HIV cure research: a formidable challenge

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Abstract

The ultimate goal of HIV cure research is to allow HIV-infected individuals to be free of disease in the absence of antiretroviral therapy. We discuss current directions and future opportunities aimed at achieving sustained virological remission, and possibly eradication. A multidisciplinary approach to HIV cure research will be important, and ethical, social and behavioural research should be conducted in parallel with basic and clinical research.

The ultimate goal of HIV cure research is to allow HIV-infected individuals to be free of disease in the absence of antiretroviral therapy. This can potentially be achieved in a number of ways. The most obvious and most difficult approach would be to eliminate all HIV-infected cells capable of producing HIV — that is, to achieve eradication of replication-competent virus from an HIV-infected individual. Today, Timothy Ray Brown (the Berlin patient) remains the only person in the world who appears to have been cured. The measures that cured him were extreme and necessary to treat his cancer, although not his HIV infection. Extensive chemotherapy and total body irradiation decreased the number of HIV-infected cells; he received a stem cell transplant with cells that lacked CCR5 (R5) HIV-1 cellular entry co-receptors, and thus, were resistant to HIV [1,2]. Moreover, the HIV quasispecies present in the patient before transplant were CCR5-dependent for viral replication, thereby eliminating the possibility for HIV propagation using the CXCR4 co-receptor [3]. This regimen has very limited applicability, even for those HIV-infected individuals with cancer, as reported CCR5-Δ32/Δ32 prevalence is no more than 1%, and frequently much rarer. Therefore, locating an HLA-matched CCR5-Δ32/Δ32 donor is a substantial challenge.

Cancer treatment and stem cell transplantation without CCR5-Δ32/Δ32 donor cells are not curative for HIV, as shown in the two ‘Boston patients’ [4]. Efforts to screen and store CCR5-Δ32/Δ32 cord blood stem cells that require less stringent HLA match are being pursued by several groups [5,6]. The low cell numbers in each cord blood unit limits their use in adults, although not necessarily in children. Indeed, it has been suggested that a paediatric recipient of such stem cells may have been a second ‘cured’ patient. Unfortunately, the child died of graft-versus-host disease shortly after transplantation, and autopsy revealed no PCR-detectable HIV (Timothy Schacker, personal communication). Reduction of CCR5 expression by gene-editing therapy using zinc finger nuclease has been pursued in HIV-infected individuals without cancer who are receiving antiretroviral therapy and have suppressed viral loads. This approach has resulted in decreased proviral DNA levels and increased CD4+ T cell counts; however, HIV re-emerged in the blood soon after antiretroviral therapy was interrupted [7]. Research in this area is now directed towards improving engraftment of CCR5-modified cells with preconditioning chemotherapy and infusing higher numbers of modified cells. In addition, attempts are being made to use additional genetic modifications, removing CXCR4 expression [8] or including a suicide gene to kill target cells. The latter has been done successfully for cancer [9].

Perhaps a more exciting prospect for HIV eradication is suggested by a recent non-human primate study. In this study, rhesus macaques were vaccinated with a replicating cytomegalovirus (CMV) vector vaccine that expressed simian immunodeficiency virus (SIV) gag, nef, env and pol genes prior to inter-rectal challenge with a highly pathogenic strain of SIVmac239. All of the macaques were infected; however, half went on to have SIV apparently eradicated from all organs [10,11]. The replicating CMV vector vaccine generated ongoing production of SIV-specific effector memory CD8+ T cell responses in blood and tissues. Unlike natural immune responses, viral escape did not occur, probably because strikingly broad CD8+ T cell responses induced by the vaccine did not target the HLA class I-restricted immunodominant epitopes that mutate readily, thereby enabling the virus to evade the immune response. This study provides compelling evidence that immune-based therapy targeting CD8+ responses could be key in eradicating HIV. It also suggests that vaccine regimens could target subdominant epitopes, at least for T cell based approaches [12].

Are there other ways to generate persistent, effective T cell responses to eliminate HIV-infected cells? In this regard, the field of HIV research could be informed by recent successes in the field of cancer immunotherapy. Today, chemotherapy-resistant acute lymphoblastic leukaemia has a 90% long-term remission and, possibly, cure rate after infusion of autologous T cells transduced with a CD19-directed chimeric antigen receptor via a lentiviral vector [13]. In HIV-infected individuals, CD8+ T cells with chimeric antigen receptor-expressing CD4 infused with a CD3 zeta signalling domain have been shown to persist for a decade [14] with the ability to reduce HIV plasma viraemia and home in rectal tissue [15,16]. The engineered CD8+ T cells express CD4, bind HIV gp120 on infected cells, and kill them. It remains unclear if, and how, this approach can clear latently infected cells that, by definition, do not express HIV. Other genetically engineered cell-based therapies that could enhance effector T cell function are artificial T cell receptors that control affinity to certain epitopes, or polyclonal T cells that recognise multiple epitopes including subdominant epitopes [17].

Sustained viral remission in absence of therapy: a more realistic goal?

