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PERSPECTIVE

International AIDS Society global scientific strategy: towards an HIV cure 2016

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Antiretroviral therapy is not curative. Given the challenges in providing lifelong therapy to a global population of more than 35 million people living with HIV, there is intense interest in developing a cure for HIV infection. The International AIDS Society convened a group of international experts to develop a scientific strategy for research towards an HIV cure. This Perspective summarizes the group's strategy.

The HIV/AIDS pandemic represents the most important global health challenge in modern history. Fortunately, when used optimally, combination antiretroviral therapy (ART) can effectively control HIV replication, prevent the development of AIDS, prolong life and reduce the risk of transmission. Despite this unquestionable success, the current treatment strategies have limitations. The operational and logistical challenges involved in delivering lifelong treatment are daunting, and the economic costs of providing ART to the more than 35 million people who are currently living with HIV might be unsustainable[1]. Lifelong adherence to treatment is challenging for many. Although rare, antiretroviral-drug resistance remains a problem, particularly for those individuals who are unable to fully adhere to treatment. Drug toxicities, complex drug–drug interactions (polypharmacy) and persistent immune dysfunction have substantial health consequences. These factors highlight the urgency of identifying an effective means of controlling the virus in the absence of ART, or finding a cure (**Box 1**). The search for a curative strategy for HIV is now a key priority for the HIV community[2], and encouraging results have already been reported (**Fig. 1** and **Box 2**).

The International AIDS Society (IAS) established the "Towards an HIV Cure" initiative in 2010. A major outcome of this initiative was the development in 2012 of a long-term scientific strategy by a large, multidisciplinary group of scientists[3]. Given the evolving nature of research into a cure for HIV (**Box 2**), the initiative expanded its scope by adding new members with unique expertise relevant to the emerging agenda, broadening the strategy beyond biomedical research to include the social and behavioral sciences (**Box 3**). This second edition of the 'Global Scientific Strategy: Towards an HIV Cure 2016' describes the crucial knowledge gaps and research questions in the field (**Table 1**).

Molecular biology of HIV latency

Background. A major barrier to curing HIV is latency, which is defined as the persistence of integrated viral DNA that is replication competent but transcriptionally silent. HIV persists primarily as a latent genome in long-lived memory $CD4^+$ T cells, and to a lesser degree, in naive $CD4^+$ T cells. Whether latency occurs in myeloid cells remains controversial. Multiple cellular mechanisms have been defined that contribute to the establishment and maintenance of latency (**Fig. 2**). A repressive chromatin environment is actively maintained at the HIV long-terminal repeat (LTR) by the activity of histone deacetylases and other regulatory proteins, and by the absence of host factors that are needed to support viral transcription, including nuclear factor kappa B (NF-κB) and positive transcription elongation factor b (PTEF-b)[4–6]. Transcriptional interference by host promoter activities also prevents successful HIV proviral transcription[7]. These multiple levels of transcriptional control confer an apparent stochastic nature to HIV proviral DNA expression, whereby even in the face of multiple activating signals, latency cannot be instantaneously disrupted in all proviral genomes[8].

The contribution of residual low-level (or 'cryptic') virus replication and spread during ART to HIV persistence is unresolved.

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Box 1 Defining cure in HIV disease

The definition of cure is important to clarify for researchers, clinicians and people who are living with HIV. The optimal outcome would be the complete eradication within an individual of all replication-competent HIV. Such a sterilizing cure will be challenging to achieve and impossible to prove with current technologies[111]. A more feasible outcome will be the achievement of long-term remission. Remission is likely to be a necessary precursor for the development of an HIV cure, and is increasingly utilized in the field to indicate the goal of long-term undetectable viremia for an as-yet-undefined period (probably of several years) in the absence of ART[112]. The concept of disease remission denotes improvement, albeit with some uncertainty, and is already well entrenched in medical settings[113].

Two controlled studies of ART intensification with the integrase inhibitor raltegravir found evidence of persistent cycles of virus replication in a subset of participants[9,10]. A study of HIV-sequence evolution within lymph node tissue found evidence of viral evolution within the first 6 months of initiating ART, a finding consistent with low-level replication[11,12], but other studies of long-term ART have failed to find any evidence of evolution[13], even in tissues[14].

The current most studied approach for eliminating latently infected T cells is based on the hypothesis that HIV latency can be reversed, which leads to the clearance of these cells through virus- or immune-mediated cytolysis ('shock and kill' therapy). The administration of latency-reversing agents (LRAs), including histone deacetylase inhibitors (HDACis) and disulfiram, to individuals with HIV who are on ART has been shown to induce an increase in both cell-associated and plasma HIV RNA levels; however, these interventions had no apparent effect on the frequency of latently infected cells[15–18]. It is unknown whether current approaches have failed because they are insufficiently potent or because the cells induced to produce the virus are not cleared[19].

Understanding blocks in HIV transcription and virus production in latently infected resting cells. Basic research on the cellular mechanisms that constitute the rate-limiting steps that control gene expression in resting CD4$^+$ T cells could be informative. Indeed, a better understanding of the factors that enable or restrict transcriptional initiation and RNA processing at the HIV LTR, and how to manipulate these factors therapeutically, is needed (**Fig. 2**).

HIV RNA transcription is not the only event that is required to disrupt latent infection effectively. HIV mRNA export, splicing and translation, viral antigen expression and/or processing and presentation are relatively understudied, especially within resting memory CD4$^+$ T cell populations. A full understanding of the steps and processes that allow the rare latently infected cell to be revealed to the immune system or to be targeted is still lacking.

Development of *in vitro* models of HIV latency. The field currently lacks validated systems through which to test and compare different LRAs[20]. The development of *in vitro* cellular models that are based on resting CD4$^+$ T cells is badly needed. These models will need to reiterate the biology that is crucial for the establishment and maintenance of latency.

