perceptions of risks or willingness to participate, donate or take risks in these studies. Few reported actual clinical or individual benefits. All studies involved some level of clinical and personal risk. This section thus focuses on clinical risk determination and reporting as opposed to clinical risk perceptions from patient-participants or clinician-researchers.

HIV cure-related research modalities

Early antiretroviral therapy (ART)

Early ART means the administration of treatment as close to HIV diagnosis as possible. This modality contributes to a smaller HIV reservoir size [11]. The literature on early ART and HIV infection remains limited by the paucity of randomised clinical trials [12]. Potential clinical advantages of early ART may include limitation of the HIV reservoir [13], preservation of immune function [12], possible CD4+ T cell restoration in the gastrointestinal lymphoid tissue (GALT) [12,14] and delayed time to viral rebound [12] among others, although more information is needed regarding long-term clinical implications. Possible physical risks include drug toxicities and drug resistance [12]. The Mississippi child is an example of a paediatric early ART case. She was treated within 31 hours of infection (birth) and rebounded after 27 months off treatment [2]. Another example is the VISCONTI cohort in which patients who received standard combination ART (cART) during acute HIV infection, maintained viraemic control for several years following treatment interruption [15]. Ananworanich *et al*. further showed that a 24-week course of megaHAART during acute HIV contributed to immune restoration, a reduced reservoir size as measured by total HIV-DNA and reduced gut T cell depletion [16]. There are considerations related to early ART for referral, inclusion and participation in studies. Some may relate to the vulnerabilities associated with acute HIV infection. Another example could include consenting issues related to early paediatric HIV cases.

Latency-reversing agents (LRAs)

Latency-reversing agents remain one of the best characterised strategies to purge latent HIV infection [17]. They usually involve a two-step strategy to 'flush out' the latent virus from resting cells, usually followed with an effective clearing mechanism. LRAs include small pharmacological molecules such as histone deacetylase inhibitors (HDACis), among others [17]. Several of these compounds are concurrently in clinical studies for the treatment of cancer or other conditions. Other compounds are being investigated at the preclinical and clinical stage. This modality appears to be relatively safe from a clinician-researcher's perspective; however, the compounds have various levels of potency and toxicities. In a study involving vorinostat, increased HIV-RNA expression in resting CD4+ T cells was seen in all eight study participants who were given a single dose of the drug, with no apparent direct clinical benefits or adverse events associated with vorinostat [18]. Participants maintained ART during the study, which may have conferred an advantage over modalities requiring analytical treatment interruption (ATI). To date, however, LRAs have not substantially reduced the size of the replication-competent proviral HIV reservoir and should not be combined with a treatment interruption. Prior to an ATI, it may be necessary to demonstrate a substantial reduction in the size of replication-competent HIV reservoir [19] in addition to frequently monitoring the participant's viral load for rebound. As current LRAs are not able to efficiently reverse HIV latency and robustly clear infected cells, it may be prudent not

to employ ATIs with LRAs. LRAs should also be paired with a robust immune strategy. At this time, the overall risk to the LRA study patient-participant may be reduced if ART is maintained; however, there may also be unknown risks.

Therapeutic vaccinations and immune-based therapies

Immune-based therapies (IBTs) aim to restore CD4+ T cell lymphocyte counts to better control HIV and disease progression [20]. This modality can be used in combination with latency-reversing agents or gene therapy approaches to stimulate HIV-specific immunity. Therapeutic vaccines are one form of immune-based therapy (IBT). One therapeutic vaccine, ASG-004, has been tested in 19 patients. An increased HIV-specific immune response was seen with a reduced viral load setpoint after treatment interruption [21]. An autologous monocyte-derived dendritic cell vaccine, pulsed with autologous heat-inactivated whole HIV particles, resulted in a significant decrease in plasma viral load (pVL), with a corresponding increase in HIV-specific T cell responses [22]. All participants saw a rebound in their viral loads to detectable levels while off cART and the effect of the vaccine waned over time. Another study using the Vacc-4x investigational product saw no benefit of vaccination and only a significant difference in viral loads for the active group at weeks 28 and 52 [23]. This study reported a change in participants' attitudes towards treatment interruption (from willing to undergo treatment interruption to unwilling). The publication of the SMART trial [24] results showing negative outcomes of treatment interruption occurred while the Vacc-4x study was under way, leading to an early stop of enrolment and a negative perception of treatment interruption among study participants. Participation considerations related to this approach may thus include the possibility that IBTs wane over time and concerns with treatment interruption if applied.

