The Challenge of Finding a Cure for HIV Infection
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The Challenge of Finding a Cure for HIV Infection

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Although combination therapy for HIV infection represents a triumph for modern medicine, chronic suppressive therapy is required to contain persistent infection in reservoirs such as latently infected CD4$^+$ lymphocytes and cells of the macrophage-monocyte lineage. Despite its success, chronic suppressive therapy is limited by its cost, the requirement of lifelong adherence, and the unknown effects of long-term treatment. This review discusses our current understanding of suppressive antiretroviral therapy, the latent viral reservoir, and the needs for and challenges of attacking this reservoir to achieve a cure.

Highly active antiretroviral therapy (HAART) for the chronic suppression of HIV replication has been the major accomplishment in HIV/AIDS medicine (*1*, *2*). Many patients are now in their second decade of treatment, with levels of plasma HIV RNA below the limits of detection of clinical assays. The impact on morbidity and mortality in the developed world has led to efforts that have brought this therapy to nearly three million people in resource-limited settings (*3*). Many patients are now enjoying a life-style little encumbered by symptoms or the side effects of medications, many of which require only once-daily administration. With the remarkable success of chronic suppression, why propose curing HIV infection—a challenging objective that requires potentially risky interventions and that may be unachievable?

Can We Do Better Than HAART?

HAART is no panacea. Current treatments must be maintained for life, with treatment interruption resulting in the rapid rebound of replicating virus. Although drug resistance can emerge because of the challenges of maintaining adherence and access to chronic antiviral therapy or owing to transmitted drug-resistant viruses, the success of HAART has been improved by the development of more potent and more tolerable therapies. Successful new drug development may not continue indefinitely, however, and HAART may never reach the majority of infected individuals in less-developed countries. Despite the prolonged suppression of HIV replication below the standard limits of detection for patients on HAART, ongoing viremia can be detected at levels of 1 to 50 copies per milliliter in the majority of patients (*4*, *5*). The origin of this viremia has not been fully characterized, but it does not appear to jeopardize the prolonged success of therapy in the adherent patient (*6*). Nevertheless, the virions may engage CD4 and chemokine receptors and may activate pathways that could lead to chronic consequences, including cardiovascular and malignant disease. The suboptimal penetration of many antiretrovirals into the central nervous system may also permit low levels of viral replication and/or release from stable viral reservoirs, resulting in neuropathology (*7*, *8*).

Despite the very low rates of toxicity of many of the newer HAART regimens, many of these drugs modulate lipid and glucose metabolism (*9*). Even modest toxicities may have cumulative effects over decades of treatment. Moreover, prolonged treatment may reveal toxicities not appreciable with animal toxicology or several years of clinical surveillance. There is already growing concern about increased rates of heart disease, diabetes, liver disease, and many forms of cancer in aging HIV-infected patients who are receiving treatment (*10*–*13*). Whether these are because of long-term HIV infection, therapeutic drug treatment, or both, is uncertain. Finally, the cost of HAART may be too much to sustain treatments on a global scale, as millions are affected.

Given the shortcomings of HAART, time-limited interventions that do not result in the resumption of viremia are a desirable but a currently unattainable objective, unlike what can be achieved with the treatment of hepatitis C virus infection. Such therapy might or might not eliminate every functional virion or infected cell, but would permit the discontinuation of HAART without the reappearance of viremia and disease. We propose that a drug-free remission should be the new goal of HIV therapeutics.

What Is the State of HIV in Successfully Treated Patients?

The source of the low-level viremia seen in most patients on HAART (*4*, *14*, *15*) may be incompletely characterized, but we do have some hints (Table 1). The failure, thus far, of treatment intensification to clear this viremia (*16*) and the lack of evidence for nucleotide sequence evolution over long periods of treatment (*17*–*19*) indicate that this phenomenon may not be driven by ongoing rounds of replication.

Patient data reveal that 1 in 10^6 CD4$^+$ T cells are latently infected with HIV, despite the durable suppression of detectable plasma viremia, although the frequency can be much lower in some patients (*20*–*22*). In vivo, it is thought that these cells are intermittently activated by antigen recognition or as bystanders in a local inflammatory process, which leads to the release of progeny virions.

