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REVIEW

HIV Persistence and the Prospect of Long-Term Drug-Free Remissions for HIV-Infected Individuals

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HIV infection can persist in spite of efficacious antiretroviral therapies. Although incomplete inhibition of viral replication may contribute to this phenomenon, this is largely due to the early establishment of a stable reservoir of latently infected cells. Thus, life-long antiviral therapy may be needed to control HIV. Such therapy is prone to drug resistance and cumulative side effects and is an unbearable financial burden for regions of the world hit hardest by the epidemic. This review discusses our current understanding of HIV persistence and the limitations of potential approaches to eradicate the virus and accordingly pleads for a joint multidisciplinary effort toward two highly related goals: the development of an HIV prophylactic vaccine and the achievement of long-term drug-free remissions in HIV-infected individuals.

Less than 15 years after HIV (human immunodeficiency virus) was discovered as the causative agent of AIDS (acquired immunodeficiency syndrome), several classes of antiviral drugs had been developed that could curb viral replication to nearly undetectable amounts and, if used in proper combinations, could prevent the occurrence of AIDS-related symptoms in infected individuals. Twelve years later, it is obvious that these highly active antiretroviral therapies (HAARTs) do not eradicate the virus, the spread of which rapidly resumes upon their cessation in all but exceptional cases. Thus, HAART can control but does not cure HIV infection. This is sobering, considering the long-term adverse effects of current therapies and their prohibitive financial burden on regions of the world where the epidemics are worst (*1*). Can HIV infection be cured, or at least is long-term drug-free remission possible? The present Review tackles this question by comparing HIV with other persistent human viral infections, by summarizing our understanding of the underlying physiopathology from both virological and immunological standpoints, by examining the potential benefits but also risks of therapies currently envisioned to eliminate the virus, and lastly, by highlighting alternative approaches aimed at inducing prolonged drug-free remissions.

How Does HIV-Induced Disease Compare with Other Chronic Human Viral Infections?

In immunocompetent hosts, most human respiratory and enteric viruses cause acute infections: The pathogen multiplies mainly at and around its portal of entry; induces transmission-promoting symptoms such as sneezes, coughs, or diarrhea; kills its target cells; is countered by innate immune responses; and is cleared by adaptive immune responses that protect against reinfection with the same viral strain. In contrast, other human viral pathogens, often less transmissible, induce persistent rather than acute infections. These include all herpes virus family members, the hepatotropic hepatitis B and C viruses (HBV and HCV, respectively), the tumorigenic papilloma and polyoma viruses, and the retroviruses HIV and human T cell leukemia virus (HTLV). Although diverse in nature and in replicative properties, these viruses can persist in the host because they all share a dual ability: limiting their cytopathic potential and escaping adaptive immune responses. How they achieve this, however, varies greatly (*2*). For example, herpes simplex virus (HSV) escapes clearance by establishing latency within cells of the central nervous system, an immunologically protected sanctuary, and undergoes sporadic reactivation bouts effectively controlled by virus-specific immune responses (*3*). In contrast, HCV does not become dormant but rather shields from and antagonizes both innate and adaptive responses, thus inducing chronic disease in close to 80% of cases (*4*). With HBV, age at the time of infection is determinant: infants typically develop chronic infections because their immature immune system is overly tolerant to the virus, whereas infection later in life, for instance through sexual contact, is spontaneously cleared in more than 95% of individuals (*4*).

HIV always induces a persistent infection, irrespective of the immune status of the host; it becomes latent in a fraction of infected cells, yet never stops replicating in others; it is highly cytopathic to $CD4^+$ T cells but exhibits modest toxicity in macrophages; lastly, it has evolved multiple mechanisms to evade immune responses, including the direct infection and killing of the very cells that should normally be key to its clearance, the $CD4^+$ helper T lymphocytes. Together, these features allow for viral persistence despite antiviral therapies capable of keeping viremia undetectable for years (*5*).

What Is at the HAART of HIV Persistence?

Newly produced HIV virions have a circulating half-life of only a few hours, thus viremia reflects the size of the pool of virus-producing cells in an infected individual. After acute infection, virus-specific T cell responses lead to a drop in viremia to a relatively stable level termed the set point, predictive of the speed at which clinically manifest immunodeficiency will occur if the patient is left untreated (*6*, *7*). After initiation of HAART, the plasma viral load undergoes a multiphasic decay, with an initial rapid decline ($t_{1/2}$ ~ days) stemming from the elimination of short-lived infected cells (mostly activated $CD4^+$ lymphocytes) by virus- and immune-mediated mechanisms (*8*). This is followed by a second phase of slower decline ($t_{1/2}$ ~ weeks) thought to reflect the loss of infected macrophages, which are more resistant to virus-induced cytopathic effects, and possibly the attrition of other viral sanctuaries (*8*). Viremia then stabilizes often below the detection limit of current tests (<50 copies of viral RNA per ml of plasma). Occasional viral blips under therapy and the rapid return of high-level viremia whenever HAART is interrupted, however, demonstrate that the virus is not eradicated (*8*). Although incomplete inhibition of viral replication is likely to contribute to this phenomenon in a subset of individuals, the heart of the problem lays in the early establishment of a stable reservoir of latently infected cells that is not sensitive to current treatments.

