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Maximising the global health impact of future HIV cure-related interventions through advance planning

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Abstract

Thinking about public health impact should inform HIV curative investigations. Should an effective HIV cure or sustained viral remission intervention emerge from ongoing investigations, implementation strategies aimed at ensuring global access will be needed if these approaches are to be impactful, and planning accordingly makes sense now. Specifically, we discuss three key access barriers to future cure-related interventions: high cost of the strategy; non-financial challenges to procurement, distribution and point-of-care delivery; and non-adherence and the need for long-term monitoring. As we argue, plans and decision-making for overcoming each of these barriers will need to be developed in advance. An evaluation of remaining barriers and likely global impact of the leading strategies under investigation should inform decisions on which strategy might receive funding priority. Among the strategies being investigated, implementation barriers for latency-reversing agents, immunotherapy and combination antiretroviral therapy (ART) may be overcome on a global scale with some effort. Overcoming implementation barriers for medically complex and high-risk interventions, such as stem cell and, to some degree, gene therapy, may be less feasible.

Keywords: HIV, cure, remission induction, genetic therapy, stem cell transplantation, immunotherapy, health plan implementation

Introduction

The US National Institutes of Health and the International AIDS Society (IAS) both prioritise research toward a cure for HIV [1]. A sterilising cure or sustainable remission would address health complications associated with long-term ART, such as renal and central nervous system toxicity [2,3], as well as expensive and burdensome life-long daily treatment, challenges of adherence, and related potential for infectiousness and for drug resistance [1].

Two broad cure-related outcomes are being pursued: a sterilising cure and controlled remission. The former is generally defined as the complete eradication of all replication-competent HIV [4]; the latter, as durable control of persistent infection in the absence of daily ART [4]. Potential cure-related interventions include stem cell transplantation and perhaps a 'shock and kill' strategy (using agents that reverse latency and eliminate all virus-producing cells). Potential remission interventions include very early ART and immunotherapy. This perspective article will assume that a successful intervention in either broad outcome category will: (1) be administered for a finite period of time (a combination dose at one time or at different times for a fixed time period); (2) work in some individuals who have accessed ART and have an undetectable viral load; (3) have acceptable toxicity and efficacy that is comparable to ART; and (4) require long-term monitoring for late rebound in HIV replication [5].

We lay out three potential barriers to global access to such interventions, if and when proven safe and efficacious: (1) high cost of the relevant cure-related strategy; (2) non-financial challenges to its smooth procurement, distribution and point-of-care delivery; and (3) non-adherence. These are not the only barriers but they struck us as among the foremost barriers to rollout of a cure intervention. We also suggest ways to overcome each barrier and argue that institutional stakeholders would need to explore how a simple, effective and sustainable delivery for future HIV cure-related interventions could emerge. We argue that one measure for greater future access is priority funding for interventions likely to become scalable. Finally, we address possible objections.

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Potential access barriers to future cure-related interventions

In 2016, only 53% of people living with HIV globally were accessing antiretroviral treatment [6]. While future HIV cure-related interventions could boost access, for example, by facilitating adherence [5], three potential barriers may delay global scale-up of these future interventions:

(1) High cost: Like many patented, novel health technologies, future HIV cure-related interventions will probably be costly immediately following regulatory approval. In some low- and middle-income countries (LMIC), first-line antiretroviral regimens cost up to US$ 23,000 per person per year when initially developed [7]. While there are no reliable estimates of the cost of cure-related strategies, estimates for autologous cell transplantation and gene therapy for other indications range from US$75,000–150,000 [8, 9]. The cost of manufacturing broadly neutralising antibodies for immunotherapy will probably remain very high, even years after approval [10]. Additional costs in any HIV cure-related intervention will come from care delivery and follow-up care to rule out viral recrudescence.

(2) Non-financial challenges to procurement, distribution and point-of-care delivery: Bureaucratic challenges and regulatory policies could also delay procurement and distribution of HIV cure-related interventions. Chronic shortages in public budgets, and supply chain challenges such as inconsistent transportation and storage, could delay distribution of cure-related interventions, primarily in LMIC [11], although these shortages are by no means absent in richer countries. Notably, these same limitations apply to standard ART regimens.

Health-care worker shortages and inadequate laboratory facilities could also hinder delivery of any intervention, particularly biologic interventions that are medically complex and currently require highly skilled health professionals, advanced medical equipment and a dependable power supply. For example, apheresis procedures, which are needed for cell isolation from blood, are medically and technically challenging [12]. In West Africa, for

example, as of 2014, Nigeria was the only West African country with the capacity to use apheresis procedures for platelet collection [12].

