The search for an HIV cure: tackling latent infection

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Strategies to eliminate infectious HIV that persists despite present treatments and with the potential to cure HIV infection are of great interest. One patient seems to have been cured of HIV infection after receiving a bone marrow transplant with cells resistant to the virus, although this strategy is not viable for large numbers of infected people. Several clinical trials are underway in which drugs are being used to activate cells that harbour latent HIV. In a recent study, investigators showed that activation of latent HIV infection in patients on antiretroviral therapy could be achieved with a single dose of vorinostat, a licensed anticancer drug that inhibits histone deacetylase. Although far from a cure, such studies provide some guidance towards the logical next steps for research. Clinical studies that use a longer duration of drug dosing, alternative agents, combination approaches, gene therapy, and immune-modulation approaches are all underway.

Introduction

Combination antiretroviral therapy has had a pronounced effect on the course of HIV infection, turning it from an infection that is typically fatal within a period of years into a manageable chronic disease. However, from a practical, public health, and economic perspective, elimination of HIV-1 infection would be preferable to long-term suppression of viral replication with drugs. Cure will probably require reduction or elimination of the HIV-1 forms that persist in the presence of antiretroviral therapy. Several factors contribute to persistent HIV-1 infection, but a major reason is persistence of a replication-competent pool of virus in resting CD4 T cells.[1,2]

The pool of latently infected cells is established very early after the initial infection with HIV-1, usually before diagnosis and antiretroviral therapy in routine practice.[3] Very early initiation of antiretroviral therapy has been associated with a reduction in the number of latently infected cells, but virus rebounds when treatment is stopped.[4–7] HIV in latently infected cells can remain dormant for the life of the cell and is not substantially affected by intensification of antiretroviral therapy.[8–10] Attempts to eliminate these cells are a key theme of eradication strategies,[2] with calls to invest heavily in innovative approaches.[11] A cure for HIV is usually defined as either a sterilising cure (by which in theory all latent HIV DNA is eliminated) or a functional cure (wherein latent HIV persists but viraemia is very low or absent without the use of antiretroviral therapy). We focus on the potential for a sterilising cure.

Antiretroviral therapy-based strategies

HIV-1 integrates into the chromosomal DNA of infected cells as part of its lifecycle. A small proportion of infected cells remain transcriptionally silent but with fully infectious virus.[12] These cells are thought to restart active HIV-1 replication when antiretroviral therapy is withdrawn, even after many years of treatment. How these cells persist for many years is not fully understood. The presence of HIV-1 DNA in very long-lived cells (particularly memory CD4 T cells) seems to be the main reason that this latent pool of proviral HIV-1 does not decay or evolve.[13–15] Some of these cells might homoeostatically proliferate to maintain the size of the viral reservoir.[16] Alternatively, even very low-level replication could result in infection of new cells and replenishment of the reservoir despite antiretroviral therapy.[8] However, the absence of viral evolution or the development of drug resistance argues against continued replication in patients on antiretroviral therapy.

Treatment intensification studies have not shown reduction in the size of the HIV-1 reservoir or prevented the recrudescence of viraemia after withdrawal of treatment.[10] One study[8] in 2010, however, showed that intensification of successful antiretroviral therapy with the integrase inhibitor raltegravir resulted in a subset of patients having increased unintegrated forms of HIV-1 DNA.[8] Although controversial,[17] these results imply that the integrase-inhibitor intensification might have slightly reduced replication. Complete blockage of new rounds of infection is likely to be an important starting point for future studies aimed at reducing the size of the latent reservoir.

