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CENTRAL NERVOUS SYSTEM AND COGNITION (SS SPUDICH, SECTION EDITOR)

HIV Eradication Strategies: Implications for the Central Nervous System

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Abstract

Purpose of Review In addition to preventive protocols and antiretroviral therapy, HIV-1 eradication has been considered as an additional strategy to help fight the AIDS epidemic. With the support of multiple funding agencies, research groups worldwide have been developing protocols to achieve either a sterilizing or a functional cure for HIV-infection.

Recent Findings Most of the studies focus on the elimination or suppression of circulating CD4+ T cells, the best characterized HIV-1 latent reservoir. The role of the central nervous system (CNS) as a latent reservoir is still controversial. Although brain macrophages and astrocytes are susceptible to HIV-1 infection, it has not been ascertained whether the CNS carries latent HIV-1 during cART and, if so, whether the virus can be reactivated and spread to other compartments after ART interruption.

Summary Here, we examine the implications of HIV-1 eradication strategies on the CNS, regardless of whether it is a true latent reservoir and, if so, whether it is present in all patients.

Keywords HIV latency · CNS · HIV cure

Introduction

More than 35 million people worldwide are infected with HIV-1, and an average of a million people die every year of AIDS-related causes. Despite immense progress in understanding the virus and its pathogenesis, the development of a preventive vaccine or efficacious treatment to permanently cure HIV-1-infected individuals has not occurred. In addition, only an average of 60% of these individuals have been treated adequately and have an undetectable viral load [1, 2]. The closest there is to a cure is combination antiretroviral therapy (cART), introduced in 1996. Since then, the number of AIDS cases have drastically declined and the lives of people living with HIV-1 have significantly improved. However, signs of chronic inflammation are still observed in a large percentage of treated patients, even when the virus remains undetectable in the blood and CD4+ T cell counts are restored to pre-infection levels [3, 4]. cART halts viral replication but does not eliminate the virus due to the presence of latent reservoirs containing HIV-1 genomes that can be reactivated and release infectious viral particles once treatment is interrupted. The central concept behind an AIDS cure is to either eliminate all functionally latent virus (sterilizing cure) or to provide absolute control of viral replication even in the presence of viral reservoirs (functional cure). In both cases, strategies have been suggested and, in some cases, tested in vivo.

The location of all latent reservoirs has not been elucidated [5]. Most HIV-1 eradication procedures focus on the elimination of the CD4+ T cell latent reservoir, which has been the best characterized and thought to be the cell carrying the majority of HIV-1 latent genomes [6]. It is possible, however, that other cells such as macrophages and astrocytes may represent an additional part of this reservoir [7, 8•, 9] and it is not known whether strategies used to eliminate lymphocytes will also eradicate other latently infected cell types [10]. The central nervous system (CNS) is specifically suited for carrying functionally latent viral genomes; in addition to being populated with HIV-1-susceptible macrophages and astrocytes [10], the brain is compartmentalized and protected by the blood-brain barrier (BBB), which selectively allows the trafficking of cells and biomolecules. HIV-1-associated cognitive disorders (HAND) are still prevalent in cART-treated patients [11, 12].

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In addition to the evident symptoms associated with neurological dysfunction, such as memory loss and neuropathy, these patients present a threefold increased risk of mortality when compared to their HIV-1-infected non-HAND counterparts [13]. A study using tissues from the National NeuroAIDS Tissue Consortium established an association between these morbidities and viral replication in the CNS [14]. A high prevalence of HIV-1 DNA and RNA was reported in 148 brain specimens of cART-treated patients, and higher levels of viral nucleic acids were detected in patients with neuropathological evidence of HIV-1 encephalitis, despite an undetectable plasma viral load [14]. These findings reaffirm the importance of the brain as a potential viral reservoir during cART.

AIDS cure strategies have been suggested since the beginning of the epidemic, even before the identification of HIV-1 as the etiologic agent. In 1983, bone marrow transplantations in AIDS patients were tried for the first time, with failed results [15]. In 2009, there was new hope for a successful transplant protocol with the functional cure of Timothy Brown, the Berlin Patient, who received bone marrow cells from a donor homozygous for the HIV-1-protective mutation CCR5-Δ32 [16]. The success seen with the Berlin patient led several governmental funding agencies, private companies, and charitable organizations to sponsored projects specifically focused on HIV-1 eradication [17]. This review will focus on how the currently proposed HIV-1 eradication strategies may affect the CNS and discuss the likelihood that these protocols will be able to eradicate potential HIV-1 reservoirs in the brain.