(3) Non-adherence: While one advantage of cure-related interventions is reduction in the burden of daily medication intake, adherence challenges remain. Combination treatment or multiple-dose regimens may threaten adherence and follow-up in resource-limited settings, where individuals are unable to pay for frequent transportation to treatment centres and face multiple additional structural and further challenges to adherence [13]. For all interventions, adherence to ongoing evaluations to detect viral recrudescence (especially crucial in sustainable remission interventions) may prove not only challenging but expensive to secure [5]. The very fact that interventions permit a break in daily adherence to oral medications – in some ways an answer to ART adherence challenges – may create loss to follow-up, another adherence hazard [14]. Finally, during the treatment interruptions, nonadherence to safer sex practices may present a major ethical challenge – the risk of onward transmission to sexual partners and to fetuses.

Ensuring equitable access to future cure-related interventions

To mitigate potential barriers to global scale-up of future HIV cure-related interventions, the following should be considered:

(1) High cost of HIV cure-related strategy

First, national and global policy-makers would need to discuss the supply of future HIV cure-related interventions. For example, by augmenting models that worked for the global rollout of ART, the delay from regulatory approval to access in many LMICs could be reduced. When antiretroviral drugs were initially priced, some countries issued TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement compulsory licences, which allowed them to produce or import generic versions at significantly reduced prices [15]. Countries with high HIV burden could similarly seek an initial agreement with global policy-makers to issue compulsory licences that enable immediate access to cure-related drugs. Alternatively, in return for guaranteed low prices for future HIV cure-related drugs, global policy-makers could extend patents for drug manufacturers' other blockbuster and 'lifestyle' drugs, or establish a pay-for-performance 'Health Impact Fund' [16] that may give pharmaceutical companies the option of selling their drugs at a uniformly low price globally, while being rewarded for the global health impact of their efforts. Global health impact can be measured in terms of impact on the HIV-related global burden of disease [17].

(2) Non-financial challenges to procurement, distribution and point-of-care delivery

A procurement agency for HIV cure-related interventions could be established in advance of drug approval. Stakeholders in HIV cure-related research and care – people living with HIV, other activists, researchers, pharmaceutical companies, funding agencies and governments – would need to be engaged in discussions of the logistical, structural and cultural challenges facing implementation [18]. Governments in HIV-endemic LMICs could review past health-care interventions whose implementation has been challenging (e.g., scaling up the use of ART) and collaborate with implementation experts to preempt similar challenges. For example, they could work with the U.S. President's Emergency Fund for AIDS Relief (PEPFAR) to strengthen supply chains and set aside resources for training health-care workers and laboratory technicians to administer cure-related interventions. However, with recent proposed cuts in PEPFAR budget, there would be fewer available resources to support early implementation planning [19].

Non-financial procurement, distribution and delivery barriers are more resolvable for medications that can be easily distributed and administered in resource-limited settings, such as the short-course oral or injectable medication that is expected in most latency-reversing treatment and immunotherapy, if successful. Even here, however, added challenges pertain to management of viral recrudescence. It would be harder to implement medically complex interventions such as stem cell therapy and, to a lesser degree, gene therapy in remote locations, including many where ART is readily available.

(3) Non-adherence

Non-adherence challenges are likely to be worse, or at least different, for some potential cure-related interventions than for others. A one-time HIV sterilising cure intervention, administered by highly skilled staff in a single visit, with little or no follow-up, would be ideal from the point of view of adherence, although this is unlikely to be achievable. Spaced out remission interventions, such as a single injection every few months or years, are also appealing, but if non-adherence to the schedule risks failure and viral recrudescence, then the public health benefit of the curative regimen as compared to standard ART will be questioned.

Adherence strategies used with the scale-up of ART in developing countries [20] could be enhanced and replicated for a short-course HIV cure-related intervention such as latency-reversing agents and immunotherapy. Some challenges to remission strategies would need to be explored further, even before approval. For example, would short message service (SMS) reminders for follow-up viral load evaluation be more, or less, effective than regular SMS reminders to take oral ART [21]? Stem cell transplantation requires prolonged immunosuppressant use and close follow-up, which would make adherence difficult in the general population. In principle, monitoring could help improve adherence even in the absence of self-motivation. In practice, however, it is hard to accomplish and user motivation is essential.

Prioritising interventions most likely to ensure equitable access

For future HIV cure-related strategies, likelihood of effectiveness could be hampered not only by failure to address the barriers listed above, but also by barriers which the above solutions are unlikely to overcome, even with substantial resources and sustained efforts. Based on recent modeling work, an antiretroviral-free viral suppression intervention would be cost-effective in a sub-Saharan African country if it costs less than US$1400 [5] or less than US$2000 [22]. Currently, excessive costs and other acute barriers are relatively likely to be removable for latency-reversing agents, immunotherapy and intensive ART-based sustainable remission for the reasons stated above. If proven safe and efficacious, and with efforts to address barriers, these interventions currently seem most promising to make the greatest impact on the global HIV epidemic. Stem cell therapy, and perhaps gene therapy, will probably have the least impact on the global epidemic, even if proven safe and efficacious and given similar efforts. The main reason is the formidable implementation barriers to their successful procurement, distribution and delivery.

