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Can HIV Be Cured, and Should We Try?

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I. Introduction

An estimated 35.0 million persons live with HIV; 2.1 million new infections occurred and 1.5 million persons died of HIV in 2013 (World Health Organization, http://www.who.int/hiv/data/epi_core_dec2014.png?ua=1). Despite effective combination antiretroviral therapy (cART), less than one-quarter of patients can access these life-prolonging medications; and despite its effectiveness, cART does not normalize life expectancy, as premature aging, metabolic complications and chronic inflammation complicate HIV therapy.

HIV is incurable due to the presence of a latent viral reservoir. During the life cycle of the virus, HIV integrates into the host DNA. A subset of integrated HIV provirus remains transcriptionally silent, producing neither viral proteins nor viral progeny, until reactivation by various physiologic stimuli. This latency of HIV allows some infected cells to escape immune detection and elimination, and these latently infected cells constitute the viral reservoir. The latent viral reservoir allows viral rebound within weeks of interruption of cART, [1,2] where the magnitude of viral replication approaches that present pre-therapy. Although it was once thought that viral rebound occurred universally following therapy interruption, several recent reports challenge that paradigm. The “Berlin patient” successfully cleared HIV after two allogeneic transplants from a donor with homozygous CCR5Δ32 mutation,[3] and he has not rebounded HIV after nearly seven years. This case likely represents a cure from HIV; yet other cases have been described where HIV rebound has been attenuated, or delayed. The “Mississippi” baby was a perinatally HIV-infected infant who initiated cART within hours of birth, and when interrupted eighteen months later, viremia remained undetectable for nearly two years.[4] The Harvard BMT cases underwent allogeneic BMT, developed undetectable HIV DNA, yet rebounded viremia within only eight months after cART discontinuation.[5] Together these cases demonstrate that control of

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viremia in the absence of cART is possible, if not durable.[4] The VISCONTI cohort of 14 HIV-infected adults who initiated antiretroviral therapy during acute infection, and in whom high level rebound viremia had not occurred several years after cessation of therapy,[6] similarly demonstrated that viral rebound following cART interruption can be attenuated.

These cases have reinvigorated research toward finding a cure for HIV, which certainly will require an exceptional investment of time, talent and resources. Thus it is prudent to question whether such resources would be better devoted to more proximate needs with proven results (such as supplying cART to those without access to it, or supplying pre/post exposure prophylaxis to reduce the rate of new infections).

II. Limitations

To target something for eradication (without inducing unacceptable collateral damage) first one must be able to define and identify it. Many details of the latent HIV reservoir remain unknown, including what cell types make up the latent reservoir, the actual size of the reservoir and its anatomic location(s). While central memory CD4 T cells contribute to the reservoir, HIV infects a number of other cell types with long half-lives, including tissue macrophages and microglia, which reside in immunologically and pharmacologically protected anatomic sites (e.g. testes and central nervous system). [7] Furthermore, HIV can infect CD34+ hematopoietic stem cells, [8,9] suggesting that potentially any cell derived from HSCs could contain latent virus.

Also it remains unknown what HIV characteristics are necessary to be considered a true reservoir, since integrated proviral DNA can be replication competent or incompetent due to fatal mutations in the viral cDNA prior to integration, and/or the presence of deletions within the viral genome. Thus, transcription has to be induced to “reactivate” viral replication and provide pharmacologic or immunologic targets – the so-called “shock and kill” hypothesis, which has three main limitations. First, while there are several models of HIV latency, none fully recapitulate what occurs *in vivo*, and experimental results in one model rarely are replicable in another.[10] Second, no potentially clinically acceptable reactivation stimulus has been described that reactivates provirus in all *in vitro* models, or even all provirus in a single model.[11] Third, up to 12% of non-induced provirus are replication competent, as determined by cloning and *in vitro* infection assays,[12] suggesting that viral reactivation with available agents is incomplete.

All cure strategies envision concurrent suppressive cART, in addition to the cure intervention. However nearly 1 in 5 HIV infected persons does not know they are infected,[13] and they continue to transmit HIV. Furthermore, less than 1 in 3 who know they are HIV infected successfully suppress viral replication with therapy. [13] Therefore, a cure would be available to less than 25% of persons in resource-rich countries, and fewer worldwide, unless significant improvements are made in HIV diagnosis, access to care, and effective treatment.