Antiretroviral Intensification

Even with highly effective cART, low-level plasma viremia can be detected using novel quantitative methods. Viral decay studies revealed a three-phase decline curve followed by a fourth prolonged phase where viral decay is negligible [18]. The addition of novel potent antiretrovirals to the already existent regimen does not seem to alter the viral reservoir, indicating that ongoing viral replication is not the principal source of persistent viremia [18–20]. These studies are limited by the lack of information on the role of reservoirs in immunologically privileged compartments such as brain and the genitourinary tract. The real-time penetrance of antiretrovirals into the CNS has not been thoroughly evaluated, and the use of cerebrospinal fluid (CSF) as a surrogate for the brain parenchyma has not been validated [21, 22]. It is possible that novel antiretrovirals (ARV) with improved CNS penetrance will provide better results for the intensification strategy. However, some ARVs are neurotoxic and may lead to an undesired effect of decreasing the CNS viral reservoir while increasing neuroinflammation or neuronal cell loss. This hypothesis is not unfounded. As an example, six percent of patients using dolutegravir, one of the most promising novel integrase inhibitors with excellent brain penetrance [23], had to be discontinued because of adverse neuropsychiatric effects [24]. Additionally, more recently, researchers detected a higher-than-expected number of neural-tube defects among infants born to women who started treatment with dolutegravir before conception [25], highlighting that we do not fully understand the impact ARVs could have on brain development. These findings suggest that the utmost caution should be used with the development of future ARVs and intensification protocols.

Latency Reversing Agents

Once it was demonstrated that HIV-1 genomes remain quiescent during cART, anti-HIV-1 research efforts started focusing on compounds to reactivate and eliminate these latent reservoirs [26]. In vivo treatment with cytokines, which were used early in the epidemic with the sole objective of improving the patient's immune responses [27, 28], were later suggested as viral transcription reactivators [29]. Other compounds, including protein kinase C (PKC) agonists and histone deacetylase (HDAC) inhibitors, were also considered and the strategy recently named "shock and kill" or "kick and kill" [30]. The basic concept behind "kick and kill" is that patients under cART carry latent genomes that can be reactivated by potent latency reversing agents (LRA), such as cytokines and phorbols. Once these genomes are activated and start producing viral particles, the previously latently infected cells can then be detected and destroyed by the immune system. Since the patient is still under cART, the released virus is not expected to spread. The efficacy of such a technique can be evaluated stepwise. Initially, compounds have to be able to activate latent genomes in vitro (cell lines) or ex vivo, with cells isolated from long-term suppressed patients. The in vivo efficacy is then examined using animal models such as humanized mice and non-human primates. Finally, the compounds are tested in humans and the decline in viral reservoirs can be measured by in vitro techniques or by analyzing the time of rebound after cART interruption. The major hurdle for the "kick and kill" strategy, however, is to find a compound that can activate all viral genomes without causing overt cell activation and cytotoxicity. Several of the products used for "kick and kill" are intrinsically toxic and, in most cases, are administered in doses that may not lead to detectable viral activation.

Many LRAs have been previously used in other maladies such as cancers and neurodegenerative disorders, and the effects of such compounds in the CNS have been reported. IL-2, one of the first cytokines proposed as LRAs [31, 32], has been used in the treatment of metastatic renal cell carcinoma and metastatic melanoma but has been avoided in patients with brain metastasis [33]. IL-2-induced capillary leak syndrome can cause increased intracranial pressure, and IL-2-associated thrombocytopenia increases the potential of brain hemorrhages. Additionally, IL-2 may induce behavioral changes,

confusion, lethargy, and (rarely) coma [33, 34]. On the contrary, IL-15 treatment seems to have positive effects in the brain, at least in animal models. Treatment with an IL-15 complex (IL-15C) prevented experimental cerebral malaria in mice through the expansion of protective IL-10 producing NK cells. IL-15C treatment also decreased CD8+ T cell activation in the brain and prevented BBB breakdown without influencing parasite load [35]. Although IL-15 has only a low level of permeation across the BBB, peripheral IL-15 can activate multiple signaling pathways in neurons widely distributed in the CNS regions, reducing anxiety and neuropsychiatric symptoms in mouse experiments [36]. ALT-803, a superagonist IL15-IL15R complex that mimics the effects of IL-15, has been tested in patients who relapsed after allogeneic transplantations, with no noticeable neurological adverse effect [37]. However, in multiple sclerosis, increased peripheral and local levels of IL-15 amplify the pathogenic potential of CD4+ CD28− T cells and contribute to tissue damage in brain lesions [38]. These data suggest that neurodegenerative disorders may be aggravated in HIV-1+ individuals receiving ALT-803 therapy.

