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Immunotherapeutics to treat HIV in the central nervous system

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Abstract

Purpose of review—The application of Immunotherapies to HIV presents a new horizon of treatment options, but little is known about what impact they may have on the central nervous system (CNS). Here we review the most promising immunotherapeutic strategies that can be used to target HIV in the CNS and focus on identifying their potential benefits while exploring the challenges that remain in their application.

Recent findings—We have identified five immunotherapeutic strategies that hold potential in managing CNS disease among HIV infected patients. These include broadly neutralizing antibodies, multi-affinity antibodies, CAR-T cell therapy, checkpoint inhibitors, and therapeutic vaccines.

Summary—Each class of Immunotherapy presents unique mechanisms by which CNS viremia and latency may be addressed but are faced with several challenges. CAR-T Cell therapy and multi-affinity antibodies seem to hold promise but combination therapy is likely to be most effective. However more human trials are needed before the clinical benefits of these therapies are realized.

Keywords

HIV-1; Central nervous system; Immunotherapy; CAR-T cell therapy; Broadly neutralizing antibodies; Therapeutic HIV-1 vaccine

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Conflicts of Interest

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Introduction

Over the past decade, immunotheraputics, including monoclonal antibodies, chimeric antigen receptor T (CAR-T) cell therapy, and checkpoint inhibitors, have emerged as important therapeutics to prolong the lives of patients with cancer. Applying these advances in the treatment of HIV-1 (HIV) is vital, because despite decades of improvement in antiretroviral therapy (ART), sustained rates of virologic suppression and cure have remained elusive [1]. This is a consequence of many remaining barriers with traditional ART including adherence, incomplete immune restoration, chronic inflammation, and HIV viral latency [2,3].

While ART has been effective at controlling viral replication in cells, it has been challenged by toxicity, resistance, and by poor penetration into immune privileged sites including the central nervous system (CNS) [4]. Specifically, in the CNS, the most important shortcomings of ART have been the neurotoxic effects, variable CNS penetration, and viral escape in the CNS. For the last decade clinicians have applied the CNS penetration effectiveness score (CPE) to help devise therapies that maximize ART concentration in the CNS[5]. The CPE score ranks ART regimens on their ability to penetrate the CNS in an effort to control viral replication and reduce the incidence of neurologic complications in HIV. However, the therapeutic efficacy of selecting ART based on a CPE score has become questionable. Studies have shown that even patients treated with high CPE score regimens still have an increased risk of developing HIV associated dementia likely as a result of increased neurotoxicity [6,7].

Targeting the CNS in patients with HIV infection has risen in importance given HIV cure can only be achieved with viral eradication from the CNS. Further, mounting evidence from aging cohorts continue to highlight the morbidity and neurocognitive sequalae of HIV infection even in the setting of virologic control [8,9]. Studies have shown that within two weeks of HIV acquisition, there is detectable virus in the CNS [4]. The resultant viral replication and its neuroinflammatory effects have been linked to worse neurocognitive outcomes, including conditions such as HIV associated dementia, HIV associated neurocognitive disorder (HAND), and myelopathy [8,9]. This chronic inflammation is observed in patients even when their plasma viral loads are undetectable. Further studies have shown that CSF viremia occurs in 10% of patieints with an undetectable plasma viral load, and an estimated 30 to 50% of supressed patieints have evidence of HAND [4,7]. Therefore, it is crucial to close the significant gaps in our understanding of the pathogenesis of HIV in the CNS as well as to seek alternative therapeutic strategies.

Better understanding of HIV neuropathogenesis is hampered by the challenges in the direct sampling of brain tissue. It remains unclear which cells are impacted by viral latency and how drugs, once in the CNS compartment, can directly target the cells harboring the viruses [10–12]. Delivering effective drug to unique cell types in the CNS, such as astrocytes, microglia, and macrophages has proved difficult [9,13]. The blood brain barrier (BBB) also poses a major barrier to ART and immunotherapeutics alike. The BBB limits the entry of immune cells and mediators due to its tissue and endothelial tight junctions. Under homeostatic conditions, trafficking of neutrophils and lymphocytes into the CNS is very low,

resulting in relative immunoprivilege [14]. In addition, molecular size restrictions and CSF efflux pump mechanisms may reduce the ability for antibody complexes or small molecule drugs to reach therapeutic concentrations in the CNS [15]. Direct neurotoxicity also remains an important therapeutic challenge seen both in ART and in the early application of immunotherapies. Novel applications of immunotherapies may be able to address some of these barriers; but there may also be many shared challenges in targeting HIV in the CNS.

