

# The Search for an HIV Cure: Where Do We Go From Here?

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Since the first case of an HIV sterilizing cure was published, remarkable progress has been made in our understanding of the mechanisms behind HIV persistence. However, our goal of achieving a safe and broadly-available treatment for sustained HIV remission has proven elusive. In this supplement, we provide a series of articles reviewing the technical hurdles facing the field, key assays to measure HIV persistence and the next-generation of therapeutics for HIV remission.

**Key Words:** HIV cure; viral remission; shock and kill; immune response.

In 2009, an article was published in the *New England Journal of Medicine* reporting the remarkable case of an individual with acute myeloid leukemia who was apparently cured of HIV after a hematopoietic stem cell transplant from a donor homozygous for the CCR5-Δ32 mutation [1]. The story of Timothy Ray Brown, also known as the Berlin patient, was the crucial proof-of-principle that an HIV cure was possible and inspired a generation of patients and researchers to search for strategies that could lead to antiretroviral therapy (ART)-free HIV remission.

Since that report, we have made tremendous progress towards solving the riddle that is HIV persistence and advancing potential curative strategies into clinical trials. However, we have yet to find an intervention, short of hematopoietic stem cell transplantation, that can sustainably deplete the HIV reservoir. In this supplement, we take stock of the state of the HIV cure field, both at the incredible progress that has been made, but also at the daunting challenges that remain. We also provide an overview of several promising strategies for achieving the elusive goal of sustained HIV remission.

In the first 2 articles of this collection, we outline the challenges facing investigators who are engaged in this field and in the next 4 articles, we provide an overview of promising approaches towards achieving sustained HIV remission. In the first article, Dr Li and colleagues [1] outline a series of challenges facing researchers, including (1) HIV-infected cells are rare and located in difficult-to-study anatomic sites; (2) the basic mechanisms underlying HIV latency and reactivation are

not yet fully defined; (3) reactivating the latent HIV provirus has proven difficult and HIV-expressing cells may not be effectively cleared by the host immune response; and (4) the impact of HIV diversity and viral escape represent additional barriers to viral eradication and control. The authors also review the success stories in the field, including cases of sterilizing cure in the Berlin and London patients [2-4], as well as the promise exemplified by spontaneous and posttreatment HIV controllers [5-8]. In the next article, Drs Robert and Janet Siliciano [9] focus on defining the size of the “true” reservoir, or the fraction of integrated proviruses that contribute to HIV persistence and can seed viral rebound. They compare the HIV reservoir assays used to quantify the HIV reservoir, with a focus on viral outgrowth assay and intact proviral DNA assay [10, 11]. They also review our understanding of HIV persistence, including exploring the importance of clonal expansion of HIV-infected cells and the difficulty in inducing the viral expression of latent proviruses, a cornerstone of shock and kill strategies for achieving HIV remission. Finally, they discuss the concept of the rebound-competent reservoir: when ART is stopped, some replication-competent viruses in the reservoir may be controlled by innate, humoral, or cytotoxic T-cell responses, which may explain why virus isolates found in plasma during treatment interruption may differ from that detected by the traditional virus outgrowth assay (which does not incorporate antiviral immune responses). The concept of the rebound-competent reservoir is likely to become increasingly important in the cure field, particularly as we design immune-based therapies to achieve sustained HIV remission.

Among the most exciting immunologic strategies for HIV remission are broadly neutralizing antibodies (bNAbs), reviewed by Dr Rossignol and colleagues [12]. In addition to their direct antiviral activity, there is tantalizing evidence that bNAbs, by

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interacting via their Fc domain with immune cells, may eliminate infected cells. This insight raises the prospect of engineering the Fc portion of antibodies to enhance their antireservoir functional activity, a novel and exciting approach to achieving HIV remission [13]. In addition to the potential for antibody-mediated reservoir reduction, there is a new understanding of how cytotoxic T lymphocytes (CTLs) may be harnessed to control HIV. Dr Kaseke and colleagues [14] detail several lines of evidence, including studies of HIV spontaneous controllers, emerging viral sequence adaptations to host immune responses, and a well-studied murine model of non-HIV viral control [15]. The authors summarize their recently published work on using structure-based network analysis to better define T-cell responses [16] and provide a roadmap on how this could be translated into the rational design of a CTL-based HIV vaccine. The implication of this work is that, by developing strategies to focus the CTL response on highly networked epitopes found in HIV spontaneous controllers, it may be possible to enhance immune control of the reservoir. Dr Zhou and coauthors [17] extend the idea of T-cell control of the reservoir by reviewing strategies for enhancing HIV-specific immune responses through adoptive T-cell therapy, including ex vivo expansion of T cells and use of T-cell receptor or chimeric antigen receptor-engineered HIV-specific T cells. They review lessons learned from oncology, provide an overview of the promise that these approaches provide, and also detail ongoing efforts to optimize this strategy, such as overcoming viral escape and protecting these engineered cells from HIV. The final report in this collection, from Drs Li, Mori, and Valente [18], highlights a completely different approach to achieving HIV remission: rather than the shock and kill strategy for HIV reservoir eradication, they propose a “block and lock” strategy involving epigenetic silencing of the HIV promoter. This group has published intriguing studies showing that the use of a Tat inhibitor, didehydro-Cortistatin A, can effectively control viral expression in the absence of ART [19] by promoting rather than reversing latency. The authors review the mechanisms of action of this latency-promoting agent, including in vitro and in vivo studies that provide proof of concept that the block and lock approach may be an alternative strategy for controlling HIV in the absence of traditional ART.

Since the first report of a sterilizing HIV cure, it is estimated that more than 20 million people have become infected with HIV [20]. Finding a sterilizing or functional cure for HIV would have a seismic impact on the health of millions worldwide. This collection of papers provides a clear look at challenges facing the field, but also provides a roadmap for the strategies that have the potential to lead us closer to our goal of sustained HIV remission and cure. Indeed, the efforts and advances highlighted in this collection represent a tribute to the memory of Timothy Ray Brown, who passed away in 2020 from recurrent leukemia,

but whose example continues to serve as an inspiration to the field of HIV cure research.

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