Neurotoxic effects have been observed in other LRA classes as well. HDAC inhibitors have been broadly used in the treatment of cancers and adverse effects on the brain have been documented, mostly occurring at doses higher than the maximum tolerated dose [39]. Grade 3 ataxia and grade 1–2 neurological events, including vertigo and memory loss, were observed in phase II trials with vorinostat [40, 41]. Those effects are generally temporary and resolved after treatment interruption. Interestingly, HDAC inhibition is associated with maintaining long-term memory and has been suggested as a potential therapeutic for Alzheimer's disease [42]. Similar adverse effects have been observed in patients treated with PKC agonists, such as bryostatin and prostratin. Both LRAs can dramatically damage the integrity of the endothelial monolayer, induce the secretion of proinflammatory cytokines, and promote upregulation of ICAM-1 expression [43], resulting in an increase in leukocyte transmigration through the BBB and potential increase in neuroinflammation [44]. Additionally, most clinical trials using bryostatin led to systemic side effects unrelated to the CNS, such as myalgia and general fatigue [45], and both PKC agonists have been proposed as positive neuromodulators for neurodegenerative disorders and anti-cancer drugs.

A direct effect of LRAs on latent reservoirs in the brain should also be considered. An effective compound should be able to cross the BBB and activate latent genomes in macrophages and astrocytes. Most compounds are assessed only in CD4+ T cells, although it is known that the HIV-1 LTR in macrophages is regulated by distinct transcription factors [46, 47]. For instance, one of the LRAs used to test the "kick and kill" strategy in human clinical trials, the acetaldehyde dehydrogenase blocker disulfiram [48], effectively activates latent genomes in CD4+ T cells, crosses the BBB, but does not induce viral transcription in macrophages [49]. In addition to concerns about efficacious viral reactivation, levels of cART in the brain must be adequate to prevent viral spread and HIV-1-associated neuroinflammation. As previously discussed, the levels of ARVs in the CNS during cART have not been adequately measured, and both macrophages and astrocytes respond differently to these compounds when compared to CD4+ T cells [50, 51]. De novo replication, however, is not a requisite for neuroinflammation since reactivation of latent genomes in the brain may lead to neurotoxicity caused by viral proteins, such as Tat and Nef [52–55], regardless of the occurrence of viral replication.

Concerns about the effects of LRAs on neuroinflammation were substantiated during the evaluation of a two-LRA combination, the PKC agonist ingenol-B and the HDAC inhibitor vorinostat, used as a "kick and kill" strategy in SIV-infected long-term suppressed macaques [8]. In one of the animals, an increase in CSF viral load after the second cycle of LRAs preceded plasma viremia, and the macaque was euthanized due to pronounced neurological symptoms. Focal sites of SIV RNA, demonstrated in situ hybridization, were identified in the occipital cortex, but not in the basal ganglia or parietal cortex. Genotypic analysis identified a unique SIV quasispecies in the CSF that could not be found in any other compartment, including lymph nodes, spleen, and blood. As in any result from animal models, we should be careful to extrapolate these findings to HIV-1-infected individuals. Nonetheless, until it is demonstrated that the CNS does not host latent HIV-1 genomes at all during cART, careful CSF monitoring should be conducted during LRA treatment in humans.

An additional concern regarding LRAs and the CNS is the possibility that other cryptic pathogens will also reactivate during treatment. Some HDAC inhibitors, such as valproic acid and vorinostat, can reactivate herpesviruses in vitro, including HSV-1, EBV, and CMV [56–58]. However, the recurrence of opportunistic infections caused by the use of LRAs has not been observed in the clinical setting.

Stem Cell Transplantation

Immunoablation and allogeneic transplantation (IA/AT) of homozygous CCR5Δ32 stem cells is the only eradication strategy thus far that has resulted in a putative functional cure [16]. CCR5 is a co-receptor needed for R5 tropic viruses to enter both CD4+ T cells and macrophages; the Δ32 mutation results in a similar protein that is no longer displayed on the cell surface [59]. This prevents HIV-1 from entering its target cells and spread of virus. The "Berlin patient" received two bone marrow transplants from a homozygous CCR5Δ32 donor which resulted in a long-term HIV-1 remission. Following the "Berlin patient" success story, other groups have attempted