Stem cell transplantation and gene therapy

Stem cell transplants and gene therapy approaches have also generated a vast body of literature. These modalities entail making immune cells resistant to HIV infection and a concomitant effort at reconstituting the immune system [25,26]. From a patient-participant's perspective, possible risks and safety concerns include: (1) imperfect efficiency with genetic modification of stem cells, and thus the risk of letting unprotected immune cells become new targets for HIV, which could contribute to immune system failure or re-establishment of viral reservoirs [27]; (2) conventional vectors being integrated randomly into the host genome and disrupting transcription of host genes, or activation of proto-oncogenes causing malignancies [27]; and (3) possible induction of mutagenesis in some loci and off-target effects that could be deleterious [27]. Additional constraints include the limited availability of CCR5 Δ-32 homozygous donors and the risks associated with irradiation and chemotherapy that constitute part of the regimen with stem cell transplants [27].

While Timothy Brown was cured of HIV via stem cell transplant [1], he underwent high-dose induction and consolidation chemotherapy as well as engraftment with allogeneic stem cells from a donor who was homozygous for the CCR5 Δ32/Δ32 mutation [1]. Timothy Brown experienced hepatic toxic effects, renal failure and viral rebound following the initial ART interruption. He experienced graft-versus-host disease (GVHD) of the skin and relapse of acute myeloid leukaemia after the initial transplantation [1]. His case report reinvigorated the hope for a cure, but his remission was not without serious side effects or risks. In turn, the two Boston patients received reduced-intensity conditioning allogeneic stem cell transplant; however, there was virus rebound following analytical treatment interruption [28]. At least six other patients with HIV and concomitant cancer who received grafts from homozygous CCR5 Δ32/Δ32 donors died shortly after their transplant owing to relapse of the myelodysplastic syndrome, pneumonia, infection, relapse of non-Hodgkin's lymphoma and GHVD. One patient experienced a chemokine (C-X-C motif) receptor 4 (CXCR4)-tropic HIV rebound [29]. Participation considerations related to stem cell transplantation and gene therapy may include high risks from the interventions. They may also be potential ethnic differences (e.g. Δ32 genetic mutation) and concerns with scalability of the approach overall.

Combination approaches

It is unlikely that one single modality will lead to an HIV cure [30]. As with cART, the future of HIV cure-related research may require finding synergies between different approaches. For example, there will be possible synergies between latency-reversing agents and immune-based therapies to augment the immunological response [30], and the factors affecting participation in those studies will likely be compounded.

An emerging social sciences literature on participation in HIV cure research

The social sciences literature on participation in HIV cure research is emerging but has not kept pace with the exponentially growing biomedical research field. This section explores three main themes: (1) reasons for wanting an HIV cure; (2) desirable future outcomes or benefits of HIV cure; and (3) patient views on analytical treatment interruption.

Reasons for wanting an HIV cure

Verdult and colleagues addressed the attitudes of people living with HIV in the Netherlands via an online survey that sought information on the importance of HIV cure research [31]. Top reasons for wanting an HIV cure identified amongst 458 respondents were uncertainty about future health problems, overall negative impacts of HIV on health, concerns about infecting others and stigma [31].

Desirable outcomes of benefits of HIV cure

A survey of 20 volunteers enrolled in a latency-reversing agent (vorinostat) study in Australia described participant expectations while in the study [32]. Researchers surveyed experiences during study participation as well as desirability of potential cure scenarios. The highest ranked future hypothetical benefit of HIV cure study participation was 'stopping HIV transmission to others' (47%), while the second highest ranking was 'unable to be re-infected with HIV' (32%) [32]. Another survey conducted primarily in the UK assessed factors affecting willingness to participate in HIV cure-related studies. This study found that health and well-being (96%) and inability to transmit HIV to others (90%) were ranked as the more desirable future possible outcomes of HIV cure-related research [33].

Patient views on analytical treatment interruption

An online cross-sectional survey administered among >2,000 people living with HIV in the United States found that 34% of respondents would be either very willing or willing to participate in HIV cure-related studies requiring treatment interruption [34]. This study also found that willingness to participate in HIV cure-related research involving treatment interruption was greatest among people who were highly motivated to participate in studies for the benefit of science or society, as opposed to individual

benefits. The UK survey [33] found that 59% of respondents would accept substantial risks and 62% deemed treatment interruption acceptable.