Development of more selective and effective LRAs. Although it is clear that LRAs can stimulate the production and release of virions from a small subset of infected cells *in vitro*, more potent LRAs are needed. This will probably require the redistribution or upregulation of several key cellular factors with combination therapies[21]. It will be challenging to identify such combinations with current *in vitro* systems because these systems fail to capture the complex signaling networks *in vivo* that maintain memory cells in a resting state (and that hence maintain latent infection). One new approach under study might function indirectly by activating antigen-presenting cells to signal and activate memory cells (for example, toll-like receptor agonists). Current systems are also unable to study LRA activity over prolonged periods, which will probably be needed, given the stochastic nature of latency reversal, and which will highlight the role of animal models in this research.

All LRAs target host cellular pathways and hence might have untoward effects on multiple other host genes[22]. LRAs that broadly activate all T cells are likely to reverse latency, but the inflammatory consequences will almost certainly prove risky[23]. LRAs that alter the epigenetic environment that silences DNA transcription could increase the risk of malignant transformation; indeed, the first generation of LRAs (vorinostat and panobinostat) studied in the clinic had mutagenic potential in common screening assays. Given their non-specific effects on the activation status of memory cells, some LRAs have the potential to stimulate cell proliferation, which could lead to the expansion of an infected cell population[24,25]. Immune-modifying drugs that mitigate this response might need to be developed along with LRAs. Finally, these approaches will have to be carefully vetted for their potential to dampen the very immune responses that are needed for viral clearance[26].

Strategies to silence the HIV provirus permanently. An alternative approach that represents a marked departure from the 'shock and kill' paradigm is to fully and irreversibly suppress HIV transcription, leading to permanent silencing and a lack of virus production upon

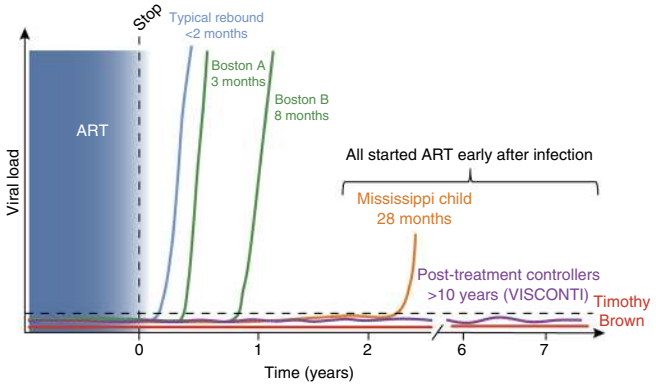


Figure 1 Cases of transient or sustained remission off ART. Viral rebound after the cessation of ART usually occurs within 2–3 weeks. In some circumstances, viral rebound has been substantially delayed in the setting of stem cell transplantation (Boston patients A and B) or of very early ART in an infant (Mississippi child). In some individuals, long-term post-treatment control off ART has been achieved. In these post-treatment controllers, ART was nearly always initiated in acute infection, and the virus was usually detected at low levels in plasma. These individuals were first described as part of the VISCONTI study (viro-immunological sustained control after treatment interruption) in France. Timothy Brown remains the only HIV-positive individual off ART with no virus detected in blood or tissue. He received a stem cell transplant from a donor who was *CCR5*Δ32 negative, and he has remained off ART for more than 7 years.

Box 2 Progress in HIV-cure research, 2012–16

There have been a number of important advances since the publication of the first 2012 Global Scientific Strategy: Towards an HIV Cure[3]. Sustained periods of aviremia in the absence of therapy were achieved in an aggressively treated infant, in at least two individuals who have received allogeneic stem cell transplantation and in adults who received several years of ART initiated soon after infection (**Fig. 1**)[58,62,63,114]. Nonhuman primate and humanized mouse models of well-treated SIV and HIV disease have been validated and used to advance the scientific agenda[64,115]. Most HIV in blood was found to be replication incompetent, and most of the apparent replication-competent virus was found to be noninducible *ex vivo*[8]. Early initiation of ART limits the establishment of the reservoir and prevents the generation of immune escape in latently infected cells[64,116,117]. New tools that can quantify the frequency of a cell that carries replication-competent virus have been developed[89,90], and some biomarkers have been shown to predict the time to viral rebound after a treatment interruption[93,94,118,119]. The central role of the T_{FH} cells and the B cell follicle in supporting SIV or HIV replication was established[35]. The central role of long-lived, self-renewing memory CD4+ T cells as a reservoir during sustained ART (>10 years) was established[33], whereas the role of macrophages as a stable reservoir during ART has been challenged[14,37]. Homeostatic proliferation induced by cytokines or HIV-integration events as a mechanism of persistence was demonstrated[25,40,41,120]. Evidence was presented suggesting that HIV continues to replicate and evolve during the first 6 months of ART[121], but not necessarily during long-term ART[13]. New LRAs and combination approaches were identified *in vitro*[21,122–124], and the capacity of more established LRAs to disrupt latency was demonstrated in a series of phase 1/2 clinical trials[15–17,22,125]. Novel vaccines were developed that contained and possibly cured SIV infection when administered before infection[47], and the safety and potential efficacy of bNabs and bispecific antibodies were demonstrated[47,48,52,53,55,126]. The safety of gene therapy with *CCR5* modification was found to be feasible and safe[10,83].

Box 3 Methodology

This second edition of the Global Scientific Strategy: Towards an HIV Cure was developed under the auspices of the International AIDS Society (IAS) to revise and update the original strategy released in 2012. The strategy was discussed and developed by the International Scientific Working Group, a global team of leading stakeholders, including basic scientists, clinical physicians, social scientists, ethicists and community leaders from around the world. The International Scientific Working Group was composed of seven multidisciplinary subgroups and included input from medical ethicists in each subgroup. The Global Scientific Strategy (GSS) was discussed, developed and finalized at a series of in-person workshops and electronic discussions from October 2014 to February 2016. In addition to discussions with the International Scientific Working Group, the Global Scientific Strategy (GSS) underwent wide dissemination for a peer-review process, incorporating comments and edits from a broad range of stakeholders, in keeping with the values of the IAS. These research recommendations represent the culmination of hundreds of hours of online and in-person meetings with community leaders, pharmaceutical-company representatives, funders and regulatory-agency representatives, as well as HIV researchers from low-income, middle-income and high-income country contexts. A number of non-HIV researchers were consulted on specific scientific issues.

the discontinuation of ART. This strategy will require approaches that specifically target the integrated HIV genome[27,28]. We lack an understanding of the molecular mechanisms that are involved in pharmacologically mediated 'deep' latency, and the durability of this state.