to reproduce the results with only partial success. Two patients, named the "Boston patients," who were heterozygous for CCR5Δ32 and received $CCR5^{+/+}$ HIV-1-susceptible stem cells, reported a dramatic reduction in peripheral blood CD4+ T cell reservoirs and undetectable viremia in the absence of cART. Unfortunately, the virus rebounded in both patients after 129 and 226 days post-ART interruption, respectively, and HIV-1 was detected in the CSF of one patient [60]. In another patient, transplanted with homozygous CCR5Δ32, a rapid rebound of a preexisting CXCR4-tropic viral isolate was observed [61]. The analysis of adverse effects of the transplant procedure in the brain of these patients is not feasible but, similar to LRAs, transplantations have been used in many other contexts, including cancers and neurodegenerative disorders. IA/AT are intrusive and high-risk procedures that are only performed as a last resort. Neurological complications are common and can occur at any step of the protocol [62–64]. Drugs used during conditioning and for graft-versus-host-disease (GVHD) prophylaxis have predictable neurological toxicities, from mild symptoms, such as tremors and insomnia, to seizures and whole-brain atrophy [64, 65]. Pancytopenia and immunosuppression, both between the infusion of stem cells and marrow reconstitution and months after transplantation, may lead to opportunistic infections and the reactivation of CNS cryptic pathogens, including toxoplasma and several herpesviruses [66, 67]. On a positive note, it is hypothesized that the efficacy of IA/AT in cure strategies will depend on the extent of GVHD, which seems to be necessary for the complete elimination of HIV-1-infected cells [68]. In mouse models, IA/AT allowed the generation of chimeric brains with microglia being originated from progenitor cells of the recipient mixed with bone marrow-derived macrophages from the donor [69]. This observation may explain the absence of HIV-1 in the CNS of the Berlin patient, who underwent two bone marrow transplants leading to intense GVHD, and the presence of virus in the CSF of one of the Boston patients who did not experience severe GVHD.

Immunotherapy—Broadly Neutralizing Antibodies and Immune Checkpoint Inhibitors

Broadly neutralizing antibodies (bNAb) against HIV have been proposed as additional tools to eradication strategies. As part of a "kick and kill" or IA/TA protocol, bNAbs could be used to eliminate latently infected cells, with or without direct antibody-induced activation [70, 71]. Although infused bNAbs have broad tissue distribution, it is not known whether they can reach the CNS in sufficient levels. Other human or humanized antibodies used in the treatment of cancers have been reported to achieve over 500 times lower concentrations in the CSF relative to serum [72], which may represent a problem for the efficient control of HIV-1 during eradication strategies. HIV-1 variants present in the CSF seem to be, in some cases, more resistant to bNAbs than their blood counterpart, suggesting that the CNS could be a reservoir of bNAb-resistant viruses [73•].

Following success in cancers and autoimmune diseases, the use of checkpoint inhibitors has also been proposed as monotherapy or adjuvant strategy for HIV eradication [74, 75]. The impact of these compounds on the CNS in the context of HIV-1 infection is still unknown, although results from clinical trials for the use of anti-checkpoint proteins for the treatment of tumors have been, in general, positive. Monoclonal antibodies against the PD-1/PD-L1 axis used to treat melanoma proved efficacious against brain metastasis as well [76] and a combination of anti-PD1 and anti-TIGIT in a murine model for glioblastoma-improved survival via modifications of both the T cell and myeloid compartment [77]. However, anti-CTL4 monotherapy has been associated with many neurologic syndromes, including myelitis, neuropathy, aseptic meningitis, and a fatal case of Guillain–Barre syndrome [78].

HIV-1 Deep Suppression

In contrast to "kick and kill," a novel strategy named "block and lock" has been proposed as a functional cure for HIV infection. It has been demonstrated that the compound didehydro-cortistatin A (dCA) inhibits Tat activity and drives the expression of HIV-1 genes into a persistent latent state [79]. Treatment with dCA would promote a state of lasting latency in HIV-infected cells ("blocking") and would inhibit the reactivation of latent reservoirs, permanently keeping ("locking") the genomes in deep latency, presumably even in the absence of cART. The compound was tested in the bone marrow-liver-thymus (BLT) mouse model of HIV latency and persistence with positive results, reducing viral mRNA in tissues [80•]. Most importantly, there was a significant reduction in HIV RNA levels in the brains of dCA-treated mice, suggesting that dCA crosses the BBB and could reduce neuroinflammation caused by viral proteins, such as Tat and Nef.