The above studies contribute to an emerging social sciences literature and demonstrate the feasibility of conducting social science research on HIV cure either as stand-alone research or embedded as part of a clinical study. These preliminary results also underscore the need to better understand the role of altruism (e.g. 'stopping HIV transmission to others') in HIV cure-related research participation decision-making. Additional similar social science studies on HIV cure are planned in the United States, Europe and China. More research will also be needed on patient-participants' perceptions of risks and benefits (and possibly how they relate to actual clinical risk determination).

Participation in HIV prevention research

While HIV prevention research is fundamentally different from HIV cure research (involving HIV-negative participants versus people living with HIV), the literature on willingness to participate in HIV prevention yielded an extensive list of possible barriers and facilitators to HIV research participation that could be applicable to the HIV cure-related field.

Dhalla and colleagues [6] focused on the motivators to participation in actual, as opposed to hypothetical, HIV vaccine trials. This review distinguished early phase studies from larger efficacy trials. Most motivators to participation in actual HIV vaccine trials were categorised as societal versus individual benefits. Societal benefits tended to be altruistic, while individual benefits were financial, physical or psychological in nature. For early-phase studies, societal benefits were common; whereas individual benefits predominated in later-phase efficacy trials.

Instead of focusing on motivators, the Mills *et al.* synthesis [35] categorised barriers to hypothetical HIV prevention trial participation using content analysis. Topics reported fell into five main categories: (1) safety concerns (side effects); (2) fear or mistrust (drug companies or treatment as 'guinea pig'); (3) concerns or misunderstandings about study design (possibility of receiving placebo); (4) discrimination and social risk (viewed as living with HIV); and (5) pragmatic obstacles (inconveniences).

Participation in HIV treatment research

The HIV treatment literature can be informative given the overlapping populations of participants living with HIV. One comprehensive review of the major barriers to participation in HIV treatment research included both qualitative and quantitative studies [36]. Major barriers to participation in HIV treatment studies were organised by safety concerns and fears of side effects, distrust of researchers, concerns around research design, logistical challenges and social discrimination. One of the major findings was the paucity of research in reference to low-income countries and 'harder-to-enrol' populations such as people from minority groups and women. The quantitative HIV treatment studies tended to focus on concerns around safety and side effects, suspicions about experimental treatment and mistrust of clinical researchers. Complementarily, qualitative studies highlighted personal inconveniences in everyday life and potential discrimination and stigmatisation resulting from lack of anonymity and inadvertent disclosure of HIV seropositivity that could result from participation.

An original study conducted among 657 people living with HIV from 1997 to 2003 evaluated the range of predictors of HIV treatment research participation using multivariate analysis [37]. The strongest predictors of enrolment related to clinical contact factors, including place of residence with respect to clinic, years on HIV treatment and percentage of appointments kept. Few personal characteristics influenced participation in research. This study suggested that the variations seen between socio-ethnic groups could be explained by confounding clinic contact factors. The authors recommended shifting the focus from the 'who' of research participation to the 'how' of clinical interactions in order to encourage meaningful engagement of people living with HIV in treatment research.

Participation in cancer research

The cancer field can provide meaningful insights to inform HIV cure research. Cox and colleagues published two reviews: one exploring the reasons for non-participation in cancer clinical studies [38] and another examining practical challenges related to entry into cancer clinical studies [39]. Factors related to non-participation in cancer clinical studies included: (1) patients deciding not to participate; (2) researchers choosing not to offer study involvement to patients; (3) lack of knowledge about studies; (4) patients not meeting eligibility requirements; (5) demands on time and practical matters such as work schedules, transportation and duration of the study; and (6) patients' concerns that studies were commercially driven [38]. Factors positively influencing participation in cancer clinical studies included: (1) existence of a trusting relationship between the clinician-researcher and the patient-participant; and (2) communication processes, particularly around provision of study information [38]. With specific reference to early phase anti-cancer drug studies, factors such as not wanting to give up, wanting to help other cancer patients, not wanting to lose support offered as part of the study, hope for tumour response and desire to help medical research were highlighted as possible motivators [38]. Another study highlighted the conflicting objectives between clinical care/treatment and scientific medical research, discussed the role of informed consent as a key step in deciding whether to participate in research, and the obligation of healthcare professionals in fostering sound decision-making [39]. One of the main lessons learned from the cancer field, also applicable to HIV cure-related studies, is that the context of the clinician-researcher–patient-participant consultation has profound effects on a person's decision to participate in a study.

