HIV cure: an acceptability scientific agenda

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Purpose of review
Recent years have seen major investments into HIV cure research, seeking a permanent cure or remission. The purpose of this review is to consider how this important research agenda could be broadened to include issues of acceptability and appropriateness for different populations.

Recent findings
We discuss how the definitions of cure such as functional cure (remission) or complete cure (viral elimination) could be interpreted differently by various populations. We also discuss the different methods of cure and the importance of including Africa in cure research to ensure that emerging remedies could be trialled and utilized on the continent that bears the brunt of the AIDS pandemic.

Summary
We propose that the social science research of HIV cure acceptability should be done concurrently with the basic and clinical sciences, to ensure that cure methods consider stakeholder preferences.

Keywords
analytical treatment interruption, HIV cure, HIV cure acceptability, HIV cure research

INTRODUCTION

Although antiretroviral therapy (ART) has been revolutionary in transforming HIV from a death sentence to a manageable chronic disease, it does not provide cure [1,2,3▪,4,5,6▪▪,7]. Patients must commit to lifelong medications and deal with issues such as incomplete viral suppression, social stigma, drug resistance, medication side effects and unsustainable costs. Therefore, an HIV cure is a highly desirable goal for patients [8,9], the reason organizations like the National Institutes of Health and the International AIDS Society have made cure a top research agenda [10–12]. An HIV cure will eliminate stigma and discrimination, reduce new infections and provide sustainable financial solution for controlling the HIV pandemic [13].

The main obstacle to an HIV cure is the persistence of transcriptionally silent and immunologically inert latent proviruses in quiescent memory $CD4^+$ T cells [4,14]. These cells serve as viral reservoir ready to respond to antigenic stimulation and replenish the virus if ART is interrupted [9,14]. On the basis of the known characteristics of the HIV-1 provirus reviewed by Cohn *et al.* [4], various methods are being investigated for an HIV cure. First, is the shock and kill approach (latency reactivation), whereby small molecules are used to force proviral reactivation from latency under the cover of ART. Induction of de-novo virion synthesis is then expected to result in cell death from viral cytopathic effects or immune clearance, after which ART can be discontinued [15,16]. Second, the block and lock approach, wherein small molecules will be used to modify the surroundings of the integrated virus to send it into 'deep latency' such that upon discontinuation of ART, the virus will not reactivate [5,7,17,18]. Third, genetic methods that will either completely excise integrated HIV-1 provirus from the genome or produce mutations that will render the virus inactive [19–21]. Fourth, immunotherapies such as the use of broadly neutralizing antibodies or chimeric antigen receptors to suppress reactivation or kill cells with reactivated virus [22]. Finally, combination approaches like shock and kill with immunological approaches are also being

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KEY POINTS

- Basic and clinical science research alone cannot provide all the evidence needed for the development and deployment of HIV cure, collaboration with the behavioural sciences is urgently needed.
- Investigation is vital to determine how patients, including those in Africa, will accept the risks and benefits associated with the types of cures being considered by researchers.
- Education and advocacy are crucial to bring home the message of HIV cure to all stakeholders, who should participate and help design effective cure strategies that will be acceptable to patients.

pursued [10,23▪▪]. Each approach may lead to treatments that differ in the range and nature of side effects, duration, intensity of treatment and type and probability of benefit.

The value that patients place on various dimensions of risks and benefits, in comparison with the current ART, will determine acceptability in clinical trials as well as ultimate public health impact in real-world settings. Patients considering cure therapies will therefore need thorough education and may have to overcome substantial uncertainties in both side effects and prospect of benefit. As all of these interventions may carry substantial risks for people living with HIV (PLWH) without any guarantee that they will provide a cure, the research agenda must also include questions such as: What does a cure mean for patients most of whom have undetectable virus on ART? Will patients agree to interrupt ART during cure trials and under what circumstances? What risks are patients willing to endure to achieve a cure given that most are doing well on ART? How applicable and acceptable are the cures being developed to patients in low-middle income countries (LMICs)? There is an urgent need to answer these questions in different geographical settings [24] to ensure that interventions being developed will be acceptable to patients around the world, especially in Africa where most PLWH reside. These answers could feed into the design of cure intervention to assure maximum participation in future trials.