The Berlin patient and bone marrow transplantation

One person is widely believed to have been cured of HIV-1 infection.[18–20] Although anecdotal, the case is instructive and provides hope that other, safer strategies could be developed in the future. The patient, a 40-year-old HIV-positive man living in Berlin, developed acute myeloid leukaemia and received a bone-marrow transplant from a donor with a homozygous mutation (Δ32) in the gene encoding C-C chemokine receptor 5, *CCR5*, which renders the donor cells highly resistant to infection from most HIV-1 strains (figure 1). He stopped antiretroviral therapy and detectable HIV viraemia did not return. Intensive efforts to detect residual HIV-1 from several tissues generally resulted in undetectable or barely detectable HIV-1 DNA or RNA.[18]

According to a report[21] from 2012, two HIV-positive patients with lymphoma who were on antiretroviral therapy received allogeneic bone marrow transplants (but from donors who were not resistant to HIV), and HIV-1 was no longer detectable in either patient.

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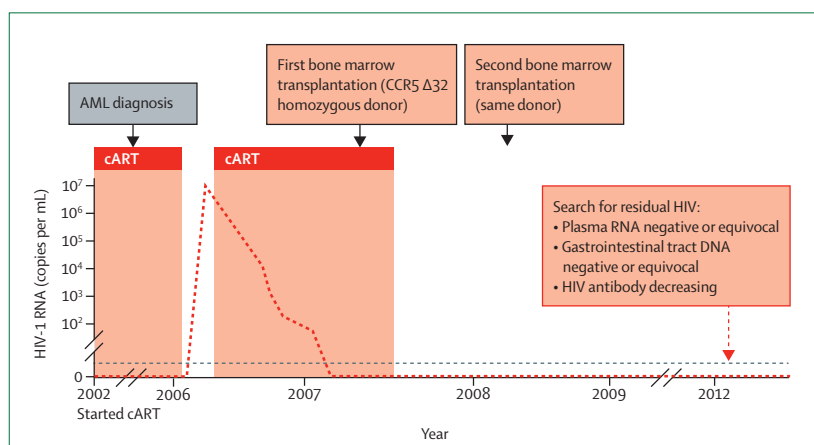**skent@unimelb.edu.au**

Figure 1: Timeline for treatment of the Berlin patient
The grey dotted line represents the limit of detection (one copy per mL) in tests used after transplantation.
AML=acute myeloid leukaemia. cART=combined antiretroviral therapy.

Although these patients have not interrupted their antiretroviral therapy and cure is unconfirmed, these additional cases raise the possibility that factors other than HIV-resistance conferred by the transplanted bone marrow could have cured the Berlin patient. Factors that could contribute to the elimination of HIV latency after bone marrow transplantation include graft-versus-host disease, the use of immunosuppressive drugs, and a possible effect of the hosts being heterozygous for the CCR5 mutation. Although bone marrow transplantation is not a method that could be implemented widely to cure HIV, investigation of the most relevant factors that reduce or eliminate HIV latency in this setting could lead to safer and more suitable alternatives.

Strategies to purge latently infected cells

Several interventions in patients who are on stable, long-term antiretroviral therapy have been studied for their effect on the latent viral reservoir. Interleukin 2 activates CD4 T cells harbouring proviral HIV-1 DNA that, in theory, could be cleared with potent combination antiretroviral therapy.[22] Interleukin-2 therapy showed promise in reducing the latent HIV reservoir in small studies,[22] but in larger clinical trials did not reduce the latent virus reservoir.[23] The anti-T-cell antibody muromonab-CD3 (also known as OKT3) also causes direct T-cell activation, but like interleukin 2 did not reduce HIV latency or improve clinical outcomes. Both agents were associated with substantial toxic effects.[24,25] Interleukin 7 can reactivate HIV-1 in vitro,[26] although clinical trials of the molecule in patients on antiretroviral therapy have not shown any reduction in the size of the latent HIV-1 reservoir.[27] Several groups are studying the ability of other agents (particularly histone deacetylase inhibitors) to activate latent HIV-1 transcription from resting CD4 T cells, and clinical trials are in progress to assess these agents.[28]

