Immunologic strategies for HIV-1 remission and eradication

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Antiretroviral therapy (ART) is able to suppress HIV-1 replication indefinitely in individuals who have access to these medications, are able to tolerate these drugs, and are motivated to take them daily for life. However, ART is not curative. HIV-1 persists indefinitely during ART as quiescent integrated DNA within memory CD4+ T cells and perhaps other long-lived cellular reservoirs. In this Review, we discuss the role of the immune system in the establishment and maintenance of the latent HIV-1 reservoir. A detailed understanding of how the host immune system shapes the size and distribution of the viral reservoir should lead to the development of a new generation of immune-based therapeutics, which may eventually contribute to a curative intervention.

HIV-1 is a retrovirus that integrates into the host genome, primarily in memory CD4+ T cells that can harbor latent, replication-competent HIV-1 DNA for many years (1–3). This latent HIV-1 reservoir is thought to be established during acute infection (4–6), although precisely when, where, and how the reservoir is seeded remains to be determined. The reservoir has a remarkably long half-life and is resistant to antiretroviral therapy (ART), resulting in lifelong infection and viral rebound in the vast majority of HIV-1–infected individuals when ART is discontinued (6, 7). Major research efforts are currently under way to understand the biology of the viral reservoir, the mechanism of viral latency, and the potential of various therapeutic approaches to target the reservoir (Fig. 1). Recent data indicate that the size of the viral reservoir may in fact be substantially larger than previously anticipated, suggesting the profound scope of this challenge (8).

Role of the immune system in shaping and maintaining the viral reservoir

HIV-1 infection causes profound and often irreversible changes to the adaptive and innate immune system. In the absence of ART, CD4+ T cells are progressively depleted, CD8+ T cells are often expanded, and much of the immune system is chronically activated. Some of these abnormalities improve during long-term ART, but the immune system rarely returns to normal, and chronic inflammation persists despite ART. This state of heightened inflammation is driven by multiple factors, including HIV-1 production, irreversible loss of the mucosal integrity, exposure to gut microbes, and an excess burden of other pathogens such as cytomegalovirus (CMV). The implications of this chronic inflammatory state for overall health and the HIV-1 reservoir are the focus of intense investigation (9).

HIV-1 preferentially infects activated memory CD4+ T cells that express the chemokine receptor CCR5, although resting CD4+ T cells, naive CD4+ T cells, and macrophages can also be infected. The majority of infected and activated CD4+ T cells die quickly (10), but a small fraction revert to a resting state and persist indefinitely as the latent reservoir. Because ART blocks all or nearly all new infection events, the reservoir that exists at the time ART is initiated becomes the reservoir that persists for the life of the individual. This viral reservoir is maintained during ART by the long half-life of infected memory T cells, homeostatic proliferation of these cells (11, 12), and perhaps low levels of cell-to-cell virus transfer (cryptic replication) (13). Recent studies suggest that the HIV-1 genome is often found integrated in host genes associated with cell growth (14), indicating that HIV-1 may promote its own persistence in part by promoting the continual expansion of latently infected cells (15, 16).

The viral reservoir in peripheral blood exists predominantly in memory CD4+ T cells endowed with regenerative potential, including memory stem cells and central memory cells (11, 17). The reservoir also persists in potentially shorter-lived CD4+ T effector cell populations, but whether these cells represent a stable reservoir or one that is constantly being regenerated via proliferation and differentiation is unknown. The distribution of the viral reservoir differs in tissues compared with blood, with the frequency of infection generally higher on a per-cell basis in lymphocyte-rich tissues such as peripheral lymph nodes, the ileum, and perhaps the spleen (18, 19).

The higher frequency of target cell infection in these tissues may reflect cell-to-cell virus spread (20) and/or the presence of other immune cells that contribute to the maintenance of latency (21).

