OPINION

Towards an HIV cure: a global scientific strategy

The International AIDS Society Scientific Working Group on HIV Cure

Abstract | Given the limitations of antiretroviral therapy and recent advances in our understanding of HIV persistence during effective treatment, there is a growing recognition that a cure for HIV infection is both needed and feasible. The International AIDS Society convened a group of international experts to develop a scientific strategy for research towards an HIV cure. Several priorities for basic, translational and clinical research were identified. This Opinion article summarizes the group's recommended key goals for the international community.

Although in the current decade the HIV epidemic continues unabated, a notable success is that more than 20 different antiretroviral drugs are now available in many countries. When these antiretroviral drugs are used in combination, they improve health and prolong life in HIV-infected individuals and reduce the rates of transmission of the virus. Indeed, HIV-infected individuals who harbour a drug-susceptible viral strain, have access to antiretroviral drugs and are fully compliant with therapy can achieve and maintain complete, or near complete, viral suppression for years to decades. However, despite these successes, standard therapies do not fully restore health or a normal immune status in HIV-infected individuals, and patients still experience co-morbidities, such as increased cardiovascular disease, bone disorders and cognitive impairment[1]. In addition, interruption of antiretroviral therapy almost invariably leads to the re-emergence of detectable viral replication and the progression of AIDS. Perhaps more importantly, only a minority of HIV-infected individuals globally have access to antiretroviral therapy.

The cost of antiretroviral therapy has decreased substantially in recent years, and the availability of these drugs in resource-poor settings has steadily increased. However, the cost associated with delivering antiretroviral drugs to the 33 million people who are now living with HIV is overwhelming many organizations and public health systems. It is estimated that for every HIV-infected person who starts antiretroviral therapy, two individuals are newly infected with HIV; this is clearly unsustainable[2]. The continued presence on a global level of a large number of untreated HIV-infected individuals — who are the main source of ongoing HIV transmission[3] — means that the infected population is likely to grow. Given these well-recognized issues, there is a growing interest in developing curative strategies to tackle HIV[4–6]. Theoretically, a safe, affordable and scalable cure could address both the individual and public health limitations that are associated with lifelong antiretroviral therapy.

The International AIDS Society (IAS) convened a team of more than 40 scientists who are active in the field of HIV research. We have met frequently over the past 2 years. Throughout this process, the IAS has engaged with a broad range of stakeholders from around the world and has exhaustively solicited advice on the steps that should be taken to develop a cure for HIV infection. These efforts include the creation of a stakeholders' advisory board, and online and in-person discussions with hundreds of community activists, representatives from pharmaceutical and biotechnology industries, funding and regulatory agencies, and key HIV and non-HIV researchers from across the world.

In this Opinion article, we provide a concise, multidisciplinary plan that identifies a set of key scientific priorities that should bring us measurably closer to our vision of developing a cure for HIV infection (BOX 2). These priorities span the areas of basic, translational and clinical investigation. Two broadly defined approaches for curing HIV infection were considered by the group: first, the elimination of all HIV-infected cells (a sterilizing cure); and, second, the generation of effective host immunity to HIV that would result in lifelong control of the virus in the absence of therapy, despite not achieving the complete eradication of HIV (a functional cure). Here, we describe how the priorities identified by the IAS can allow us to achieve a sterilizing or functional cure for HIV.

Basic science aspects of HIV cure research

Multiple mechanisms are likely to contribute to HIV persistence during long-term, otherwise effective, antiretroviral therapy. These include the persistence of pools of latently infected $CD4^+$ T cells[7], *de novo* infection of target host cells (ongoing viral replication)[8,9] and the failure of the host immune system to recognize and eliminate infected cells. In the following sections, we discuss the mechanisms that we need to understand in order to identify a strategy that will lead to an HIV cure.

Mechanisms that establish HIV latency. Most $CD4^+$ T cells that are productively infected with HIV are likely to die from virus-induced cytopathic effects, but a small subset of long-lived 'resting' memory T cells that harbour integrated HIV DNA persist indefinitely[7] (a phenomenon generally referred to as latent infection) (FIGS 1,2). Although less well characterized, latent HIV infection may also occur in cell populations other than memory $CD4^+$ T cells, including naive $CD4^+$ T cells, tissue macrophages, astrocytes, thymocytes and perhaps haematopoietic progenitor cells[10–14]. The establishment of latency in resting memory T cells is due either to the infection of resting $CD4^+$ T cells (which is difficult to achieve *ex vivo*)[15–17] or to the infection of highly susceptible activated $CD4^+$ T cells followed by their reversion to

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a resting state[18–20] (FIG. 2). A more precise description of where the virus exists during effective therapy and how these reservoirs acquire HIV is needed. In addition, it will be important to determine the form of the virus in such reservoirs; for example, it could be present as pre-integrated DNA, integrated DNA, virions adsorbed on the surface of follicular dendritic cells or virions in the intracellular compartments of macrophages.

