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Latency reversal and viral clearance to cure HIV-1

David M. Margolis[1,2,*], **J. Victor Garcia**[1], **Daria J. Hazuda**[3], and **Barton F. Haynes**[4]

[1]University of North Carolina HIV Cure Center, Department of Medicine, and Center for AIDS Research, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

[2]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

[3]Merck Research Laboratories, White Horse Junction, PA, USA

[4]Duke Human Vaccine Institute, Department of Medicine, and Department of Immunology, Duke University School of Medicine, Durham, NC, USA

Abstract

Research toward a cure for human immunodeficiency virus type 1 (HIV-1) infection has joined prevention and treatment efforts in the global public health agenda. A major approach to HIV eradication envisions antiretroviral suppression, paired with targeted therapies to enforce the expression of viral antigen from quiescent HIV-1 genomes, and immunotherapies to clear latent infection. These strategies are targeted to lead to viral eradication—a cure for AIDS. Paired testing of latency reversal and clearance strategies has begun, but additional obstacles to HIV eradication may emerge. Nevertheless, there is reason for optimism that advances in long-acting antiretroviral therapy and HIV prevention strategies will contribute to efforts in HIV cure research and that the implementation of these efforts will synergize to markedly blunt the effect of the HIV pandemic on society.

The human immunodeficiency virus (HIV) has been a major burden on society since the virus emerged over 30 years ago. But in less than 2 decades, a remarkable investment and the resultant scientific progress across the biomedical research enterprise and the pharmaceutical industry produced the spectacular success that is now modern antiretroviral therapy (ART) (1). These advances transformed HIV infection from a fatal disease into a manageable chronic illness. The global implementation of ART and HIV prevention efforts are now showing signs of blunting the HIV pandemic (2).

Despite these successes, the stigma of HIV infection and its long-term societal and resource costs remain a substantial challenge. Suppressive, lifelong antiviral therapy alone cannot be the final solution to the HIV pandemic, and thus, recent efforts have focused on interventions that can yield a drug-free remission of HIV infection or even its cure. Drug-free immune control of chronic HIV infection may exact a toll on the host, and many may prefer the complex goal of HIV eradication. At the individual level, ART provides substantial long-term health benefits, and so compared with other foreseeable goals such as

*Corresponding author. dmargo@med.unc.edu.

drug-free immune control of chronic HIV infection, perhaps only the challenging goal of HIV eradication may be acceptable to some. A number of diverse and novel approaches aimed at finding a cure for HIV are being explored, and encouraging advances have emerged.

The challenge at hand is considerable and is well illustrated both by a singular success and several failures. In the case of Timothy Brown, the Berlin patient, it seems that a series of complex clinical events after the transplantation of CCR5-deficient cells innately resistant to HIV infection led to the complete clearance of infected cells (3, 4). Although limited studies did not detect latently infected cells in the Boston patients after stem cell transplantation (5), or in the Mississippi child (6) treated with potent antiretroviral therapy in the first hours of life, the absence of a durable and potent anti-HIV immune response may have allowed viral rebound. There is little doubt that a considerable and sustained effort will be needed in both basic and translational research to transform these clinical anecdotes into therapeutic approaches that are safe and effective enough to be deployed broadly against the HIV pandemic.

The beginnings of HIV cure research

The initiation of efforts to develop therapeutic strategies to clear HIV infection has led to advances overcoming the obstacles to viral eradication and has illuminated new challenges. Proviral latency—the persistence of quiescent but replication-competent proviral genomes in resting $CD4^+$ T lymphocytes, and to an unknown extent in other cell populations such as myeloid cells—is a central problem for curative strategies (7). A central approach to this problem envisions targeted approaches to reverse latency so that viral antigen is expressed by a formerly latently infected cell and becomes vulnerable to immune clearance mechanisms. Further, such viral clearance mechanisms may require therapeutic or immunomodulatory enhancement strategies such as reversal of anti–HIV-1 effector cell exhaustion.