Low amounts of viral replication seem to contribute to HIV persistence particularly in individuals displaying immune activation in organs such as the gastrointestinal tract (*5*, *9*). Although more potent or penetrating antiviral drugs might succeed in suppressing residual viral replication in this and other anatomical sites such as the central nervous system and the genital tract, they will not affect individual latently infected cells. It is estimated that an HIV-infected individual with no detectable viremia can harbor up to 10^7 latently

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infected cells, mostly CD4+ memory T lymphocytes (*10*). This reservoir is established from the earliest times of infection and is maintained in part by homeostatic proliferation (*11–13*). Although its size may be reduced when HAART is initiated very early, mathematical models predict that viral eradication could take up to several decades under conditions of complete viral suppression (*14*). This has led to the proposal of combining HAART with "purging regimens," that is, therapeutic approaches aimed at forcing viral expression by latently infected cells to induce their destruction by virus- or immune-mediated mechanisms. A good comprehension of the molecular mechanisms of HIV latency is necessary to understand the rationale and evaluate the prospects of such therapeutic interventions.

What Are the Molecular Mechanisms of HIV Latency?

When HIV infects resting CD4+ T cells in vitro, it stalls before integrating. This preintegration latency probably occurs in vivo, but is unlikely to represent a functionally significant reservoir given the short half-life of episomal viral DNA (<10 days) (*15*). In contrast, integrated viral genomes (proviruses) can be durably yet reversibly repressed by a combination of mechanisms (*16*). First, the provirus can be subjected to repression via neighboring cis-acting sequences. The HIV preintegration complex is normally tethered to expressed genes by the transcription factor LEDGF/p75, presumably to foster viral expres-

