The Journal of Infectious Diseases

INTRODUCTION

Towards an HIV Cure: a View of a Developing Field

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Keywords. HIV; Latency; cure; eradication; persistence; provirus; reservoir; antiviral immunity.

Since the earliest days of antiretroviral therapy (ART), human immunodeficiency virus (HIV)–positive people, those that care for them, and those that care about them have hoped for the day when HIV infection could be cured. The emergence of the first effective ART combinations was soon followed by early efforts to cure infection through what became known as "shock and kill" therapy. However, direct activation of HIV-infected cells resulted in frightening toxicities. Because of this as well as the emerging understanding of proviral latency in the 1990s, any consideration of efforts toward an HIV cure were viewed as fruitless and even irresponsible in the scientific and medical community.

But in 2006, Timothy Brown's bone marrow transplants and cancer treatments resulted in what is still the only known HIV cure, as his immune system was replaced with cells carrying the HIV-resistant Δ32 CCR5 gene. This singular event, combined with alternating waves of hope and frustration in the quest for an effective prophylactic HIV vaccine and daunting challenges faced by societies tasked with the provision of life-long ART to populations across the globe, galvanized new efforts in the scientific community to reconsider the idea of HIV cure.

The National Institutes of Health funded 3 groups, the Martin Delaney Collaboratories, to work together on HIV cure research in 2011. The first demonstration of reversal of HIV latency in a human study was reported in 2012, and the International AIDS Society, led by Nobel Laureate Francois Barre-Sinoussi, initiated a global effort to galvanize HIV cure research in the same year.

In parallel with the accelerating and expanding effort in research, HIV cure has been much discussed and debated in many scientific, public health, and social forums in the few years that have followed. The goals of these efforts have become compartmentalized into 2 camps. Some doubt that a retroviral infection can ever be cleared and thus seek an acceptable middle ground: functional cure, a state of autonomous control of HIV infection without the use of ART, in which viremia is undetectable, there is no disease progression, immunodeficiency, or HIV transmission, and life expectancy is unaltered from those without infection. Others seek the eradication of HIV infection altogether and an escape both from medical concerns and the stigma of an HIV-positive identity. In truth, it would seem that if success is achieved in the near term, it will be difficult to tell one outcome from the other, and, as with oncological cures, it will be difficult to immediately assure an individual of the finality of the outcome. Nevertheless, it is easy to see how achieving any progress toward a cure for HIV infection could revolutionize the management of the pandemic around the world and increase the chance of creating a truly AIDS-free generation.

For this supplemental issue, we invited clinicians and scientists who represent the newly funded and restructured Martin Delaney Collaboratories for HIV Cure Research to discuss developments, challenges, and priorities in each of 7 key areas of HIV cure research. These discussions are representative of many of the advances made in the last few years in this nascent field and of the new directions under investigation in the Collaboratories and other key research groups across the globe.

Henrich and colleagues discuss the methodological challenges of quantification and characterization of the whole-body burden of replication-competent HIV individuals of receiving effective ART. The ability to sensitively, specifically, and precisely measure the size and distribution of the cells encoding persistent HIV infection in blood and tissues is a key unmet need that must be addressed to allow HIV cure research to progress and, ultimately, provide validation of cures, when achieved.

Mullins and Frenkel highlight the recently recognized challenge posed by the clonal expansion HIV-1 provirus within HIV-infected cells. Clonally expanded cells appear to comprise an expanding fraction of the residual infected cell population in individuals that remain on ART for years, although the fraction of these viral genomes that can generate a threatening, replication-competent virus has yet to be precisely quantified. Boritz and Douek review their recent findings documenting the uneven distribution of cell subsets that harbor HIV during ART across the blood and tissue compartments. They point to the need for studies that can reveal the key anatomic sanctuaries for persistent infection.

The Journal of Infectious Diseases® 2017;215(S3):S109–10

DOI: 10.1093/infdis/jiw633

My colleague and collaborator Nancie Archin and I discuss the challenges inherent in the development of latency reversing agents (LRAs), a key tool to reveal persistently infected cells and create a window of vulnerability within the latent reservoir to allow its targeted clearance. We hope that the steady advances in the development of LRAs may soon be paired with emerging immunotherapeutics to clear persistently infected cells and allow measurable clinical advances toward an HIV cure. In this vein, Montaner and Riley review leading HIV cure strategies to harness cell-mediated control against HIV in stably suppressed ART-treated participants. The researchers focus on their efforts to bring the antiviral activity of gene-modified T cells bearing chimeric antigen receptors (CARs), which are resistant to infection, to bear as potent tools to clear infection or result in a sustained remission in the absence of ART.

Ferrari and colleagues focus on other immunotherapeutic work engaging humoral and innate antiviral immunity as tools to clear persistent HIV infection. Their work focuses on the use of HIV-1 Env-specific antibodies that can bind the surface of infected $CD4^+$ T cells and promote their elimination by recruiting cytotoxic effector cells such as natural killer cells, monocytes, and polymorphonuclear neutrophils cells. Finally, Garcia and Silvestri review the 2 leading animal models under study in HIV cure research—humanized mice and nonhuman primates—to provide much-needed preclinical modeling of HIV latency disruption and cure strategies.

As with other challenging problems facing society, the HIV pandemic requires a broad, multifaceted approach. Among the many important goals for future HIV research is the development of temporally contained therapies capable of achieving an HIV cure, by any name. The quest for "a cure" for cancer has been undiminished over decades, rewarded in recent years with significant progress. There is now hope for a future in which the risk of acquiring HIV infection is reduced by behavioral and vaccine approaches; disease progression is halted by simple, inexpensive, durable, and nontoxic ART; innate control of HIV infection is improved by novel immunotherapies; and eradication of infection is possible in a gradually growing number of people across the world with HIV infection.

Notes

Supplement sponsorship. This supplement was supported by grants from Merck & Co., Inc. and Gilead Sciences, Inc.

Potential conflicts of interest. The authors: No reported conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.