General medical research literature

The general medical research literature on participation in research can also inform HIV cure-related studies. One review [40] comprised qualitative and quantitative studies of the barriers and motivators to research participation among African Americans, Latinos, Asian Americans and Pacific Islanders. Among barriers to participation, mistrust, competing demands, fear of unintended consequences, lack of access to information and stigma were the most commonly cited reasons for not participating in research. A study by Verheggen *et al.* [41] found that individuals make 'personal balance accounts' before entering studies, defined as the physical and emotional benefits participants hope to gain minus the risks and burdens expected from the study. This study found that long-term patients have slightly different motivators to participate in clinical studies versus short-term, newly diagnosed patients.

Discussion

This scoping review is unique because it offers a trans-disciplinary methodology to begin to understand factors that may affect participation of people living with HIV in cure-related studies. The distinctive approach is the use of proxy fields (such as HIV prevention, HIV treatment and cancer) to anticipate some of the

facilitators or barriers to participation. Our main argument is that the social sciences on HIV cure research can benefit from drawing from these proxy fields of study.

The scoping review presented a snapshot of some HIV cure-related research modalities that will become more important in biomedical research and that will require human participation. The review reported actual risks and clinical endpoints of HIV cure-related studies from the published literature that may affect future participation. The review discussed that HIV cure-related research strategies involve risks, some of them significant, and personal and clinical benefits may be negligible. Consequently, researchers do need to remain vigilant to not over-appeal to people's altruistic motives and inflate hopes for an HIV cure. Altruistic motives in the context of high-risk/low-benefit HIV cure-related studies do need further empirical exploration. Patients contemplating participation in HIV cure-related studies do need to weigh the known benefits of ART against the known and unknown risks of studies to advance the search for an HIV cure. While some of the interventions confer risks, the means of testing whether they have an effect (e.g. analytical treatment interruption) may have a greater degree of risk. Thus, 'personal balance accounts' [42] may become more relevant as patient-participants evaluate possible risks *vs.* benefits scenarios.

Furthermore, the heterogeneity of HIV cure-related research strategies may require a multi-disciplinary approach to understanding factors affecting participation. Scientists will need to incorporate lessons learned from the past, since these studies of novel interventions are not emerging in a vacuum. In this review, the HIV prevention research field revealed that there are recognisable societal and individual risks and benefits affecting participation in HIV research studies. The construct of personal versus societal risks and benefits can be helpful in the context of HIV cure-related research as well, since most benefits of early-phase studies will accrue to science and society instead of the individual. In turn, the HIV treatment field highlighted the importance of perceptions and education about clinical research, along with possible fears of side effects and perceived risk–benefit ratios.

Learning from the cancer field, this review highlighted the importance of a trusting relationship between the clinician-researcher and the patient-participant, communication and informed consent in decision-making and the context in which potential participants are approached for studies. The cancer analogy was found to be instructive and this finding is consistent with a recent paper about the language of HIV cure research whereas authors opted for 'clinical remission' (similar to that used in oncology) because it denoted 'improvement with some uncertainty' [8]. None the less, the cancer analogy is imperfect, as there can be significant health differences between cancer patients (some of whom may be at the end of life) versus people living with HIV, the majority of whom are now able to lead relatively healthy lives due to the availability of potent antiretroviral treatment. Undoubtedly, communications processes around provision of study information, literacy and meaning of HIV cure-related research will remain important to make decisions as to whether to participate.

The multi-disciplinary approach used in this scoping review mirrors that used in the biomedical sciences towards an HIV cure. In fact, the HIV cure-related field is highly influenced by oncology (e.g. via the use of anti-cancer drugs or gene transfer) and immunology and vaccinology (to prevent viral rebound). Proxy fields have also proven useful in informing ethical considerations in HIV cure research [42,43] and stakeholder engagement [44]. This review is consistent with earlier literature on HIV cure-related research that found value in incorporating considerations from related fields, since novel interventions are not emerging in an ahistorical clinical research vacuum [42,43]. While the field of HIV cure-related research has distinctions from the HIV prevention, HIV treatment or cancer research, the use of the analogies is certainly helpful in deriving empirical comparisons and ethical considerations and to inform the planning of studies. The review also discussed emergent themes in the social sciences of HIV cure-related research. More research will be needed to understand patient-participant perspectives regarding HIV cure-related studies, including perceptions of risks and benefits for the different research modalities.

