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PAPER

Why cure, why now?

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ABSTRACT

Combination antiretroviral therapy (cART) is highly effective at preventing morbidity and mortality due to infection with human immunodeficiency virus (HIV), but does not eradicate the virus. Consequently, cART must be administered life-long. Recent progress has stimulated research towards a cure of HIV infection. Approaches under investigation include hematopoietic stem cell transplantation, latency reactivating agents, immune based therapies, and cell-based therapies. Each of these approaches carries potential risks that must be weighed against the availability of safe and effective cART. Balancing the risks and benefits of this research poses unique challenges to potential study participants, clinicians and investigators.

INTRODUCTION AND BACKGROUND

HIV is the causative agent of AIDS. Since the recognition of AIDS and the discovery of HIV in the early 1980s, HIV infection has become pandemic with approximately 37 million people currently living with HIV/AIDS.¹ The advent of combination antiretroviral therapy (cART) has reduced dramatically the morbidity and mortality due to HIV infection worldwide. Progress in HIV therapeutics since zidovudine (also known as azidothymidine (AZT)) was first approved for the treatment of AIDS 30 years ago has led to the development of highly effective, safe, generally well tolerated and convenient cART regimens, several of which are available as single-tablet regimens, allowing patients to take a single pill once a day to prevent the complications of HIV/AIDS. Studies suggest that persons infected with HIV who are diagnosed early (before significant damage is done to their immune systems) and initiate cART can expect essentially normal life-span.² What was once a death sentence has been transformed into a manageable chronic disease, akin to hypertension or diabetes.

Despite these extraordinary advances in the treatment of AIDS, problems remain. Although cART is highly effective at suppressing HIV, it does not eliminate the virus, which remains in a latent, or dormant, state in lymphocytes of infected persons.³ Treatment must be taken daily to maintain viral suppression. Interruption of treatment for more than a few days risks the rebound of viral replication, and with it the chance for selecting drug resistance. Thus, strict adherence to daily cART is essential for the long-term success of treatment. Patients who face challenges in adhering to their antiretroviral regimens may develop virus that is progressively more and more resistant to available drugs. Substance use, homelessness, psychiatric disease, incarceration, loss of insurance and drug

stock-outs (in low-income and middle-income countries) are common reasons that patients may be unable to adhere to their cART regimen. Drug-resistant virus requires a more complex regimen, which in turn increases the challenge of adherence, giving rise to a vicious cycle with increasing levels of resistance and diminishing efficacy of ART. Intermittent adherence also carries with it the risk of transmission to sex partners during periods of viral rebound.

Even among successfully treated patients in whom virus replication is fully suppressed, the ongoing release of virus from the reservoir of long-lived infected cells results in inappropriate immune activation that can damage various organs, resulting most notably in a substantially increased risk of cardiovascular disease among HIV-infected persons as compared with uninfected adults.⁴ Added to these biological risks, the need to take daily antiretroviral medications is a constant reminder for many patients of their HIV-infected status, and a source of considerable stigma.

For these reasons, interest in finding a cure remains high among patients, clinicians and investigators. Developing a cure for HIV infection has proven elusive, however, and substantial barriers must be overcome if cure, or durable treatment-free remission in the majority of patients is to be achieved. Chief among these obstacles is the fundamental biology of HIV itself. HIV is a retrovirus, a type of RNA virus, that infects lymphocytes known as T helper cells (also called CD4 T cells). Upon entering a CD4 T cell the viral RNA is first converted to DNA, the genetic material of human cells, through the process of reverse transcription. (This process is carried out by a viral enzyme called reverse transcriptase, the target of antiretroviral drugs such as AZT.) The DNA form of the virus is then inserted into the chromosomes of the host cell. If the cell is in an activated state, the DNA is transcribed to produce more viral RNA, which directs the production of viral proteins, resulting in the release of new virus particles and death of the cell. However, some infected cells revert to a resting state and continue to harbour the virus in a silent, or latent state, dormant in much the same way as a computer virus can lie dormant until triggered by a specific signal or event. Because the virus is dormant, it is not affected by antiretroviral drugs. Similarly, because no viral proteins are expressed in a latently infected cell, such cells are not recognised as infected by the host immune system and escape destruction. Thus, these latently infected CD4 T cells persist for the life of an infected person and, if ART is interrupted, lead to resumed virus replication and disease progression.⁵