In the absence of therapy, the frequency of activated T cells is associated with the level of viremia. During long-term suppressive ART, a similar albeit less consistent association

Fig. 1. “Shock and kill” strategies. Latent HIV-1 reservoirs in resting CD4+ T cells can be activated (“shocked”), which might make them more susceptible to be eliminated (“killed”) by immunologic effector mechanisms.
exists, with the frequency of activated CD4+ T cells expressing human leukocyte antigen—DR (HLA-DR), CCR5, and programmed cell death protein-1 (PD-1) correlated with the frequency of cells containing HIV-1 RNA or DNA (22, 23). The mechanism for this association is unknown but likely is bidirectional and multifactorial. Low levels of virus replication and/or production may lead to T cell activation. When stable ART is intensified with the addition of a potent HIV-1 integrase inhibitor, markers of low-level HIV-1 replication and inflammation decline at least in some individuals, indicating that replication persists during ART and triggers an inflammatory response (32, 33).

Alternatively, an inflammatory immune environment may contribute to the persistence of the viral reservoir by a number of mechanisms (25). T cell activation promotes cell-to-cell virus transfer because activated cells are more likely to produce virus and to become infected. T cell receptor engagement by cognate antigen or cytokines [e.g., interleukin (IL)-17] stimulates CD4+ T cell proliferation and the expansion of the infected cell population (22). CD4+ T cell proliferation may in fact be the most important mechanism leading to the stability of the reservoir (Fig. 2) (26). A chronic inflammatory environment would also be expected to prevent the generation of optimal HIV-1-specific immune responses. Chronic inflammation stimulates potent and sustained immunoregulatory responses, including expansion of T regulatory cells and up-regulation of PD-1 and other negative regulators on effector cells (11, 26). HIV-1-associated inflammation also stimulates the deposition of collagen in secondary lymphoid organs, which in turn leads to tissue fibrosis, persistent immunodeficiency, and poor host clearance mechanisms (27).

Understanding the complex virus-host interactions that lead to the establishment and maintenance of the latent HIV-1 reservoir will require advances in our fundamental understanding of T cell biology. How are memory CD4+ T cells generated and maintained? What are the life spans of the various CD4+ T cell subsets? How are the properties of T cells in the blood different from those in lymphoid tissues? How do the fates of CD4+ T cells activated via cognate antigen differ from those stimulated to proliferate by homeostatic mechanisms? How do myeloid cells, including dendritic cells, contribute to the generation and maintenance of T cell memory and latency? How will inhibitors of the pathways that regulate T cell survival and function change the life span of individual cell types?

There are also a number of critical unanswered questions related to the immunology of HIV-1 persistence. Because the size, distribution, and stability of the viral reservoir during ART are determined in part by the host immune system, factors that influence immune function—including gender, ethnicity, chronic inflammatory diseases, chronic infectious diseases, obesity, and substance abuse—are all likely to have important but unknown effects on the viral reservoir. The age at which the virus is acquired and ART is initiated is also likely to be important. ART administered at 30 hours of age in a perinatally infected infant resulted in sustained remission and a possible cure (28), and the administration of ART in the first 3 months of life was associated with a sustained decay in the reservoir (29). Given that the development of memory CD4+ T cell responses generally occurs after birth, perhaps limited by immunoregulatory responses (30), it is possible that seeding the viral reservoir may be less efficient in infants (31). This hypothesis remains a largely unexplored area of HIV-1 cure research.

The Berlin and Boston patients

Much of the enthusiasm for HIV-1 cure research is derived from the case of the “Berlin patient” (32). In 2007, an HIV-1-infected adult living in Berlin developed acute myelogenous leukemia and received an allogeneic hematopoietic stem cell transplant from a donor who carried a homozygous deletion of CCR5, which renders cells highly resistant to HIV-1 infection. The procedure worked, and the patient has appeared to be free of both cancer and HIV-1 for over 5 years (33). Despite intense efforts, this outcome has not yet been repeated. Finding suitable HLA-matched donors homozygous for the CCR5 deletion is challenging, and the few transplants that have been performed have failed because of recurrence of the underlying cancer or emergence of CCR5-tropic viruses. Nevertheless, this case has galvanized gene therapy efforts to modify CD4+ T cells (34) and potentially also stem cells (35, 36) to render them resistant to HIV-1 infection.