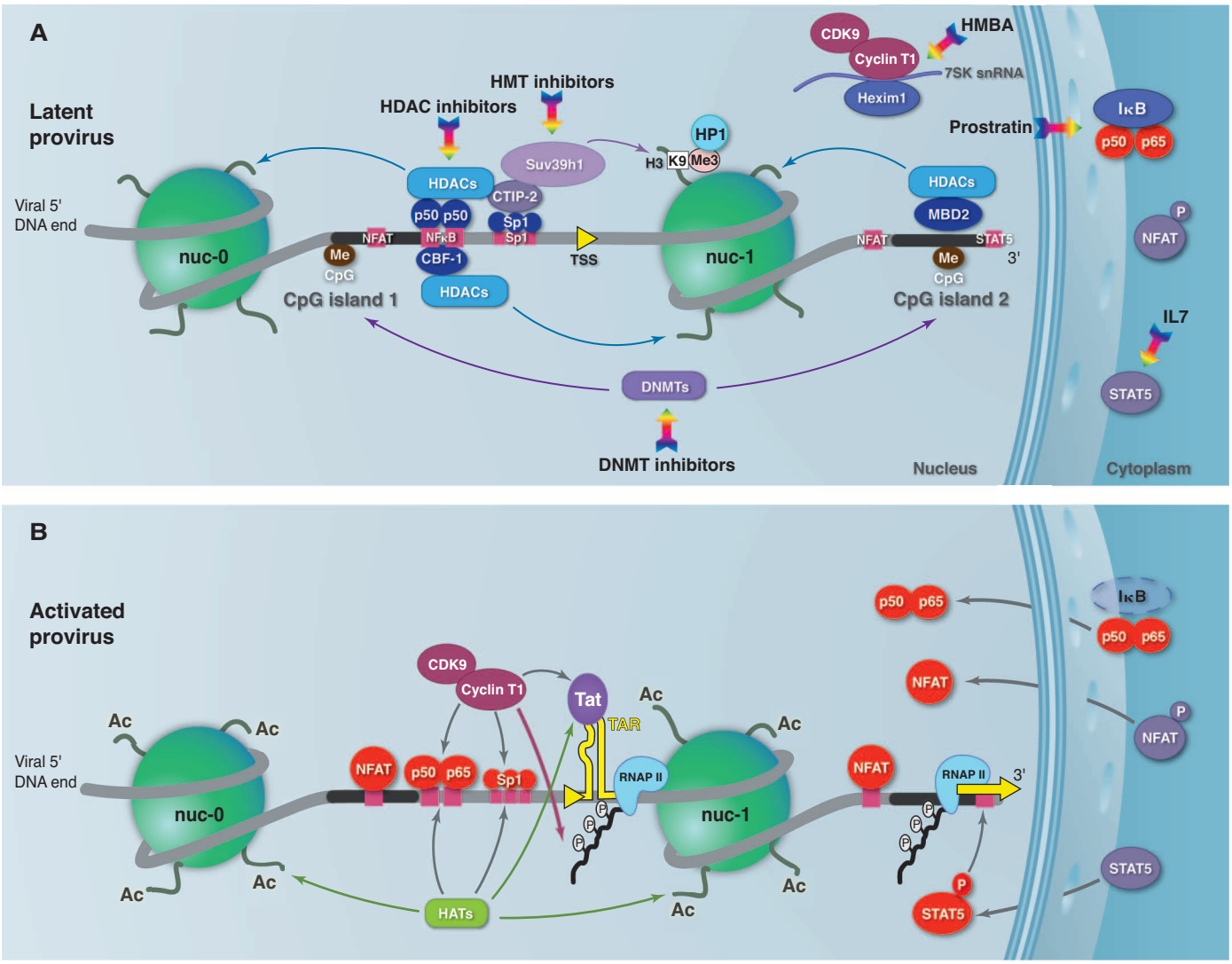

Fig. 1. The yin and yang of HIV transcription in CD4+ T cells. The viral DNA 5′ end is depicted as a light gray ribbon wrapped around nucleosomes Nuc 0 and Nuc 1, with CpG islands in dark gray; sequences binding transcription factors NFAT, NFκB, Sp1, and STAT5 as pink boxes; transcriptional start site (TSS) as a yellow triangle. Gray arrows depict protein movements; color-coded arrows link enzymes and their targets; rainbow arrows indicate potential pharmacological interventions leading to HIV transcriptional activation. (**A**) In resting T cells, HDACs and HMTs (such as Suv93h1) are recruited to the HIV promoter via p50 homodimers and CBF-1 bound to the NFκB sites and via the Sp1-binding CTIP-2 and the methylated DNA-binding MBD2 proteins. Deacetylation and indicated histone methylation on Nuc 0 and Nuc 1 induce a state of heterochromatin. Methylation of two CpG islands by DNA methyltransferases (DNMTs) can further repress transcription. Moreover, the cyclin T1/CDK9-containing pTEFb is sequestered by the Hexim1/7SK RNA complex, whereas the active form of NFκB (p50-p65 heterodimers) is kept by IκB in the cytoplasm, where the phosphorylated and unphosphorylated forms of NFAT and STAT5, respectively, are also retained. (**B**) In activated T cells, HATs and the cyclin T1/CDK9 complex are recruited to the viral promoter by NFκB p50-p65 and Sp1 bound to their cognate sites, and by Tat bound to the TAR (Tat responsive) sequence of nascent RNA transcripts. Histone acetylation of nearby nucleosomes and phosphorylation of the RNAPII C-terminal domain ensue, leading to more accessible chromatin conformation and increased transcriptional elongation, respectively. HIV gene expression is further stimulated by the binding of NFAT and phosphorylated STAT5 to their cognate sites.

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sion (*17*). However, integration can occasionally occur within less favorable chromatin environments, leading to latency. Second, the transcriptional status of HIV is tightly coupled to the activation state of its host cell (Fig. 1A). In resting T cells, nucleosomes adjacent to the HIV promoter, notably one situated at the transcriptional start site (Nuc 1), bear markers of silent heterochromatin, such as lysine 9 trimethylated histone 3 (H3K9me3), heterochromatin protein 1 (HP1), and low levels of histone acetylation (*18*). The 5′ long terminal repeat (LTR) of HIV harbors sequences that, in resting T cells, can bind negative regulators. For instance, two adjacent nuclear factor κB (NFκB) sites recruit either p50 homodimers or the C-promoter binding factor-1 (CBF-1), both of which bring in histone deacetylases (HDACs) that act on Nuc 1. Sp1 binding to the basal promoter similarly tethers the corepressor CTIP-2, which recruits HDACs and the histone methyltransferase Suv39h1 (*19*), leading to histone deacetylation and H3K9 trimethylation at Nuc 1 with secondary recruitment of HP1 and promoter repression. Silencing is reinforced by methylation of two CpG islands, possibly through stochastic influences exerted by neighboring cis-acting sequences (*20*, *21*). Methyl-CpG binding domain protein 2 (MDB2) and HDAC-2 bind to the most distal of these methylated CpG islands, a process that negatively correlates with HIV transcription. Lastly, latency can be strengthened by posttranscriptional mechanisms, such as impaired HIV mRNA nuclear export, be-