Identification of appropriate strategies for viral reactivation has proceeded in two ways. First, new drug discovery has been aimed at identification of agents that through minimum signalling can activate virus expression from latently infected cells without cellular or immune activation. This approach depends on appropriate models for latency. The gold standard for cellular target remains cells that were latently infected in vivo. However, this approach is not always practical and screening assays that use resting primary CD4 T cells infected in vitro have also been used.[29,30] Latently infected cell lines, although useful for defining the mechanisms that control latency,[31] are oligoclonal and poorly mimic the variation in viral integration sites seen in vivo and in primary cell models.[32] Until comparisons of in-vivo and in-vitro effects are available through clinical trials, the relative usefulness of drug screening assays for inhibition of HIV-1 latency will remain unclear. Despite these limitations, candidate agents have been identified, including those that act on NF-κB pathways of DNA transcription (eg, prostratin), epigenetic modifiers (eg, histone deacetylase inhibitors), inhibitors of DNA methylation, and agents (eg, disulfiram) that target the protein kinase AKT, which is involved in cell proliferation.[33] A large array of small molecules that inhibit HIV-1 latency in at least some in-vitro models is now available.[34]

The second strategy is to move rapidly to clinical trials with existing, licensed therapeutic drugs that have the ability to reactivate the virus. Patients whose infections are suppressed with antiretroviral therapy are currently being enrolled in early clinical trials for treatment with viral activators. Preliminary results of one such study are promising,[35] and further research should be done to define the appropriate doses and durations needed to achieve effective clearance of the latent reservoir. The histone deacetylase inhibitor valproic acid was one of the first drugs used, but it is a weak inhibitor of histone deacetylase at doses achievable in the clinic.[36] Valproic acid showed promise in an initial investigation[37] in which it was used together with intensified antiretroviral therapy. However, subsequent studies showed that valproic acid had no effect on the reservoir, emphasising that the relation between in-vitro and in-vivo activity of latency-activating agents is as yet unclear (table).[35,37–41] Potentially more potent histone deacetylase inhibitors, such as vorinostat, have recently been assessed in clinical trials in the USA with a single dose[35] and in Australia with a regimen of 400 mg per day (the licensed daily dose of the drug when used for the treatment of cutaneous T-cell lymphoma) for 14 days (NCT01365065). The histone deacetylase inhibitors panobinostat and romidepsin are both more potent than vorinostat in the activation of latent HIV-1 in vitro, and a clinical trial of panobinostat has started in Denmark (NCT01680094).

Inhibitors of DNA methylation such as decitabine are used in cancer chemotherapy and can modify HIV-1 expression,[31] but are not yet in clinical trials for HIV-1. Disulfiram, a drug long used to treat alcoholism because of its inhibition of acetaldehyde dehydrogenase, might

	Drug	n	Design	Results
Lehrman et al,[37] 2005	Valproic acid	4	Proof of concept study—treatment analysis of infectious units per million cells	Reduced viral reservoir after valproate given in combination with antiretroviral intensification
Siliciano et al,[38] 2007		9	Observational study of patients on combined antiretroviral therapy and valproate	No differences in infectious units per million cells
Sagot-Lerolle et al,[39] 2008		11/13	Case-control study	No effect
Archin et al,[40] 2010		3	Follow-up of Lehrman et al[37] at 48 and 96 weeks	No long-term effect of valproate in initial responders
Routy et al,[41] 2012		56	Randomised study (27 given valproate in weeks 0–16, 29 given valproate in weeks 16–32)	No effect on infectious units per billion cells at 16 or 48 weeks
NCT01319383	Vorinostat	30	400 mg single dose; later investigation to use 400 mg daily for 3 consecutive days per week (maximum 8 weeks)	Initial analysis[35] of single dose in eight patients showed an increase in cell-associated HIV RNA in resting CD4 T cells
NCT01365065		20	400 mg daily for 14 days; initial follow-up to 24 weeks	NA
NCT01680094 (CLEAR study)	Panobinostat	16	20 mg on days 1, 3, and 5, every other week for 8 weeks; viral load, proviral DNA, and infectious units per million cells recorded for 32 weeks	NA
NCT01286259	Disulfiram	20	500 mg daily for 1 month	NA