The application of immunotherapy in HIV not only presents a wider array of treatment options, but importantly offers potential mechanisms to eradicate or functionally cure HIV. There may also be opportunities to reduce morbidity in HIV patieints by blocking inflammation, improving immune restoration, and addressing viral latency. This article will focus on how novel immunotherapeutic strategies could target HIV in the CNS and will highlight what challenges still remain.

Immune strategies

Several immunotherapeutic strategies have been developed and tested in clinical trials to understand their efficacy and potential for clinical applications. Here we will review the most promising areas of therapeutics and their applicability to the treatment of CNS disease in HIV.

Broadly neutralizing antibodies

Broadly neutralizing antibodies (bNAbs) function by targeting various epitopes on the surface of the HIV-1 envelope as well as CD4 cell receptors which effectively blocks viral entry into cells. Over the past several years HIV specific bNAbs have evolved to gaining increasing potency and breadth [16]. These bNAbs have shown promising effects on decreasing viral loads *in vitro* and in animal studies [17,18]. These early studies paved the way for Ibalizumab, a broadly neutralizing antibody targeting the CD4 cell receptor, now FDA approved for the treatment of multidrug resistant HIV-1 [19].

More research continues to emerge on the potential of bNAbs and a recent clinical trial demonstrated significant bNAb efficacy in suppressing HIV viremia. Caskey et al showed a single infusion of a monoclonal antibody, 3BNC117, showed a mean drop of 1.48 log10copies/ml in patients viral loads, and suppression was maintained up to 28 days [20]; and combination of dual bNAb therapy demonstrated decreases of 2.05 log10copies/ml in viremia, which remained significantly reduced for 3 months [21]. However, there were no CSF viral loads or neurological outcomes assessed in these trials. Although infused bNAbs have a large volume of distribution, it is not known whether they can reach the CNS in sufficient levels. Studies of intravenously infused monoclonal antibodies to treat CNS lymphoma have demonstrated poor CSF concentrations, with CSF levels 100-fold lower than serum [22].

The poor penetrance of bNAbs into the CNS may be a crucial limitation in their ability to treat CNS disease. The CNS penetrance of anti–HIV-1 bNAbs has yet to be measured in human studies; but other human immunoglobulins have demonstrated significant serum to CSF discordance: achieving 500 to 1000 times lower concentrations in CSF relative to

serum [16]. Our data on CSF concentrations of intravenously infused bNAbs in non-human primate studies showed similar low concentrations. Studies of serum and CSF concentrations of rituximab have shown strikingly poor penetration into the CNS, with concentrations reaching only 0.1% of the serum level [23]. Interestingly, intrathecal delivery has been studied with rituximab, and although higher concentrations were achieved in the CSF, they were limited by rapid clearance and very short terminal half-lives [23]. Non-human primate studies looking at the kinetics of intravenously infused human neutralizing monoclonal antibodies in simian immunodeficiency virus (SIV) infected infant macaques in plasma and tissue, have further shown no quantifiable levels in the CNS when examined over a two week period [24]. In response, longer lasting bNAbs are being engineered to help address these issues but it is unclear whether longer half-lives will translate into increased CNS concentrations. Alternative modes of delivery that can bypass the BBB are worth exploring in combination with modifications to promote *in vitro* longevity.

Multi-affinity antibodies to cross blood brain barrier

The incredible genetic diversity of the HIV-1 envelope has created practical challenges in the development of neutralizing antibodies. A new generation of multi-affinity antibodies has emerged in response [25,26]. Not unlike the evolution seen in the development of ART, initial monotherapy provided proof of efficacy, but dual and triple drug therapy has provided durable virologic control.