ACCEPTABILITY OF A FUNCTIONAL CURE

Understanding the concept of cure as far as HIV is concerned is crucial to determining what will qualify as cure. Researchers anticipate the two forms of cure. The first, termed 'eradication cure' or 'sterilizing cure' involves complete eradication of all replication-competent provirus from the infected person, including removal of viruses in cellular and anatomical reservoirs [2,3▪,10,25,26]. The second form is termed 'functional cure' or long-term remission whereby the viral reservoir is depleted to the extent that cessation of ART will not result in immediate viral rebound [2,3▪,10,25,26]. The gold standard of infectious disease cure is elimination of the pathogen; therefore, everyone will take eradication cure as the ideal. However, given the enormous difficulty that eradication of HIV presents to researchers, a more likely scenario will probably be some form of functional cure. Indeed, methods such as shock and kill, block and lock and immunological strategies mentioned above are aimed towards some form of functional cure. Will patients see a functional cure as cure, as there is some risk of virus return even if it is very low? A functional cure also presupposes that patients will need periodic evaluation to ensure that the virus has not come back. Will patients rather take their ART once a day, instead of subjecting themselves to such uncertainties? Few studies have examined the specific question of desirability of functional cure. In a study involving 356 men who have sex with men (MSM) in Hong Kong, Kwan *et al.* [6▪▪] showed that although 58% of participants were not aware of functional cure, when it was explained to them, 90% were willing to participate in long-term remission trials. In qualitative interviews done in Australia, Netherlands, South Africa or USA, participants envision cure as being a virus-free state. Sustained remission is not considered as cure because it does not take away concerns such as stigma, fear of transmission and potential future ill health [27,28▪,29–32]. These studies show that the concept of functional cure is not intuitive to patients. More patient education and studies are needed to determine the acceptability of long-term remission as a form of cure. Ultimately, researchers may need to abandon the term 'functional cure' and use the more appropriate term of long-term remission, especially given the advent of long-acting ARTs.

ACCEPTABILITY OF TREATMENT INTERRUPTIONS

To evaluate the efficacy of any cure strategy, patients may be asked to stop taking ART while being closely monitored, a process called analytical treatment interruption (ATI) [33▪▪,34▪▪]. Two types of ATI are used to assess potential cure therapies: time to viral rebound (TVR) studies and viral set-point studies [34▪▪]. The TVR determines the time taken for viral load to become detectable (50 copies/ml) after participants stop ART and the time taken for the viral load to reach the threshold for restarting ART (which can range from 1000 to 10 000 copies/ml) depending

on the study [34▪▪]. Set-point studies evaluate the participants' immune systems' control of HIV during treatment interruptions. These are much longer studies with months of ART withdrawal during which researchers allow participants' viral loads to increase to high levels (100 000 copies/ml) to determine if the immune system can control the virus and decrease the load to a level below the initial spike. Whichever type is used in HIV cure trial, ATI is currently an indispensable part of the process to evaluate the efficacy and performance of HIV cure strategies [35–38]. Already, there are at least two reported cases of sexual transmission during ATI for vaccine studies [39,40]. Implementation of ATI during HIV cure-related clinical trials is a necessity, yet the modalities are complex and the outcomes unpredictable [41,42]. There are currently no biomarkers to predict viral rebound, despite ongoing research [38,43,44]; therefore, frequent viral load measurements, often once week, must be done to inform when ART should be resumed [45]. This may inconvenience trial participants who must visit the clinic several times a week during the trial [46]. Due to the complexity and ethical dilemmas involved, expert groups have issued guidelines for ATI, which will help streamline the procedure in different trials [42,47].

Studies on ATI show that there may be sex and regional differences in acceptability. An international online survey comprising mainly PLWH in Europe and America found that patients were willing to take substantial risks without guarantee of benefit including 62% who would undergo ATI [48]. Being an online survey, motivated participants may have self-selected to influence the results. This is because in almost all qualitative in-depth interviews published from South Africa, USA, Netherlands and other places, ATI is a main concern for participation in cure trials [42,46,47,49,50]. It is possible that in-depth face-to-face interviews help participants to understand what ATI really entails. In addition, most of these studies recruit MSM who are the majority of patients in the developed world. Few studies about perspectives of patients and other stakeholders have been performed in Africa where the majority of HIV patients live and where the demographic of the disease has twice as many women as men. In two qualitative studies performed in South Africa, treatment interruption was a major concern, as patients felt they may get sick again [31,51]. In a survey of 251 patients living with HIV in Ghana, although most patients expressed enthusiasm about participating in cure trials, they were not willing to take substantial risks [3▪]. For instance, most participants (87%) said 'no or maybe' to ATI with 67% saying a definite 'no' even if their physician will follow up closely [3▪]. This study did not explore the reasons for such high resistance to ATI, but it may have something to do with fears of getting sick and distrust in the medical establishment.

It is important to emphasize that many stakeholders in the fight against HIV do not fully understand the modalities involved in ATI, the implications and the risks associated [37,48], while those who know about it have limited understanding of the full implications [52]. One mitigation factor for ATI is when patients know their partners will be protected from getting infected [47,52,53,54▪▪]. Therefore, there is the need to find ways to involve trial participants' partners and offer them preexposure prophylaxis (PrEP), as a way to assuage the fear of transmission to sexual partners [53,54▪▪].

