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HIV beyond HAART: Current Strategies for HIV Eradication

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Abstract

Novel HIV-1 eradication strategies have arisen due to a deeper understanding of the nature of HIV-1 persistence in patients taking highly active antiretroviral therapy (HAART). In this review we discuss current approaches and challenges to HIV-1 eradication in the HAART era, the limitations of HAART, characteristics of the latent reservoir and the rationale for research targeting HIV-1 eradication.

Keywords: HIV eradication; HIV latent reservoir; HIV elite suppressors; Highly active antiretroviral therapy

Why Look for a Cure?

The introduction of highly active antiretroviral therapy (HAART) represents a landmark achievement in the global effort to combat HIV-1 infection. Durable blockade of viral replication by combinations of antiretroviral drugs transformed HIV-1 infection from an untreatable, highly morbid condition into a chronic, manageable medical problem for most patients with access to therapy. Unrelenting international efforts have helped foster the economic resources, infrastructure and political will necessary for widespread dissemination of these treatments to areas of the world most affected by the HIV-1 epidemic.

Despite these significant gains, the epidemic continues to spread. According to the Centers for Disease Control, at the end of 2008 an estimated 1.1 million persons over 13 years of age were living with HIV-1 infection in the United States [1]. Overall, HIV incidence in the United States was stable from 2006 to 2009. However, among men who have sex with men(MSM) incidence rates increased [2]. According to the World Health Organization, 33.3 million people are living with HIV-1 worldwide with 2.6 million new infections and 1.8 million deaths from AIDS in 2009 alone [3]. The provision of effective, lifelong treatment for a majority of infected individuals worldwide may yet prove to be an insurmountable goal.

Alongside the complexities inherent to global resource allocation and outreach to vulnerable populations, there is a growing recognition of the potential long-term toxicities of chronic HIV-1 infection [4] and of prolonged antiretroviral therapy itself [5]. Despite the success of HAART, normal life expectancy for people living with HIV has not been fully restored. This is particularly true in patients diagnosed or treated in later stages of the disease. In the United Kingdom Collaborative HIV Cohort Study, life expectancy for people treated for HIV-1 infection increased by over 15 years during 1996-2008 but was still 13 years less than the population at large [6]. Despite the potential for early diagnosis and treatment to close this gap, a majority of patients continue to present for care late in their illness [7-9].

The inability to curb the HIV-1 pandemic through preventative strategies, the daunting logistics of worldwide HAART rollout and the recognition of the long-term consequences of both HIV-1 infection and its current management have contributed to a growing consensus that the pursuit of a cure for HIV-1 represents a worthy scientific and humanitarian objective. A 2009 case report [10] and subsequent studies [11,12] describe viral eradication in an HIV-1 positive man treated for acute myeloblastic leukemia with stem cells impervious to HIV-1 entry have provided further support for research and clinical trials aimed at HIV-1 eradication. We present here an overview of the current concepts and future directions of translational research on HIV-1 eradication.

What are the Limits of HAART?

The beginning of the HAART era conjured enthusiasm for the potential eradication of HIV-1 with novel combination treatments that reduced the viral load below the limit of detection [13-15]. All antiretroviral drugs target specific steps in viral replication. The logarithmic decay of viral RNA in the blood combined with the rebound of the circulating $CD4^+$ T cell population, the primary cellular target of HIV-1, provided strong evidence that active replication was effectively blocked. However, descriptions of a pool of resting memory $CD4^+$ T cells containing replication competent HIV-1 DNA in aviremic patients on HAART followed soon after the initial reports of the potency of antiretroviral combination therapy [16,17]. This discovery demonstrated that preventing active viral replication alone was not sufficient to cure HIV-1 infection [18].

Despite continuous viral suppression on HAART for years or even decades, patients who stop taking these drugs develop viremia within a matter of weeks and will eventually progress to overt immunodeficiency if not restarted on therapy. The source of this rebound viremia appears to be a minority of cells among the resting memory $CD4^+$ T cell population that harbor unexpressed HIV-1 proviral DNA stably integrated into the cellular genome [19].