Table: **Clinical studies of drugs to reduce viral latency by activating the latent virus**

inhibit DNA methyltransferase and activate latent HIV.[42] It is currently being assessed in a clinical trial with a regimen of 500 mg per day for 14 days (NCT01286259). Recent in-vitro work has shown that disulfiram activates latent HIV-1 via activation of the protein kinase AKT.[33] Prostratin activates the NF-κB pathway and latent HIV-1 in vitro, but because of its serious toxic effects cannot be assessed in clinical trials. Development of activators of protein kinase C such as bryostatin or bryostatin analogues could be an alternative approach.[43] Synergistic effects between histone deacetylase inhibitors, methyl-ation inhibitors, histone methyltransferase inhibitors, activators of NF-κB, and interleukin 7 have all been shown in vitro,[30,44] but such combinations remain unexplored in clinical studies so far.

Gene therapy approaches

The curing of the Berlin patient suggests that clearance of HIV-1 can be achieved through repopulation with CCR5-deficient haemopoietic cells, even in the presence of what seemed to be small amounts of virus using CXCR4 before bone marrow transplantation.[18] This finding raises important questions about the relative contribution of the total body irradiation used during transplantation compared with the contribution of low CCR5 expression per se. The 2012 report[21] of the clearance of HIV-1 DNA after allogeneic stem cell transplantation for lymphoma (in the absence of CCR5 mutations in the donor) raises the possibility that transplantation, potentially enhanced by graft-versus-host disease, could contribute to clearance of latently infected cells.

Two separate but related approaches for gene therapy are also being explored (figure 2). The first uses zinc-finger nucleases transfected into either autologous CD34-positive stem cells or expanded populations of CD4 T cells that are reinfused back into the patient.[45] The zinc finger targets *CCR5* and permanently modifies it or truncates it within the genome of the transduced cells, thereby providing a pool of cells permanently resistant to HIV-1 infection (figure 2). CCR5 depletion with zinc-finger nucleases that target CCR5 effectively reduces HIV-1 in mouse models.[46] An initial clinical trial showed a possible reduction in viral rebound after infusion of CCR5-deficient cells and structured treatment interruption in six patients.[47] Reduction of CCR5 expression was associated with control of viraemia—one patient who had the most substantial CCR5 depletion had undetectable plasma viraemia by week 12. Although an important first step, larger studies with more robust reductions in setpoint viral load in patients who are off antiretroviral therapy are needed. A second approach is to knock down translation of CCR5 by use of a short interfering RNA (siRNA) that is retrovirally transduced into autologous CD34-positive or CD4 T cells (figure 2); this approach has also shown promise in preclinical investigation.[48] Phase 1 trials of this method are expected to start in 2013.

An alternative gene therapy-based approach is to enforce latency so that viral rebound does not occur if antiretroviral therapy is stopped. This outcome could be achieved by targeting the HIV-1 promoter with siRNAs or short hairpin RNAs that induce transcriptional gene silencing of the virus via induction of stable epigenetic changes in the integrated viral genome, particularly in the viral promoter or 5′ long terminal repeat (figure 2).[49] Sustained expression of these constructs in immune cells might allow a functional cure through the induction of long-term latency of the virus, resistant to reactivation by inflammatory, proliferative, and homoeostatic stimuli. Although this approach is encouraging in vitro, it is many years away from reaching the clinic.