Mechanisms that maintain viral quiescence in persistently infected cells. True latency is defined as the maintenance in the host genome of integrated viral DNA that is replication competent but transcriptionally silent. The transcription of HIV DNA is regulated by the same pathways that regulate host DNA transcription, as well as by the HIV-encoded regulatory protein Tat[21]. Several mechanisms for latency have been proposed. One, there could be insufficient levels of host transcription factors — such as positive transcription elongation factor B (PTEFB)[22], nuclear factor-κB (NF-κB), nuclear factor of activated T cells (NFAT) and signal transducer and activator of transcription 5 (STAT5)[23] — coupled with the presence of negative transcriptional regulators (such as NF-κB1 homodimers)[24,25]. Two, restrictions at the HIV promoter region could prevent the access of host transcription factors. Three, transcription could be prevented by post-latency chromatin remodelling of HIV DNA and epigenetic silencing[26–29]. Four, there could be transcriptional interference by host promoter activities[30].

In addition to these molecular mechanisms acting in the nucleus, latently infected cells may be maintained by factors that result in an extended lifespan and/or homeostatic proliferation of the cells[31,32]. Of note, the host pathways that enable lifelong immunological memory also result in lifelong infection; hence, it is expected that advances in our understanding of latency will be informed by and contribute to our understanding of the basic immunology of T cell memory. Therapies (such as valproic acid, vorinostat and disulphiram) that promote the expression of viral proteins from latently infected cells by modifying these pathways have been or are currently being tested[33–37].

Cellular and tissue sources of viral persistence. It is well established that HIV-infected cells persist in the blood and in specific anatomical compartments, such as the gut mucosa, genital tract, lymph nodes and central nervous system[14,38,39]. Based on non-human primate studies, other tissues (such as the spleen and liver) are also likely to be enriched in HIV-infected cells[40–42]. Many of these tissues represent distinct biological compartments that may be resistant to standard treatments. For example, the central nervous system, the genital tract and possibly other tissues are difficult to access with certain antiretroviral drugs, and the nature of the virus population in these compartments is likely to be biologically distinct from that in the systemic circulation[43,44].

Distinct cellular reservoirs of HIV also exist. The best characterized and to date the only proven cellular reservoir of HIV during long-term HIV treatment are memory $CD4^+$ T cells that lack activation markers. However, the population of resting $CD4^+$ T cells is highly heterogeneous and includes several distinct subsets (for example, naive, stem cell memory, central memory, transitional memory and effector memory T cells). These subsets have specific biological features that may have a substantial impact on the long-term *in vivo* persistence of latent HIV infection[31,32,45]. For example, it is likely, although not yet formally proven, that it will be more difficult to eliminate HIV from less terminally differentiated memory T cells

that have a longer lifespan and greater proliferation potential than from more terminally differentiated cells with a shorter lifespan and more limited proliferative potential.

To identify the tissue and cellular source(s) of HIV persistence, sensitive phylogenetic analyses of HIV DNA or RNA should be conducted on multiple compartments. Non-T cell HIV reservoirs — such as astrocytes, dendritic cells and tissue macrophages — will also need to be studied. The impact of antiretroviral drug penetration in these tissues and the nature of the reservoir will need to be defined. It is expected that advances in this area will be accelerated by the establishment of an invasive biopsy and autopsy network aimed at obtaining relevant samples, as well as by studies of simian immunodeficiency virus (SIV)-infected non-human primates that are treated with antiretroviral therapies[42,46].