Characterization of these cells, known as the latent reservoir, followed soon after their discovery. Resting memory $CD4^+$ T cells represent a fundamental pillar of adaptive immunity, allowing humans to recognize and respond appropriately to foreign antigens years after initial exposure. The qualities that allow these cells to function as our immunologic memory also promote environment conducive for viral persistence. These cells are among the longest-lived in the body and are not thought to be subject to immune clearance. They circulate between the peripheral blood and lymph nodes. Resting memory T cells are in a generally repressive state with regard to gene expression compared to activated T cells. Roughly one in one million circulating resting

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memory CD4+ T cells harbor replication competent proviral HIV-1 genomes [20]. This reservoir in patients on HAART has been shown to be stable over a period of many years [21]. These cells are thought to sporadically re-activate leading to derepression of silenced HIV-1 proviral genes and the production of virions that are released into the plasma. This process likely gives rise to the low-level viremia observed in patients on HAART and is thought to be the source of productive infection and viral rebound in those who stop taking antiretrovirals [19,22].

A series of trials have examined the role of HAART initiation soon after HIV-1 diagnosis as well as the role of intensifying antiretroviral therapy beyond the standard three drug / two drug class regimens with respect to viral persistence and the latent reservoir. In several clinical trials administering HAART to patients early in the disease course appeared to result in smaller viral reservoirs by a variety of measurements compare to those who started later [23-25]. The clinical significance of these findings is unclear however, as HAART 'early treatment' trials that included treatment interruption have described viral rebound in patients who stopped therapy even among patients with very small or undetectable latent reservoirs [26,27]. The latent reservoir can be detected within months of primary HIV-1 infection [16,20] and expands exponentially upon treatment cessation. Therefore reduction, but not elimination, of this reservoir through early treatment would not be expected to lead to long-term control of viremia [24,27]. In contrast to these findings, a recent retrospective study of patients treated early after HIV-1 diagnosis demonstrated long-term virologic control in a minority of subjects after treatment cessation [28]. This phenomenon is being studied in an ongoing randomized controlled trial (ClinicalTrials.gov NCT000908544). It remains to be seen whether a subset of patients can be identified who would benefit from immediate therapy.

The opportunity to test the efficacy of intensifying HAART with additional agents has arisen with the advent of new, well-tolerated antiretroviral in novel drug classes in the last several years. Five separate trials have made use of raltegravir [29-33], a novel integrase inhibitor, as an intensifying agent in virally suppressed patients on stable HAART regimens. None of these trials demonstrated a decrease in low-level viremia. Other intensification trials using different antiretrovirals have reported the same results [34,35] supporting the conclusion that the limits of viral suppression have been reached with current antiretroviral combinations. Adding more drugs to currently recommended HAART appears to do little to address viral persistence. Rather, strategies that directly target or suppress the latent reservoir, perhaps in combination with HAART, will be necessary to eradicate HIV-1 infection.

Engineering Immune Control: Gene Therapy

In 2007, a medical team in Berlin performed an allogeneic hematopoietic stem cell transplant in an HIV-1 infected patient with acute myeloid leukemia using stem cells from a donor who was homozygous for the C-C chemokine receptor 5 (CCR5) delta32 deletion [10]. An analysis of HIV-1 co-receptor phenotype prior to transplant revealed CCR5 tropism in this patient. CCR5 is one of two co-receptors that allows for HIV-1 entry into human cells after the virus binds to the CD4 receptor on the cell surface. A minority of healthy individuals who are homozygous for this naturally occurring 32 base pair deletion in the CCR5 gene will produce a defective gene product that makes CD4+ T cells non-permissive to HIV-1 infection [36]. The patient was taken off of all antiretrovirals prior to his conditioning regimen and subsequent transplant. At the time of the original report, HIV-1 had remained undetectable for 20 months. A follow up report described no detection of HIV-1 RNA or DNA in blood, cerebrospinal fluid or gut mucosal tissue three and a half years post-transplant [11] prompting many in the field to consider this patient the first to be cured of HIV-1 infection.

As this patient underwent myeloablative chemotherapy and whole body irradiation prior to allogeneic stem cell transplant, it remains unclear which component ultimately led to long-term viral eradication. However, previous reports provide evidence that chemotherapy followed by stem cell transplant are not sufficient to suppress HIV-1 [37-42] and raise the distinct possibility that the re-population of this patient's immune system with CCR5-deficient target cells played a major role in eradication. HIV-1 infected cells that survived chemotherapy, radiation and graft-versus-host mediated clearance would be unable to propagate infection due to lack of target cells, as the donor cells re-populating the immune system are inherently non-permissive to HIV-1 virion entry. In theory a latently infected stem cell that survived myeloablative therapy and stem cell transplant could re-populate the immune system with latently infected cells. Analysis of the Berlin patient's bone marrow after therapy did not reveal any stem cells harboring HIV-1 proviral DNA [11]. Either such cells were eliminated, or were not a significant population prior to therapy. The role of hematopoietic stem cells as a long-lived HIV-1 reservoir remains a topic of much debate. Regardless, the results of this case report have given rise to a novel approach to viral eradication making use of gene therapy techniques.