Defining the role of HIV replication as a cause of persistence. The role of ongoing HIV replication in maintaining HIV persistence remains controversial. HIV might continue to spread, despite ART, as a consequence of insufficient drug potency, pharmacologic barriers that prevent the distribution of treatment to all tissue reservoirs and/or a lack of effective immunity, particularly in potential immune-privileged sanctuaries. Assays that can assess new infection events—rather than simply the production of virions—will need to be developed; these assays will presumably need to be validated using lymphoid tissues. Novel strategies that overcome potential mechanisms for persistent replication (for example, more potent ART and enhanced T cell immunity) will need to be studied in animal models—and eventually, people—to determine whether replication persists and whether it can be inhibited.

The immunology of HIV persistence

Background. Untreated HIV causes irreversible harm to the immune system. Effective ART reverses many of these abnormalities, but a state of persistent inflammation and immune dysfunction typically persists. This immune state during ART is characterized by chronic low-level inflammation in the adaptive and innate immune systems, elevated immunoregulatory responses and CD4+ and CD8+ T cell dysfunction. It is thought that this compromised immune state contributes to HIV persistence on ART, and that efforts to control HIV in the absence of ART might require interventions that reverse some or all of these immunological abnormalities[29].

Characterizing and quantifying the total-body burden of replication-competent HIV is challenging, because most of the virus resides in difficult-to-access lymphoid issues. In blood and tissues, HIV persists primarily in either latently or productively infected memory CD4+ T cells[30–32]. Over time, the virus may become enriched in memory cells with self-renewing stem cell–like capacity[33]. T follicular helper (T_{FH}) cells might also be highly enriched for replication-competent virus, perhaps because they reside largely in B cell follicles, which are relatively inaccessible to HIV-specific CD8+ T cells[34–36]. Although macrophages are productively infected during untreated HIV infection, it has proved difficult to demonstrate conclusively that replication-competent HIV persists indefinitely in these cells during ART[37], or that HIV persists in those tissues that are rich in macrophages, particularly the central nervous system[38,39].

It is generally accepted that the biology of CD4+ T cell memory determines the fate of latently infected cells. Major knowledge gaps exist in this area. The lifespan of these cells *in vivo* is unknown. Clonal expansion of HIV in memory CD4+ T cells is apparently common, perhaps because the site where HIV integrates enhances cell proliferative or survival capacity[14,40–43]. The relative contributions of cytokine-mediated T cell turnover (T cell homeostasis) versus

Table 1 Priority areas for research towards an HIV cure.

Molecular biology of HIV latency	Immunology of HIV persistence	Models for HIV cure or sustainable remission	Remission in the pediatric population	Gene and cell therapy	Novel biomarkers to quantify HIV persistence	Social-science and health-systems research
Further develop and refine resting CD4+ T cell models that reflect the diversity of proviral latency to decipher the molecular mechanism of HIV latency and to ensure that they are sufficiently tractable for use in therapeutic testing and development	Characterize in a diverse population of children and adults with HIV the distribution of the replication-competent virus in all tissues	Establish an ethical balance between scientific gain and the interests of study participants in testing invasive or potentially risky interventions, considering medical and nonmedical risks and benefits for individual participants, as well as broader societal benefits	Understand the development of the innate and adaptive immune systems in the systemic and mucosal compartments	Explore the potential of engineered T cells to target HIV-infected cells	Systematically and impartially determine the performance characteristics of all assays of putative biomarkers	Promote patient-focused research to understand the perceptions, attitudes and beliefs of individuals with HIV, their partners and communities toward HIV cure
Apply new tools, including single-cell analyses, to explore the diversity of proviral latency, and identify pathways and factors that could be targeted in therapeutic testing and development	Characterize the impact of the host immune environment on the size, distribution and inducibility of the reservoir, focusing on the most relevant tissues	Develop iterative animal and clinical studies to understand the anatomical and cellular components of the reservoirs, the responses to novel interventions and the utility of candidate biomarkers for predicting viral recrudescence	Understand latent-reservoir dynamics and factors associated with the establishment and maintenance of latency, including the central nervous system as a reservoir	Develop methods to deliver gene therapies to reservoir cells	Develop nonhuman primate and human sample repositories and clinical databases to validate single or composite biomarkers of the duration of ART-free remission	Measure and promote stakeholder engagement in HIV-cure research among a diverse group of individuals from a range of local contexts
Explore the contribution of HIV restriction factors in controlling the establishment and maintenance of HIV latency	Determine in animal models, and ultimately, in humans, the effects of immune-modifying drugs on latency reversal	Understand the impact of the timing of ART on HIV persistence and remission by in-depth characterization of the immunological and virologic profiles at the time of ART initiation	Understand pre-existing immune responses against HIV and the role of immunotherapeutics in eliminating latently infected cells	Develop methods to boost immune responses in combination with cell and gene therapies	Assess biomarkers of HIV persistence in different populations, including children, adolescents, the elderly, women and transgender individuals	Use decision analysis and related modeling strategies to optimize clinical trials, enhance HIV-cure strategies and demonstrate budgetary impact
Develop assay systems in patients' cells to assess a range of responses: enforcement of latency, RNA expression, antigen expression and virion production	Develop therapies that enhance the capacity of the immune system to target and eliminate virus-producing cells during ART, and to control residual HIV in the absence of ART	Construct an operational definition for HIV remission, for use in both clinical research and community communications	Identify ways to appropriately conduct HIV-cure research in children, including studies that involve new interventions, invasive procedures and treatment interruption	Understand the consequences of myeloablative conditioning to enhance HSC engraftment, and develop alternative approaches	Leverage technological advances in genomics, metabolomics, proteomics, imaging and single-cell analyses to identify new potential biomarkers of the persistence of replication-competent proviruses in blood and tissue, and identify a phenotypic marker of a latently infected cell	Determine optimal health systems and policy strategies to promote HIV-cure research

For each section of the strategy document, the priority areas of research are described.

antigen-mediated T cell activation on the persistence of the replication-competent reservoir are unknown, but massive and sustained clonal expansion of cells containing an intact provirus that is capable of sustaining infectious viremia has been reported[43].