Another source of virion production, which does not require ongoing replication, is the episodic production of HIV by long-lived cells. In situ hybridization of lymphoid tissue in simian immunodeficiency virus (SIV)–infected macaques and HIV-infected humans revealed that, in addition to the activated and infected CD4$^+$ T cells that produce large numbers of virions with a short cellular half-life, many lymphocytes can be visualized that produce small amounts of viral RNA, yet do not display markers of activation (*23*). Such cells are not seen in vitro, and whether such cells occur in vivo during prolonged antiretro-

Table 1. HIV latency.

- Latently infected resting memory CD4$^+$ T cells are the best-characterized latent reservoir for HIV-1.
- Less than 1 cell per 1,000,000 resting CD4$^+$ T cells from patients on HAART harbor latent HIV-1 provirus.
- Sequence of latent proviruses does not evolve, which suggests no ongoing viral replication.
- Discontinuation of HAART allows viral relapse from latent reservoir.
- Patients successfully treated with HAART for longer than 10 years exhibit no appreciable decrease in the size of the latent reservoir.
- The persistence of latently infected memory CD4$^+$ T lymphocytes precludes their elimination by HAART alone for the lifetime of the patient.
- Other drug-insensitive reservoirs, including brain, macrophages, and hematopoietic stem cells, may also exist.
- Latency is likely established and maintained by numerous blocks at multiple steps in the HIV-1 replicative pathway, which potentially complicates eradication strategies.

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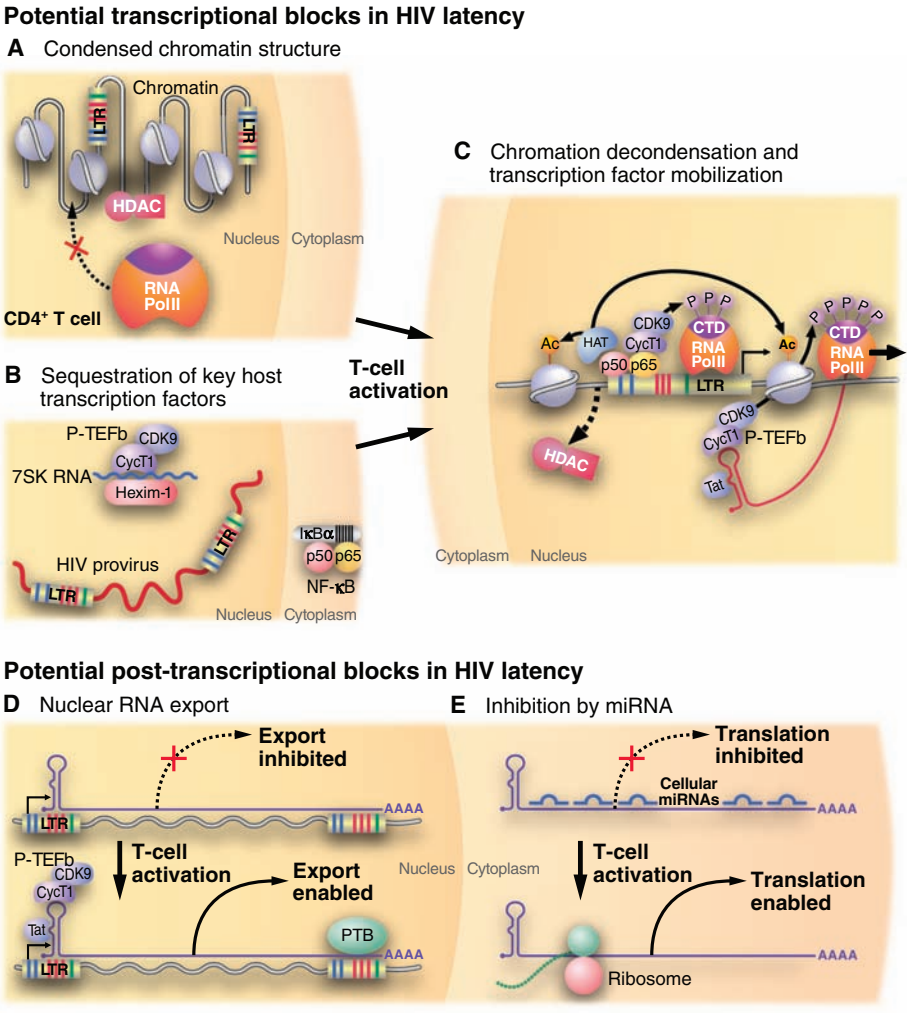