Immune modulation and immune effector mechanisms

Immunity is also likely to have an important role in controlling HIV latency. Several studies have examined therapeutic vaccines for their ability to control HIV in
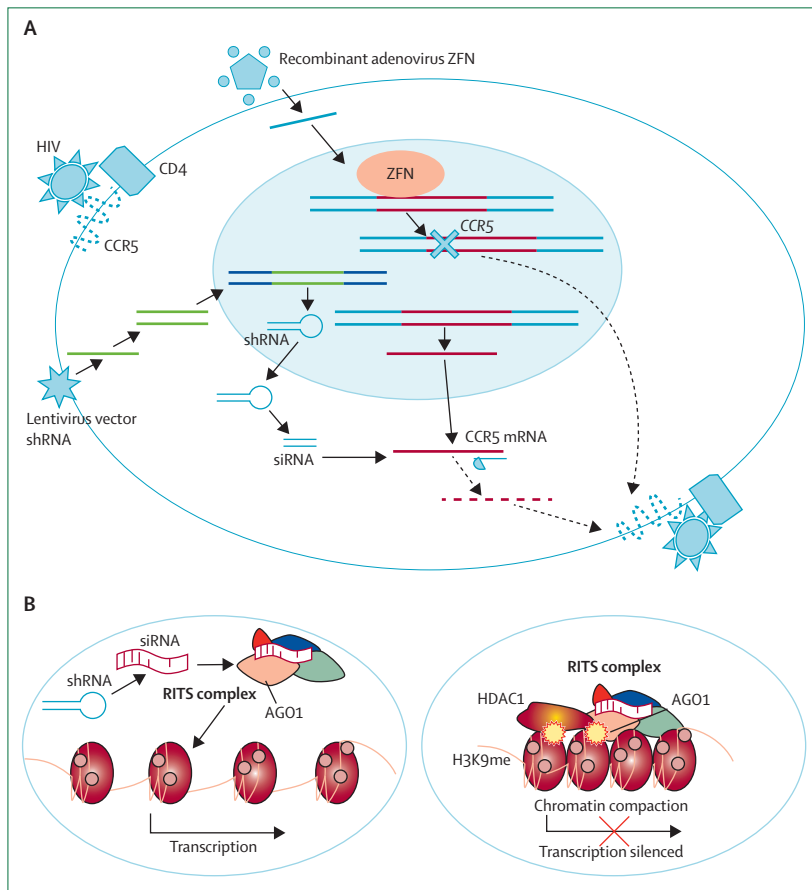
Figure 2: Gene therapy approaches to reduce HIV latency and cure HIV
HIV usually enters cells by use of the CCR5 and CD4 coreceptors (A). Zinc fingers nucleases (ZFN) expressed by recombinant adenoviruses can block CCR5 gene expression, rendering the cell devoid of CCR5 and resistant to HIV. Alternatively, short hairpin RNAs (shRNAs) expressed by lentivirus vectors can degrade CCR5 RNA, also rendering the cell devoid of CCR5 and resistant to HIV, through expression of a short interfering RNA (siRNA) that binds to the CCR5 messenger RNA (mRNA). Transcription of HIV is favoured by an open chromatin structure in the nucleus, shown by widely spaced histones (B, left). siRNA can bind to the RNA-induced transcriptional silencing (RITS) complex, which can result in chromatin compaction and silencing of HIV transcription (right), potentially leading to a permanent latent state for HIV in the cell. AGO1=argonaute RISC catalytic component 1. HDAC1=histone deacetylase 1. H3K9me=trimethylation of histone H3 at lysine 9.

the absence of antiretroviral therapy. Most studies into therapeutic vaccines have focused on cytotoxic T-lymphocyte responses by attempting to boost and broaden HIV-1-specific CD4 and CD8 T-cell responses, but with little success to date.[50–57] In the context of virus reactivation by drugs such as histone deacetylase inhibitors, antiretroviral therapy blocks the infection of new cells after reactivation. However, little is known about the fate of the reactivated cells. Reactivated latently infected CD4 T cells might die as a result of viral cytopathic effect or elimination by the host immune responses, but without active elimination of the cell, a risk remains that the reactivated virus-expressing cells will return to latency.