A related approach is to use ART to protect transplanted donor cells until full chimerism occurs. This strategy is illustrated by two cases of HIV-1–infected adults in Boston who received hematopoietic stem cell transplants for treatment of refractory lymphoma (37). Under the coverage of ART, full donor chimerism was apparently achieved, with the donor immune cells eventually replacing the original immune cells over a period of years. As that occurred, HIV-1 DNA gradually declined to undetectable levels. Therapy was then interrupted in both individuals. Virus failed to rebound within the first few weeks, leading to initial optimism that these individuals may have been cured. Unfortunately, virus then dramatically rebounded at weeks 12 and 32 after treatment interruption, indicating that the transplant caused a profound but incomplete elimination of the viral reservoir. This failure highlights the need either to eradicate all replication-competent virus or to enhance the capacity of the host immune system to contain the limited residual virus that may persist after a curative intervention. These observations also illustrate the limitation of our current biomarkers for HIV-1 persistence. The development and validation of a highly sensitive biomarker that can reliably detect and quantify the total body burden of replication-competent HIV-1 during ART is one of the highest current priorities of the field.

Comparing the outcomes of the Berlin and Boston cases is informative. Graft versus host disease (GVHD) occurred in all three cases and likely contributed to reductions of the viral reservoirs. As has been observed with beneficial graft-versus-tumor effects, allogeneic donor cells targeting hematopoietic cells likely reduced the number of recipient CD4+ T cells harboring latent HIV-1. These cases have also led to increased interest in modifying host responses with immune-based therapeutics as part of a curative strategy (38). Assuming that the Berlin patient achieved a complete sterilizing cure and that ART was fully effective in the Boston cases, why was the virus eradicated only in the former case? One key difference in the transplant protocols was the extent of pretransplant myeloablation, which would be expected to reduce the size of the reservoir. The Berlin patient received an aggressive regimen of chemotherapy and total body irradiation, whereas a milder approach was used in the Boston cases. The Berlin patient also received more aggressive immunosuppressive therapies for GVHD, and, as outlined below, suppressing T cell activation and proliferation might result in further control of the reservoir.

“Shock and kill”

Hematopoietic stem cell transplantation is too risky and too complex for the majority of HIV-1–infected individuals worldwide. Other approaches that have generated considerable enthusiasm include pharmacologic strategies to induce latently infected cells to produce virus (“shock”) together with interventions that would enhance the ability of the host to clear these virus-producing cells (“kill”) (Fig. 1). Histone deacetylase (HDAC) inhibitors have been shown to increase production of HIV-1 RNA and, to a lesser degree, virus particles from the viral reservoir in vivo (39). However, the magnitude of the effect of HDAC inhibitors has to date been modest, and this class of drugs has not yet demonstrated a consistent effect on the frequency of cells that harbor replication-competent HIV-1 (40–42). Other classes of antilatency drugs and immunomodulators are therefore being explored for their capacity to stimulate the viral reservoir (40, 42, 43).

To augment the capacity of the host to eliminate reservoir cells after activation, several immunologic strategies are being explored. These strategies include therapeutic vaccines, monoclonal antibodies, and immune checkpoint inhibitors (Fig. 2).

Therapeutic vaccines

It is likely that a latency-reversing agent will need to be coupled with an immunologic strategy to clear virus-producing cells. One approach is to expand HIV-1–specific CD8+ T lymphocyte responses (44). As has been well-established in natural control of HIV-1 (i.e., “elite” control), potent CD8+ T lymphocytes can control HIV-1 by selectively killing virus-producing cells (45). This concept has led to a renewed interest in therapeutic vaccines, namely the administration of candidate HIV-1 vaccines to HIV-1–infected individuals typically on suppressive ART, with the goal of augmenting virus-specific immune responses and either
accelerating the decay of the reservoir during ART or improving the control of viral rebound after interruption of ART. Several therapeutic vaccines have been evaluated in HIV-1–infected subjects, including vector-based vaccines that express HIV-1 antigens from harmless or attenuated viruses such as canary pox (ALVAC) or adenovirus serotype 5 (Ad5), as well as plasmid DNA vaccines (46–51). Although these vaccines generally proved immunogenic, most therapeutic vaccines have to date failed to show virologic or clinical benefit, and a few have suggested harm, potentially as a result of increasing immune activation. Infusion of antigen-pulsed autologous dendritic cells has shown potentially greater promise but requires confirmation (52).