Fig. 1. Proviral latency is the result of multiple restrictions on HIV expression. (**A**) Proviral latency is maintained, in part, by the action of several transcription factors that recruit HDACs and other complexes to the HIV-1 long-terminal repeat (LTR) promoter, which results in histone modifications within chromatin at the HIV promoter that limit the ability of RNA polymerase to initiate transcription. (**B**) Key cellular factors that are required for robust HIV transcription, such as NF-κB or the P-TEFb–cyclin complex, are sequestered in resting $CD4^+$ T cells by cellular regulatory complexes [inhibitor of nuclear factor κB (IκB) and HEXIM–7SK RNA, respectively). Release and mobilization of these factors is required for proviral expression. (**C**) When histone acetyltransferases (HATs) supercede the effect of HDACs, coactivators such as NF-κB can recruit RNA polymerase (RNA Pol) complexes. Production of Tat allows the recruitment of P-TEFb, mediating an explosive increase in transcription and the escape of provirus from latency. (**D**) The initial wave of Tat production may be further restricted by inefficient export of multiple spliced HIV mRNAs, relieved upon cellular activation by enhanced expression of PTB. (**E**) Cellular miRNAs that bind HIV mRNAs may also restrict translation of early expressed HIV mRNAs and so reduce Tat production. CDK, cyclin-dependent kinase; CTD, C-terminal repeat domain; and CycT1, cyclin T1.

viral therapy is unknown. Further, the life span of and the kinetics of viral expression in such cells remain undefined.

Low-level plasma viremia cannot always be linked to activation of latently infected $CD4^+$ T cells. In a longitudinal analysis of cloned RNA from plasma-derived virions of a subset of HAART-suppressed patients, the Siliciano group identified distinctive homogeneous viral subpopulations (*24*). These observations raise the possibility of a chronically infected clonal reservoir, analogous to a persistently infected stem cell. How a persistently infected cell population could produce virions at a steady state for years, in the presence of some level of cell-mediated immunity, remains unexplained. Other cellular or tissue sources of virus, such as cells of the monocyte and macrophage lineages, may also contribute to low levels of viremia.

Can Mechanisms That Drive Latency Be Therapeutically Exploited?

Activation from latency to completion of the replication cycle should result in lytic cell death of $CD4^+$ T cells. Multiple mechanisms may contribute to the maintenance of proviral latency [reviewed in Williams and Greene (*25*)], and so, combination approaches could be required to eradicate infection (Fig. 1 and 2). Such strategies would depend on current or future antiretroviral therapy to completely inhibit all new infection events. Antilatency agents would be given, intermittently and for a limited period of time, to purge the last sanctuaries of HIV infection (Fig. 3).

Chromatin remodeling enzymes like histone deacetylases (HDACs) play a critical role in HIV latency (Fig. 1A) (*26*–*29*). HDACs are recruited to the highly conserved initiator region of the HIV promoter by several distinct complexes, by means of factors that are both ubiquitous in cell types infected by HIV and also participate in basal and activated viral gene expression. The existence of multiple mechanisms that recruit repressive HDAC complexes to the proviral promoter raises the possibility that HDAC inhibitors might lead to the activation of HIV in latently infected cells (Fig. 2).

In addition to HDACs, HIV expression is limited by other cellular barriers to effective mRNA transcription, which the virus overcomes through the action of its own activator, Tat. Tat recruits the positive transcription elongation factor b (P-TEFb) kinase to the integrated viral promoter, inducing viral gene expression (Fig. 1B and C) (*30*). Several kinase agonists, including hexamethylbisacetamide (HMBA)—a compound previously tested in human cancer trials (*31*), activate intracellular signaling cascades that mobilize P-TEFb in the absence of Tat (*32*, *33*) and can induce the expression of HIV in latently infected cells (Fig. 2) (*34*).

The HIV promoter responds to coactivators that are abundant in activated cells, but, in the context of the resting T cell, inadequate nuclear levels of nuclear factor κB (NF-κB) and nuclear factor of activated T cells (NFAT) may contribute to the establishment of latency (Fig. 1B) (*35*). Diminished binding could be the result of changes in chromatin structure, in part mediated by the action of HDACs. Prostratin, a nontumorigenic phorbol ester isolated from the Samoan medicinal plant, *Homalanthus nutans*, induces HIV expression in latently infected cell lines and cells isolated from HIV-infected, HAART-treated patients in the absence of cellular proliferation (*36*). In cell-line models, prostratin stimulates HIV expression through protein kinase C–mediated activation of NF-κB and so provides an approach to activation and clearance of latently infected cells (Fig. 2) (*37*).