Upregulation of Innate Immune Responses

Interferon-stimulated genes (ISG) are pivotal in the fight against viral infections [81], and exogenous type-I interferons (IFN) have been used in the treatment of both hepatitis B and C and some cancers [82–85]. Several anti-HIV restriction factors are upregulated by IFN, including SAMHD1, tetherin, and members of the APOBEC3 family [86, 87]. Long-term use of in vivo IFN led to decreased levels of HIV DNA and cell-associated RNA in CD4+ T cells [88, 89]. However, IFNα is highly neurotoxic [90, 91] and seems to be naturally downregulated in the brain during SIV infection [92, 93]. It has been

reported that many cancer patients who receive high doses of IFNα either alone or in combination with other cytokines, such as IL-2, develop an acute confusional state frequently consisting of disorientation, lethargy, somnolence, psychomotor retardation, difficulties with speaking and writing, and psychotic symptoms, such as hallucinations [85, 94, 95]. These symptoms typically resolve with discontinuation of treatment but may persist in some individuals [96]. Additionally, in HCV-treated individuals, IFNα treatment is highly correlated with the development of severe depression [97]. Currently, there are several pegylated IFNα phase I and II trials being conducted in HIV-1-infected individuals [98]. The results from this trial will help inform on the safety and efficacy of these compounds and as to whether they should be used in future HIV-1 eradication strategies.

Gene Therapy

The first documented HIV-1-eradication case, the "Berlin Patient," involved the transplantation of cells from a homozygous CCR5Δ32 donor. This inspired research groups to develop protocols for the ex vivo genetic engineering of CD4+ T cells with the goal of rendering them refractory to HIV-1 infection with subsequent reinfusion into the patient. Varied gene editing nucleases, including transcription activator-like effector nucleases (TALEN), clustered regularly interspaced short palindromic repeats (CRISPR), and zinc-fingers (ZNF), have been used in vitro to manipulate CCR5 and CXCR4 with positive results [99–101]. A phase I clinical trial utilized the ZNF system to generate CCR5 deleted autologous CD4+ T cells ex vivo and then reinfused the modified CD4+ T cells back into virologically suppressed patients [101]. The intervention was found to be relatively safe and somewhat successful. Of the four patients studied, one became HIV RNA undetectable in the blood after ART interruption. Additionally, the number of CCR5-modified CD4+ T cells declined at a slower rate than unmodified CD4+ T cells, suggesting that they were indeed resistant to HIV-1 infection. The effect of ZNF gene editing in the CNS has been studied in other settings. ZNF has been used in conjunction with an AAV viral vector to look at expression of the gene editing tools in terminally differentiated cells in the mouse brain [102]. According to this study, long-term ZFN expression in the CNS neurons did not impair essential neuronal functionality and did not cause inflammation or neurodegeneration, suggesting that this technique may be expressed safely in the brain. A phase II trial using the ZNF approach in HIV-infected individuals is now ongoing and will help to further determine this technique's effectiveness and safety.

Another intriguing approach is the in vivo excision of HIV proviruses using viral vectors that express editing enzymes. The CRISPR/Cas9 system has emerged as a new promising technique that uses guide RNAs to specifically target integrated HIV sequences of DNA and remove them from the cellular genome. This technique may be promising because it can tackle multiple reservoirs throughout the body since it is not cell-specific, but instead virus-specific [100]. Thus far, the effect of the CRISPR system on the CNS is not fully understood, but there have been a few studies that have evaluated CRISPR in astrocytes, microglia, and perivascular macrophages [103, 104]. In an astrocyte cell line, researchers were able to successfully excise integrated HIV provirus using the CRISPR system as confirmed by a GFP reporter and cell genomic DNA PCR [103]. Additionally, a similar method was used to test CRISPR effectiveness in both microglia and perivascular macrophage cell lines and in both cases CRISPR successfully eliminated latent HIV genomes in these cells [104]. These studies suggest that this method of gene editing would work in the CNS but there is not clear evidence that CRISPR would have the same effectiveness on these cells in vivo or would efficiently cross the BBB.

Final Considerations

The role of the CNS as a latent reservoir is still controversial. However, the CNS is specifically suited for carrying functionally latent viral genomes. In addition to being populated with HIV-1-susceptible macrophages and astrocytes, the brain is compartmentalized and protected by the BBB, which selectively allows the trafficking of cells and biomolecules. Additionally, HAND is still prevalent in cART-treated patients despite the absence of viremia in the blood. These data strongly suggest that the brain contains HIV-1 whether or not it is in a "true" latent state and that HIV-1 eradication strategies should take their effects on the CNS into consideration prior to implementation. As demonstrated in this review, most eradication protocols may have some adverse effects on the brain given the potential toxicity of the proposed strategies and the inflammatory nature of HIV-1 reactivation and elimination, indicating that the key to successful outcomes will be to find a balance between efficiently eliminating the reservoir and preventing negative effects on the CNS.

Compliance with Ethical Standards

Conflict of Interest Dr. Veenhuis and Dr. Clements declare no conflicts of interest. Dr. Gama reports grants from NIH, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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