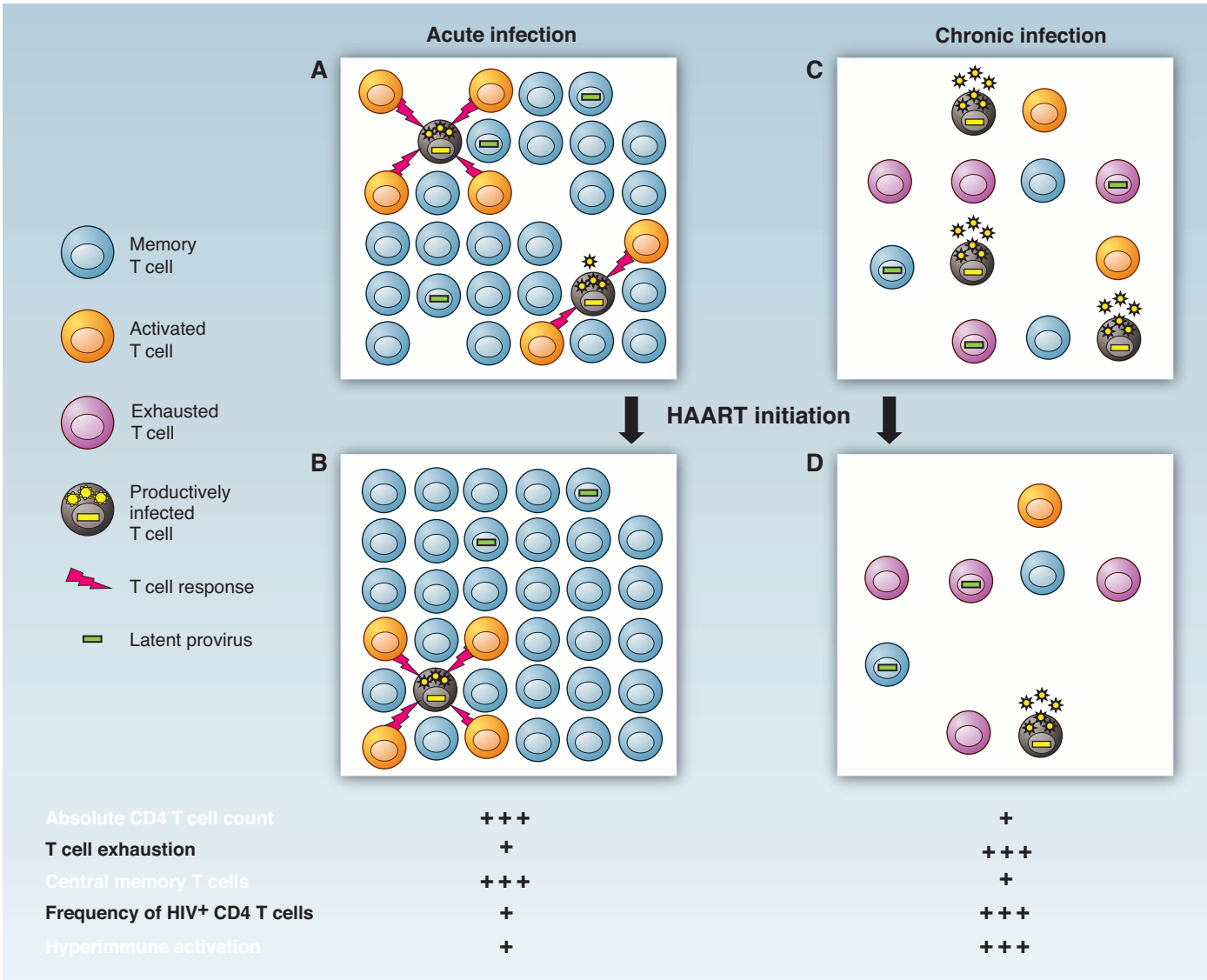

Fig. 2. HIV–T cells dynamics, on and off HAART. (**A**) During acute infection, HIV replication is partially controlled by T cell responses, and depletion of the $CD4^+$ T cell compartment is limited. Because of viral cytopathic effects or immune mediated killing, productively infected activated T cells do not generally survive for long enough to revert to a memory state. A small pool of latently infected memory $CD4^+$ T cells harboring integrated HIV DNA, however, is established. (**B**) HAART initiation during the acute phase generally results in the normalization of $CD4^+$ T cell counts and the preservation of memory T cell responses, which can subsequently contribute to the control of viral replication upon reactivation from stable reservoirs. (**C**) Chronic infection is accompanied by depletion of the $CD4^+$ compartment and exhaustion of HIV-specific T cells, leading to uncontrolled viral production. (**D**) HAART initiation during the chronic phase of the disease generally abrogates viral replication, but $CD4^+$ T cell reconstitution is limited. This is associated with hyperimmune activation of T cells of diverse specificities even in the absence of their cognate antigen. The profound depletion of memory $CD4^+$ T cells along with the exhaustion of HIV-specific $CD8^+$ T cells result in the incapacity of the immune system to control sporadic reactivation events. Although viral dissemination is limited by HAART, de novo infection can occur and may contribute to HIV persistence.

