Seven years ago, Hutter et al. [1] reported the unique case of a 40-year-old HIV-infected man who was cured of HIV infection following an allogeneic bone marrow transplant. Timothy Ray Brown, also known as the ‘Berlin Patient’ is until today the only person from whom HIV has been eradicated. This extraordinary and largely unexpected success fostered HIV cure research by opening novel therapeutic possibilities that could potentially surpass combination antiretroviral therapy (ART). Indeed, although ART has dramatically reduced the death rate from AIDS and improved the quality of life of many HIV-infected individuals, the possible long-term toxicity associated with ART, stigma and cost all contribute to the necessity of finding a cure.

A ‘sterilizing cure’, in which the virus is completely eradicated, would require the elimination of all replication-competent viruses throughout the body. An alternative approach, probably more realistic, would be to aim for what we might consider a ‘cancer model’ of cure, in which an individual would enjoy long-term health in the absence of ART, with perhaps low-level viremia. This is commonly referred to as a ‘functional cure’ in which the viral reservoir is naturally controlled by the host. Both forms of cure (sterilizing and functional) would require eliminating, or at least reducing, the reservoirs of HIV infection.

Since the report of the first HIV cure, the field of HIV reservoirs has evolved rapidly. Several strategies have been proposed to interfere with HIV persistence during ART. The development of these novel approaches has benefited from the tremendous progresses that have been made at the molecular level, including the key cellular viral and immunological mechanisms that regulate the magnitude of the persistent HIV reservoirs. This issue aims to address the challenges that should be overcome to develop a safe, scalable and affordable cure for HIV infection.

Although it is well established that HIV persists in individuals receiving suppressive ART, the precise cellular and anatomical locations that are primarily responsible for HIV persistence are still debated. Yuki et al. (pp. 362–370) review studies describing tissue reservoirs by organ system with particular attention to the nature of the infected cell types in each compartment, evidence for viral compartmentalization if any, and evidence for differences in antiretroviral concentrations. Among the potential tissue reservoir, the brain has been largely neglected, as access to this tissue is obviously limited. Gray et al. (pp. 371–375) provide evidence supporting the concept that the central nervous system (CNS) viral reservoir is unique and presents a distinct set of challenges that needs to be overcome to ensure successful viral elimination within this compartment. The CNS fulfills the major criteria to be classed as an HIV reservoir and is mainly confined to macrophages, microglia and astrocytes. The existence of this CNS reservoir supports the needs to investigate the mechanisms by which HIV persists in alternative cellular reservoirs (i.e. non-CD4+ T cells). Sacha et al. (pp. 376–382) reviewed possible interventions that could be used to target these unconventional, often neglected cellular reservoirs. The authors anticipate that a unique solution may be required for each cell type, and that delivery mechanisms or targeting strategies will need to be tissue-specific tailored. In addition to the diversity of these unconventional cellular reservoirs, the CD4+ compartment, which is often considered as the major cellular reservoir for HIV during ART, also presents considerable heterogeneity. Recent advances have increased awareness for the profound diversity and complexity of CD4+ T-cell subpopulations serving as sites for HIV-1 persistence. Lee et al. (pp. 383–387) review recent evidences indicating that in addition to the long-lasting CD4+ memory T-cell populations that contain the majority of latently infected cells in the peripheral blood, functional polarization toward a Th17, a T-follicular helper cell or a regulatory T-cell lineage may also be associated with an increased ability to

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serve as a viral reservoir. Emerging data also indicate that atypical T cells such as \( \gamma \delta \) CD4\(^+\) T cells or tissue-resident memory CD4\(^+\) T cells may be predestined to serve as sites for HIV persistence in specific tissues.