Host cell–mediated molecular mechanisms maintain the quiescence of HIV-1 gene expression in infected resting $CD4^+$T lymphocytes, and these mechanisms are potential therapeutic targets for disrupting latency (Fig. 1). One well-defined mechanism contributing to maintenance of latency is the recruitment of histone deacetylases (HDACs) to the HIV promoter in the long terminal repeat (LTR), mediating the formation of a repressive chromatin environment that inhibits LTR transcription and viral production (8–13). The relevance of this mechanism has been validated in resting $CD4^+$ T cells obtained from ART-treated, aviremic, HIV-infected individuals (10, 11, 14, 15–19). The potent HDAC inhibitor, vorinostat induces HIV chromatin acetylation and promoter expression in cell lines and elicits virus production ex vivo from the resting $CD4^+$ T cells of HIV-infected patients on suppressive ART. This effect is achieved without cellular activation, up-regulation of HIV coreceptors, or de novo HIV infection, all of which could increase the number of infected cells in the host (20, 21). Direct proof-of-concept of latency reversal has also been achieved in clinical studies, in which increases in cell-associated HIV-1 RNA production and/or plasma viremia was observed after in vivo administration of the HDAC inhibitors vorinostat, panobinostat, or romidepsin (22–25)—and in one study, the drug disulfiram (26)—to ART-

suppressed patients. However, thus far none of these interventions alone has been found to reduce the frequency of latently infected cells.

Although these data are encouraging, challenges for the effective implementation of so-called “latency-reversing agents” (LRAs) have emerged. Several studies have suggested that LRAs, at least when tested after a single drug exposure in vitro, may disrupt latency in only a subset of the population of latently infected cells (27, 28). On the basis of these in vitro studies, combinatorial LRA strategies are widely assumed to be needed to effectively and comprehensively purge the pool of replication-competent, integrated, persistent HIV. Concepts include combining HDAC inhibitors with histone methylation inhibitors (29), and protein kinase C (PKC) agonists with HDAC inhibitors or bromodomain (BRD) inhibitors (30). Toll-like receptor agonists, whose mechanism of action as an LRA is not yet fully defined (31, 32), have appeared promising in nonhuman primate studies. Human trials to test these concepts are in development.

More problematic for the discovery and development of new LRAs is the challenge that the preclinical models used for their study respond in diverse ways to signals known to reverse latency (33). Further, assays using cells from HIV^+, ART-treated patients may not fully recapitulate the complexity of latency in vivo (34) because a single pulse of maximal mitogenic activation in vitro does not disrupt latency in all infected cells. This surprising observation suggested that there might be absolute limitations to the effectiveness of a single exposure to even the most potent LRAs. Although serial stimulation in vitro induces expression of a larger proportion of the latently infected population over time (35), the challenge of developing single or combinatorial therapies that safely disrupt latency in all infected cells over a clinically tractable period of time may be considerable. An additional complication is the recent appreciation that the majority of species of cell-associated HIV RNA expressed in latently infected cells contains substantial mutations and deletions, largely because of the action of APOBECs (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like), a family of cytidine deaminase proteins that efficiently restrict HIV expression (36). Therefore, although the detection of HIV RNA within these cells reveals past infection, many viral genomes detected by means of RNA expression are replication-incompetent. The predominance of defective HIV DNA genomes (37) and incompetent HIV RNA transcripts (34) pose a challenge for investigators wishing to quantify the latent reservoir and evaluate strategies to deplete it.

Replication-competent HIV can be measured by using the quantitative viral outgrowth assay (QVOA). Although QVOA can measure the frequency of truly latent proviral infection in cohorts of stably treated patients, as documented by independent studies carried out over more than 2 decades (38, 39), the output represents a minimal estimate of the frequency of persistent, latent HIV infection (34). This leaves investigators in a conundrum: Measures of integrated HIV DNA vastly overestimate the frequency of true latent HIV infection, as do (to a lesser extent) measures of cell-associated HIV RNA, whereas the QVOA underestimates the size of the latent reservoir.

We suggest that these problems could be circumvented by the development and implementation of more sensitive tools that could assess latency reversal at the level of viral

protein production, or the presentation of viral antigen to the immune system. Cells that are capable of expressing viral proteins are more relevant than cells that simply contain replication-defective HIV DNA genomes or or express HIV RNA transcripts. Such cells are likely to be more frequent and more easily assayed than those that produce functional virions. This is perhaps the most relevant metric by which to evaluate latency reversal because the current goal of latency reversal is to create targets for immune-based clearance.

