HIV has accounted for more than 35 million deaths globally since the HIV/AIDS epidemic began in 1981. According to the latest UNAIDS figures, at the end of 2017, an estimated 36.9 million people were living with HIV. Most of the infected population is dependent on life-saving combination antiretroviral therapy (cART) that suppresses HIV replication, prevents the development of AIDS, and reduces the risk of transmission.

However, cART is not a cure, and providing lifelong daily treatment to all infected individuals is no easy feat to achieve. Daily treatment can be challenging and lead to adherence interruption, thus resulting in a rebound of the virus and potential progression to AIDS. Moreover, one in ten individuals receiving cART have been reported to experience adverse effects due to several factors, such as complex drug-to-drug interactions, underlying comorbidities, and drug toxicities arising from concomitant medication use.

In a bid to overcome challenges of daily adherence to cART, development of a long acting antiretroviral injection (combining cabotegravir and rilpivirine) that offers once-monthly administration was reported in two independent 48-week trials (NCT02951052 and NCT02938520) on March 7, 2019, at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, WA, USA. Early data from these trials suggested promising results in viral control with the monthly regimen and participant satisfaction in over 85% cases compared to taking daily dose cART.

Notwithstanding the remarkable efficacy of cART, the so-called latent reservoir of HIV represents the main barrier to HIV cure. HIV is thought to establish latency by infecting primarily the long-lived CD4 + T cells and by integrating into the host’s genomic DNA. Once established, HIV latency can shut off viral transcription in infected cells, allowing the provirus to remain undetected by the host immune system, and can hinder effective treatment by antiretroviral medication.

A latent reservoir of HIV can persist for the host’s lifetime.

The main research focus in identifying a cure for HIV has been directed at defining and eliminating the viral reservoir. The so-called “kick and kill” (alternatively referred to as “shock and kill”) approach was developed to remove the entire reservoir by forcing viral replication of the latent virus with latency-reversing agents and subsequently eliminating the infected cell population via antiviral immunity or cytopathic effects. This scheme focuses on identifying ways to adopt the host antiviral immunity to ensure complete eradication of reactivated virions. This idea has led to several key developments, including anti-HIV vaccination, HIV-specific broadly neutralising antibodies, and transduction of anti-HIV natural killer cells. The main limitations that have prevented this advance from being realised are the challenges of inducing expression from the entire HIV latent reservoir and ensuring complete limitation of viral rebound. Therefore, alternative strategies are being pursued.

In an article published in Nature, on March 5, 2019, Ravindra Gupta and colleagues at University College London, UK, reported the second-ever man, referred to as the London patient, who appears to have achieved sustained remission from HIV following successful haemopoietic stem-cell transplant from a CCR5 delta-32 donor (who is naturally resistant to HIV due to the mutation), for the treatment of Hodgkin’s lymphoma and HIV. The first patient (known as the Berlin patient) similarly achieved sustained remission from HIV a decade ago. This breakthrough has created considerable excitement within the field and beyond, because it suggests that the now-repeated success of this transplantation was not a one-off and may offer real potential for an HIV cure. There are already reports of a third patient from Düsseldorf, Germany, achieving HIV remission, although it is still too early to confirm long-term remission status in both patients. Despite the remarkable outcome offered by this stem-cell transplantation application, several challenges remain.

Gupta and other experts in the field, including Gero Hütter (the doctor who treated the Berlin patient), admit that this type of bone-marrow transplant is not feasible on a large scale and is unsuitable for most people living with HIV on cART. This is due in part to the complexity of the procedure, which involves aggressive chemotherapy to make space for the donor stem cells and may present a high risk of health complications and risk of death in those undergoing the therapy.

Recent advances in genetic modification systems and significant improvements in specialised delivery techniques are also giving rise to alternative therapies that do not rely on bone-marrow transplantation. One promising implementation is the use of engineered zinc finger nucleases (ZFN) to suppress expression of CCR5 on HIV-targeting cells, leading to inhibition of HIV-1 entry into host cells to cause infection and thereby conferring HIV resistance. Early testing of modified ZFN (SB-726-T) designed to disrupt expression of CCR5 in HIV-infected individuals showed prolonged survival; however, viraemia was insufficiently controlled (NCT00842634). Initial data from the follow-up trial (NCT01543152) presented on March 5, 2019, at the CROI showed that cyclophosphamide boosted SB-728-T engraftment in HIV-infected patients and led to delayed viral rebound and low viraemic levels while patients were on analytical treatment interruption. These encouraging results suggest that improved CCR5 modifications may provide a potential strategy for an HIV cure. Other promising advances that stem from this idea to disrupt CCR5 expression can be read in more depth in the linked commentary published in this issue of EbioMedicine, by Peluso, Deeks and McCune at the University of California San Francisco, CA, USA, and the Bill & Melinda Gates Foundation, Seattle, WA, USA.
This is an exciting time in the field of HIV research, but the goal of developing a cure still seems to be a distant prospect. To reach this important milestone, a multidisciplinary, collaborative scientific tactic will be needed to improve understanding of the challenges that must be overcome. In this quest, *EBioMedicine* will continue to welcome cutting-edge HIV research studies that offer novel mechanistic insights that will contribute to the development of a cure for HIV.

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