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cause of low amounts of polypyrimidine tract-binding protein (PTB) (*22*) and expression of host or viral micro-RNAs (miRNAs) [reviewed in (*23*)].

Upon T cell activation, a series of events inverts this flow of repressive inputs (Fig. 1B). Degradation of IκB (inhibitor of NFκB) allows the nuclear migration and HIV promoter binding of p50-p65 heterodimer, the active form of NFκB, which stimulates HIV expression, notably through the recruitment of histone acetyltransferases (HATs) that remodel Nuc 1. Similarly, intracellular calcium fluxes activate the enzyme calcineurin, which dephosphorylates and thus induces the nuclear localization of NFAT (nuclear factor of activated T cells), another positive regulator of HIV transcription. HIV expression is also dependent on the viral Tat protein, which recruits the cellular positive transcription elongation factor b (P-TEFb) complex onto the nascent viral transcript. P-TEFb comprises cyclin T1 and cyclin-dependent kinase 9 (CDK9), which stimulates transcriptional elongation by phosphorylating the C-terminal domain (CTD) of RNA polymerase II (RNAPII). In quiescent T cells, P-TEFb is sequestered by the HEXIM-1 [hexamethylene bisacetamid (HMBA)–induced protein 1]/7SK snRNA (7SK small nuclear RNA) complex. Upon activation, P-TEFb is liberated and tethered to the HIV 5′ LTR, first by p65/NFkB and Sp1 and second by Tat bound to the 5′ end of the nascent RNA transcripts (*24*). Lastly, whereas T cells constitute the most quantitatively important HIV reservoir in HAART-treated individuals, other targets may contribute to viral persistence—for instance, brain microglial or hematopoietic stem cells, in which molecular mechanisms of viral latency are yet to be deciphered (*25*).

Intervention	Impact on the HIV reservoir	Impact on immune functions
HAART initiation during acute HIV infection	Limits the frequency of latently infected cells	Preserves HIV-specific T cell responses
HAART intensification	May decrease ongoing viral replication in anatomical reservoirs (but is unlikely to affect the pool of latently infected cells)	May reduce immune activation and increase absolute CD4 T cell counts in a subset of individuals
IL-7 therapy	May induce viral reactivation but also homeostatic proliferation of latently infected cells	Increases both CD4 and CD8 absolute T cell counts and improves HIV-specific responses
HDAC inhibitors and other chromatin modifiers	May reactivate HIV production thereby decreasing the pool of latently infected cells	Unknown
Therapeutic vaccination	May achieve natural control of HIV reactivation after HAART cessation	Should induce potent and long-lasting HIV-specific T cell responses

Impact has been clearly demonstrated in several studies; Limited number of observations, needs further investigation; Hypothetical impact, not yet tested/achieved

Fig. 3. Possible strategies for the long-term control of HIV infection.

What Are the Shortcomings of the Immune Response?

After acute infection, the development of HIV-specific T cell responses leads to suppression of HIV replication and to a decrease in viral load, although the latter is modest, indicating that productive viral replication goes on in spite of the immune response. This sharply contrasts with the situation observed with herpes viruses, where only latently infected cells are preserved in the immediate aftermath of the acute infection. With HIV, a pool of productively infected cells is constantly replenished, and the continuous exposure to viral antigens during the chronic phase of infection leads to T and B cell exhaustion and ultimately to a broad and severe dysfunction of antigen-specific immune responses (*26*–*30*). The viral and immunological mechanisms underlying the lack of control of HIV replication are numerous and probably synergistic, including (i) the extraordinary capacity of HIV to escape immune pressure through mutations and virus-mediated down-regulation of key molecules such as major histocompatability complex class I (MHC-I) from the surface of infected cells (*26*, *27*), (ii) the depletion of $CD4^+$ T cells through direct and indirect cytopathic effects and the subsequent loss of T helper activity (*31*), (iii) defects in the priming and function of HIV-specific effector T cells, and (iv) the skewed development and maintenance of HIV-specific memory T cells (*32*). Together, these mechanisms result in an immune system unable to control HIV replication in a context of continuous and sustained hyperimmune activation attributed to high levels of viral replication and to the translocation of microbial products from the gut, an apparent consequence of the early immunological damage inflicted on this organ (*33*).