The calculus of viral persistence: Forces that drive the decay of the latent reservoir

Because latent, persistent HIV infection was described within the resting $CD4^+$ memory T cell, viral quiescence was initially thought to derive principally from the quiescent cellular state of the host T cell, an environment unfavorable to HIV expression (40–43). Over the next decade, studies of HIV transcriptional regulation did not refute that view but modified it, as several specific cellular mechanisms were described that served to enforce proviral quiescence (44). Some cellular mechanisms that enforce proviral latency have now become the rational targets of latency-reversing agents, seeking to inhibit these silencing mechanisms and allow expression of latent provirus (45, 46).

However, recent findings have reignited the debate around two additional mechanisms that could contribute to the persistence of replication-competent provirus: cellular proliferation and ongoing viral replication. HIV-infected patients on long-term ART have now been found to have identical HIV sequences integrated at the same position in the host genome in multiple cells, suggesting that the infected cells had descended from an identical clone via cellular proliferation (47, 48). However, the replication-competence of these proliferating clones remains in question. One study found that all of 75 integrated genomes that were fully sequenced contained lethal mutations or deletions and were replication-incompetent (49). However, this finding should be replicated and expanded because even a small fraction of proliferating but replication-competent HIV genomes could contribute substantially to viral persistence.

The contribution of other cell populations that sequester HIV in a quiescent state and persist for years despite ongoing ART also requires further examination. Latent infection can be established in vivo in naïve and transitional CD4 T cells, stem memory T cells, and γ-δ T cells (50–54). But the durability of these potential reservoirs in vivo is not understood. Similarly, whereas it is clear that various myeloid cell populations can be infected during untreated HIV viremia (54), the contribution of the persistence of latent infection in these populations to the HIV reservoir in ART-suppressed patients is unclear (55, 56).

Last, the potential contribution of residual virus replication and spread, despite ongoing ART, to HIV persistence remains controversial. Multiple controlled studies of ART intensification have found that additional inhibitors of entry, reverse transcription, integration, and viral protease function had no effect on low-level viremia, arguing that low-level viremia was generated by chronically infected cells and not by ongoing rounds of replication (57–63). However, in several studies that added an integrase inhibitor to ART-suppressed patients, transient changes in forms of HIV 2-LTR DNA and/or reductions in

immune activation were seen, potentially because of ongoing replication (64, 65). HIV sequence evolution might be expected in treated patients in whom replication was ongoing. One study reported this within lymph node tissue in patients treated for 6 months (66), a relatively short period of time after initiating ART, but other studies found no evidence of evolution in plasma or tissues in participants in whom durable suppression of viremia had been established for years (67, 68).

Regardless of the final adjudication of these issues, the overall calculus of persistent infection is clear: Once durable and suppressive ART is implemented, all measures of persistent HIV infection are either stable or decay slowly over time. Therefore, although any new persistent infections founded by cellular proliferation or residual replication on a daily basis have the potential to increase the number of latently infected cells, this contribution is apparently slightly outweighed by the number of cells that reactivate or die and leave the quiescent pool on a daily basis (Fig. 2). If this were not the case, the frequency of latent infection would increase over time.

Although not the only possible approach to eradicate HIV infection, the tools are now at hand to implement latency-reversal strategies that create a window of vulnerability within the pool of latently infected cells. LRAs must be implemented effectively in combination with immunotherapeutic approaches that can clear HIV-infected cells that present viral proteins in the context of latency reversal. Such combination eradication approaches, even if only modestly effective, should result in substantial, measurable, and reproducible depletion of persistent infection, the next major step in the development of HIV eradication strategies.

Current approaches to clearance of persistent HIV infection after latency reversal

The clearance of residual HIV infection in the context of prolonged suppression of viral replication by ART is a major challenge for the immune system and for immunotherapeutics. The targets for clearance are rare populations of cells, induced to express HIV proteins in quantities that are likely to be limited, for which the duration and kinetics of antigen presentation are unknown. Further, these cell populations may be widely distributed across anatomical compartments, and in many patients, the HIV-specific immune response may have waned in the absence of recent antigen exposure and/or may be dysfunctional or depleted owing to the effects of HIV infection on the immune system. Although CD8 T cells are highly effective in targeting and clearing virus-infected cells, and in HIV infection contribute to control of viremia, Deng *et al.* highlighted the widespread prevalence of CD8 T cell escape mutations in viral genomes found in the resting CD4 T cell reservoir (69). However, within these subjects, CD8 cells capable of targeting other epitopes that lacked mutations were detectable in all patients after peptide stimulation. This suggests that although HIV can rapidly evade the immune system in the setting of unchecked viremia, HIV-infected individuals on ART possess effector cell populations that may be capable of clearing viral species within the latent reservoir.

