Over the past decade, there has been rapid evolution and expansion in scientific and community interest in HIV curative strategies. The initial report of the cure of Timothy Brown (The Berlin Patient) following CCR5 Δ32/Δ32 stem-cell transplantation in 2009 [1] was a major catalyst in bringing together various stake-holders, including government funding agencies, private foundations, community and advocacy groups, ethicists, regulatory agencies, pharmaceutical companies, scientists and clinicians, to work towards the goal of achieving a sterilizing cure or durable control of HIV after stopping antiretroviral therapy (ART). Dedicated funding opportunities provided support for those working towards these challenging goals, leading to an exponential increase in the number of scientific articles, public articles and media coverage. The status of these efforts was extensively summarized by the International AIDS Society global strategy towards an HIV cure in 2016 [2]. Although additional cases such as Timothy Brown have yet to materialize, the HIV cure field has rapidly expanded to include work on discovering biomarkers of persistent HIV infection, development and implementation of immunological approaches to controlling HIV following ART cessation, cell and gene therapy approaches, early initiation of ART, latency promoting or reversing strategies and development of novel assays to locate, quantify and characterize persistent HIV reservoirs. Although working towards an HIV cure has been met with many scientific and practical challenges, there has been recent, palpable progress. For example, durable control of simian immunodeficiency virus (SIV) has recently been reported in nonhuman primate studies including the use of therapeutic HIV vaccine combined with Toll-like receptor agonists and mAbs directed towards viral envelope proteins or α4β7 integrin, to name just a few [3–5]. Additional cases of prolonged HIV remission prior to viral recrudescence, sometimes lasting many months, have been reported in small, proof-of-concept human studies, although none have lead to unequivocal, sustained HIV cure [6,7]. Work on other strategies has also accelerated, including the search for biomarkers of residual HIV-infected cells or the development of clinical trials incorporating combination therapies to target or modulate various aspects of HIV persistence. Of course, there have been, and always will be, growing pains and false starts while embarking upon novel and innovative cure science, but there is no disputing that the past decade has seen a dramatic increase in the understanding of HIV persistence.

However, there are several fundamental questions within HIV curative persistence research that remain unclear. Defining what is meant by an HIV ‘cure’ has undergone several iterations with an emerging consensus that achieving control of HIV following cessation of ART will require immune control in addition to reservoir reduction. This is different from a ‘sterilizing’ cure achieved with Timothy Brown, but nonetheless offers the hope of reducing or eliminating the need for life-long ART. Other questions remain. For example, how do we define HIV latency, and what specifically defines and makes up the viral reservoir? Are all infected cells that remain in the setting of ‘suppressive’ ART important to identify and target, regardless of the degree of transcriptional or translational activity? What level of reservoir reduction will be required to allow immune or other control of HIV replication following treatment interruption? What is the total body distribution and activity of persistently infected cells? Regardless of these ongoing questions, a more robust framework now exists on which HIV eradication and control studies can be designed and evaluated.

In several other infectious disease contexts, alternative therapeutic approaches are also urgently needed to circumvent failures or insufficiencies.

*Division of Experimental Medicine, University of California, San Francisco, San Francisco, California, USA. †Department of Clinical Immunology and Infectious Diseases – Henri Mondor Hospital and Vaccine Research Institute, Université Paris Est Créteil, Paris, France

Correspondence to Timothy J. Henrich, Division of Experimental Medicine, University of California, San Francisco, 1001 Potrero Avenue, San Francisco, CA 94110, USA. E-mail: timothy.henrich@ucsf.edu

Curr Opin HIV AIDS 2018, 13:381–382
DOI:10.1097/COH.0000000000000492
associated with existing antimicrobial agents [6,7]. Lessons for achieving an HIV cure must be drawn from the evolution of these therapeutic strategies and those developed in the fields of oncology and solid organ and stem cell transplantation. For example, immunosuppressive agents such as rapamycin may have unexpected positive impacts on tuberculosis (TB) or HIV infection, and other drugs that are already clinically approved and ready to enter clinical trials, such as metformin, may also have potential impact on TB infection. Immune checkpoint blockade is another example of an immune modifying therapy primarily developed for various cancers that may have some beneficial impact on HIV infection in certain individuals, but also carries significant potential risks.

In this issue of Current Opinion in HIV and AIDS, experts in HIV persistence and eradication efforts cover recent findings in topics such as biomarkers of HIV reservoirs, genital reservoirs, posttreatment control of HIV infection, therapeutic vaccination, mathematical approaches to understanding persistence and viral eradication, immunomodulatory therapies for HIV, chimeric antigen receptor T-cell approaches and analytical treatment interruptions. Ethical and clinical issues of trials to achieve functional cure are also addressed which are critical to achieving a well tolerated and scalable HIV cure. In contrast to standard antiretrovirals, which are well tolerated, many HIV curative strategies are not devoid of potential deleterious effects. Moreover, treatment interruptions alone as a means of assessing the effectiveness of these strategies may also carry risks, including viral recrudescence and exposure to secondary transmission risks. The establishment of clinical cure trials leads to a paradigm shift in the management of HIV of which participants, clinicians and researchers must be aware.

Clearly, the HIV curative field is much larger and more involved than what can be summarized in just a few articles, but the breadth and depth of the research presented attests to the importance and durability of searching for a cure. Although progress towards HIV cure has yet to achieve the number or breath of these successes, it is much easier to be an optimist in this exciting era of scientific and community research. However, momentum will only continue if there are continued interest and support from all parties involved.

Acknowledgements
None.

Financial support and sponsorship
T.J.H. is supported by NIH/NIAID R01AI122862 and R33AI116205.

Conflicts of interest
T.J.H. provides consulting services to Merck and receives grant support from Gilead Biosciences.

REFERENCES