Resting CD4 T cells latently infected with HIV-1 in vitro do not die after virus reactivation by the histone deacetylase inhibitor vorinostat,[58,59] which suggests that

reactivation alone will not purge the viral latent reservoir. However, Shan and colleagues[58] have shown that when HIV-specific cytotoxic T lymphocytes were first stimulated in vitro, they efficiently killed latently infected cells reactivated by the histone deacetylase inhibitor. Although data are limited to one in-vitro study, this finding adds credence to the idea of using therapeutic vaccines to activate cytotoxic T lymphocyte responses together with agents that reactivate latently infected cells. The induction of potent cytotoxic T lymphocyte responses in HIV-infected patients might, however, be difficult with present HIV vaccine strategies. The improvement of therapeutic vaccines for the induction of such responses is one possible approach that could be pursued.[60,61] For example, dendritic-cell-based vaccines have shown promise in this respect, although these can only be given in highly specialised centres.[62] Conjugation of vaccines to anti-dendritic-cell antibodies to target the induction of potent cytotoxic T-lymphocyte responses is a simpler approach that showed promise in preclinical studies[63] and is being investigated in a clinical trial (NCT01127464). The efficacy of live cytomegalovirus vector vaccines for the control of simian immunodeficiency virus (SIV) infection in macaques suggests a possible role for similar cytomegalovirus vectors as therapeutic vaccines for HIV-1 in future studies.[64] Unfortunately, some of the most effective HIV-specific cytotoxic T lymphocytes are restricted by fairly uncommon HLA class I alleles (eg, *HLA-B*27, HLA-B*57*) and many existing responses in patients will have already forced viral escape early in the infection.[65]

An alternative, non-MHC-restricted immune response that might recognise and eliminate reactivated latently infected cells is antibody-dependent cellular cytotoxicity (ADCC). HIV-specific ADCC antibodies mediate the killing of infected cells by binding to viral antigens on the surface of infected cells and engaging innate immune cells such as natural killer cells or monocytes through their Fc receptors.[66] However, little is known about the effect of long-term antiretroviral therapy on HIV-specific ADCC. HIV-specific ADCC antibody responses are often high in patients with very slowly progressing HIV infection.[67,68] Natural killer cell effectors are, however, decreased in number and can become dysfunctional in patients with progressive HIV disease, although results of recent studies suggest that function of natural killer cells is largely preserved, particularly in patients on effective antiretroviral therapy.[69–77] We speculate that HIV-specific ADCC antibodies could potentially be induced to help to clear reactivated latently infected cells by use of protein therapeutic vaccines combined with potent adjuvants.

Another approach is to target cell-surface molecules that are highly expressed on cells that harbour latent HIV. The programmed cell death receptor PD-1 (also known as PDCD1) is highly expressed on so-called exhausted CD4 T cells that are resistant to activation and harbour latent HIV infection.[78–80] The use of antibodies to

inhibit PD-1 and its ligand has recently shown substantial activity in cancer trials[81,82] and some promise for the reduction of immune activation in macaques infected with SIV.[83] Although such agents will have toxic effects, they could prove useful adjuncts to latency-eradication strategies.

Immune activation and latent HIV

Active HIV-1 infection is associated with increased immune activation. Antiretroviral therapy reduces immune activation, but not to normal. The residual immune activation is associated with residual long-term morbidity, despite antiretroviral therapy.[84] Immune activation despite antiretroviral therapy might have a role in the promotion of low-level HIV replication and reseeding of the latent HIV-1 reservoir, although this idea remains controversial. The investigators of the study of raltegravir intensification of antiretroviral therapy noted that the increase in non-integrated HIV-1 forms after the intervention (which implies continued low-level replication) was largely confined to patients with increased immune activation despite antiretroviral therapy.[8] This finding lends support to the idea that immune activation might drive continued viral replication in patients on antiretroviral therapy.