Scalability is among the reasons why there is increasing interest in developing interventions for sustainable virologic remission [23]. In general, directing more resources to studying cure-related interventions most likely to be globally impactful would increase expected impact and global equity. Such priority should not be absolute, and can take the form of added 'points' in funders'

calculations for relatively scalable strategies, where other 'points' are given for success in preclinical studies [24], innovation and other desiderata.

These funding priorities would also help keep HIV cure-related studies fair to study subjects. Many early phase cure-related trials are risky for participants, compared to the alternative of remaining stable on ART [22,25] – a major ethical challenge [26]. The primary justification of the social resources and risk to participants in all clinical studies comes from social value, primarily in terms of potential for substantial medical effects [27]. In this context, that means a substantial decrease in the global HIV burden [28]. While general contribution to human knowledge is also valuable, when the resources and opportunity cost are high, as are risks to individuals (such as in many cure studies, which are both risky and prioritised over other important investigations into infectious disease), especially high social value is needed for justification, and the surest way to achieve this is through the potential for high public health impact.

Possible objections

This call for early action on these matters could meet with three objections. First, we may be many years away from an approved HIV cure-related strategy. Before any intervention is approved, access barriers may wane without the need for special efforts, or specific efforts may become ineffective. By analogy, ART prices dropped dramatically in the late 1990s and early 2000s, by about 98% within a few years [29]. At the same time, one might add, removing implementation barriers is expensive for LMICs, and worth undertaking only once a specific cure-related intervention is already known to be safe and efficacious – not now.

However, some access barriers may take years to resolve, as the histories of negotiating price reduction at the global level and strengthening health-care systems clearly illustrate. With nearly 37 million people currently living with HIV worldwide, and about 17 million of them without access to ART [6], every year of delay in global rollout of approved HIV cure-related interventions would contribute substantially to the number of AIDS-related deaths, complications and new transmissions. In addition, eliminating implementation barriers through strengthening health-care systems, procurement and delivery, results in improvement of other health outcomes not limited to the HIV field. These additional benefits may even be realised before an HIV cure-related intervention is ready for rollout.

Finally, one might argue that even non-scalable HIV cure-related interventions may inspire scalable ones, or still other medical breakthroughs. This is not a wholly fanciful assumption for stem cell and gene therapy where, for instance, advances in scalability could be expected over the coming few decades [30]. However, in a time of financial crunch [19], it is hard to justify allocating substantial financial resources to research that lacks potential major global impact [28].

Conclusions

This perspective article describes three access barriers to successful rollout of future HIV cure-related interventions globally. It recommends measures to overcome these barriers, and thereby facilitate equitable access to these interventions. In particular, we have stressed that strategies and infrastructure used to expand ART access could also help resolve some of these implementation barriers. Planning and decision-making on drug prices, personnel training and short-term research priorities during the early phases of HIV cure-related research would also be advisable. A recently proposed decrease in US HIV/AIDS funding [19] may undermine this advance planning.

Even if the recommended measures are taken in earnest, removing implementation barriers will be challenging. Relatively medically complex and high-risk interventions like stem cell therapy and, to a lesser degree, gene therapy would be especially difficult to fully scale up globally, best efforts notwithstanding. Combination ART regimens, latency-reversing agents and immunotherapy, if proven safe and efficacious, are more likely to produce a scalable cure-related strategy.

Although not discussed in this perspective article, certain population groups, such as pregnant women and children, may face additional access barriers. For example, there is a lag time of 8 to 10 years for the development of optimal pediatric formulations of HIV treatment [31]. Technical complexity and a small, fragmented pediatric market are barriers to developing these formulations [31]. We expect that a scalable HIV cure-related strategy will require even more advance planning for attaining optimal pediatric formulations that are scalable globally.

The IAS has published a Global Scientific Strategy towards an HIV cure, tasked to coordinate global efforts in developing and rolling out HIV cure-related interventions that are safe, affordable and scalable [1]. A similar policy strategy document would be needed on how to build an effective and sustainable delivery system for future cure-related interventions. Such a document would render any intervention ultimately developed for HIV cure or sustained remission more likely to make a major impact on the global HIV epidemic.

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Authors' contributions

RB and NE initially conceived this manuscript and prepared the first full draft. All authors contributed to subsequent drafts. NE and SGD approved the final draft of the manuscript.

Declaration of interests

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