It is also important to consider the effects of agents used to reverse latency on the various host immune mechanisms that are required to recognize and clear the infected cells. The

window of vulnerability induced by latency-reversing agents must be judged not only by the extent of antigen expression within the latent reservoir of ART-suppressed, HIV-infected individuals, but by the ability of immune mediators to act after LRA exposure. One in vitro study suggested that romidepsin and panobinostat—two HDAC inhibitors, the leading class of LRAs—might inhibit the HIV-specific T cell response and thereby reduce the ability of the immune system to clear infection after the reversal of latency (70). But in this study and two others using autologous cells from aviremic, HIV-infected patients on ART, the antiviral activity of effector cells was unaffected by exposure to the HDAC inhibitor vorinostat (71, 72). Data from an ongoing study of pulsatile vorinostat therapy given several times a week revealed no evidence that vorinostat exposure reduced the ability of $CD8^+$ T cells or natural killer cells to recognize and clear latently infected cells induced to express HIV ex vivo (73, 74). Similarly, Søgaard (25) found that three weekly doses of romidepsin failed to measurably blunt the HIV-specific T cell response in vivo. Nevertheless, the possibility that, because of the very nature of their cellular targets, LRAs may affect immune function and therefore clearance of infected cells in which latency has been reversed, is an important issue that must be systematically assessed.

However, although LRAs can be selected for minimal impact on the immune response, in many individuals on stable, suppressive ART, the low frequency of HIV-specific $CD8^+$ T cell responses may be insufficient to clear the latent reservoir (75). As described above, this deficiency may be related to $CD8^+$ T cell escape mutations archived in the latent reservoir that arose before the implementation of ART (69, 76-78) and/or to the dysfunctional, or “exhausted,” state of the HIV-specific T cell seen in chronic infection (79). Thus, strategies to strengthen HIV-specific T cell immune responses may be needed.

A number of therapeutic HIV-1 vaccines that might fill this need have been tested, including whole inactivated virus, recombinant proteins or viruses, DNA vectors, or dendritic cell presentation of autologous antigens (80-84). Some vaccines improved HIV-specific immune responses (85), but none to date has allowed sustained ART interruption. However, in such studies the vaccine-induced immune response is asked to fully restrain all HIV replication in the absence of ART, an as-yet unmet milestone. However, for the goal of eradication in the setting of ongoing ART and antilatency therapies, the bar may be much lower because viral replication and therefore viral escape is blocked in the presence of ART.

Further, a small number of vaccine trials have measured the impact of the vaccine on the size of the latent reservoir and seen either no sustained impact on the reservoir (86) or, at best, a small, transient decline in the frequency of replication-competent latent infection (87), below a threshold predicted to be clinically relevant (38). This is most likely due to the lack of viral expression in latently infected cells, making these reservoirs insensitive to any immune response (7).

Last, such vaccines have not yet been tested for specific characteristics that may be critical to allow effective clearance of persistent HIV infection: recognition of relevant epitopes in the context of infection emerging from the latent state; reduction of low-level viremia that persists during ART; or decrease in the frequency of latently infected cells (88, 89). These endpoints should be considered in future studies as well as use of those HIV-preventive

vaccines that have induced the greatest level of HIV-specific $CD8^+$ cytotoxic T lymphocyte (CTL) in man (90). Vaccines that induce T cell responses against conserved viral epitopes may contribute to the ability to clear persistent HIV (91-94). Recent data have demonstrated that attenuated cytomegalovirus (CMV)–vectored SIV genes can induce CD8 CTL, which might eradicate SIV-infected CD4 T cells, as 50% of macaques appeared cured of acute infection (95, 96). A portion of CMV-induced CD8 T cells recognize SIV-infected CD4 T cells atypically via major histocompatibility complex class II and human lymphocyte antigen E, potentially representing a new approach to the clearance of retroviral infection (96, 97). Understanding the mechanisms of atypical CD8 T cell killing of retroviral-infected CD4 T cells and validation of the safety and efficacy of CMV-vectored approaches in humans is needed.