ACCEPTABILITY OF DIFFERENT CURE MODALITIES

Cure strategies such as shock and kill, block and lock, immunotherapy and gene therapy, may have different side effects, time commitment for trial participation, length of trial and frequency of monitoring, factors that may determine whether patients want to participate. Few studies have examined stakeholder preferences for specific cure modalities and trial characteristics. The most extensive of these is discrete choice experiment conducted by Protiere *et al.* [55] among 195 virally controlled PLWH and 160 physicians from 24 French HIV centres. Participants were made to choose and make tradeoffs between cure types (immunotherapy, latency reversal, gene therapy and combination therapies) and trial characteristics, namely trial duration, consultation frequency, trial outcomes and moderate and severe side effects. Overall, patients preferred immunotherapy, and trials that were less burdensome for them in terms of time commitment and frequency of physician evaluation. A recent focus group study to determine preferences for gene therapy however showed that most were not willing to participate in potential gene therapy cure trials [56]. They felt they were happy with their current treatment and health status and unwilling to undergo a procedure that was invasive, has unknown side effects and potentially irreversible. A lot more research is needed to determine how patients feel about the different types of cure being considered by researchers to help feed patient and provider inputs into the design of these therapies.

ACCEPTABILITY OF CURE TRIALS IN AFRICA

Most of the studies conducted to determine the acceptability of the cure agenda and risk of

participation in cure related clinical trials were done outside Africa where the greatest burden of HIV exists. Therefore, it is not clear what people living in Africa want from an HIV cure. Some of the strategies such as gene therapy, for example modification of T cell *ex vivo* and reinfusion into the patient, and some types of immunotherapy such as chimeric antigen receptor may not be feasible in Africa [2]. Although patients everywhere may be hesitant to undergo ATI, PLWH in Africa may have a lot more hesitation for unclear reasons [3▪]. We recently showed that patients in Ghana may be more risk averse than patients in the USA or Europe [3▪] and this needs further study. In addition, majority of PLWH in the USA are men and most studies aimed at understanding perception of PLWH regarding HIV cure trials were done among MSM. Given that HIV affects mostly women in Africa, it is imperative to engage PLWH in Africa, as the risk perception and tolerability may be different from those in developed countries [57].

HIV cure researchers must therefore engage and work with affected communities, local scientists and local HIV care advocates to define what is acceptable. Engaging the communities is also critical in determining the type and levels of risk they are willing to take during participation in HIV cure trials so that trials are designed with participants' specification.

ADVANCING THE ACCEPTABILITY CURE AGENDA

The NIH strategic plan for HIV and HIV-related research identifies 'Cure Ethics and Acceptability' as a priority research area for 2021–2025. To accomplish this goal will require deliberate collaborations among basic scientists, economists, implementation scientists, clinical trialists and social and behavioural scientists. Collaboration is critical because true identification of patient cure preferences requires careful experimentation using different approaches such as mixed methods qualitative design, discrete choice experiments (DCE), best worst scaling and human-centred design (HCD). Although mixed methods will deliver in-depth qualitative understanding of patient choices, DCEs will allow stakeholders to weigh different cure intervention characteristics, make trade-offs and select appropriate options [58,59▪]. The HCD borrowed from economics and gaining grounds in healthcare and HIV research is an iterative process that narrows the gap between an intervention being planned and end user preferences [60,61▪▪,62]. Thus, bringing together scientists working on HIV cure, patients, ethicists, economists and socio-behavioural scientists could yield new ideas that can feed into the design of cure interventions, and early termination of approaches that are likely to be rejected by patients and caregivers. In addition, methods like best worst scaling could help determine the extremes of cure trial preferences for patients and caregivers [63,64]. Although investigators from different backgrounds could come together to perform these important studies, the NIH and other funders could 'force' collaborations by issuing special FOAs for cure ethics and acceptability that require cross-cutting interactions.

CONCLUSION

As biomedical scientists work to find an effective, well tolerated, affordable and scalable HIV cure, there is a need to engage other stakeholders, including PLWH and their healthcare providers, to determine their acceptability of HIV cure and willingness to participate in trials. Most studies show that patients and caregivers know little about the HIV cure strategies that are being developed [48,52]. Education and advocacy is therefore crucial to bring home the message of HIV cure to stakeholders so they are involved in proposing strategies and designs of cure that they are willing to accept. The HIV cure field urgently needs experts such as implementation scientists, ethicists, economists and social scientists to help bring out patient and provider preferences more clearly.

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Conflicts of interest

There are no conflicts of interest.

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