Effects of antiretroviral therapy on the immune system and consequences for HIV persistence. The interplay between HIV-associated immune responses and HIV persistence during effective antiretroviral therapy is complex and largely unknown. Despite long-term suppression of HIV replication, several immunological abnormalities persist, including a higher than normal frequency of activated and perhaps dysfunctional T cells. Multiple mechanisms that as yet are poorly defined contribute to this persistent state of immune dysfunction. Such mechanisms include lymphoid tissue fibrosis, an irreversible loss of gut mucosal integrity, an excessive burden of co-infections and a loss of immunoregulatory cells[47–49]. High levels of tissue inflammation and immune cell activation might, in turn, increase the number of potential HIV target cells that are susceptible to infection[50], increase the homeostatic proliferation of latently infected cells[31], increase the expression of molecules that alter T cell survival and/or function (such as programmed cell death protein 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4)) and reduce the ability of host immune responses to effectively recognize and kill infected cells (FIG. 2). Thus, studies are needed to determine how host responses affect HIV persistence. In addition, we should investigate several other areas: first, the optimal biomarkers for quantifying immune activation; second, the relative contribution of overall levels of immune activation or dysfunction in distinct subsets of treated individuals (such as those treated during the acute or chronic phases of infection); and, third, the factors that distinguish beneficial inflammatory responses from those that are harmful. Furthermore, there is a growing interest in defining the role of inflammation in causing cardiovascular and other non-AIDS diseases in antiretroviral-treated adults[51]. These studies should be designed to determine how such inflammatory responses contribute to HIV persistence. Again, studies in validated models of natural SIV infections and/or antiretroviral-treated non-human primates will prove to be informative for these questions.

Control of HIV reservoirs in natural models of HIV infection. An alternative to eliminating all infected cells (a sterilizing cure) is to enhance the host capacity to control persistent viral infection without achieving complete eradication of HIV (a functional cure). These are not mutually exclusive approaches, as it is likely that effective host responses will be needed to help clear the virus once latency is reversed and that efforts to reduce the size of the reservoir therapeutically will make host control more feasible[52]. To advance the field in these areas,

Box 2 | **Seven key scientific priorities for HIV cure research**

- Determine the cellular and viral mechanisms that maintain HIV persistence during prolonged antiretroviral therapy and in rare natural controllers. This includes defining the role of mechanisms that contribute to the establishment and maintenance of latent infection, as well as defining the role of ongoing viral replication and/or homeostatic proliferation.
- Determine the tissue and cellular sources of persistent simian immunodeficiency virus (SIV) or HIV in animal models and in individuals on long-term antiretroviral therapy.
- Determine the origins of immune activation and inflammation in the presence of antiretroviral therapy and their consequences for HIV or SIV persistence.
- Determine host mechanisms that control HIV replication in the absence of therapy.
- Study, compare and validate assays to measure persistent HIV infection and to detect latently infected cells.
- Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection in animal models and in individuals on antiretroviral therapy. This includes strategies aimed at reversing latency, as well as strategies aimed at clearing latently infected cells.
- Develop and test strategies to enhance the capacity of the host immune response to control active viral replication.