Darcis et al. (pp. 388–393) describe another level of complexity to HIV persistence: the molecular mechanisms responsible for HIV latency within resting CD4\(^+\) T cells are complex, and several mechanisms operating at the transcriptional level are involved in the establishment and maintenance of HIV latency. Progress made toward the understanding of the molecular mechanisms of HIV-1 transcriptional repression has led to the identification of latency-reversing agents that activate HIV transcription, such as histone deacetylase inhibitors and protein kinase C agonists. Several of these molecules have already been tested in HIV-infected individuals for their capacity at reversing HIV latency. In this issue, Rasmussen et al. (pp. 394–401) performed a systematic review of these recent clinical trials. They note that in single-arm clinical trials, short-term administration of disulfiram or a histone deacetylase inhibitor (vorinostat, panobinostat or romidepsin) increased cell-associated HIV RNA, and in some cases also plasma HIV RNA, in HIV-infected individuals on ART. However, despite reversing latency, none of the interventions to date have had a demonstrable effect on the size of the latent HIV reservoir.

A likely reason for these failures is the possibility that cells in which HIV is reactivated are not killed. Martrs et al. (pp. 402–408) describe several strategies that may facilitate the elimination of the reactivated latently infected cells, including vaccines, administration of neutralizing antibodies or dual-affinity re-targeting antibodies and enhancement of natural killer (NK) cell functions. In her review, Trautmann (pp. 409–416) proposes several strategies to boost preexisting HIV-specific T-cell responses to induce killing. This may be achieved through early ART initiation, adoptive cell transfer, therapeutic vaccination and immunoregulatory interventions. Importantly, these immune-boosting strategies may have a significant impact on viral persistence even in the absence of a ‘shock’ component. Indeed, several recent studies strongly suggest that HIV may still actively replicate at low levels during ART, at least in a subset of individuals (reviewed in this issue by Martinet-Picado et al., pp. 417–423), which may provide preexisting target to a boosted HIV-specific cytolytic response. Although the degree to which HIV replicates during ART remains controversial, limited drug penetration within tissues and the presence of immune sanctuaries have been argued as potential mechanisms allowing HIV to spread during ART.

Nonetheless, a clear answer to this fundamental question (‘Does HIV replicate during ART?’) has not been provided yet. This is mostly attributed to our inability to precisely quantify rare latently or productively infected cells, particularly in tissues. Banga et al. (pp. 424–431) propose a comprehensive review of the virological assays that have been developed to measure HIV persistence both in quantitative and qualitative manners. Although the quantitative viral outgrowth assay is still considered as the gold standard method to measure the frequency of cells harboring replication competent HIV, it is well established that this assay largely underestimates the ‘real’ size of the reservoir. Alternative assays have been developed, but they are likely to overestimate the magnitude of the latent reservoir. There is still a need to develop a reliable and sensitive assay that will effectively predict the time to viral rebound upon treatment interruption and/or precisely measure changes in the size of the replication competent reservoir in clinical trials aimed at viral eradication.

In addition to more precise and sensitive assays, the field of HIV reservoir is in need of relevant animal models not only to describe the location and mechanisms of viral persistence, but also to test novel therapeutic strategies. In this issue, Kumar et al. (pp. 432–441) describe the most recent findings using animal models of HIV persistence. Both the humanized mice and nonhuman primates represent valuable models to study viral persistence during ART, although their relative value may vary depending on the question to be addressed. For instance, simian immunodeficiency virus or Simian-Human Immunodeficiency Virus infection of rhesus and pigtail macaques receiving effective ART may represent the most faithful animal model of HIV persistence, and may be more adequate to describe novel persistent cellular or anatomical reservoirs. In contrast, HIV infection of humanized mice provides a useful and practical model to assess the toxicity and efficacy of new strategies in a uniquely mutable system.

Timothy Ray Brown has inspired the field of HIV cure research. Several recent advancements in cellular and gene therapies have emerged at the forefront of HIV cure research (summarized in this issue, by Spraag et al., pp. 442–449). In addition to their original purpose [protecting cells from new infection through C-C chemokine receptor type 5 suppression or disruption], cell and gene therapies are now being used to boost HIV immune responses through vectored delivery of antibodies or T-cell therapies.

The road to an HIV cure is long and arduous. Precisely defining obstacles and potential solutions...
to each barrier, as described by the authors of 12 articles in this issue, will undoubtedly contribute to our progress in this extraordinary difficult mission.

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Conflicts of interest
There are no conflicts of interest.

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