One such technique involves CCR5 gene knockout in T cells andhematopoietic stem cells using zinc finger nucleases (ZFN). These CCR5-deficient cells will effectively suppress the replication of CCR5-tropic HIV-1 in animal models [43]. Harvested CD4+ T cells or CD34+ stem cells from humans can be genetically engineered ex vivo to become CCR5-deficient through ZFN targeting of the CCR5 gene open reading frame [44]. The current clinical strategy is to harvest, genetically modify and re-infuse CD4+ T cells into HIV-1 infected individuals [45,46]. Three early phase clinical trials are in progress evaluating the safety of these genetically modified T cells in humans (NCT00842634, NCT01044654, NCT01252641; clinicaltrials.gov). These trials will also measure the persistence of these modified cells, their anatomic distribution and their effect on HIV-1 replication as determined by brief structured HAART interruption. Early results presented in February 2011 suggested that this is a well-tolerated intervention [47,48]. Concerns remain about the potential role of viruses that are not CCR5-tropic with regard to HIV persistence and the long-term safety of genetically altered stem cells in general. While this strategy in its current form is unlikely to be generalizable to the millions of HIV-1 infected individuals worldwide, it has potential to shed light on immune mechanisms of long-term endogenous HIV-1 control [12].

Human Models of Functional Cure

Elite suppressors (ES) represent a distinct subset of HIV-1 infected patients who maintain stable CD4+ T cell counts and low-level viremia (<50 HIV-1 RNA copies / mL) without the use of antiretroviral drugs [49]. These patients maintain viral loads below the limit of detection of commercial assays [50,51] and do not manifest clinical signs of disease progression. Phylogenetic [52] and *in vitro* analyses [53] of virus from ES have demonstrated that these patients harbor pathogenic HIV-1, strongly suggesting that a host immune phenomenon is responsible for long-term viral suppression in ES rather than a consequence of defective or replication incompetent virus.

The mechanisms by which these patients control HIV-1 infection are incompletely understood [54]. Neutralizing antibodies do not seem to play an important role in viral control in ES [55]. Large genome-

wide analyses have revealed specific HLA class I alleles, particularly B*57 and B*27, are highly associated with HIV-1 control [56]. This supports a central role for an efficient cytotoxic T lymphocyte (CTL) response in mediating elite suppression. In particular, lytic granule loading and granzyme B-mediated cytolysis by CD8+ T cells are both more efficient in ES than in HIV-1 progressors [57]. While ES remain HIV-1 infected, their ability to control viral replication and maintain health without medications or other interventions serve as a model of functional HIV-1 cure. Further studies into the mechanisms of HIV-1 elite control are likely to inform vaccine efforts that can serve both as primary prevention and as a means of immune boosting for those who are chronically infected.

Purging the Latent Reservoir

A promising area of research in HIV-1 eradication focuses on the mechanisms by which HIV-1 establishes and maintains latency in order to develop methods to induce viral gene expression. The goal of this strategy is a reduction in the size of the latent reservoir by converting latently infected cells into virus-producing cells that would presumably be cleared by the immune system or undergo apoptosis as a byproduct of active viral replication. *In vitro*, latently infected $CD4^+$ T cells that undergo T cell activation will reliably begin to express HIV-1 genes and generate virus particles. An analogous process is thought to occur on a sporadic basis *in vivo* that contributes to low-level viremia. If a patient remains on HAART while latently infected cells become activated and produce virions, no new cycles of replication can occur due to the suppressive effects of antiretroviral therapy. Activated T cells have a half-life of one to two days, and therefore global T cell activation in combination with HAART would be expected to deplete the latent reservoir. This line of thinking led to early clinical trials in which patients were given agents known to induce global T cell activation [58,59]. Some of these agents proved toxic and have sparked the search for ways to induce viral gene expression without concomitant T cell activation.

In vitro models of the latent reservoir have allowed for a better understanding of the mechanisms that contribute to induction and maintenance of HIV-1 proviral latency [60-62]. Regulation of HIV-1 proviral gene expression is a complex process involving multiple host and virus interactions. Several potential targets have emerged from these *in vitro* models that may be exploited to potentially reverse latency [63]. In particular, the primary cellular transcription factors that govern HIV-1 gene expression have been identified and several cellular epigenetic processes that promote gene silencing including histone de-acetylation and methylation also appear to play important roles [62,64,65]. Several excellent reviews that provide further details on this topic have recently been published [66-68]. The recognition of the role of histone deacetylases (HDACs) in latency led to a pilot clinical trial administering the HDAC inhibitor valproic acid to a group of patients on HAART [68]. A modest decrease in HIV-1 DNA in resting $CD4^+$ T cells was observed in this trial but not in a subsequent study [69]. Clinical trials with more potent HDAC inhibitors are currently under way.