HIV mRNA export may also be impaired in resting T cells because of the low levels of polypyrimidine tract–binding protein (PTB) available in resting cells (Fig. 1D) (*38*). MicroRNAs (miRNAs) endogenously expressed in human cells may further impede HIV mRNA expression or translation (Fig. 1E) (*39*, *40*). If such mechanisms contribute to proviral persistence, entirely new classes of therapeutic agents able to safely alter host RNA expression or transport will be required.

Given the intimacy of the interaction between the retrovirus and the host cell, therapeutic approaches that disrupt latent infection are also likely to affect host cell function. Although mild host toxicities for limited periods of time might be acceptable, global immune activation must be avoided. Once quiescent virus is successfully induced to complete a round of replication, virus-induced cytolysis and cytotoxic T cells need to be able to clear HIV antigen–expressing cells. The viral progeny generated by such activated cells have to be prevented from successfully infecting other cells by the presence of HAART (Fig. 2).

How Are Interventions to Be Investigated?

Undoubtedly, there are other factors that regulate latency occurring in primary cells in vivo. Although we need to be aware of the potential for additional reservoirs of infectious virus, addressing the latently infected T cell reservoir may be the most direct way of exposing an even smaller additional reservoir, like infected macrophages, or anatomic compartments, such as the central nervous system, that may be suboptimally exposed to HAART. Careful in vivo testing of therapeutic agents capable of antagonizing the different mechanisms underlying HIV latency identified in $CD4^+$ T cells is important for establishing the proof of concept.

An animal model is not required for antiretroviral drug development because, thus far, activity in vitro has correlated with activity in vivo. In contrast, an animal model could be invaluable in the development and testing of antilatency therapies and would guide clinical trial design. Given the excellent outcomes of HAART, initial studies of new antilatency therapies in humans might be difficult to design and execute, because volunteers in such early studies may have little to gain, and the candidate interventions will have unproven efficacies and uncertain toxicities. SIV infection in the rhesus macaque gives rise to latent infections in $CD4^+$ T cells that mirror HIV latency (*41*), although it remains unknown whether the pathways and molecular targets promoting postintegration latency in macaques are the same as in humans.

BLT (bone marrow-liver-thymus) mice provide a second animal model. These immunodeficient mice (which lack endogenous T and B cells) are transplanted with human thymus and liver tissue and injected with hematopoietic stem cells, giving rise to systemic repopulation with human T and B cells, monocytes-macrophages, and dendritic cells capable of antibody production, activation by human antigen-presenting cells, and potent human major histocompatibility complex–restricted T cell immune responses (*42*). BLT mice have already been used to study HIV transmission and to test preexposure antiretroviral prophylaxis (*43*). Determining whether this model can be used to study HIV latency is a high experimental priority. Despite the availability of animal models for preliminary testing, clinical studies in HIV-infected patients are ultimately required.