Defining the distribution of HIV during ART. We need to better define and quantitate the anatomical and cellular sites of HIV persistence on ART and assess their evolution over time. For accessible tissue sites (for example, lymph node and gut), the spatial distribution of the replication-competent virus should be defined, and the degree to which active replication persists within putative 'sanctuaries' (for example, the B cell follicle or variable sites of antiretroviral penetration) should be determined[12,35]. For tissue sites that are less accessible (for example, spleen, brain, genital tract and thymus), tissue banks should be accessed because these contain samples from both biopsies and autopsies of people with HIV who died while on ART. It is expected that further validation of nonhuman primate models will complement these human studies.

A number of questions persist regarding the memory CD4+ T cell populations that harbor HIV during ART. Is HIV enriched in cells with certain antigen specificity during ART? Can replication-competent HIV be found readily in all CD4+ T cell populations, including T regulatory cells, T_H1, T_H2, T_H17 and T_{FH} cells? Does the distribution of virus across these populations change over time? What is the nature of the tissue-resident CD4+ T cells that harbor latent HIV and cannot be sampled readily in humans? Does signaling between antigen-presenting cells (for example, dendritic cells and macrophages) and neighboring infected cells in lymphoid tissues contribute to latency[44]?

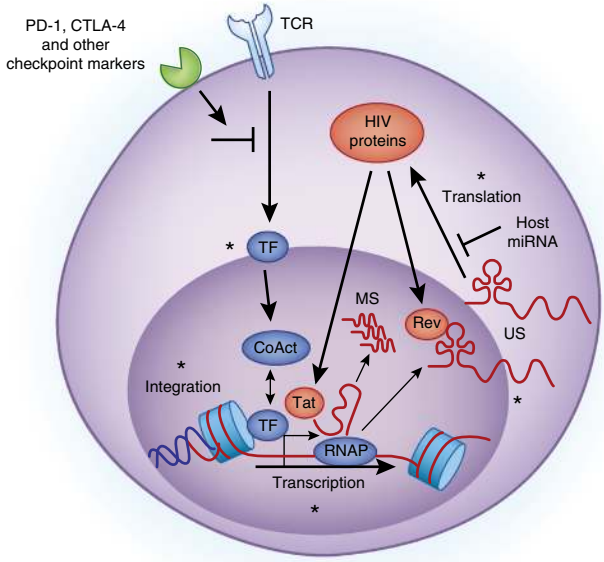


Figure 2 Mechanisms that maintain HIV latency in resting CD4+ T cells. There are multiple blocks to viral production in latently infected resting CD4+ T cells (asterisks), including the site of integration, epigenetic silencing of transcription, lack of cellular transcription factors, incomplete elongation of viral transcripts, nuclear retention of transcripts and microRNAs (miRNA) limiting the translation of viral proteins. TCR, T cell receptor; TF, transcription factors; co-Act, co-activators; MS, multiply spliced; US, unspliced; Rev, HIV Rev protein; RNAP, RNA polymerase.

Emphasis should be placed on exploring how human variability (for example, host genetics, age, gender, co-morbidities, co-infections, HIV-disease-progression state and the microbiome) affects HIV persistence on ART. Given that the majority of those infected with HIV are chronically co-infected with other pathogens, such as malaria, *Mycobacterium tuberculosis*, hepatitis B or C virus or helminthic worms, the impact of such co-infections on the persistence of HIV should also be studied. In addition, as the epidemic matures, more people will have been on suppressive ART for longer—up to two decades. Although the reservoir in blood seems to be remarkably stable over time, recent data suggests that it continues to decay (or becomes less active) over many years in the lymph nodes[36]. The long-term (decade-length) stability of the reservoir in terms of size, distribution, response to activation and replication competence should be defined.

Defining the biology of the reservoir. How CD4+ T cell memory is established and maintained in humans has not been fully characterized. These efforts are likely to involve transcriptomic and proteomic analysis of infected cells, as well as analysis of the transcriptional state of the virus. The impact of anatomical site, the microenvironment, cellular metabolism and the microbiome on T cell dynamics should be defined.

Enhancing the capacity of the immune system to clear or control HIV. Most cure strategies will require the active elimination of infected cells or the control of HIV persistence by T cells, antibodies, natural killer (NK) cells and/or macrophages. With regard to enhancing T cell function, a number of approaches should be pursued. T cell vaccines that are able to enhance HIV-specific immunity remain a priority. There is specific interest in approaches that stimulate responses against novel, nondominant epitopes, given that cytotoxic T lymphocyte (CTL) escape to standard (canonical) epitopes probably exists in most individuals, and given that most vaccines seem to stimulate pre-existing memory responses[45]. A potent cytomegalovirus (CMV) vector re-engineered to stimulate sustained responses to novel, nonimmunodominant epitopes has shown promise in nonhuman primate models[46–48].

Broadly neutralizing antibodies (bNabs) may also play a part[49–53]. The degree to which such antibodies might target latently infected cells that go on to express viral antigens spontaneously or after induction by a LRA, or that to which they are able to overcome the sequence diversity that emerges in chronic infection, needs to be defined. The optimal effector pathway (for example, NK cells, macrophages and complement) for the clearance of infected cells is unknown[54]. Therapies that target effector cells that home to lymphoid tissue, including chemokine blockade and/or the disruption of B cell follicles, should also be pursued. Bispecific antibodies that enhance virus production and that simultaneously recognize and eliminate virus-expressing cells have shown promise in preclinical models and should be advanced into the clinic, with the recognition that potentially harmful off-target effects could occur[55,56].