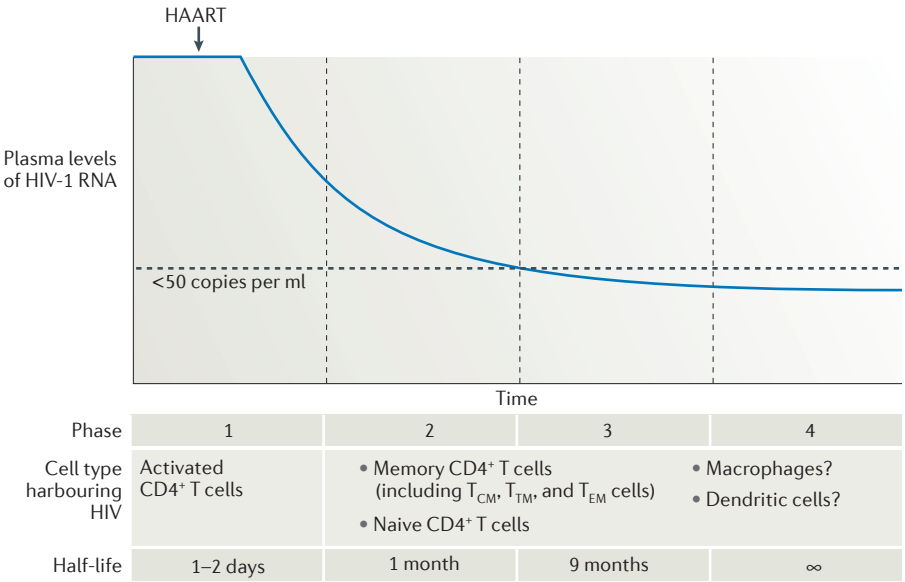

Figure 1 | **The impact of antiretroviral therapy on HIV reservoirs.** Most patients who adhere to antiretroviral therapy have dramatic and rapid decreases in plasma levels of HIV RNA. Persistent viraemia largely reflects the release of the virus from stable cellular reservoirs. The source of the virus during effective antiretroviral therapy is primarily defined by the half-life of the cells that were infected before therapy was initiated. After several years of therapy, long-lived populations of resting CD4+ central memory T (T_{CM}) cells become the dominant source of HIV persistence. Some of the data illustrated are based on REF. 55. HAART, highly active antiretroviral therapy; T_{EM}, effector memory T; T_{TM}, transitional memory T.

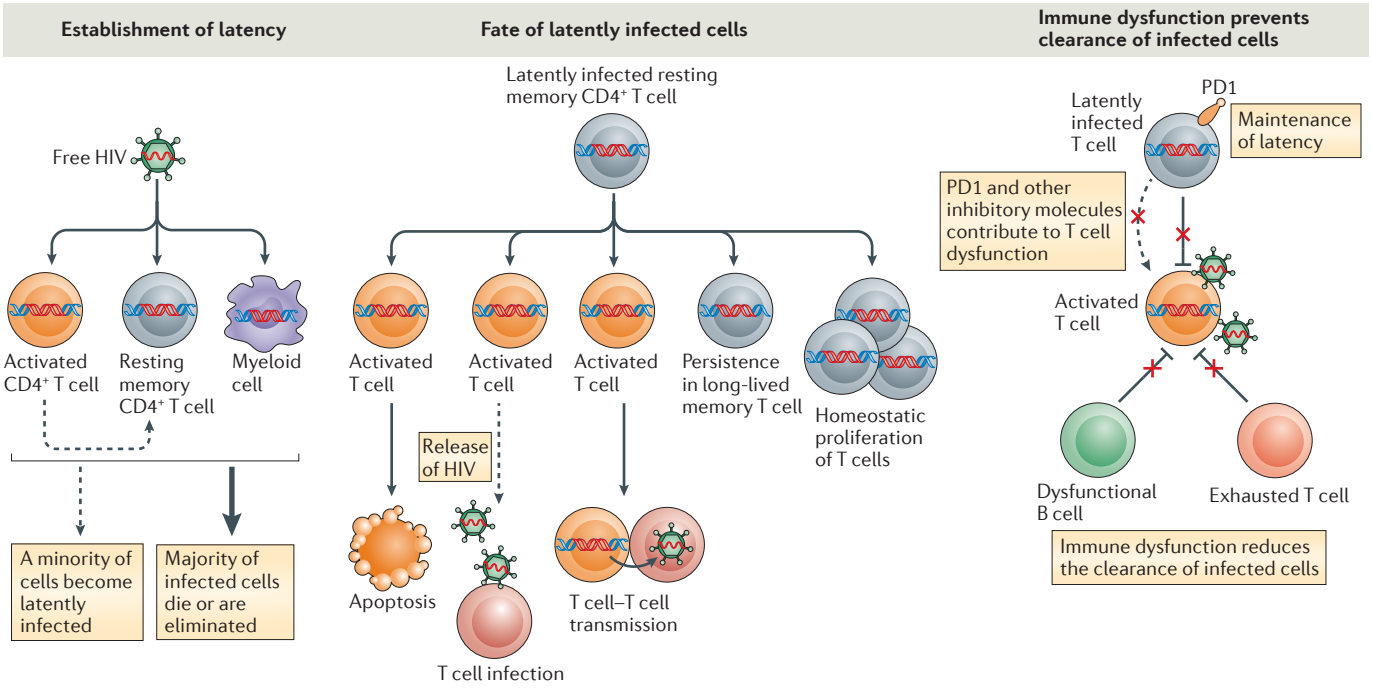

Figure 2 | **Mechanisms of HIV persistence during antiretroviral therapy.** The left panel illustrates how latent HIV infection can be established in T cell and myeloid cell reservoirs. The primary mechanism is probably infection of activated memory CD4+ T cells. Most of these cells die, but a minority revert to a resting state. The centre panel illustrates the fate of these now resting 'latently infected' memory CD4+ T cells. These cells either die slowly, become a source of new infections, persist as long-lived cells or expand through homeostatic mechanisms. The right panel depicts some immune mechanisms that contribute to persistence. These include mechanisms that maintain cells in a resting state (for example, the upregulation of programmed cell death protein 1 (PD1)). Immune dysfunction during therapy probably reduces the efficient clearance of infected cells.