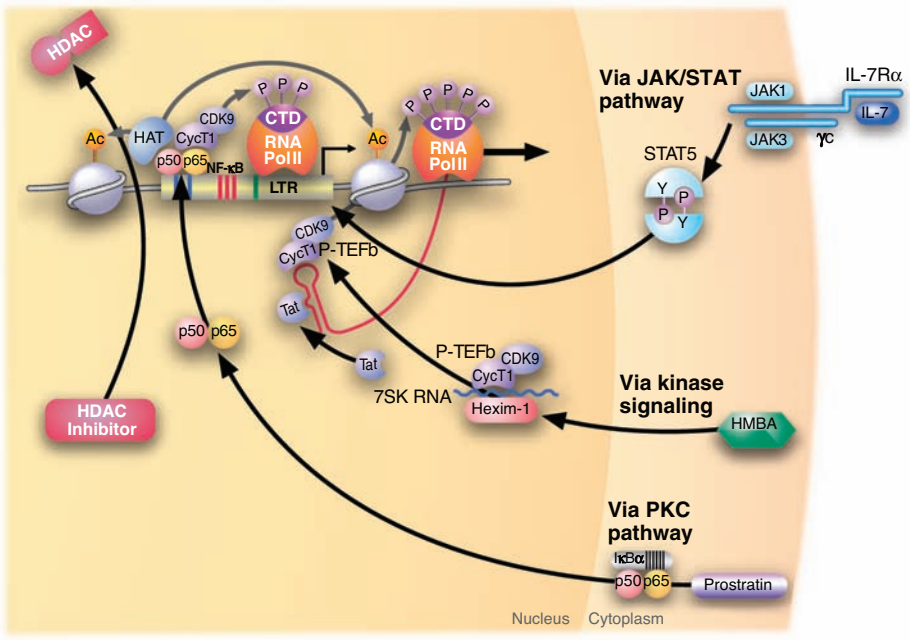

Fig. 2. Potential therapies to disrupt latent proviral HIV infection. HDAC inhibitors may relieve repression by HDACs and may allow histone acetylation by HAT, which results in HIV expression. Via kinase signaling, HMBA stimulates the release of P-TEFb from sequestration within a ribonucleoprotein complex containing HEXIM and 7SK snRNA (small nuclear RNA). Tat then recruits P-TEFb to an HIV RNA structure (TAR), present at the 5′ end of all nascent HIV RNAs, which allows for phosphorylation and activation of RNA Pol II and other factors, leading to processive transcription. Prostratin stimulates HIV through protein kinase C (PKC)–mediated release of active NF-κB. Interleukin 7 (IL-7), a cytokine essential for maintenance of T cell homeostasis, can induce HIV expression from quiescent resting cells without global T cell activation, via the JAK/STAT5 signaling pathway.

Phase I trials to deplete persistent HIV infection have demonstrated that these approaches can be tested safely (*44*–*46*), and studies using novel inducers of HIV expression such as interleukin 7 (*47*) may soon be feasible (Figs. 2 and 3).

Quantifying the latent HIV reservoir in humans is challenging when less than 1 in a million $CD4^+$ T cells are latently infected, and there are approximately 100 copies of integrated provirus for each latently infected $CD4^+$ T cell (*48*). After amplification by the polymerase chain reaction, measurements of integrated proviral DNA might serve as a surrogate marker for changes in the latent reservoir (*18*). However, the small size of the reservoir and the imprecision of current assays require improved techniques to assess the effectiveness of interventions. Moreover, once the reservoir is reduced by 10- to 100-fold, the remaining latently infected cells may be concealed below the limit of detection of any assay yet described.

Access to lymphoid tissue or most anatomic compartments in otherwise healthy subjects is difficult. Although such studies may fail to detect an infected reservoir, they cannot prove its eradication. When an intervention or combination of interventions is considered sufficiently compelling, the ultimate test of efficacy will be the withdrawal of HAART. Antiretroviral therapy is effective and relatively safe. As a result, the administration of any experimental intervention in either a proof-of-concept feasibility trial or in a trial incorporating treatment interruption raises significant ethical, regulatory and study design issues, because antiretroviral therapy is so effective and relatively safe. Therefore, involvement of various stakeholders in thoughtful deliberations is necessary. Such studies are required if we wish to cure HIV; but, although the potential benefit to humanity is great, the benefit to the early trial volunteers is nearly nonexistent. The appropriate volunteers in a trial involving treatment interruption might be those who initiated HAART before significant immune depletion. This criterion would minimize risk of treatment interruption, especially with close monitoring to resume treatment should virus replication be detected. A second rationale for selecting such subjects is that their infected-cell reservoir may be smaller and thus more amenable to intervention (*18*, *49*).

Do We Need a New Approach to Develop a Cure?

The recent disappointing results from the trials of HIV vaccine and microbicide candidates have prompted a renewed commitment to basic research to identify effective approaches to these critically needed prevention strategies. We advocate a similar impetus for new approaches to purge the latent reservoir in order to cure HIV infection.

Years of effort have led to public health strategies to reduce the risk of cancer, a vaccine