Targeting T cell homeostasis and T cell dysfunction. Therapies that aim to reverse chronic inflammation could contribute to cure or remission by (i) altering the chronically dysfunctional immunoregulatory environment with an aim at enhancing T cell function; (ii) reducing T cell proliferation (homeostatic and antigen driven); and (iii) reducing virion production and the generation of new target cells, thereby reducing virus spread. Proof of concept for these approaches was demonstrated recently in nonhuman primates[57]. Potentially targetable pathways that could be informative if blocked or enhanced include immune checkpoints (PD-1, CLTA-4, TIGIT and others), indoleamine-pyrrole 2,3-dioxygenase (IDO), interleukin (IL)-18, mTOR, JAK/STAT, IL-10 and TGF-β, among others.

Many of these approaches have substantial risks, which makes studies in generally healthy adults who are positive for HIV and on ART challenging from an ethical perspective. More interaction between HIV specialists and other disciplines working with these approaches is urgently needed. There may be particular synergies between HIV experts and those who are working in oncology, autoimmune disease and transplantation. Indeed, careful studies of adults with HIV who are undergoing transplant surgery have revealed novel insights regarding HIV persistence on ART and the potential role of immune-modifying therapies[58,59]. Careful studies of adults positive for HIV with cancer who are receiving immune-checkpoint blockers or other emerging immunotherapies should prove to be particularly informative, and these could lead to the identification of novel curative strategies for HIV infection[60].

Developing and maintaining well-characterized cohorts. Studies of those who control HIV naturally ('elite controllers') have provided the strongest evidence to date that HIV-specific CD8+ T cell immunity can contribute to virus control[61]. More recently, some individuals who might have been destined for poorly controlled HIV were turned possibly into long-term controllers by early introduction of ART that was subsequently discontinued[62,63]. The development of larger cohorts of these 'post-treatment controllers' will be needed to confirm these provocative findings. Other cohorts that should prove valuable include those of individuals undergoing solid-organ transplantation[59] or of

individuals receiving immunotherapy and other treatments for the management of cancer and other chronic disease[60].

Models for HIV cure or sustainable remission

Background. Animal models, including nonhuman primates infected with simian immunodeficiency virus (SIV) and humanized mice infected with HIV provide numerous important advantages, including the ability to control experimental variability, definition of the identity, size, timing and route of the virus inoculum and the flexibility of experimental and therapeutic interventions. The ability to perform extensive tissue sampling in animal models, including elective necropsy, is a key advantage, because the vast majority of virus that persists on ART resides in tissues that are difficult or impossible to sample in a clinical setting. These models contribute substantially to the overall research effort aimed at achieving HIV remission. Studies in animal models have informed the field about the rate at which latency is established, the anatomical and cellular components of the reservoirs and the responses to novel interventions[35,64,65]. Recently, ART regimens have been developed that can achieve and maintain clinically relevant levels of viral suppression in nonhuman primate models, and, encouragingly with regard to the potential predictive value of such studies, results in nonhuman primate studies of LRAs have paralleled results from clinical studies of the same agents[66].

Humanized mouse models have also been used for studies in this area, but limitations on sampling from individual animals, the relatively short duration of feasible studies (weeks) and graft-versus-host disease in many models restrict the utility of such models to addressing only certain questions[65,67]. However, these models permit the rapid evaluation of selected strategies in the context of HIV infection of human immune cells.

Development of models. Because of the high bar to clinical testing of unproven and potentially hazardous interventions in a population that is doing well with standard-of-care ART, animal models provide an important pathway for the evaluation of novel strategies to achieve cure of or sustained off-ART remission from HIV infection, serving as a key step for proof-of-concept study *in vivo* and safety testing. Key research questions in this setting include further efforts to establish whether these models recapitulate known and newly discovered features of HIV persistence in humans, including cellular and anatomic sites of residual virus, cellular and molecular factors influencing latency, the nature of immune dysregulation, and responses of the infected hosts to experimental interventions. Results so far have been encouraging, although some important aspects, such as the impact of very long ART (longer than a decade), will probably prove impossible to model in these animal studies[36]. Iterative studies in which the cycles of preclinical experiments in animal models are informed by emerging clinical data offer great promise to provide insights into the most relevant and most effective approaches.

Identify viable combination regimens. It is unlikely that any single intervention will result in a durable remission or cure. Most long-term strategies now being pursued involve combinations of various approaches. Examples include combinations of two or more LRAs with shock-and-kill therapies that aim to enhance the clearance of latently infected cells or combinations of therapeutic vaccines with adjuvants and/or immune-modifying agents (for example, immune-checkpoint inhibitors). It will be challenging to identify, develop and optimize such combinations in humans, given that many combinations will need to be tested and that characterizing the safety and pharmacology of individual interventions will probably need to be completed before such combinations can even be considered. Once animal models are fully optimized, well-resourced, iteratively designed and adequately powered studies of single and combination approaches should be adopted, with the most promising combinations advanced to humans.

HIV remission in the pediatric population

Background. Worldwide, there are almost 4 million children living with HIV, and 250,000 more are infected every year[62]. Children face the prospect of lifelong ART along with the added challenges associated with ART throughout childhood and adolescence (for example, limited appropriate drug formulations and poor adherence). As such, HIV remission represents an especially desirable goal for the pediatric population.

Perinatal HIV infection offers a unique opportunity to assess prompt control of HIV replication because of the known timing of HIV exposure through maternal infection. Other factors that may potentially further reduce the frequency of latently infected cells include immune tolerance in infancy, lower immune activation relative to adults and slower T cell memory development[68–70].