a more thorough understanding of how the host can control HIV is needed. This work should include studies of those rare individuals who control HIV replication and do not experience a loss of CD4+ T cells and progression to AIDS (known as elite controllers or long-term nonprogressors). There should also be focused interest on identifying and characterizing those rare individuals who once had poorly controlled HIV but who remain aviraemic after interruption of long-term antiretroviral therapy (known as post-antiretroviral therapy controllers)[53]. Finally, the growing number of experimental SIV models as well as SIV and HIV vaccines that allow durable control after acute infection might prove to be an informative platform for these types of study[54]. There is, however, a strong need to move beyond conventional CD4+ and CD8+ T cell responses in order to better define the role of innate and other immune effector mechanisms in controlling HIV. For example, it will be important to address the functions of B cells, natural killer cells, dendritic cells, γδ T cells, natural killer T cells, regulatory T cells, T helper 17 cells and T follicular helper cells during HIV infection.

Host factors that determine the size of the HIV reservoir. Although not well studied, there is likely to be significant person-to-person heterogeneity in terms of the size and distribution of the viral reservoir. Large observational studies that involve the collection and banking of cell and tissue samples would be informative on this issue. We need to define the effects on HIV persistence of gender, race, treatment regimens, pre-therapy disease characteristics and treatment outcomes (such as optimal versus suboptimal CD4+ T cell gains and low versus high levels of inflammation).

The use of genomics technologies and other population-based high-throughput approaches should be considered in these analyses. An extensive number of genomic and proteomic studies have been conducted to define the correlates of virus control in the absence of therapy. These approaches should include as outcome measures the level of HIV persistence during therapy and the level of virus control after treatment interruption. Such studies might identify crucial determinants of outcome during long-term suppressive therapy, which presumably will be different from the determinants of outcome in untreated disease.

Translational research and cure research

Prospective plans to translate any basic science findings to the clinic in a rapid and efficient manner are needed. Findings from basic research should be translated into reagents that can be tested in validated models of HIV persistence and, ultimately, in clinical trials. Assays need to be developed and validated such that they can be used to monitor the impact of a potential therapy on the HIV reservoir. It has been proposed that a large collaborative network of academic, industry and regulatory experts will be required to support such translational research[4]. Our summary of the scientific priorities for such work is provided below.

Identify assays to measure viral burdens in patients on antiretroviral therapy. There are several assays that are now routinely used to quantify HIV persistence. These include measures of plasma HIV RNA (the single-copy assay), cell-associated RNA, episomal DNA (that is, extrachromosomal DNA, including two-long-terminal-repeat (2-LTR) circles), ratios of non-integrated to integrated DNA and levels of culturable replication-competent virus[55,56]. Many of

these approaches can be applied to tissue samples[38]. However, none of these assays is standardized, and the relationships between these measurements and the amounts of residual latent virus, the degree of persistent low-level replication and the extent of persistent immune activation or dysfunction are currently unknown. Although the definitive test of a cure will require interruption of antiretroviral therapy, it will be necessary to identify therapeutic interventions that reduce the size of the viral reservoir even as therapy is continued if clinical trials are to proceed in an efficient and ethical manner. Prospective comparative and validation studies that assess measures of HIV persistence are of high importance[56]. The key objectives of this work are to develop three types of assay: a high-throughput, scalable assay that quantifies the level of residual latent and replication-competent virus in relevant tissues; a method to quantify residual viral replication (as compared to residual viral DNA or antigen production); and treatment-specific assays that reflect the biological activity of potentially curative interventions.