In vitro models of HIV-1 latency have also been used to perform screening assays of drug libraries to identify agents that are able to induce proviral gene expression without inducing T cell activation [61,70]. A variety of compounds appear capable of triggering HIV-1 gene expression *in vitro*, leading to mechanistic studies as well as pilot clinical trials. Much of this work has focused on latently infected $CD4^+$ T cells obtained from the peripheral blood of patients. The role played by latently infected cells in tissue reservoirs such as the gut-associated lymphoid tissue and the central nervous system is much less understood and are not entirely accounted for in current *in vitro* models. Given the complexity of the molecular mechanisms that govern latency as they are currently understood, a combination approach analogous to HAART may be necessary to purge the latent reservoir.

Targeted Apoptosis of Latently Infected Cells

An anti-apoptotic phenotype is one of the defining characteristics of the latent reservoir. These cells persist despite undergoing HIV-1 entry, reverse transcription and subsequent proviral integration into the cellular genome and appear to have a half-life of 44 months [21]. One conceptual approach to HIV-1 eradication is to consider this population of cells analogous to a tumor [71]. While HAART prompts a form of chronic remission, treatment interruption results in almost immediate relapse. The corresponding treatment strategy for these 'tumor' cells follows along the cancer chemotherapy paradigm: to target this population for cell death as specifically as possible while inducing minimal damage to uninfected cells.

Chemotherapy is frequently designed to target abnormal or over expressed cell surface markers found on tumor cells but not healthy bystander cells. One of the challenges of applying this paradigm to HIV-1 persistence is the lack of defining cell surface characteristics that distinguish the latent reservoir from uninfected resting memory $CD4^+$ T cells. Despite this limitation, promising *in vitro* work has demonstrated that targeted apoptosis of chronically infected cells may represent a feasible eradication strategy [72,73]. HIV-1 has been shown to manipulate cellular biochemical pathways that alter the apoptotic threshold of these cells [74,75]. Better understanding of these pathways may allow for specific targeting of latently infected cells despite their lack of unique cell surface markers.

This strategy may be of particular importance for reservoirs other than resting memory $CD4^+$ T cells. Macrophages have been described to harbor replication competent HIV-1 despite HAART [76], and these cells may play an important role as tissue-based reservoirs of HIV-1 particularly in the central nervous system and the gastrointestinal tract [77,78]. It is unclear whether HIV-1 infected macrophages undergo true latency or whether they continue low-level replication throughout their lifespan. The longevity of these cells is unknown, as is their relative contribution to long-term HIV-1 persistence in patients on HAART. Macrophages are resistant to the cytopathic effects of HIV-1, and in fact, may take on a pronounced anti-apoptotic phenotype upon infection [79]. A directed apoptosis strategy may prove to be useful in addressing non-T cell sources of HIV-1 persistence.

Challenges and Future Directions

A significant number of challenges must be addressed in the course of pursuing HIV-1 eradication. Though the biology of latency is becoming better understood, it has proven to be a highly complex process that *in vivo* involves a small population of indistinguishable; quiescent cells circulating in the blood and less well characterized tissue-based reservoirs. While the gold-standard lab technique for quantification of the size of latent reservoir has been well described [80], it requires a large amount of blood from patients and significant resource allocation with regard to trained personnel and a specialized lab environment. Alternative latent reservoir measurements currently in use have not been fully standardized between laboratories and further work remains to ensure that these different measurements are comparable to one another. A recent review provides an excellent summary and comparison of these techniques [81]. Another crucial

research priority is to develop a better understanding regarding the degree to which *in vitro* models recapitulate the nature of HIV persistence. This will be particularly important as discoveries in the lab are translated into clinical trials focused on HIV-1 eradication.

Both the success and the limitations of HAART have led to a new frontier in HIV-1 research. The complexity of HIV-1 persistence continues to strain the boundaries of scientific understanding. While eradication of this virus presents a formidable challenge, it will be essential to maintain a global perspective. The early advances toward HIV-1 eradication presented here will represent truly revolutionary scientific and humanitarian achievements when their beneficiaries include all of those involved in this epidemic.

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