While viral eradication would be ideal, achieving a “functional cure” is considered more realistic, wherein altering host susceptibility to infection, or through boosting immune control of viral replication, a new homeostasis is achieved between virus and host, and

progression to AIDS is prevented without the need for antiretroviral therapy. A small percentage of HIV infected persons already control disease as natural variants to the expected clinical course of the disease. Long-term non-progressors (LNTPs) are characterized by having preserved CD4 T cell counts over a long period of time (typically >10 years), despite ongoing, moderate to high level viral replication. Elite controllers (ECs) also maintain preserved CD4 T cell counts, but in the setting of immune-based control of viral replication to low levels. However LNTPs eventually progress, and some ECs eventually lose virologic control, both situations requiring initiation of antiretroviral therapy.[14] Furthermore, LTNPs and ECs still suffer from complications of chronic inflammation, suggesting that patients with "functional cure" may not escape all of the consequences of persistent HIV infection.[15] Therefore, if the goal of HIV cure is to avoid lifelong cART and chronic inflammation, the clinical experience of LTNPs and ECs suggest that viral eradication should ultimately be the target, which is arguably more difficult to attain than a "functional cure."

III. Hope for the future

Nevertheless, the fact that the "Berlin patient" has been cured means *ipso facto* that HIV can be cured. As research seeks to recapitulate that cure in a more generalizable way, it is prudent to keep in mind the desirable attributes of a cure. The cure must be less toxic than lifelong cART; that cure must be generalizable and not only available in a handful of specialized institutions; and the cure must be scalable to reach a majority of infected patients worldwide. Failure to achieve these criteria will necessarily limit the access to and uptake of the cure in a global setting. While stem cell transplantation with donor cells genetically resistant to infection has resulted in the only HIV cure to date, and infusion of autologous CD4 T cells genetically engineered to become resistant to infection have been shown to persist in HIV infected patients,[16] it is our opinion that stem cell transplant related strategies and complex gene therapies are effectively impractical as large-scale interventions, but maintain value as a means of testing proof of concept. Below, three broad approaches are discussed which in our opinion offer better hope for a *generalizable* HIV cure in the attainable future.

i. Prime, shock, and kill. An early theoretical approach to HIV eradication was based upon the premise that since many HIV encoded proteins are intrinsically cytotoxic, reactivating HIV from a formerly latent CD4 T cell, would result in the intracellular expression of these cytotoxic proteins and result in cell death by apoptosis (often incorrectly referred to as lysis or cytolysis).[17] However when this "shock and kill hypothesis" was tested, cell death did not occur.[18,19] Since latent HIV resides principally in central memory CD4 T cells which function as a long lived archive of immune responses, the resistance of these cells to death following HIV reactivation may simply be due to these cells being destined to longevity and thus resistant to death. Thus, we (ADB) have proposed a modification wherein chemosensitization (instructed by years of oncology chemosensitization strategies) of central memory cells towards an apoptosis-prone phenotype prior to HIV reactivation will achieve a decreased in latently infected cell number. [20]

ii. Broadly neutralizing antibodies (with cellular cytotoxicity mechanisms). Prophylactic and therapeutic vaccines have shown promise in non-human primate models of HIV infection.[21,22] However, human trials of vaccine based approaches to control of HIV have been widely disappointing, with the exception of one trial which showed a modest reduction in HIV acquisition rates. [23] Reasons why so many vaccine trials have failed, and the Thai trial succeeded (despite using the same immunogens that failed in previous trials) are unknown but may be illuminated by studies in macaques, which show that vaccine response, and protection from infectious challenge is impacted by genetic background.[24] Thus the successful Thai trial might have succeeded whereas the same vaccine had failed previously, since it was tested in a new genetic background. Vaccine studies might therefore best be tested in a design that controls for HLA background; doing so might allow discrimination of a beneficial effect in select subgroups.