The introduction of HAART had raised hope for viral eradication or at least for a natural, long-term control of HIV replication. The reproducible observation of viral rebounds during structured treatment interruptions (STI) trials, however, indicates that the immune system, even after a long "antigen-free" period, is unable to control HIV resurgence (*34*). By comparison, reactivation bouts of herpes virus infections are swiftly put to rest, probably often before they even become detectable, except in immunocompromised individuals. Immune hyperactivation and suboptimal priming of T cells during the viremic period might preclude the establishment of long-lasting memory T cells, explaining why viral rebounds during STI cannot be tamed (*32*, *35*, *36*). There could also be depletion of HIV-specific $CD4^+$ T cells early in the disease and creation of an immunological "hole," as viral antigen-mediated stimulation of these cells renders them highly susceptible to infection (*31*). Supporting both of these models, initiation of HAART shortly after the primary infection, before immune activation and exhaustion reach their maximal level, increases the breadth and the magnitude of HIV-specific memory $CD4^+$ T cells in virally suppressed participants, suggesting that early treatment could be a prerequisite to the natural control of HIV replication (*37*, *38*) (Fig. 2).

Recent observations in both humans and nonhuman primates indicate that long-lasting central memory $CD4^+$ T cells (T_{CM}) might play a particularly important role in the control of HIV replication. Through their expression of the chemokine receptor CCR7 and the selectin CD62L, T_{CM} preferentially home to secondary lymphoid organs and readily proliferate and differentiate into effector cells in response to antigenic stimulation (*39*). Furthermore, they are long-lived, ensuring long-term immunological memory (*40*). HIV infection is characterized by defects in the generation and maintenance of T_{CM} cells (*32*, *35*, *41*). $CD8^+$ T_{CM} have a shorter half-life and are less abundant in HIV-infected individuals than in controls (*42*). Also, the frequency of detection of both $CD4^+$ and $CD8^+$ HIV-specific T cells decreases rapidly after HAART initiation (*43*, *44*). Nevertheless, early treatment of simian immunodeficiency virus (SIV) infection is associated with a restoration of $CD4^+$ T_{CM} cells in the gut, suggesting that a fraction of T_{CM} cells generated during an acute infection could be preserved so as to constitute a functional pool when viral replication is suppressed by HAART (*45*).

Increased frequency and survival capacity of high interleukin (IL)-2–producing $CD4^+$ and $CD8^+$ T_{CM} cells were measured in elite controllers (ECs), a rare population of HIV-infected individuals who control viral replication in the absence of therapy (*46*, *47*). ECs most likely represent a

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heterogeneous group, with contributions of identified host factors (e.g., HLA alleles B27 and B57) in some but not all. ECs' $CD4^+$ T_{CM} cells appear protected from viral infection, as do those from SIV-infected sooty mangabeys, a model of natural resistance to disease progression (*48*, *49*). All together, these observations indicate that both $CD4^+$ and $CD8^+$ T_{CM} cells contribute to the natural control of HIV and suggest that a drug-free control of HIV replication may be achieved by preventing the elimination of these cells through early treatment interventions and specific vaccination strategies.

Is Long-Term Drug-Free Remission Possible?

The latent reservoir is established from the earliest times of infection. Rare patients, when placed on HAART at this time, exhibit prolonged viral control after treatment interruption (*50*). This suggests that early treatment may help to preserve immune responses. Furthermore, HAART with STIs in acutely infected macaques increases SIV-specific responses, and the capacity of the immune response to temporarily control viral rebounds (*51*). Whether such an outcome is restricted to particular genetic backgrounds in humans remains to be determined (*52*).

A recent longitudinal study of the rebounding virus in patients subjected to multiple 2-week STIs revealed that its clonal origin differed between episodes. Furthermore, assembled phylogenies indicated no temporal structure between the rebounding viruses and their pretreatment counterparts, sequences obtained during different STIs clustering with different pretreatment clones (*53*). In another group of patients, the sequences of rebounding viruses were distinct from those of proviral DNAs detected in the circulating latent reservoir before HAART interruption (*54*). Most likely, only a fraction of the total pool of HIV-infected clones is represented in the blood, and T cells residing, for instance, in the gut are more susceptible to undergo antigen-induced immune activation and reignite the infectious process (*55*). HIV thus appears to reemerge from the stochastic activation of long-lived clones rather than from the expansion of viral populations replicating at low levels during treatment. Correspondingly, treatment intensification trials with new and potent antiretroviral drugs have failed to eliminate residual HIV viremia. In several instances where ultrasensitive assays capable of detecting as low as one copy of HIV per ml of plasma were used, no clear benefit of HAART intensification could be demonstrated in patients who had previously achieved undetectable (<50 copies per ml) viremia (*56*–*59*). Recently, addition of a potent integrase inhibitor to a cocktail of antiretrovirals induced a transient increase in episomal viral DNA in 30% of HAART-treated participants, a sign that this drug was curtailing some ongoing replication, yet it did not lead to any measurable change in their viral loads (*60*).