This new generation of multi-affinity antibodies have several advantages over single bNAbs. They have demonstrated improved breadth, potency, and potentially provide a higher barrier to viral escape [27,28]. Studies with bNAb monotherapy have demonstrated that bNAbs designed to target a single epitope may not optimally treat HIV as their selective pressure can prompt the emergence of resistant mutants [29]. Thus, bNAbs with a single target are not likely to maintain durable suppression of HIV due to viral escape mutants that ultimately result in viral rebound [30]. Trispecific antibodies - bNAbs that bind three unique sites - have demonstrated higher potency and breadth than previously studied single bNAb in several non-human primate studies [31,32]. They show similar pharmacokinetics to those in human single bNAb trials, and have also demonstrated complete immunity against SIV in two recent trials [27,31]. However, there are currently no human trials to date that have demonstrated their efficacy or evaluated them for safety in humans.

An advantage of multi-affinity bNAbs is that they can also be engineered to engage both immune effector cells and targets on the blood brain barrier. This facilitates entry into the CNS using the receptor mediated transcytosis system, while delivering effector cells to the infected cells. Studies in non-human primates have shown that antibodies specific to the transferrin receptor on the BBB can enhance crossing of large molecules, such as multi-affinity antibodies, into the CNS [33]. This combination of antibodies allows the engagement of immune effector cells and cellular targets in a variety of ways and can both enhance the killing of latently infected cells or add a direct cytotoxic effect [28]. While these properties hold great promise, data on their safety and efficacy are currently limited to non-human primate studies.

Due to early stage of their development, little is known about the challenges we might expect with multi-affinity antibodies. Their increased complexity and ability to bind multiple epitopes may come with more off target effects than what has been reported previously with single affinity bNAbs. Though there are interesting mechanisms by which they may be engineered to enter the CNS, penetration into the parenchyma will remain a central challenge to overcome in their application to treat HIV in the CNS. The bNAbs have the potential to be efficacious in prophylaxis and treatment of HIV in the CNS, if these barriers can be surmounted.

Chimeric Antigen Receptor T cells (CAR-T cells)

Chimeric antigen receptor T cell therapy (CAR-T) utilizes genetically engineered T-cell receptors to redirect T-cells towards specific antigens of interest. They are comprised of a single-chain variable fragment attached to a transmembrane domain and intra-cellular signaling complex. These chimeric receptors reprogram T-cells so they no longer require antigen presentation by MHC molecules, but instead can bind specific epitopes directly. This selection of surface epitopes on target cells serves to redirect cytotoxic T-cell response towards an intended cellular target while avoiding destruction of off target host tissues.

CAR-T cell therapy in HIV predates its applications in clinical oncology [34]. Studies in the 1990s and early 2000s demonstrated that first generation anti-HIV CD4-based CAR-T cells could inhibit viral replication *in vitro*, and survived for prolonged periods *in vivo* in humans, but ultimately had minimal clinical efficacy [35,36]. They did not provide any durable virologic control nor could they be proven to reduce viral reservoir size. Second generation CAR-T cells were developed with added intracellular co-stimulatory domains that greatly improved their efficacy [37,38]. Building upon the success of CAR-T cells for hematologic malignancies, new generations of anti-HIV CAR-T cells have been developed and tested by a number of groups [39,40]. Among these are duo CAR-T cells which have been engineered to target multiple sites on the HIV viral envelope thus increasing their breadth and potency over mono CAR-T cells. Early data using duo CAR-T has demonstrated potent reductions of HIV-1 infected cells *in vitro*; and *in vivo* studies using HIV-1 infected mice models have demonstrated the elimination of up to 97% of HIV infected cells using duo CAR-T cells [39].

CAR-T cells have a number of advantages when it comes to the targeting of infected HIV cells. Importantly, they function independently to MHC and can target cells that are latently infected or have been ineffectively cleared by endogenous CTL responses. This cytotoxic specificity may circumvent the challenges of inducing viral escape mutants in the CNS seen in other forms of immunotherapy. Though more data from human studies with CAR-T in HIV treatment are needed to better assess this potential benefit. CAR-T cells are also long lived *in vivo*, and maintain activity for at least 6 months, and can be detected in peripheral blood for up to ten years, in some studies [41,42]. More recent studies examining concentrations of CAR-T in the CNS demonstrate that they are able to cross the BBB [43]. In addition, clinical studies in oncology have shown favorable results in treating primary CNS malignancies including CNS lymphoma and glioblastoma, further validating their ability to traffic to the brain [42]. Preclinical studies have begun to look at the use of

hematopoietic stem cells rather than peripheral immune cells modified with CAR receptors. These studies have shown success in engineering hematopoietic stem cells with anti-HIV T-cell receptors that allow for the differentiation of HIV specific T-cells capable of viral suppression [44]. Such CAR-T stem cells have the advantage of potentially providing prolonged immunity and may represent an important step towards cure.