Most of these early-generation therapeutic vaccines involved relatively weak or suboptimal immunogens. Moreover, as was demonstrated in a study of DNA priming followed by Ad5 boosting, these therapeutic vaccines typically expand preexisting T cell clones, which by definition had already failed to control virus replication before ART (53), either because they were dysfunctional or because they selected for a virus population containing CD8+ T cell escape mutations. A successful therapeutic vaccine would ideally induce functional CD8+ T cells specific for novel HIV-1 epitopes. The next generation of therapeutic vaccines will also likely be combined with reservoir-activating agents.

Several novel therapeutic vaccines may be evaluated in clinical trials over the next several years. Such strategies include CMV vectors; Ad26 prime, modified vaccinia Ankara (MVA) boost regimens; and lymph node–targeted amphiphilic peptide vaccines. Prophylactic vaccination with CMV vectors has been shown to result in the induction of broad cellular immune responses against novel epitopes and apparent clearance of a stringent challenge with simian immunodeficiency virus (SIV) in about half of vaccinated rhesus monkeys (54–56). The persistently replicative nature of CMV vectors is likely critical for the highly functional effector memory T cells that appear to persist indefinitely. Moreover, the ability of CMV vectors to induce unconventional class II–restricted CD8+ T cell responses provides a potentially important benefit because they target novel epitopes that likely were not previously subject to immune selection pressure (56). Clinical development of CMV vectors will presumably require attenuated vectors, and manufacturing and regulatory issues for CMV vectors remain to be determined.

Another therapeutic vaccine platform that will likely be evaluated in clinical trials involves Ad26 vectors. Prophylactic vaccination with Ad26-based prime-boost vaccine regimens, such as priming with Ad26 and boosting with the pox vector MVA, has proven highly immunogenic and has afforded partial protection against acquisition of infection as well as reduced setpoint viral loads after stringent SIV challenges in rhesus monkeys (57, 58). Ad26 has several advantages over Ad5 as a vaccine vector, including the induction of different innate immune profiles that may reduce undesirable inflammatory responses and result in more
functional T cell phenotypes. Moreover, Ad26-based prime-boost regimens have demonstrated partial protective efficacy in the stringent rhesus monkey challenge models in which Ad5-based regimens have failed (57–59), suggesting their potential for greater clinical utility.

Use of amphiphilic peptides, which have been shown to target antigen to lymph nodes and aim to induce cellular immune responses simultaneously to two or more coevolving regions of immunologic vulnerability of HIV-1, is another potential therapeutic vaccine strategy (60, 61). The extent to which these and other next-generation vaccine candidates will afford therapeutic efficacy in preclinical and clinical studies remains to be determined.

**Broadly neutralizing monoclonal antibodies**

Potent broadly neutralizing HIV-1-specific monoclonal antibodies (mAbs) are also being explored as a potential HIV-1 eradication strategy. Prior studies using the earlier generation of neutralizing mAbs were generally unsuccessful in both preclinical and clinical studies (62–64), but the identification of a new generation of mAbs with improved potency and breadth has led to a resurgence of interest in this approach. In particular, two studies in rhesus monkeys demonstrated that infusion of mAb cocktails, as well as certain individual mAbs, in chronically SHIV-infected rhesus monkeys resulted in substantial, albeit transient, suppression of viremia (65, 66), building on previous studies in humanized mice (67). Moreover, a subset of animals with the lowest starting viral loads did not exhibit viral rebound even after mAb titers declined to undetectable levels, suggesting the potential for a durable therapeutic effect in certain circumstances (65). Infusion of one particular mAb, PGT121, resulted in not only rapid and profound suppression of plasma viral RNA but also substantial reductions of proviral DNA in peripheral blood, lymph nodes, and gastrointestinal mucosa (65). These data suggest that certain mAbs may be able to target virus-infected cells in tissues, although it remains to be determined whether these mAbs can impact the viral reservoir.