Recent efforts have therefore focused on the possibility that latent viruses could be "purged" by pharmacological manipulations. For this, whether in vitro or, for selected agents, in the setting of controlled clinical trials, HAART has been combined with interventions aimed at forcing viral expression from the latent reservoir. It was reasoned that HIV induction would expose latently infected cells to virus- and immune-mediated killing, whereas HAART would block any further viral spread. Owing to the molecular mechanisms at play in the establishment and maintenance of HIV latency, three categories of agents have been tested: T cell activators, inhibitors of histone-modifying enzymes, and inhibitors of DNA methylation (Fig. 1). Early clinical studies assessing the potential benefit of combining T cell activating agents, such as IL-2 or antibodies specific to the T cell receptor CD3 subunit (OKT3), with antiviral drugs demonstrated a transient drop in the apparent size of the viral reservoir, but patients experienced rapid plasma viral rebound upon HAART cessation (*61*). IL-7, an important controller of T cell homeostasis, can reactivate latent HIV in vitro through the induction of the Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathway (*62*). But IL-7 also promotes the homeostatic proliferation of HIV latently infected cells, which questions its usefulness for purging viral reservoirs (*13*). An initial report that valproic acid (VPA), an antiepileptic agent with weak histone deacetylase inhibitory activity, may decrease the size of the pool of latently infected resting $CD4^+$ T cells was not subsequently confirmed (*63*, *64*). In vitro and ex vivo analyses have further demonstrated that the transcriptional activity of latent HIV proviruses can be induced by combining various types of activators, including the NFκB-inducer prostratin, with HDAC inhibitors such as VPA or suberoylanilide hydroxamic acid, and inhibitors of DNA methylation such as 5-aza-2′-deoxycytidine (*20*, *21*, *65*).

Although these data indicate that latent HIV proviruses can be forced out of transcriptional silence, evidence that latently infected, resting $CD4^+$ T cells are destroyed upon exposure to purging agents is still lacking both in vitro and in vivo (*66*). Furthermore, many of the mechanisms involved in the establishment and maintenance of HIV latency are also responsible for keeping endogenous retroelements at bay. More than 40% of the human genome is derived from such ge-

Table 1. Some of what we want to know and should dare to ask.

1. What are the relative contributions to HIV persistence under HAART of:
   - Long-lived latently infected $CD4^+$ T cells?
   - Other latently infected cells (microglia, hematopoietic stem cells)?
   - Ongoing/residual viral replication, including in anatomical territories less accessible to antiviral drugs (e.g., the brain)?
2. Can HAART intensification completely suppress residual viral replication?
3. Is there a functionally important decay of the latent reservoir under intensified HAART?
4. Are rebounding viruses in STI:
   - Immunological escape mutants?
   - Viruses for which specific memory immune cells were previously lost?
   - Virologically and immunologically different depending on the time of HAART initiation?
5. Is early HAART initiation capable of:
   - Limiting the pool of latently infected cells?
   - Preserving immune functions?
   - Reducing damage to the GALT (gut-associated lymphoid tissue) and hence subsequent inflammation triggered by systemic leakage of microbial products?
6. Can chronic gut inflammation be curtailed in HIV-infected individuals, and does this affect viral control?
7. Are the gut microbiome and virome altered in chronic HIV infection, and can they be manipulated to minimize antigenic stimulation by intestinal microbial products?
8. Can therapeutic strategies aimed at reactivating latently infected $CD4^+$ T cells lead to a decreased HIV burden in infected individuals receiving HAART without prohibitive adverse effects (e.g., mobilization of endogenous retroelements)?
9. Is pathogenic SIV infection a reliable model to evaluate therapeutic strategies aimed at interfering with HIV persistence? What is the effect of HAART on virological and immunological parameters of (nonpathogenic) SIV infection in its natural hosts?
10. Can a combination of early HAART initiation and therapeutic vaccination lead to subsequent drug-free HIV control?

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netic invaders, whether endogenous retroviruses or non-LTR retrotransposons such as LINEs (long interspersed nuclear elements) and SINEs (short interspersed nuclear elements, which include *Alu* repeats). Endogenous retroelements are formidable motors of evolution, yet their uncontrolled spread could have deleterious consequences, as demonstrated by their occasional involvement in both hereditary and acquired human diseases, including various forms of cancer. Accordingly, retroelements are tightly repressed by histone deacetylation, histone methylation, and DNA methylation. These epigenetic marks are established early in embryogenesis and are maintained throughout life (*67*). The combination of drugs aimed at purging latent HIV reservoirs will likely activate endogenous retroelements, the propagation of which will not be reliably suppressed by HAART. Thus, the potential benefit of purging latent HIV from patients otherwise stably maintained on HAART should be carefully weighed against the risk of retrotransposition-induced insertional mutagenesis.