Antibodies that can specifically direct immune clearance of HIV-infected cells are a new area of HIV cure research. Cocktails of broadly neutralizing antibodies derived from HIV-infected individuals can bind to virions and virus-infected CD4 T cells and may be useful tools for curative strategies (98, 99). Other non-neutralizing HIV antibodies have been isolated that selectively target virus-infected CD4 T cells. Engineering of these Env-targeting antibodies into bispecific antibodies or chimeric dual-affinity retargeting antibodies (DARTS) that can target CD8 effector cells to HIV-infected CD4 T cells is a promising new strategy (72, 100, 101). Novel immune-augmenting strategies, such as adjunctive treatment with immune checkpoint inhibitors, might reawaken an extant but exhausted or diminished immune response and facilitate clearance of viral reservoirs (102).

Testing latency reversal and clearance

Although informative studies of latency reversal and clearance strategies can be executed in ex vivo tissue culture models, a full analysis of curative strategies must be performed in animal model studies and human clinical trials. Like all HIV-infected cells, latently infected cells exist predominantly in tissues, and some anatomic compartments may differ in drug penetrance or in the access of components of the cellular and humoral immune response. Therefore, comprehensive studies of latency reversal and clearance strategies require extensive tissue monitoring and sampling that is both practically and ethically untenable in human studies. Although it is fortunate that both humanized mouse models and nonhuman primate models have recently been advanced so that infection and ART can be reliably used, both models could benefit from further optimization in order to address the most relevant questions related to HIV cure research.

Novel humanized mice models such as the bone marrow–liver-thymus (BLT) mouse, the T cell–only mouse (ToM), and the recently described Myeloid-only mouse (MoM) serve effectively in this capacity (54, 103). Humanized BLT mice exhibit systemic human reconstitution, including in the brain, gut, and vaginal mucosa, with a complete and functional human immune system. By virtue of only having human T cells, ToM allow for the investigation of latency purely in this important compartment. In both of these models, HIV establishes a chronic, lifelong infection from which latently infected cells can be isolated after suppression of viremia ART (104, 105). Similarly, the availability of a model devoid of human T cells but with a full complement of myeloid cells (MoM) allows for the

investigation of the contribution of macrophages to HIV latency and persistence in the complete absence of human T cells. The utility of humanized mice for the in vivo analysis of LRAs and clearance strategies has been demonstrated (99, 103, 106). BLT and ToM mice allow (i) the evaluation of different types of highly relevant viruses for infection, (ii) the analysis of latency and persistence by virtually all human cell types that are targets of HIV infection in both the periphery and tissues, (iii) the evaluation of new and established antiretroviral drug interventions, and (iv) the evaluation of novel induction and killing approaches (106). Other humanized mouse models have been successfully used to evaluate broadly neutralizing antibodies and combination induction therapy, with encouraging results (99, 107, 108). In addition, because humanized mice represent a complex system featuring virtually all cell types that are important for adaptive immune responses, they can be useful for the in vivo evaluation of novel approaches to curing HIV that are based on biological molecules as well as gene and cell therapies.

Pathogenic models of SIV infection in the rhesus macaque have also been used in HIV cure research, following the formulation of ART similar in composition, safety, and efficacy to those that have been used in humans. ART regimens now consistently suppress SIV viremia to levels below detection (less than three copies per milliliter of plasma) of the most sensitive assays, thus reaching viral suppression comparable with that in HIV-infected humans (109–111). The availability of such sensitive viral detection assays in both animal models may now allow the field to address critical questions in the context of ongoing ART in vivo.

Thus, human testing of latency reversal and clearance strategies is needed. In selected settings, experimental agents that have already advanced to human testing in venues such as oncology may be more rapidly brought forward for proof-of concept studies in man. But initial evaluation of novel agents or combinations will still likely require testing in animal models. Where exhaustive analysis of tissue is needed, animal models will continue to be integral to research advances, although when possible, immune tissues in human clinical trials should be examined. For example, specialized structures in lymph nodes called lymphoid follicles are enriched for viral infection, and CTL responses have recently been shown to be restricted at these sites (112). The ability of diverse eradication strategies to deliver effectors to such potential sanctuaries can be carefully tested only in such in vivo models.