Identify effective methods to monitor ongoing viral replication in patients on antiretroviral therapy. The extent to which HIV continues to replenish its reservoir through ongoing cycles of replication remains controversial. The lack of readily apparent viral evolution during therapy and the inability of additional drugs (that is, treatment 'intensification') to reduce the level of viraemia argue against the occurrence of residual replication[57–60]. By contrast, the ability of treatment intensification to affect virus levels and T cell activation in those tissues with the highest concentrations of virus and target cells indicates that the virus may indeed be replicating, albeit at very low levels[8,61,62]. As incomplete suppression of viral replication will allow reseeding of reservoirs when latency is reversed therapeutically (and new virions are produced), defining the degree to which viral replication persists during therapy is widely considered to be a crucial question. Efforts should probably focus on tissue reservoirs in which most of the virus is thought to reside, particularly where there are dense collections of target cells that might support the cell-to-cell transfer of the virus. Given the difficulty in accessing relevant tissues (such as the spleen and central nervous system), the role that myeloid cells have in shaping and maintaining the viral reservoir is largely unknown. Specifically, understanding the role of macrophages as a viral reservoir and the way in which signalling between myeloid cells and $CD4^+$ T cells leads to HIV persistence should be a focus of non-human primate and, when feasible, human studies[31,63,64]. Strategies that could potentially address these questions include whole-body non-invasive imaging in humans or whole-body tissue sampling in non-human primates. Increased collaboration among physicists, imaging experts, immunologists and virologists would assist this challenge.

Determine new cellular markers that identify latently infected cells in vivo. The best-characterized reservoir for latent HIV is resting central memory $CD4^+$ T cells. These cells — and other cell reservoirs — are highly heterogeneous, but it is likely that other phenotypical markers will allow for the identification of those cell populations that are enriched for latent HIV. For example, a presumed major pathway for the generation of latency is the reversion of activated and recently infected cells to a resting state. $CD4^+$ T cell activation is controlled and reversed, in part, by the expression of certain negative regulators of immune function, including the inhibitory receptor PD1. PD1 expression may therefore mark cells that are more likely to harbour HIV[31]. Knowledge about such markers will provide needed insights into how latency is established and maintained, and might lead to the development of new therapeutics that target latency in a specific manner. PD1-specific antibodies have shown efficacy in cancer studies and are slowly being advanced into HIV curative studies[65]. As another example, it is also probable (but as yet unproven) that HIV-specific $CD4^+$ T cells are more likely than non-HIV-specific $CD4^+$ T cells to contain latent HIV during long-term antiretroviral therapy. This is especially true in lymphoid tissues, where virus production and virus-specific $CD4^+$ T cells are likely to be concentrated. Progress in this area can be accelerated by the use of single-cell assay technologies and *ex vivo* models of latently infected cells.

Develop strategies to safely eliminate persistently HIV-infected cells in individuals on antiretroviral therapy. Over the past several years, several strategies aimed at eliminating persistently HIV-infected cells have been proposed. Most of these strategies involve deliberately inducing viral expression. Although such strategies assume that virus production would lead to cell death, the fates of such virus-producing cells are unknown[52]. An intensive screening and validation of agents that might eliminate persistently infected cells is of paramount importance. Such strategies might use agents that recognize viral antigens on the cell and deliver a secondary signal causing cell death. Similarly to ongoing strategies for cancer treatment[66], targeted T cell therapies that selectively kill subsets of cells harbouring the largest quantities of HIV DNA may have a profound impact on the size of a persistent reservoir. Moreover, immunotoxins directed at virus-producing cells have been advocated[67,68].

Develop strategies to enhance host immune-mediated control of active viral replication. The development of immune-based strategies that control viral replication would be very relevant for defining the path to a functional cure. Such strategies might also limit the replenishment of viral reservoirs that may occur through ongoing replication in treated subjects (particularly in tissues) and hence could help to achieve a sterilizing cure. The development of therapeutic vaccines aimed at enhancing immune-mediated clearance of virus-producing cells is therefore of high priority. Towards this end, focused efforts are needed to develop therapeutic immunization strategies (or comparable approaches) that generate effective responses against the autologous virus (or against regions of the HIV genome that are well conserved). In addition to therapeutic T cell vaccines — which so far have largely failed to control viral replication in untreated disease — efforts should be aimed at enhancing dendritic cell function, as promising data have been generated in this area[69]. Given the growing interest in antibody-mediated protection against HIV acquisition[70], it is hoped that the immense resources directed at developing a preventive vaccine might lead to the identification of novel ways to control established infection. This control might occur via the generation of antibodies that can neutralize cell-to-cell transmission of the virus or via antibody-dependent cellular cytotoxicity. Several therapeutic vaccine candidates are currently in the pipeline and should be developed further. These approaches could also be combined with adjuvants or cytokine-based agents, such as interleukin-7 (IL-7), that could potentiate cytotoxic T cell activity or restore $CD4^+$ T cell homeostasis[71].