What Can Be Done?

In sum, the prospect of achieving a sterilizing cure, where all functionally important HIV-positive cells are eliminated from an infected individual receiving HAART, is rather remote. Accordingly, we propose that an increased emphasis be placed on efforts aimed at achieving a functional cure (Fig. 3). Reaching this objective may be facilitated by the rapid initiation of potent antiretroviral drug regimens, which could minimize the size of the latent reservoir and the amount of damage inflicted on the immune system, particularly in the gut, during the early times of infection (*68*). Remarkably, natural SIV infections are characterized not by low viremia, but rather by levels of immune activation considerably reduced compared with those of pathogenic SIV and HIV infections, with preservation of mucosal immunity and absence of significant microbial translocation (*49*). Whether this parameter can be favorably manipulated in HIV-infected individuals should be assessed (Table 1). As well, we need to understand better why a viral clone that resurges from latently infected cells succeeds so reproducibly in reestablishing an infection that is within weeks uncontrollably propagated by broad viral quasi-species. What is the immunological nature of the initially rebounding virus? Is it an early viral clone, the virus-specific helper T cells of which were eliminated during the acute phase of the infection (*31*)? An escape mutant unrecognized by preexisting virus-specific antibodies and cytotoxic T cells (*69*)? Or is reemergence of latent viruses the result of exhausted HIV-specific B and T cell responses due to chronic antigenic exposure? Accordingly, does the lack of such exhaustion when HAART is instated early change the genetic, biological, and immunological profile of rebounding viruses upon subsequent treatment interruption?

Therapeutic HIV and SIV vaccination trials in humans and nonhuman primates, respectively, have so far given mixed results, with boosting of virus-specific immune responses in some cases but no clear prolonged reduction of viremia in any (*70*, *71*). However, much fewer efforts have focused on this goal than on the development of a prophylactic HIV vaccine. As the latter is now recognized as critically needing a more in-depth and scientifically sophisticated research investment (*72*), we propose that the two lines of investigation be pursued jointly. Both will benefit from an increased understanding of antiretroviral immunity, whether innate or adaptive, and will have to rely on similar experimental tools and models. Furthermore, the comparable degrees of clonality of transmitted/founder and rebounding viruses suggest that the immunological challenges posed in both situations bear some similarities, even though the founder virus is selected from a broad quasi-species present in the inoculum through the action of a naive yet intact immune system (*73*), whereas the rebounding virus faces immune responses that have been primed but also damaged by the preexisting infection. Moreover, owing to the integrative properties of HIV and its ability to enter latency, it is likely that a successful prophylactic vaccine will not be sterilizing but will rather minimize the systemic spread of the virus, the very goal of a therapeutic vaccine. Of note, testing the latter is logistically easier, because HAART interruption immediately provides the proper challenge in all enrolled individuals.

What leads could one follow for developing a therapeutic HIV vaccine? The study of ECs and nonhuman primates points to interesting avenues. Although it appears that neutralizing antibodies do not have a major role in ECs, the immunological profile of these individuals speaks for the critical influence of a strong polyfunctional $CD8^+$ T cell response to essential immunodominant epitopes, resulting in effective granzyme B-mediated killing of HIV-infected T cells (*74*). Moreover, the relative resistance of sooty mangabeys and ECs $CD4^+$ T_{CM} cells to viral infection suggests that a virus-free T_{CM} compartment may be a major correlate of protection during lentiviral infection, including for controlling reactivation from latent reservoirs. Understanding how this compartment is established and how its expansion can be stimulated may lead to the development of approaches for the long-term, drug-free control of HIV infection. Experience acquired while trying to develop an HIV vaccine, however, indicates that this will require wandering off the beaten paths (*72*). More provocatively, innate and adaptive responses do not significantly control SIV in its natural hosts, yet these animals rarely develop disease (*49*). Whether the accompanying and probably explanatory limited immune activation and preserved mucosal immunity can be obtained only at the price of a long and costly evolutionary adaptation, or whether it can be induced by external interventions, warrants investigation.

When the first signs of the AIDS disaster became apparent and a human retrovirus was discovered as its cause, few would have predicted that barely 20 years later one would be discussing how to keep HIV-infected individuals healthy without medication. The very topic of the present Review is thus a tribute to the extraordinary achievements of the past two decades. Still, the challenge ahead is tremendous and reflects the depth of our remaining ignorance on many fundamental aspects of the interactions between HIV and the human body, and as a consequence our current inability to devise rational approaches to tilt irreversibly the balance in favor of the infected host. Similar to developing an HIV vaccine, obtaining long-term drug-free remissions for HIV-infected individuals should be defined as a top strategic priority, and proper incentives and programs should be put in place to recruit the broad and multidisciplinary scientific research community that will be indispensable to succeed in this endeavor.

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