Conclusion: The synergies of cure and prevention

Research toward HIV eradication began with the success of ART, followed closely by the description of latent, persistent infection. The daunting problem of proviral latency and the failure of initial eradication efforts (113) led to a long hiatus in such efforts, but these were renewed after the report of an HIV cure in the Berlin patient (3) and the initial description of a LRA (22). The next major advance will likely be the demonstration, outside of the context of bone marrow transplantation, of substantial depletion of persistent infection when effective LRAs are appropriately paired with a viral clearance strategy that delivers active effector cells to the sites of induced viral expression. Years of longitudinal measurements have suggested a benchmark for such trials: a decrease by a factor of at least 6 of the

frequency of replication-competent HIV within the resting $CD4^+$ T cell reservoir after an intervention, a decline that is rarely seen on ART alone. Such a depletion of latent infection shown by means of QVOA would be expected to correlate with a depletion of the total replication-competent latent reservoir, a meaningful step toward the goal of HIV eradication (38). Already, the decades of investment in the development of a prophylactic HIV vaccine and other preventive strategies have paid unexpected dividends; this research pipeline provides key knowledge and research tools needed to implement effective HIV clearance strategies.

However, it is very likely that additional advances will be needed to allow durable remission of viremia in the absence of ART or, eventually, eradication of HIV infection. This challenge is poignantly illustrated by the case of the "Mississippi child," in whom ART was interrupted after treatment for the first 18 months of life, and a remission of viremia lasted 27 months before a robust viral rebound mimicking primary infection (6). In this child, the viral reservoir was too small to measure, and aviremia in the absence of an HIV-specific immune response presumably was maintained by the intrinsic quiescence of latently infected cells.

This scenario also suggests a third intervention that should be added after therapeutic disruption of HIV latency and clearance of cellular reservoirs of persistent infection: protection against viral rebound and new HIV infection. As the field of HIV vaccine development moves forward, prophylactic vaccines should be deployed as the last step in an HIV latency reversal and clearance strategy, both to prevent viral rebound that might emanate from rare latently infected cells that have survived the initial rounds of latency reversal and clearance, and to protect against new HIV infection in this at-risk patient population. The prevention of reinfection is an important public health measure, given the substantial health care investment likely to be needed to achieve durable remission or cure of HIV infection.

The past 5 years have seen a substantial new investment in HIV cure research from governments, foundations, and industry. Advances and new insights into the nature of the problem have marked the founding of this new field of endeavor. Key insights into the diverse and complex biology of persistent HIV infection have been made. A diverse portfolio of LRAs is under study, and a pipeline for the development, testing, and validation of new agents now exists. A variety of approaches to imbue an effective anti–HIV-1 response to mediate viral clearance are under study, and some are entering clinical testing. 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 ART may be followed by one in which ART is no longer a lifelong necessity. And as HIV vaccine science contributes to efforts to eradicate persistent HIV infection, the fields of HIV prevention, treatment, and cure will create the tools to move us toward a world without AIDS.