Box 3 | **The Berlin patient**

The growing global interest in curing HIV infection is due, in part, to a remarkable case report. A 40-year-old HIV-infected man who was responding well to antiretroviral therapy developed acute myeloid leukaemia and eventually needed an allogeneic bone marrow transplant. Recognizing that a small proportion of people lack a functional CC-chemokine receptor 5 (CCR5), which is a key receptor for HIV entry, his Berlin-based clinical team identified an HLA-matched donor who was homozygous for the *CCR5* Δ32 deletion. After extensive conditioning to deplete his haematopoietic system, the patient was successfully transplanted. Antiretroviral therapy was discontinued at the time of transplantation. Remarkably, viraemia remained undetectable throughout the post-transplant period, which has now lasted for more than 5 years. In addition to the reconstitution of the immune system with CCR5-deficient cells, factors that may have contributed to this apparent cure include the use of extensive pre-transplant conditioning (which may have reduced the size of the HIV reservoir) and the use of immune-based therapeutics after the transplant (which may have altered the host environment, preventing low-level HIV replication and subsequent virological rebound).

Develop strategies to interfere with host mechanisms that contribute to viral persistence. The complexity of the interplay between immune activation (and its different causes) and viral persistence (and its various measurements) suggests that immune-based therapeutics aimed at reducing chronic immune activation may complement other strategies being considered[8,50]. As many potential interventions are potentially toxic and of uncertain benefit, it is expected that animal models will be needed to advance progress in this area. Agents that should be tested in these models include immunosuppressive or immunomodulatory agents, which may reduce residual inflammation and/or immune activation in individuals on antiretroviral therapy. This would block the potentially continuous replenishment of viral reservoirs that may be fuelled by ongoing immune cell activation. Alternatively, immune-based treatments that promote the differentiation of cells harbouring the virus from longer-lived to shorter-lived cells should be evaluated. For example, IL-15 is known to promote the differentiation of central memory $CD4^+$ T cells into shorter-lived transitional or effector memory $CD4^+$ T cells.

Develop relevant models to allow preclinical testing of therapeutic strategies. Several robust and highly promising primary cell and animal models of HIV latency have been developed[18,42,72–74]. It is expected that such models will be used to study the feasibility of eliminating persistently HIV-infected cells. However, several challenges still remain. First, the cell lines and *ex vivo* cultures of primary cells that are designed to mimic HIV latency have non-physiological features. Second, there are difficulties in maintaining treatment-mediated viral suppression for extended periods in animals. Third, only limited amounts of peripheral blood and tissue specimens can be obtained from these animals to perform various immunological and virological assays. Nonetheless, recently developed animal models are improving the feasibility of using such models to test HIV eradication strategies (including both single and combination treatment approaches). As the development of animal models of viral suppression is recent, studies aimed at demonstrating their validity should be conducted, and detailed comparative studies of sites of viral persistence in human and non-human primate systems are warranted.

Clinical trial aspects of HIV cure research

Eradicating HIV from an infected person was previously perceived as an unachievable task. The recent demonstration of a single individual who was apparently cured following an allogeneic $CCR5^{\Delta32/\Delta32}$ haematopoietic stem cell transplant has sparked interest in studying curative interventions in the clinic[75,76] (BOX 3). The following are key strategic questions and areas of research that we think should guide future hypothesis-driven clinical interventions.

Determine the effects of early antiretroviral therapy on HIV reservoirs. With the possible exception of the individual who was apparently cured by a haematopoietic stem cell transplant, there are no known cases of HIV-seropositive individuals seroreverting in the absence of antiretroviral therapy. However, rare HIV-infected individuals were recently identified who failed to control HIV during acute infection, received long-term antiretroviral therapy, and then remained aviraemic (according to conventional assays) for months to years after interrupting therapy[53]. These individuals appear to be immunologically different from the prototypical elite controllers, in that they lack protective HLA alleles and do not develop strong HIV-specific T cell responses. As such, they may provide unique insights into how early and aggressive antiretroviral therapy might influence the natural course of the disease. The effects of very early treatment on the evolution of viral diversity, reservoir size and cellular distribution requires further research, as it is likely that curative interventions may depend on the stage of disease at the time of antiretroviral therapy initiation[77,78]. Studies in appropriate non-human primate models may also contribute to these investigations, given the relative ease of tissue sampling and the control of experimental variables in these models.