A growing number of potent and broadly neutralizing mAbs now exist that target various epitopes on the HIV-1 envelope protein. However, a central question for HIV-1 eradication strategies is whether mAbs will be able to target the viral reservoir and clear virally infected cells, potentially via Fc-mediated mechanisms such as antibody-dependent cellular cytotoxicity or antibody-dependent cell-mediated virus inhibition. Another possibility is that direct neutralization of free virions will reduce chronic antigen stimulation and augment the functionality of host virus-specific T cell responses, resulting in improved virologic control. Supporting this latter possibility is the observation that, after PGT121 infusion in SHIV-infected rhesus monkeys, HIV-1 Gag-specific T cells exhibited decreased activation and exhaustion and improved capacity to suppress virus replication in vitro (65). A potential caveat regarding broadly neutralizing mAbs is their limited accessibility to certain anatomic reservoir sites, such as the central nervous system.

**Immune checkpoint blockade**

Another potential strategy to augment host immune control involves the blockade of immune checkpoint molecules. Activated T cells express a series of receptors that when engaged by their ligands result in suppression of function and return to a nonactivated state. The best-characterized immune checkpoint molecule is PD-1, which is a marker of functional T cell exhaustion. The ligands for PD-1, PD-L1 and PD-L2, are widely expressed in tissues. Inhibitors of the PD-1 pathway restore T cell function and have shown efficacy in the cancer field (68). These inhibitors may also enhance the capacity of the host immune system to clear chronic viral infections. Indeed, a single dose of an antibody against PD-1 appeared to cure hepatitis C virus infection in a small subset of individuals (69). It is thought that inhibitors of other immune checkpoint molecules (such as CTLA-4, LAG-3, TIM-3, TIGIT, and 2B4) may also prove effective.

PD-1 inhibitors and other checkpoint blockers may also have direct effects on the establishment and maintenance of the viral reservoir (70). Because activated cells are more likely to become infected than resting cells, previously activated cells—including those expressing PD-1—might be expected to be enriched for HIV-1 (71). Indeed, the size of the reservoir is positively correlated with the frequency of PD-1—expressing cells (72, 73), and HIV-1 is enriched in PD-1—expressing memory cells (74). Clinical trials of PD-1 inhibitors in treated HIV-1 disease have been initiated.

**Immune-modulating drugs**

After years of suppressive ART, the vast majority of the residual population of replication-competent virus resides in long-lived memory CD4+ T cells. The estimated size of the reservoir during ART is directly associated with the frequency of activated and proliferating cells (11, 12, 22, 23, 25), and in some studies activated and proliferating cells also contain more HIV-1 (11, 14, 75). Clinical trials of PD-1 inhibitors in treated HIV-1 disease have been initiated.

**Cure strategies**

As a result of the correlation between markers of T cell activation or dysfunction and the size of the viral reservoir, it is possible that immunomodulatory interventions may also contribute to a cure. It should be noted, however, that the most direct way to “shock” HIV-1 out of a state of latency may be nonspecific and potent activation of infected CD4+ T cells (76–80). In murine models of chronic lymphocytic choriomeningitis virus (LCMV) infection, inhibition of type I interferon leads to decreased viral clearance (82, 83). Although chronic type I interferon stimulation might be harmful, supratherapeutic doses of type I interferon have also been shown to have sustained anti–HIV-1 effects in untreated chronic infection (84) and may affect reservoir size in treated disease (85). Proof-of-concept studies involving interferon-α and inhibitors of interferon-α are both planned.

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T cell activation and proliferation are controlled by a number of signaling pathways, including those that inhibit the Janus kinase/STAT pathway (75, 76) and those that inhibit the mTOR signaling pathway (77–80). Specific inhibitors of these pathways might prove useful in a combination therapy (81). However, the development of new drugs to target the viral reservoir and clear virally infected cells in tissues, although it remains to be determined whether these mAbs can impact the viral reservoir.

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therapeutic agent will invariably lead to complex and difficult-to-predict counterregulatory responses, it is difficult to predict how such interventions will affect the viral reservoir. The complexity of attempting to use an activating agent to reverse latency is illustrated by recent studies with IL-7. Preclinical studies suggested that this approach would reverse latency (89). Although a proof-of-concept clinical study found that IL-7 caused production of virions in vivo (90), the overall impact of the approach was an increase in the estimated reservoir size, presumably because of proliferation and expansion of infected cells (12). Experiments in improved preclinical models of ART-suppressed virus infection and proof-of-concept clinical trials will hopefully provide clarity on these and other issues.