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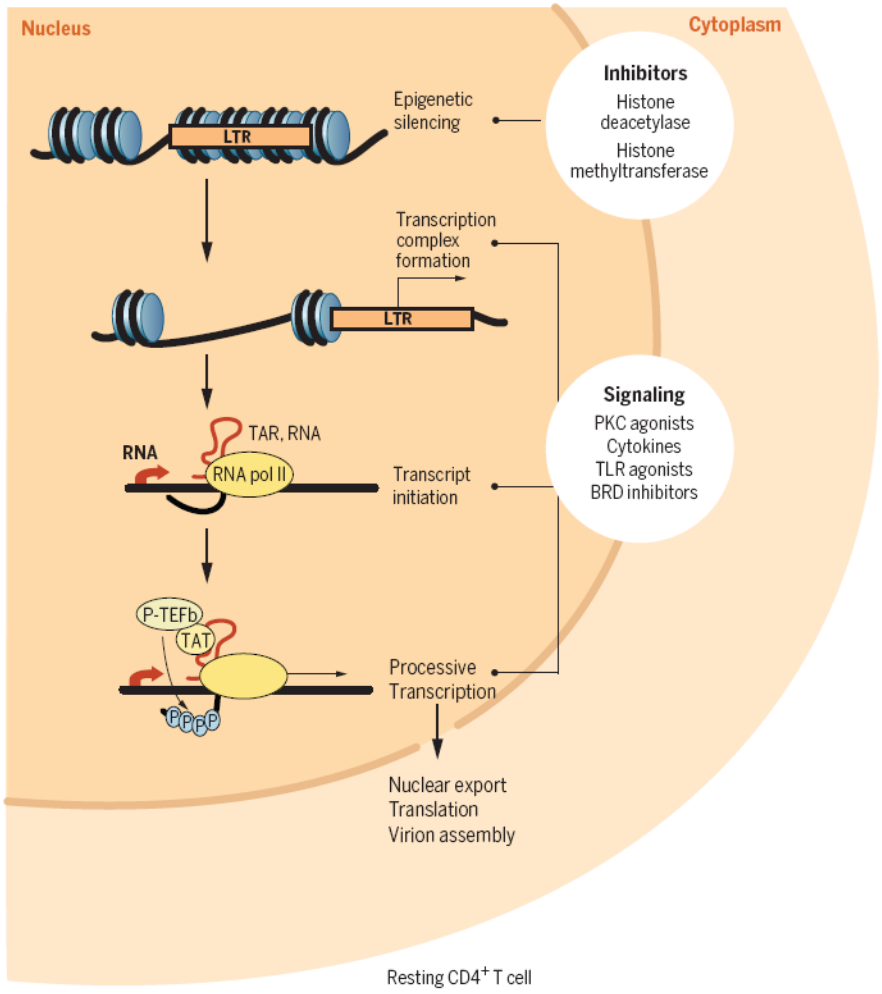

Fig. 1. HIV latency

Cellular pathways that enforce HIV latency are targets for LRAs. The escape of the integration provirus from the latent state is restricted at several levels: epigenetic silencing of the proviral promoter, transcription complex formation, transcript initiation, and transcription complex processivity. Examples of inhibitors and inducers currently under study as potential LRAs are displayed.

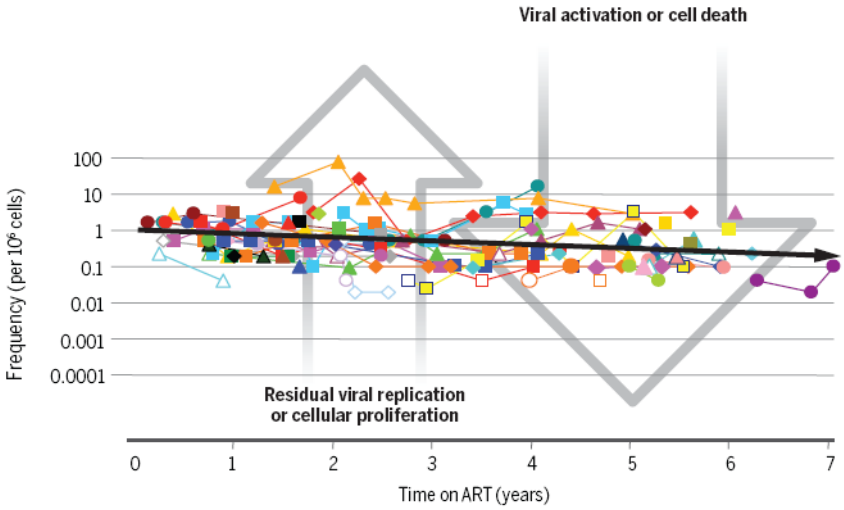

Fig. 2. Persistent, latent infection of memory CD4 cells decays slowly over time

Residual HIV replication and proliferation of latently infected cells might increase the frequency of latent infection, but these forces must be slightly outweighed by those that naturally deplete latent infection because a slow decay of latent infection is uniformly seen in stably treated patients. The goal of antilatency therapy is to effectively accelerate the clearance of persistent infection across all reservoirs of persistent infection. This data, collected over 10 years ago (35), has recently been precisely reproduced in a contemporary patient cohort using improved ART (36). [Adapted by permission from Macmillan Publishers, *Nature Med*. 2003.]