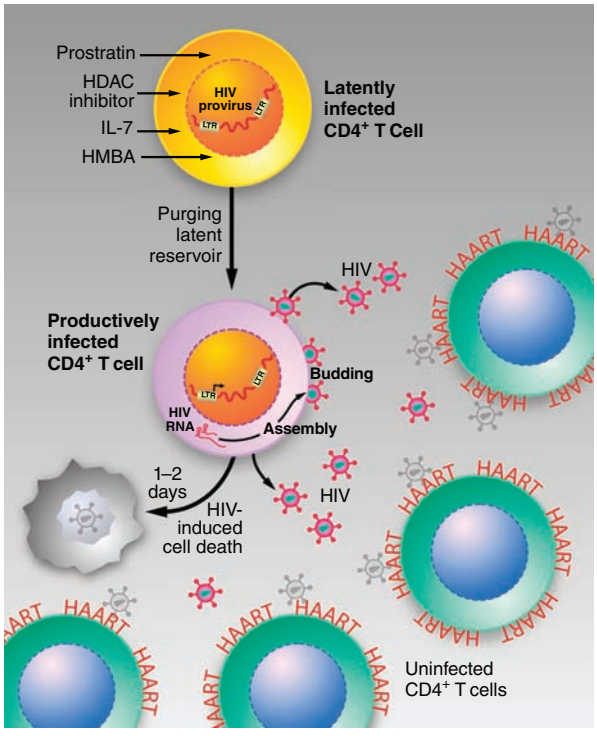

Fig. 3. Purging persistent proviral infection. If targeted approaches, alone or in combination, succeed in activating latent HIV proviruses present in differentiated CD4+ T cells, the life span of these cells should be short. These inductive agents must be used in combination with HAART to prevent further HIV spread to uninfected CD4+ T cells.

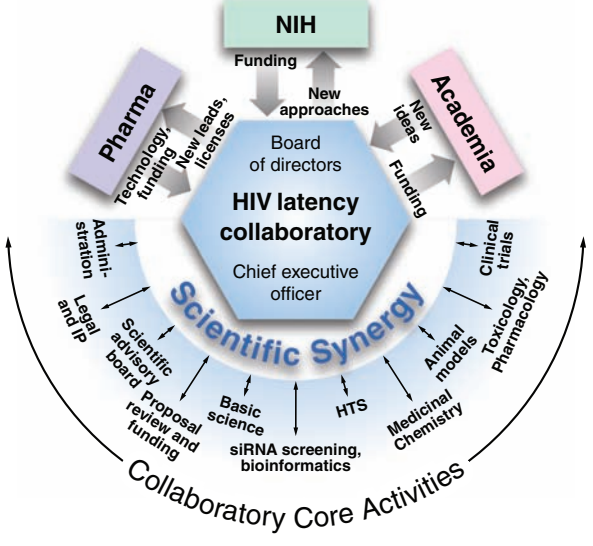

Fig. 4. Overview of an HIV Latency Collaboratory representing a joint research venture between the U.S. National Institutes of Health (NIH), the pharmaceutical industry (pharma), and academia. The goal of this collaboratory is to accelerate basic discovery and the clinical translation of these discoveries that allows for eradication of HIV in infected patients or at least a stable drug-free remission. This collaboratory is designed to include all interested investigators with meritorious ideas. These investigators will be funded via the collaboratory and will have access to a range of core technologies provided by the collaboratory that should promote scientific synergy and enhanced experimental efficiency. The collaboratory would be governed by a Board of Directors comprised of representatives from each of the partners in the joint venture. HTS, high-throughput screening; IP, intellectual property; and siRNA, small interfering RNA.

that prevents cervical cancer, better therapies to treat malignancies, and curative therapies for some cancers. Such a multifaceted approach should also be applied to the effort to cure HIV infection. This will require behavioral and biological tools to prevent HIV infection; safe, affordable, and nontoxic therapies for initial control of HIV infection; and new interventions that can achieve a drug-free remission of viremia in some patients.

The challenge of developing an HIV vaccine spans the need for new basic research insights to product development to clinical trials. The complexity of fostering and coordinating these efforts has led to the creation of major NIH intramural (Vaccine Research Center) and extramural (Center for HIV/AIDS Immunology) programs and of an international, multi-institutional effort (The Global HIV Vaccine Enterprise). Our understanding of HIV latency has chiefly resulted from independent, investigator-initiated efforts. In order to translate these academic accomplishments into clinical treatments similar initiatives are required. Antilatency therapies will require the drug discovery capabilities of industry, like high-throughput drug candidate screening; medicinal chemistry; product synthesis, production, and formulation; toxicology; and pharmacology. A coordinated initiative involving academia, industry, government, and patient advocates could greatly accelerate the identification of potential interventions and their clinical assessment (Fig. 4). We conceive an initiative, termed here a collaboratory, in which the government contributes funding, regulatory oversight, and coordination; industry contributes funding, drug discovery, technology, and expertise; and academia contributes ideas and investigative capacity. Long-term support for a flexible, collaborative public-private joint venture might improve efficiency and conserve resources, while at the same time catalyzing progress that no single group could achieve. Clearly much work and many challenges lie ahead, but if novel scientific insights can be brought to bear in clinically effective ways, the era marked by the benefits of HAART may be followed by one in which HAART is no longer a lifelong necessity.

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