Characterize mechanisms of persistence. The major knowledge gaps for perinatal HIV infection are in understanding the mechanisms of latency in infants and children. The dynamics of HIV persistence in children are probably different than those in adults, owing to a number of factors, such as the types and numbers of target cells, the efficiency in clearing HIV-infected cells and pharmacokinetics of ART in blood and tissues. Little is known about the development of the newborn and infant innate and adaptive immune systems, or about the role of immune activation, homeostasis, inflammation and viral and host factors in the establishment and maintenance of HIV latency[71]. Early ART can preserve normal development of B and T cells, as demonstrated by the ability of children on ART to mount immune responses against childhood vaccines. However, there is limited understanding of the development of HIV-specific B and T cell immunity, including neutralizing and non-neutralizing antibodies and effector and polyfunctional T cell responses. The development of techniques for virologic and immunological characterization that require small blood volumes is crucial to advancing pediatric cure research. Given the difficulties in studying young children, development of infant animal models should be pursued.

Cell and gene therapy

Background. There is growing interest in the potential of gene and cell therapies to treat HIV infection (**Fig. 3**). This has been driven in part by recent technological advances and successes in other disease areas, especially in inherited immune deficiencies and cancer, and as seen in the successful outcome for Timothy Brown[72]. This individual received a hematopoietic stem cell (HSC) transplant as part of treatment for acute myeloid leukemia from a donor who was homozygous for the *CCR5*Δ32 deletion and therefore resistant to HIV infection. Mimicking this approach, most gene therapies to date for HIV have been based on the engineering of a patient's own (autologous) cells to confer HIV resistance, either by removing *CCR5* (ref. 73) or by introducing genes that encode anti-HIV proteins[74,75].

Gene therapies are also being considered as a way of directly removing HIV-infected cells while an individual is on ART, although daunting technical barriers exist. Other approaches seek to target integrated HIV genomes for inactivation using engineered nucleases such

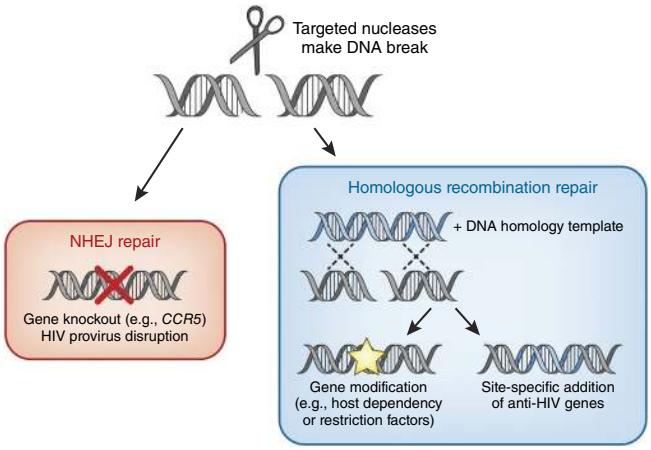


Figure 3 The use of targeted nucleases against HIV. Targeted nucleases, such as ZFNs and CRISPR–Cas9, provide more precise methods of gene therapy. They create site-specific DNA breaks, whose subsequent repair by the nonhomologous end-joining (NHEJ) pathway can be exploited to disrupt a gene, such as *CCR5*, or even an integrated HIV genome. Alternatively, repair can occur through homologous recombination, and a co-introduced DNA homology template can be designed to create small mutations in host genes or to direct the site-specific insertion of an anti-HIV gene.

as zinc-finger nucleases (ZFNs), TAL effector nucleases (TALENs) or clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 (ref. 76), although directing such treatments to latently infected cells *in vivo* poses substantial challenges, including the potential for off-target mutations. More practically, immune cells could be modified to recognize and destroy HIV-infected cells that express HIV antigens[77], in the same way that engineered T cell receptors or chimeric antigen receptor (CAR) T cells have proved successful against certain cancers[78,79]. Finally, cells could be turned into factories for the long-term production of anti-HIV molecules, such as bNabs[80] or protein mimetics of CD4 or CCR5 mimetics[81].

Because fully myeloablative conditioning will not be acceptable in noncancer settings, the percentage of gene-modified cells present immediately after transplant will represent a minority of the cells in the body. Although it is assumed that there could be some selection for gene-modified, HIV-resistant cells as the virus depletes those that remain genetically unmodified—and hence susceptible to HIV—this may not be effective if ART is maintained and if there is little or no replicating virus in the individual. Such selection could be temporarily induced with a treatment interruption, although the duration of uncontrolled virus replication required to select for a sufficient number of gene-modified cells is unknown, and there will be limited support for studies that require prolonged periods of viremia.

Explore the potential of engineered T cells to eliminate HIV-infected cells. The field of T cell engineering is moving rapidly, with great successes in the area of immunotherapies for cancer. In a similar approach, it is possible that the engineering of T cells to express modified TCRs or of CARs that recognize HIV antigens could provide control of HIV or eliminate infected cells. Other immune effector cells are also being developed as candidates for these methods[82].

Develop an HIV-resistant T cell population. There are a number of gene modifications that might render a T cell resistant to HIV infection. To achieve lifelong remission, it will probably require the protection of all possible target cells, including $CD4^+$ T cells and perhaps monocytes and macrophages. The ideal population to target is that of HSCs because they are long-lived precursors for multiple cell types; however, these cells are rare and technically challenging to isolate, genetically modify and engraft. Given that re-engineered stem cells have the potential for malignant transformation, the use of 'kill switches' (genes that can be activated to cause cell death) will need consideration.

Develop methods for delivering targeted nucleases to latently infected cells. Targeted nucleases such as ZFNs and CRISPR–Cas9 can disrupt HIV proviral DNA in cell-culture models, but their application to individuals with HIV will require enhanced methods of delivery. This includes the challenge of delivery to the rare, latently infected cells that may not express HIV antigens. Achieving delivery *in vivo* is a challenge for the field of gene therapy in general.

Apply methods to boost immune responses in combination with cell and gene therapies. It is uncertain whether genetically modified HSCs or T cells, even if resistant to HIV infection, could mediate the eradication of other infected cells. Consequently, some additional mechanisms will probably be required to control or eliminate persistent HIV while the gene-modified HIV-resistant cells protect against re-infection. Cell and gene therapies could therefore be combined with other treatments that boost HIV-specific immune responses, including novel therapeutic vaccine strategies, drugs—such as PD-1 inhibitors—that modulate T cell responses and LRAs. There are already some indications that engineered HSC-derived $CD4^+$ T cells or peripheral T cells can boost the endogenous immune system to control HIV[75,83], but this needs to be understood better.