The PrEP, PEP, and cure continuum

Treating HIV-1 with ART shortly after infection may also contribute to HIV-1 eradication. ART during acute HIV-1 infection reduces the size of the reservoir (91, 92), limits the generation of escape mutants, and preserves immune function. For these reasons, it is thought that HIV-1-infected individuals who initiate ART during acute infection have the best chance for HIV-1 eradication, although this group represents only a small fraction of total HIV-1-infected individuals. It is also possible that very early ART may even be curative, as illustrated by the case of the HIV-1–infected infant who was started on ART at 30 hours of life. Therapy was discontinued after 18 months, and virus remained undetectable (through at least month 30), suggesting that very early initiation of ART may prevent establishment of a long-lived reservoir (28). However, the applicability of these findings to sexual HIV-1 transmission in adults remains uncertain.

The potentially curative role of ART when administered within days of infection blurs the traditional distinction between preexposure prophylaxis (PrEP), postexposure prophylaxis (PEP), and a cure (Fig. 3). It is well established that treating adults with ART within hours of HIV-1 exposure (e.g., a needlestick injury in a healthcare worker) substantially reduces the risk of acquiring HIV-1. However, antiretroviral drugs inhibit active virus replication in host cells, and thus the clinical success of PEP strategies indicates that the first HIV-1–infected cells after viral exposure can be eradicated. Indeed, if intensive virologic monitoring were used in these individuals, then it is possible that some might exhibit transient low levels of virus in blood or tissues and thus would be considered “cured.” From this perspective, the use of very early ART to eradicate HIV-1 infection may not be uncommon.

Early ART that fails to block the establishment of the viral reservoir might still prevent some of the immunologic damage that typically occurs during acute HIV-1 infection, thus augmenting the capacity of the host immune system to control viral replication. Such an ART-induced shift toward a more effective host immune response and a smaller viral reservoir may in rare cases lead to sustained control of the virus (a functional cure). Among a cohort of adults in France who started ART during acute HIV-1 infection and then discontinued therapy after several years (the VISCONTI cohort), about 10 to 15% did not exhibit detectable viral rebound, although replication-competent virus still persisted in these individuals and they lacked protective HLA haplotypes (93). This observation has not yet been confirmed, and the mechanism for the posttreatment controller phenotype remains to be determined. As compared with elite controllers who naturally control HIV-1 infection without ART, the posttreatment controllers demonstrate remarkably small viral reservoirs and low levels of T cell activation, both of which may have contributed to the lack of rebound viremia when therapy was discontinued.

Conclusions and perspectives

Advances over the past several years have suggested that HIV-1 might be eradicated or controlled under specific conditions. Thus, the increasing enthusiasm for HIV-1 eradication research and the growing public and private investment in the HIV-1 cure agenda are justifiable. However, as described in detail elsewhere (94, 95), major scientific challenges remain. A more detailed understanding of the biology of the latent viral reservoir and the partially effective virus-specific immune responses is critical. As the Boston patients demonstrate, improved assays are needed to quantify the viral reservoir, and predictive biomarkers for viral rebound are also needed. Reliable and predictive animal models should also be developed to evaluate concepts and to inform clinical research strategies.

The establishment and maintenance of the viral reservoir appears to be affected at least in part by the immune system. Immunotherapy approaches will therefore likely have an increasing role in HIV-1 eradication strategies in the future. However, the optimal strategies to stimulate viral release from latency, to augment host immune responses, and to limit negative inflammatory responses remain to be determined. Although a small number of case reports suggest that it might be possible to eradicate HIV-1 infection in unusual circumstances, no proof of concept yet exists that chronic HIV-1 infection can be cured by a safe and scalable intervention. Over the next few years, multiple novel and promising HIV-1 eradication concepts will be evaluated. It is likely that progress will be steady but unpredictable, and reaching the final goal may take many years. Regardless, substantial expansion of rigorous basic research, preclinical studies, and clinical trials in this field will undoubtedly lead to important advances in our understanding of the biology of the HIV-1 reservoir and the challenges that face HIV-1 eradication strategies.

REFERENCES AND NOTES

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