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For many years, this central feature of retrovirus biology led most scientists and clinicians to assume that curing HIV infection (eradicating all traces of the virus from an infected person) was an unrealistic goal. Research towards a cure received an enormous boost by the report that a patient (known as the 'Berlin patient' before he identified himself as Timothy Ray Brown) had apparently been cured of HIV by a bone marrow transplant (more formally called a haematopoietic stem cell transplant (SCT)).⁶ In this case, the patient had long standing HIV infection for which he was receiving standard ART when he developed a form of leukaemia. Anticipating that the patient might require SCT for treatment of the leukaemia, his haematologist, Dr Gero Hütter, searched for a potential donor who carried a mutation that inactivates one of the receptors (chemokine receptor 5 (CCR5)) needed by HIV to enter a CD4 T cell. Approximately 1% of people of northern European origin lack the CCR5 receptor due to this mutation but are perfectly healthy.⁷ Their CD4 T cells are resistant to infection by most strains of HIV.⁸ Dr Hütter reasoned that if the HIV-infected cells in Mr Brown could be reduced or eliminated by the chemotherapy and radiation therapy needed to kill off the leukaemia cells in preparation for a bone marrow transplant, then reconstituting his immune system with stem cells that were intrinsically resistant to HIV infection could prevent return of the virus. Events unfolded precisely as predicted, and Mr Brown has now been free of any detectable HIV without the need for ART for at least 7 years.⁹

Although it is impossible to state with certainty that all traces of HIV have been eradicated from Mr Brown, his apparent cure has galvanised the field and sparked a resurgence of interest in HIV cure research. The expansion of HIV cure research has been fuelled by a significant increase in targeted funding provided by the National Institutes of Health, American Foundation for AIDS Research (amfAR), the Bill and Melinda Gates Foundation and other organisations. Results of this work have already identified a number of promising leads that are now poised for testing in proof-of-concept pilot studies in patients with HIV infection.

APPROACHES TO HIV CURE

Despite the apparent success of SCT in the Berlin patient, this approach is too risky to be considered for use in patients other than those who require SCT for treatment of an otherwise fatal leukaemia or lymphoma. Moreover, SCT is far too complex and expensive to be scalable for delivery to the 35 million persons living with HIV infection worldwide. Alternative approaches currently under investigation include the use of latency reversing agents to stimulate virus production by latently infected cells; immune-based interventions to bolster anti-HIV immune responses in order to enhance the elimination of latently infected cells that harbour the HIV reservoir and cell-based therapies using genetically modified T cells or haematopoietic stem cells engineered to be resistant to HIV (eg, by introducing a deletion in the CCR5 gene).

Latency reversing agents

Advances in cancer research and studies in basic immunology provided a new understanding of the mechanisms by which HIV is maintained in a latent state in resting lymphocytes, and identified possible targets for drugs that might reawaken the virus, potentially purging the reservoir. The theory behind this approach is that reactivation of virus from latently infected cells will lead to their death, either directly or because they become targets for destruction by the immune system. Repeated cycles

of such treatment could deplete the reservoir of latently infected cells. Continued administration of ART would protect uninfected cells from becoming infected by the newly released virus, thereby preventing the reservoir from being repopulated. Several drugs known as histone deacetylase (HDAC) inhibitors have been approved for the treatment of various cancers. Small pilot studies in patients with HIV infection on stable ART have demonstrated the ability of these HDAC inhibitors to stimulate virus production, although to date there is no evidence that such treatment leads to a significant reduction in the size of the viral reservoir.^{10–13} Other activators of HIV transcription are being studied in clinical trials and animal models.^{14 15}

Immune-based interventions

In vitro studies and work in animal models suggest that a variety of immune-based interventions might stimulate the host anti-HIV response. These include inhibitors of so-called checkpoint blockers, therapeutic vaccination and broadly neutralising antibodies. Inhibitors of checkpoint blockers non-specifically activate the immune system to overcome the state of immune exhaustion characteristic of cancer and chronic virus infection, such as HIV.^{16 17} Therapeutic vaccines are intended to enhance pathogen-specific immune responses in patients already infected with a particular microbial agent. Broadly neutralising antibodies target a wide variety of different HIV strains and may help the immune system destroy infected cells expressing HIV antigens.^{18 19}