Another promising approach involves concept of broadly neutralizing antibodies. Although not a novel concept in infectious disease therapy, only recently have several broadly neutralizing antibodies have been identified which neutralize >90% of clinical HIV isolates.[25] Moreover there has been recent recognition that modifications to the Fc domain of antibodies greatly impact the engagement of cells which bind antibodies and affect the cellular mechanisms of immune clearance following antibody binding (eg antibody-dependent cellular cytotoxicity, phagocytosis etc). Thus creation of a synthetic antibody whose Fab domains neutralize >90% of HIV isolates, merged with an optimized Fc domain which optimally activates ADCC and other cellular clearance pathways, offers promise as a long lasting antiviral. [26,27] How it might be used remains to be determined, but whereas pharmacologic antiviral intensification fails to suppress HIV replication to <1 copy/ml, neutralizing antibody therapy might – and thereby prevent low level viremia repopulating the HIV reservoir.

iii. Immune boosting strategies– it is now widely accepted that persons infected with HIV mount a broad immune response to the virus, but that immune response fails to control viral replication, or kill the majority of virally infected cells. Reasons why the immune response is ineffective are likely multiple, but clearly include inappropriate expression of immune inhibitory receptors such as PD-1, CTLA4 and others. With this background, inhibitors of the ligand for PD1 (PDL1) which have recently been FDA approved for immune boosting during therapy of refractory melanoma, are likely to augment the quality of the anti-HIV T cell response, possibly achieving meaningful reductions in HIV burden. [28] Similarly studies of CTLA4 inhibitors will be of great interest as complementary immune boosting strategies. It is notable, though, that other immune based strategies, including administration of stimulatory cytokines interleukin-2 interleukin-7, actually increased the size of the latent HIV reservoir.[29,30]

IV. How low is low enough?

A critical challenge facing the cure initiative is to understand when interventions have reduced the HIV burden low enough that HIV will not come back after antiretroviral therapy

is stopped. In fact, recent mathematical modeling suggests that the latent viral reservoir would need to be reduced more than 10,000 fold to achieve an eradication cure.[31] Even in the case of the only patient cured of HIV to date, both HIV RNA and DNA were detectable at various times.[32] Thus absence of HIV nucleic acid is not necessary for cure. This is perhaps understandable, given that ~80% of integrated proviruses are defective, i.e. un-inducible.

What then is the measure which we should use to predict when a "cure" has been achieved? One possibility lab surrogate for HIV cure is Quantitative Viral Outgrowth Assay (QVOA), which measures how much replication competent HIV is present in peripheral blood. The predictive ability of QVOA will of course depend on how many input cells are tested. Ultimately the benchmark test of cure will be absence of HIV rebound following antiretroviral stoppage.

V. How best to achieve a cure?

It is likely that several, or even many, strategies will be identified that can reduce HIV burden to some degree. By acting on different pathways to reduce HIV burden, or by applying sequential interventions, these different treatment modalities may be additive, or possibly synergistic in their anti-HIV effects. For instance, there are substantial data that treatment with cART during acute HIV infection significantly restricts the size of the latent viral reservoir. [33,34] These patients may ultimately then benefit from subsequent curative interventions with otherwise modest effects on the reservoir. Much as antiretroviral effects were only optimized by the additive effects of different drug classes, the likely path to HIV cure will involve multiple different HIV reservoir reducing agents, given with maximally suppressive cART, until such time that a predictive assay such as QVOA suggest that cure might have occurred, at which point the patient and their physician decide whether antiretroviral therapy should be stopped and the patient monitored closely for viral rebound.

Conclusion

It is our opinion, and we think most in the scientific community would agree, that finding a "cure for HIV" is indeed a laudable goal and that expanding research effort in that direction is warranted. It remains debatable whether an actual cure is within reach. However, basic science, clinical and epidemiologic research in HIV over the past 33 years has afforded a significant number of insights and methods that have translated across fields and advanced many other areas of science, such as development of lentiviral vector-mediated gene delivery; plerixafor for mobilization of HSCs prior to stem cell transplantation; treatment protocols for opportunistic infections in non-AIDS immunocompromised patients; and adaptive clinical trial design. It is likely this will ancillary benefit will continue to occur moving forward. However, we caution against irrational exuberance, and suggest that the limited resources devoted to other proven prevention strategies (e.g. prevention of mother-to-child transmission; pre-exposure prophylaxis; early post-exposure treatment; male circumcision; screening and education programs), the search for an effective vaccine, and expanding access to antiretroviral therapy, should not be diverted from these worthy causes.

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Abbreviations

BMT	Bone marrow transplantation
cART	Combination antiretroviral therapy
ECs	Elite controllers
HIV	Human Immunodeficiency Virus
LNTPs	Long-term non-progressors
QVOA	Quantitative Viral Outgrowth Assay

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