An alternative approach to absolute eradication of all replication competent virus in achieving a ‘cure’ of HIV infection is the induction of sustained virological remission following discontinuation of antiretroviral therapy. The recent HIV viral rebound in the Mississippi child who was thought possibly to have
been cured after receiving early antiretroviral therapy instituted at 30 hours of life was sobering [18,19]. This case forced the field to reconsider that a feasible goal of a ‘cure’ effort for HIV infection may not necessarily be eradication of virus but could be sustained virological remission following discontinuation of antiretroviral therapy in the absence of absolute eradication. Since rebound of HIV viraemia upon discontinuation of antiretroviral therapy emanates from the, often latent, reservoir of HIV, greater understanding of the nature, characteristics, cell types and anatomical distribution of the body’s HIV reservoirs is critical. Early initiation of antiretroviral treatment currently appears the most effective way to attenuate the size of latent reservoirs of HIV [20]. However, this approach has not been shown to eradicate the virus, most likely due to the very early establishment of reservoirs in long-lived memory CD4+ T cells soon after infection [21]. Indeed, rapid viral rebound was observed in two children after 3 years of antiretroviral treatment even though therapy was initiated within the first 24 hours of life [22,23]. These two cases provide clues to possible predictors of viral rebound. In contrast to the Mississippi child, these children had evidence of ongoing viral replication with detectable cell-associated HIV RNA, HIV-specific T cells or immune activation. The cases also show that initiating antiretroviral therapy within 24 hours after birth (probably at the time of onset of infection), was not early enough. This observation provides a basis for evaluating therapy initiated even sooner — immediately after birth — particularly in babies at high risk for HIV infection (i.e. those born to mothers who received no antiretroviral treatment) to prevent HIV reservoir seeding. This approach of therapy initiated even sooner – immediately after birth – particularly in babies at high risk for HIV infection (i.e. those born to mothers who received no antiretroviral treatment) to prevent HIV reservoir seeding. This approach of initiation of therapy to the newborn immediately after birth would be most relevant for babies infected perinatally; however, it would theoretically be less effective for babies who may have been infected weeks earlier in utero. The lack of detectable proviral DNA and replication-competent HIV prior to treatment interruption in these cases [22,23] illustrate the limitation of current assays in detecting low numbers of HIV-infected cells [24]. Moreover, the bulk of replicating HIV persists in tissues such as the lymph node and gut where antiretrovirals have limited penetration; it will be important in the future to more carefully examine these sites [25,26]. In this regard, improving measurements of the HIV reservoir in peripheral blood and tissues is a research area under intense investigation. Recent studies in non-human primates underscore the rapidity with which the lentiviral reservoir is established and the inadequacy of combination antiretroviral therapy alone in sterilising viral reservoirs [27].

Early initiation of antiretroviral therapy is a critical step in any pathway towards an HIV cure. In addition, novel therapeutic approaches may be needed. In particular, some have advocated approaches that activate latent reservoir cells, thereby allowing them to be destroyed. Clinical trials of such latency-reversing classes of drugs such as histone deacetylase inhibitors suggest that they can induce some expression of latent HIV although not its clearance [28]. Other drug classes, such as activators of protein kinase C or toll-like receptors, may be more effective [29]. Given potentially large HIV reservoirs [30,31], the extent to which these agents could provide adequate awakening of latent virus is unclear. Their potential role, if any, would most likely be together with an immune-based therapy to kill the re-activated cells. Recent work has shown that broadly neutralising antibodies can clear cell-free virus and infected cells that express HIV [32]. Proviral DNA was reduced in macaques treated with these antibodies [33,34]; however, the extent of the ability of antibodies to clear latently infected cells is not well understood. Several human studies are planned to evaluate the effects of passively infused antibodies on the HIV reservoir. Immune checkpoint blockers such as anti-programmed cell death-1 antibody could improve function and persistence of effector T cells [35]. Targeted cytotoxic therapy using immunotoxin is another potential approach [36]. Although therapeutic HIV vaccines have had little success in the past, newer vaccines such as the prime boost adenovirus26/modified vaccinia Ankara vaccine in macaques have shown promise in blunting plasma viraemia and achieving persistent viral control [37].

What are our opportunities going forward? The latest developments in HIV cure research were recently discussed at the US National Institute of Allergy and Infectious Diseases’ Strategies for an HIV Cure meeting in October 2014 (www.blsmeetings.net/hivcuremeeting2014). It became clear at that meeting that a concerted effort towards an HIV cure is being made on many fronts.

Are we on the right track? Only time will tell. We are making progress and many approaches to a cure have a sound scientific rationale. However, basic and clinical science are not enough; we must also consider important ethical, social and behavioural research questions in parallel [38]. Many of the interventions pose significant health risks with modest (at best) benefit to trial participants. Treatment interruption of antiretroviral therapy is the ultimate test for HIV remission. Still, it presents medical risk without close monitoring and prompt resumption of antiretroviral therapy if a patient’s HIV viral load rebounds. Most of the trial participants so far are young white men. Equity in trial participation for gender, transmission risk groups, age and race remain important issues [39]. Low- and middle-income countries, where the majority of people living with HIV reside, should be encouraged to participate in HIV cure research. This is particularly important for interventions for which efficacy is HIV clade-dependent, such as broadly neutralising antibodies and therapeutic HIV vaccines. The initial trials for HIV cure modalities are generally not longer than 1–2 years. Post-trial access to these experimental interventions may become an important consideration if prolonged HIV remission could be maintained with repeat administrations. The concepts of HIV eradication and remission may be confusing to trial participants. Behavioural research on patient expectations, and willingness and decision making to participate in cure research will guide interactions with trial volunteers and the community along with adoption of approaches from normative bodies such as the UNAIDS/AVAC Good Participatory Guidelines [40]. With the rapidly moving science of HIV cure research and its high risk and uncertainty for success, stakeholder engagement should be done early to facilitate its sustainability and should include national and international regulatory and funding agencies, the scientific community, clinicians, the pharmaceutical industry and civil society.

Ultimately, for HIV cure research to have significant public health impact, the interventions must be effective, simple, safe and scalable [6]. We are still in the discovery phase of research toward a cure, and there will be many disappointments. Moving forward it will be critical to put forth our best efforts, collaborate widely and be guided by the best science and highest ethical standards.

Conflicts of interest
The authors declared no potential conflict of interest relevant to this work.
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