Drug treatments to reduce chronic inflammation are of interest for several diseases,[85] and such treatments are being investigated for HIV-induced immune activation in several small studies. These studies have two goals: to improve long-term morbidity and to reduce the continuing low-level HIV-1 replication that occurs despite antiretroviral therapy, which would allow more efficient decay or clearance of latently infected cells. The gut-associated lymphoid tissues are damaged during HIV-1 infection and probably contribute to persistent immune activation. Drugs being investigated in clinical trials to reduce gut-damage associated immune activation and so potentially to reduce latent HIV-1 reservoirs include probiotics (NCT01439841),[86] anti-lipopolysaccharide antibodies,[87] the bowel anti-inflammatory agent mesalazine (NCT01090102), and the antibiotic rifaximin (NCT01466595). Research into treatment with agents such at valganciclovir to reduce herpesvirus-induced immune activation common in patients with HIV-1 is at the early proof-of-concept stage.[88] Another approach being investigated in a clinical trial is the reduction of inflammation and thereby the HIV reservoir by use of the angiotensin-converting-enzyme inhibitor lisinopril (NCT01535235). Whether approaches to reduce immune activation in HIV-1 infection will reduce the latent reservoir of HIV DNA is unknown.

Timing of interventions to reduce HIV latency

The timing of when antiretroviral therapy is started after HIV-1 infection might affect the extent of latency during treatment. Patients with acute HIV-1 infection treated with antiretroviral drugs have fewer latently infected cells, and the extent of latent infection seems to be associated with the size of the viral load and duration of viraemia before antiretroviral therapy.[7] Additionally, a small subset of patients given antiretroviral therapy during acute infection can control HIV well when treatment is stopped.[4,7] Although such individuals are difficult to identify for recruitment to clinical trials, they could represent an opportunity to explore more effective interventions against latency.

A second question is when to give interventions to reduce latently infected cells relative to the timing of antiretroviral therapy. Studies are currently done in patients who are on long-term antiretroviral therapy. This approach has the advantage of minimising the risk that any HIV-1 activation could reseed the latent reservoir. On the other hand, this approach might mean that the latent pool is targeted at a time when it is more resistant to activation. Indeed, the notion of a stable population of latently infected CD4 T cells has historically been defined in the context of long-term antiretroviral therapy. However, some researchers have questioned whether such a stable reservoir of HIV-1 DNA is also present during active infection,[89] because of the high immune activation. If the latent HIV-1 DNA pool is much more labile during active infection, then this possibility presents a potential avenue for intervention.
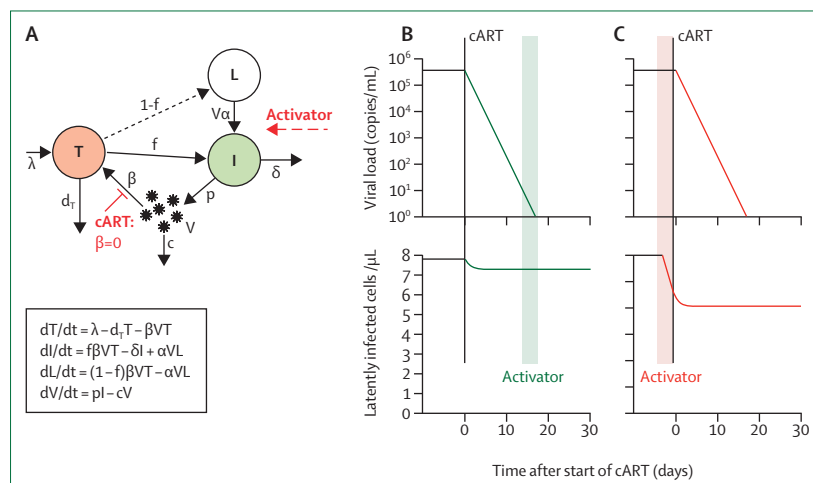