Assess new strategies that can be tested clinically. Rationally designed pilot clinical studies aimed at identifying agents that reduce the size of the viral reservoir are needed, assuming that the potential risk to study participants is known and deemed acceptable. The first generation of clinical trials are expected to inform the optimal design of curative studies and will test the behaviour of potential virological outcome measures in a clinical trial setting. It is also expected that insights from such studies might inform and direct future basic science investigations. Several questions and follow-up studies from the single case of the apparently curative allogeneic stem cell transplant illustrate how pilot clinical trials can support basic science[76]. Strategies that are now being actively studied in the clinic include drugs that induce HIV production from latently infected cells (such as vorinostat, disulphiram and, possibly, cytokines such as IL-7) and drugs that act to modify host immune responses that might promote latency (such as PD1-specific monoclonal antibodies).

Replace cells that are susceptible to HIV infection with cells that are resistant. There are several approaches that might lead to the generation of HIV-resistant cells, including the selective deletion of genes encoding crucial host proteins (such as CCR5) that are necessary to support viral entry and replication, and the delivery of genes that encode antiviral proteins[79,80]. Although formidable scientific, logistical and ethical issues persist when considering aggressive gene therapy approaches, it is hoped that advances in other fields of medicine will soon lead to new approaches that are safer (for example, that have a reduced risk for malignant transformation after gene modification) and that do not require aggressive pre-therapy conditioning regimens.

Assess combined strategies to reduce HIV reservoirs. Given the multiple mechanisms that may contribute to HIV persistence, it is unlikely that a single intervention will result in a therapeutic cure. New combination therapies will need to be developed and tested, but progress will be challenging given that single drugs might prove ineffective. The simultaneous development of multiple drugs will probably require close collaboration between different pharmaceutical companies at the earliest stages of drug development (perhaps even during the preclinical development process). It is expected that validated *ex vivo* primary cell models and animal models will be needed to identify optimal combination approaches. Non-human primates are now being used to test combinations of histone deacetylase inhibitors with prostratin (an activator of protein kinase C). Preliminary efforts are already being taken by the IAS to promote and enable cross-company collaborations.

Ethical considerations. Clinical research on pathways to HIV eradication poses substantial ethical challenges. Although the potential benefit to humanity of eradicating HIV is great, the benefit to early trial volunteers is likely to be small. Importantly, studies that involve reactivating agents, treatment interruptions, invasive procedures, bone marrow conditioning, stem cell transplantation or combination therapies carry unknown and possibly significant risks to volunteers. In addition, the participants in these trials either will be on effective antiretroviral therapy and have good to excellent health status or will be healthy uninfected volunteers. Careful informed consent is essential, as research aimed at a cure may raise expectations among participants, and such expectations need to be fully and carefully discussed. The balance of risks and benefits will need to be detailed and explained. Sponsors should make their best efforts to identify appropriate protections for individuals who may become injured in the course of clinical studies. Appropriate research design, methods and conduct should be agreed upon through engagement with relevant communities, including scientific and regulatory bodies and government stakeholders. Research on HIV eradication should not be limited to developed countries, and the highest ethical standards recognized by the international community should be applied worldwide. A discussion involving community advocates, clinicians, medical ethicists and regulatory leaders has already started and will continue under the auspices of the IAS.

Conclusion

The vision of the IAS for an HIV cure is straightforward. A safe, affordable and scalable cure will improve the health and quality of life for those with established infection, reduce the risk of viral transmission to those not infected and ultimately allow resources to be shifted to other needs. A cure will thus achieve what preventive and therapeutic approaches aim to do, which is to essentially stop transmission of HIV to those who are uninfected and restore immunological function and normal health to those who are infected. To reach that goal, the IAS and its partners will foster international research collaborations for an HIV cure and monitor progress made in the roll-out of the scientific strategy. In particular, the IAS will develop systems for global information and data sharing, to ensure good coordination of HIV cure efforts and research funding in both the public and private sectors. Finally, the IAS will strengthen research on ethical questions that are linked to HIV cure strategies and be an advocate for reinforced investments in this area.

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Competing interests statement

The authors declare no competing financial interests.

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000 **Towards an HIV cure: a global scientific strategy**

The International AIDS Society Scientific Working Group on HIV Cure

The development of effective antiretroviral therapies has greatly improved the disease prognosis for patients with HIV. However, the limitations of these therapies have renewed interest in developing alternative treatment strategies. Here, a group of experts from the International AIDS Society discuss the research steps that need to be taken to achieve the ultimate objective — a cure for HIV.

Subject categories
Immunity, infection, HIV