Development of less toxic immunosuppressive conditioning regimens. Although the efficiency of rendering T cells or HSCs resistant *ex vivo* has improved substantially during the past few years, there is still an enormous problem of getting these cells to engraft without the use of toxic conditioning regimens. Although chemoablation increases the efficiency of engraftment of gene-modified HSCs and T cells, there are concerns about its toxicity. One mitigating approach is to do such studies first in HIV-positive individuals who have cancer, but this patient population is small—and getting smaller. More investigation is needed into the long-term effects of such treatments, because the risks of ablation in the autologous-gene-therapy setting are unknown. Novel, less toxic regimens therefore need to be developed. These include safer (nonmutagenic) methods of conditioning and the possibility of positive selection for engineered cells *in vivo* after transplantation[84].

Novel biomarkers to quantify HIV persistence

Background. The quantitative viral-outgrowth assay (QVOA) has long been considered to be the gold standard for measuring the size of the replication-competent reservoir[85–87]. The assay is labor intensive, expensive and requires large numbers of cells. Recent advances in measuring the levels of inducible virus include a similar limiting-dilution format, but measure the production of cell-associated RNA or the release of viral RNA in supernatant[88,89]. The amplification of latent infectious virus using a humanized mouse model—the murine viral-outgrowth assay (MVOA) can also be used[90].

HIV-infected cells can also be quantified using PCR-based assays. Total or integrated HIV DNA are both high-throughput assays that are more easily standardized; however, they overestimate the number of latently infected cells, because most proviruses that persist during

ART have lethal mutations or deletions[8,91]. The quantification of low-level plasma viremia by single-copy assay is useful in studies of latency reversal, but its relationship with the frequency of latently infected cells is unclear (**Box 4**)[91].

It is possible that measuring the immune response to HIV could be a more sensitive strategy for detecting residual virus than measuring the virus itself. The avidity and concentration of HIV antibodies seem to change with declining numbers of latently infected cells[92], and markers of T cell activation and proliferation have been shown in multiple studies to be correlated with the number of latently infected cells[29].

No biomarker has been identified that can accurately and consistently predict either time to viral rebound after ART discontinuation or the duration of ART-free remission, although progress is being made[93,94]. In the absence of predictable biomarkers of virologic rebound, the assessment of HIV remission requires the interruption of ART.

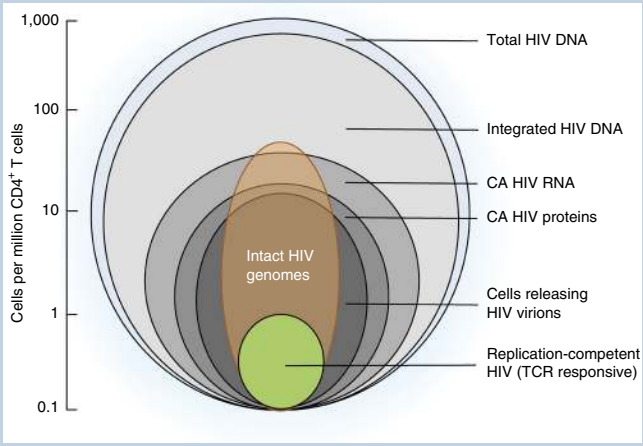
Define the performance characteristics of existing and evolving biomarkers. The performance characteristics of putative biomarker assays need to be much better characterized through an unbiased assessment of sensitivity, specificity, precision and accuracy, by testing blinded panels of clinical samples that are prepared and distributed by a central organization. Impartial, centralized distribution of test panels and data analysis are crucial components of the research infrastructure needed to determine biomarker-assay performance accurately. These efforts should include both blood-based and tissue-based biomarkers.

Develop highly sensitive biomarkers of HIV persistence. Biomarkers in blood might be too insensitive to represent adequately the extent of HIV persistence in tissue[35]. Indeed, previous case reports of prolonged remission after HSC transplantation—in Boston[58] and of very early ART administration to a child born to an untreated mother with HIV in Mississippi[95]—provide evidence that blood sampling alone, perhaps because there is a limit to how much blood can be collected, is not sufficiently sensitive to detect HIV persistence. Less cumbersome and more scalable means of sampling tissue need to be achieved as a potential means of increasing the sensitivity of biomarkers of HIV persistence. Advances in whole-body imaging technologies, such as immune positron-emission tomography (PET) scanning[96] and stereotactic guided tissue sampling, hold promise, but the reduction of risk and the simplification of the sampling process to that equivalent to phlebotomy are formidable challenges. Animal models, such as humanized mice and the MVOA, can enhance the lower limit of sensitivity to detect infectious HIV; these models will be limited both by the amount of cells that can be infused and by costs.

Identify specific markers of an infected cell. There is a compelling need to identify phenotypic markers for latently infected cells *in vivo*. It has been argued that HIV is enriched in cells that express markers of T cell activation and function, including HLA-DR, CCR5, CCR6, CXCR3 and PD-1 (refs. 30,97–99), although it is likely that only a fraction of cells expressing such markers harbors latent HIV. Whether persistent virus in activated cells differs from resting cells remains unclear. The identification of markers for the infected population could result in more targeted therapies.

Box 4 Measuring HIV persistence in virally suppressed individuals

The estimated number of cells infected with HIV that persist on ART differs depending on the methodology used. Approximately 100–1,000 CD4$^+$ T cells per million cells contain HIV genomes (HIV DNA). Only a fraction of these cells make cell-associated (CA) HIV RNA, and a smaller fraction have detectable HIV proteins or release virions into supernatant. A smaller fraction of cells generates replication-competent HIV *in vitro* after stimulation by T cell receptor (TCR) ligation (green circle; ~1/106 cells). However, sequencing of viral genomes indicates that the 'real' size of the reservoir (intact genomes, brown oval; ~60/106 cells) might be much larger than this.