Figure 3: **Possible effects of early or late treatment with latency activators**
We used a mathematical model of viral replication to explore how the timing of administration of a latency-activating drug could potentially affect the latent reservoir (A). The model is based on the assumption that the drug triples the activation rate and is given for a short time (3 days), either immediately before initiation of or after long-term use of combined antiretroviral therapy (cART). If the latency activator is given after long-term use of cART (B) it has a small effect on number of latently infected cells, because the cells are mostly quiescent. If the same latency activator is given for 3 days immediately before the start of cART (C), it causes a large decrease in the number of latently infected cells, because the cells already have a high reactivation rate. The model is adapted from the standard model of HIV infection[96,97] such that a proportion of infected CD4 T cells (1-f) enters the latent pool (L). Latent cells do not produce virus or die, but can be activated to become productively infected cells at a rate proportional to the viral load (αV, where α is the activation constant). cART blocks new infections—the equivalent of setting susceptibility β to zero (on the assumption that the treatment is 100% effective). Parameters used in the figure: λ=10 cells/mL per day; f=0·95; d_T=0·01 per day; α=1·25 × 10⁻⁷; β=8 × 10⁻⁸ mL/copy per day; p=800 copies/cell per day; δ=0·8 per day; c=20 per day.

Search strategy and selection criteria

We searched PubMed and ClinicalTrials.gov for reports about cures for HIV and about HIV latency to identify clinically applicable approaches. We used the search terms "HIV latency", "HIV cure", and "latent HIV" and reviewed articles published in English between Jan 1, 1990 and Dec 1, 2012.

We recently studied the turnover of viral DNA in resting CD4 T cells in active SIV infection of macaques.[90] When viral loads were low, the turnover of the putative latent reservoir was very slow (many years), which is consistent with the low turnover of virus in patients with HIV-1 on treatment. However, in animals with high viral loads, the turnover of SIV DNA within resting CD4 T cells was fast (days), which suggests that high immune activation during active infection might prevent the establishment of true latency. This idea is supported by findings from a study in patients after the initiation of antiretroviral therapy that suggested rapid exchange between productively and latently infected cell pools during both chronic and acute infection.[91] Additionally, studies in HIV-infected patients show a delay between the appearance of mutations in plasma and their appearance in the proviral DNA, both for immune-adaptive mutations[92] and drug-resistance mutations.[93–95]

These findings suggest a new strategy to address the reduction or elimination of the viral reservoir. Since many agents currently under investigation aim to purge the latent reservoir through activation of latent cells, targeting the reservoir when it is already turning over rapidly during active infection might be easier to achieve than when it is stable under long-term antiretroviral therapy. The possible effects of giving a latency-activating drug at different times relative to antiretroviral therapy can be investigated by use of a simple model of HIV infection (figure 3).[96,97] The model predicts that the short-term treatment with latency activators would have the strongest effect on latent HIV-1 DNA if given immediately before commencement of antiretroviral therapy, when it enhances the already existing high activation rate of latent cells caused by the high viral load. Of course, the precise mechanisms of action of a putative latency-activating drug are uncertain, as is whether these would work synergistically with immune activation (as is assumed here). Moreover, whether the reduction in latent HIV would be sufficient to reliably yield a functional cure in the absence of antiretroviral therapy remains unknown, but studies aimed at the incremental reduction of the reservoir size should ultimately answer such questions.

The timing-of-cure approaches with respect to initiation of antiretroviral therapy could hold some promise, but they are not without their own risks. A very real potential exists for toxic effects from attempts to cure at the time of starting antiretroviral therapy, since cellular activation, the loss of a key subset of immune cells, and potentially further increases of HIV-1 replication could be transiently induced. Paradoxically, the results of our previous study[90] and our model (figure 3) suggest that the patients who could benefit the most from such an intervention would be those with high levels of viral replication—ie, those who are likely to have a high turnover of HIV-1 DNA within resting CD4 T cells, making this reservoir more vulnerable.

Conclusions

Innovative strategies to reduce or eliminate latent HIV-1 infection are being pursued to reduce the global burden of HIV and costs and adverse effects associated with lifelong antiretroviral therapy. Several different strategies are in early stage clinical trials. Approaches that attempt to reduce latent HIV at the time that antiretroviral therapy is started should also be investigated.

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