Limitations

This scoping review relied on evidence from research on the willingness to participate in HIV prevention, HIV treatment and cancer research to inform the implementation of HIV cure-related studies and future social sciences on HIV cure. Motivators and deterrents to study participation could be inferred across the range of studies. Limitations of the review included retrieval of journal articles from a single English-language source (PubMed) and possible selection bias due to the scoping methodology. Furthermore, correlates of retention or withdrawal from studies and patient referrals were not assessed. The review summarised considerations from a range of studies, including systematic reviews, cross-sectional and prospective studies, and qualitative research. Since this is a scoping review aimed at guiding future research, we did not employ a systematic approach that adjudicated the quality of studies or the strength of evidence [10] and this is a limitation of the review. Instead, the broad focus was paradigmatic of the scoping approach geared towards providing an overview of extant literature without extensive data synthesis, different from the systematic review methodology [10]. The scoping review gathered background information about possible factors that may affect participation in HIV cure-related studies, using a trans-disciplinary approach. While the reliance on analogies may have been speculative, the expanded search yielded insights into factors facilitating and hindering participation in clinical research that could inform the planning and design of HIV cure-related studies. Even with an attempt to incorporate an inclusive view, the scoping exercise may have omitted useful medical analogies, such as gene transfer research or medication-free research used in schizophrenia or rheumatology. Paradoxically, while the literature on participation in clinical studies seems to over-emphasise barriers to participation, there remains a paucity of research on non-participation or refusal to participate, due to the practical difficulties in accessing non-participants. The scoping review did not delve into factors affecting non-participation.

Implications for future social sciences research on HIV cure

Themes explored in this review have implications for future social sciences research on HIV cure. Table 1 summarises the key lessons learned from the proxy literatures to inform future research on participation and willingness to donate or take risks in the HIV cure research space. Factors affecting participation in clinical studies will likely transcend distinct medical boundaries. Decisions to participate in HIV cure-related studies will be complex and multi-faceted. Factors will vary from individual to societal determinants. While the existing literature remains focused on patient-participant-reported intentions, it will be important to understand clinician-researchers' perceptions, the values of communities and society, and the perspectives of policy-makers, regulators and bioethicists towards HIV cure-related research. Furthermore, it will be important to engage these stakeholders

Table 1. Key lessons from proxy literatures to inform future research on participation in HIV cure studies

- HIV and cancer clinical studies have several similarities with ongoing and planned HIV cure clinical research, providing an opportunity to anticipate some of the ethical and logistical challenges
- HIV cure clinical research incorporates a wide range of types of studies and risks to the individuals, obviating the need for cure-specific ethical guidelines
- Many early HIV cure clinical studies will have substantial individual risks and negligible individual benefits, increasing the importance of external institutional review board (IRB) review as part of the research process
- Societal, cultural, and study-specific contexts from HIV prevention and HIV treatment studies demonstrate the importance of qualitative research to assess issues related to participation in research
- Cancer clinical studies underline the need for a strong foundation of patient-researcher trust to facilitate recruitment of cancer patients into ongoing studies
- Further empirical social science and ethics research are necessary to inform the implementation of HIV cure research

around the actual and perceived barriers of participation early to prepare for the conduct and exponential growth of HIV cure-related studies around the world.

In order to produce satisfying answers as to the factors affecting participation in HIV cure-related studies, we will need different study designs and the meaningful involvement of people living with HIV to establish validity of constructs. In light of this review, we recommend a hierarchy of studies based on the specific research questions, such as prospective (or retrospective) study designs nested within actual HIV cure clinical studies to yield longitudinal and/or retrospective information about actual patient-participant's experiences. This will require the close collaboration of social scientists and biomedical researchers as well as an open dialogue across traditional disciplinary boundaries. These nested collaborative studies may provide more valid answers compared to cross-sectional surveys about hypothetical intents to participate; however, they will be more difficult to implement. We will also need adequate formative, qualitative research to understand the perspectives of patient-participants, clinician-researchers and other stakeholders. With respect to appreciating the individual journey and prognosis of people living with HIV with their illness, it may be important to adopt a fluid, open and humanistic view, particularly with regards to assessing how quality of life, resilience, hopes, co-morbidities, and illness trajectories can affect participation in and attitudes about HIV cure-related research. Finally, as biomedical and social sciences research evolve, further ethics research will be necessary to inform the implementation of HIV cure-related research.

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