Develop methods for detection of replication-competent proviruses. These methods might involve nucleic acid detection of signature proviral sequences that are present in intact proviruses only, and not in defective ones; high-throughput, full-length, single-genome sequencing to identify intact proviruses; or simplified viral-outgrowth assays that induce the complete reactivation of latent but intact proviruses, potentially using additional stimuli other than activation of the T cell receptor[100]. Recent innovations in high-throughput analyses of single cells should be applied with the goal of quantifying rare cells that contain inducible, intact proviruses.

Develop nonvirologic biomarkers that quantify the total-body reservoir. Potential biomarkers of this type include the levels of antibody to specific HIV proteins, the affinity of antibodies for such proteins or the frequency of B cells that are responsive to specific HIV antigens. Similarly, assays to assess the frequency of CD4$^+$ or CD8$^+$ T cells that are responsive to specific HIV antigens should be sought as markers of HIV persistence. Host transcriptional or metabolic signatures of continued innate or adaptive immune response to HIV nucleic acids or proteins might also prove to be sensitive markers of HIV persistence.

Validate biomarkers for use in studies of HIV cure and/or remission. Any putative biomarker needs to be validated as a predictor of the duration of ART-free remission. A major repository of biological samples of various types (blood, body fluids and tissues) and a robust clinical database of individuals who suspend

ART in a controlled manner are essential for the validation of candidate biomarkers.

Characterize and validate biomarkers for all HIV subtypes. An infrastructure to support biomarker development at a global scale will be needed to ensure that assays are optimized to detect common circulating HIV clades, in addition to subtype B.

Social-science and health-systems research

Background. Given the complexity of cure science outlined in the preceding sections, research on science translation and public engagement is crucial. Social-science research on an HIV cure has the potential to guide meaningful community engagement, ensure ethical conduct of research, mitigate the risks of behavioral disinhibition and therapeutic misconception, enhance patient–physician communication, engage global key populations, ensure economic viability and reduce pervasive HIV and sexual stigma. Health-systems research can facilitate policy-relevant research synergies, assist with health-systems preparedness, spur public–private collaboration and inform effective community-engagement strategies.

Identify perceptions of individuals with HIV. The voices of people living with HIV have always been central to the HIV response, and this must extend to cure research[101]. For many people living with HIV, their serostatus has been the basis for a number of decisions that influence their health (for example, serosorting and other sexual behaviors) and well-being (for example, participation in community groups and advocacy). How they understand the meaning of HIV cure is important, because these beliefs may influence their participation in clinical trials, their trust in HIV-service delivery systems, their engagement in care and treatment, serostatus disclosure and ongoing risk and protective behaviors.

The personal, behavioral, ethical and social implications of participating in HIV cure clinical research warrant greater attention in the context of clinical research. Examples of this type of research include research about how to effectively communicate the science; benefits and risks of HIV-cure trials as part of informed consent[102,103]; qualitative research among trial participants with HIV and their partners about how participation in cure studies affects the participant's HIV identity, sexual behaviors and social relationships; and research into how people living with HIV understand (or misunderstand) ongoing HIV-cure research[104,105].

Measuring and increasing stakeholder engagement. There are multiple stakeholders in cure research, including individuals with HIV, key affected populations, health professionals, scientists, funding agencies, international agencies, public-health and regulatory authorities, pharmaceutical industries and civil-society organizations. The history of HIV intervention research shows how early stakeholder engagement at multiple levels can help to increase the likelihood of success and to mitigate failure[106]. However, there are many key research areas that require further investigation, including better and more standardized tools for measuring stakeholder engagement and its downstream effects (for example, changes in retention rates and recruitment pace in cure-research projects); optimal timing and substance of HIV community and noncommunity stakeholder engagement, including investigation of the role of community advisory boards in representing the community research interests; and ensuring the affordability of community-engagement strategies, especially in resource-constrained contexts.

Clinical-trial equity and inclusiveness. To ensure an equitable distribution of cure strategies, it is essential to incorporate a diverse group of participants in terms of sex, ethnicity and nationality, location, age and other characteristics. However, the optimal mechanisms and tools for achieving such inclusiveness are unclear. This field could benefit from understanding the experience of the HIV-vaccine research field over the past several decades[107]. Research opportunities in this realm include community-based research on how to ensure inclusiveness and representativeness in HIV-cure studies and approaches to improve the likelihood of equitable implementation of and access to efficacious HIV-cure strategies, especially in resource-limited settings.

Health-systems research. Modeling research could help researchers to understand which individual cure strategy or group of strategies would be optimal for achieving population-level effects[108]. Both cost effectiveness (i.e., will the strategy be worth paying for?) and budgetary-impact research (i.e., will the strategy be affordable?) will be important, especially in resource-limited settings[109]. Identifying who will pay for a cure and how prices will be established is also crucial. Studies on how best to enhance public–private collaboration toward an HIV cure could alleviate some of the regulatory and logistical challenges associated with drug development.

Global perspectives. The local context of HIV-cure research is likely to prove crucial. For example, previous examples of ineffective HIV 'cures' in sub-Saharan Africa[110] may influence how individuals with HIV perceive HIV-cure research moving forward. The cost of delivering a cure would probably be different in these resource-constrained contexts. Yet, to date, none of the existing literature has focused on low-income-country contexts that have a disproportionately high burden of HIV and would potentially have the most to gain from a cure.

CONCLUSION

The development of a safe, affordable and scalable strategy that results in the complete eradication of HIV or sustained virus control in the absence of therapy is a key priority of the IAS, funders and the broader HIV community. There are now a number of potential therapeutic strategies that could conceivably achieve this goal, once considered aspirational. The challenges, however, remain substantial. A central premise of the IAS Global Scientific Strategy is that a multidisciplinary, collaborative and sustained effort will be needed to overcome these challenges. The strategy outlined here highlights the priority areas for research and will hopefully guide a global strategic research effort and inspire new investigators to engage in the challenge.

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COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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