Cell-based therapies

Another potential approach for eliminating the HIV reservoir is through the use of cell-based therapies. Several different types of cell-based treatment are being investigated. Each involves collecting large numbers of lymphocytes or haematopoietic stem cells from the blood through a procedure called leukapheresis, genetically modifying the cells, expanding the modified cells in the laboratory, and then reinfusing them into the patient. The genetic modification can either be designed to make the cells resistant to HIV infection, or to target cytotoxic T lymphocytes ('killer' T cells) to HIV-infected cells with the goal of destroying the viral reservoir. A number of pilot studies have demonstrated the feasibility of these approaches, but further studies are needed in order to establish efficacy.^{20 21}

RISKS OF HIV CURE RESEARCH

Each of the hypothetical approaches to HIV cure described above carries substantial risk. For example, the HDAC inhibitors are mutagenic (in the case of vorinostat and panobinostat) or teratogenic (in the case of romidepsin), raising concerns about long-term risk of cancer or harm to an embryo, respectively. In addition, these drugs can have cardiac, haematological and gastrointestinal toxicities that may be life threatening.^{22–24} Immune checkpoint blockers such as nivolumab and pembrolizumab can cause serious autoimmune reactions due to the non-specific activation of cytotoxic T cells, including significant lung and liver inflammation.^{25 26} In some patients who have received these drugs for cancer treatment (their currently approved use), autoimmune attack has resulted in diabetes and heart failure.^{27 28} Although cell-based therapies generally have been well tolerated, some of the approaches to gene modification carry with them the risk of inducing malignant transformation of the modified cells.²⁹ Successful engraftment of modified stem cells may require a preconditioning treatment to 'make room' for these cells in the bone marrow.³⁰ Because of the serious toxicities associated with such conditioning regimens, most studies

with genetically modified stem cells for HIV eradication have been restricted to patients in need of an SCT for treatment of a life-threatening malignancy.

Another risk of HIV cure studies relates to the ‘test of cure’. A consensus has emerged in the field that the ultimate test of an intervention, or combination of interventions, targeting the HIV-1 reservoir is an analytical treatment interruption, in which ART is discontinued and the patient monitored closely for signs of virologic rebound. However, treatment interruptions also pose potential risks for study participants, including the possibility of severe primary infection-like symptoms, a possible decline in CD4 cell count, increased risk of AIDS-related and cardiovascular events, potential emergence of antiretroviral drug resistance and increased risk of HIV transmission to sex partners.^{31–34}

ETHICAL CHALLENGES IN HIV CURE RESEARCH

The potential risk of investigational approaches to HIV cure juxtaposed against the success and safety of ART captures the central dilemma facing potential participants, clinicians and investigators. How can this essential research move forward while maintaining an acceptable risk:benefit ratio? In early phase studies, the risk of potential harm may exceed any prospect of benefit. Historically, studies with greater risk have recruited patients thought to have the greatest immediate medical need. ‘Salvage therapy’ studies in highly treatment-experienced patients with drug-resistant HIV-1 were cases in point. However, studies aimed at reducing the viral reservoir will likely require patients to be on a suppressive ART regimen; patients with advanced HIV disease may be less likely to respond to immune-based therapies and may be at higher risk of toxicity and serious adverse events. How to assure equitable selection of participants for studies of HIV cure poses a significant challenge, as does assuring that the fruits of this research, if successful, are equitably distributed to those in need.

The informed consent process for HIV cure studies requires particular scrutiny, so that participants fully comprehend the potential risks and benefits. Although it may be appropriate to frame the goal of an individual study as contributing to the search for a cure, the word ‘cure’ must be used with great caution. It could provide false hope to participants or lead to miscalculation of study risks, especially in early phase and proof-of-concept studies in which cure is unlikely. In this respect, the danger of therapeutic misconception mirrors that of early-stage cancer trials, with the key difference that unlike advanced stage cancer, safe and effective treatment for HIV infection is already available.

Persons living with HIV/AIDS, clinicians, investigators, institutional review boards, funding agencies, pharmaceutical companies and governmental regulatory authorities may each have different perspectives on how research towards an HIV cure should proceed. Broad discussion that is inclusive of all stakeholders is essential in order to arrive at consensus on these complex issues. Throughout the process we should be guided by the basic pillars of human research: beneficence, equity and autonomy. In this way we can ensure that this vitally important research proceeds with the utmost attention to patient safety and adheres to the highest ethical standards.

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