However, several challenges remain with chimeric antigen receptor T-cell therapy. CAR-T cell related encephalopathy syndrome (CRES) and cytokine-release syndrome (CRS) are among the most common; and occur in more than half of patients. Symptoms can range from mild constitutional signs to multisystem organ failure or hemophagocytic lymphohistiocytosis (HLH) [45,46]. CRES tends to be milder in its presentation and accounts for about 12% and 55% of all reactions [47]. CAR-T cell therapy has also been associated with other significant neurotoxic effects including confusion, delirium, aphasia, seizure, and in severe cases loss of consciousness [48]. Estimating neurotoxicity among patients is challenging due to the diversity of CAR-T cell therapies and the variability in co-stimulatory domains used. Disruption of the blood brain barrier is thought to play a role in neurotoxicity, but more studies are needed to determine the CNS complications of CAR-T cell therapy specifically in the treatment of HIV.

Therapeutic vaccines to enhance HIV-specific CTL response

The success of ART over the last decade has spurred renewed interest in the development of an HIV vaccine. The persistence of a viral reservoir and the variability in adherence, access, and delivery of ART have underscored the importance of these efforts. Despite several decades of determination there has been limited success in therapeutic and preventative vaccine trials [49]. The RV-144 trial demonstrated only modest efficacy against the acquisition of HIV but advanced the understanding of what immunologic strategies may be successful going forward [50]. Using a prime and boost strategy with the combination of ALVAC-HIV (canarypox vector) and AIDSVAX B/E (gp120 vaccine), it demonstrated an efficacy of 31.2% in preventing the acquisition of HIV [51,52]. Based on the immune responses knowledge gained from this trial, there are currently several vaccine strategies under active investigation [53]. Traditionally, prevention strategies have focused on the production of bNAbs, whereas therapeutic strategies have focused on non-neutralizing functional antibodies that direct HIV specific cytotoxic CD8 responses [54,55].

Of particular interest to HIV infection in the CNS are therapeutic vaccine strategies that enhance cytotoxic T-cell responses [56]. Given the viral latency in the CNS, boosted CTL responses can be used to augment the detection and cell specific destruction of cells harbouring HIV DNA. Several studies have demonstrated the ability of non-neutralizing antibodies to elicit a remarkably broad array of responses from innate immune effector cells that result in the targeted destruction of latently infected cells [57]. However, the efficacy and adverse effects of boosting the HIV specific CTL responses in the CNS is not yet known. To date, there are no clinical studies examining this. Despite this lack of clinical data, there are many challenges that are likely to be encountered.

Among these, viral latency and reversal, along with immune compartmentalization are likely to be the most important. Vaccines present an appealing option for the prevention of HIV, but cannot address viral latency once established [58]. This is due to the inaccessibility of genetic material that has already integrated into the host genomes. Patients who have been virally supressed with ART have quiescent viral reservoirs with low levels of proviral DNA replication. This ultimately makes it difficult for vaccine boosted CTL responses to target cells with a robust CD8+ cytotoxic T lymphocyte response. The use of latency reversal agents to upregulate replication of proviral DNA have been tried [59]. However, little is known about the effect of these agents on cells in the CNS and to what extent the specific cell types like microglia and astrocytes can be effectively reactivated. Clinical studies have highlighted the potential toxicity of some latency reversal agents and concerns remain about the clinical effects of neurotoxic viral proteins along with inflammation that may result from reactivation in the CNS [4].

Immune compartmentalization also poses a challenge for the ability of therapeutic vaccines to eradicate HIV in the CNS. The low number of HIV specific CD8+ T-cells within immune privileged sites, including the CNS, is thought to be due to blockade by the BBB[60]. The resulting compartmentalization limits effective trafficking of HIV specific CD8+ T-cells to the CNS -- preventing the elimination and clearance of infected cells. This has been well described in non-human primates infected with SIV which have demonstrated a lack of direct access to lymphoid follicles, resulting in HIV persistence [61,62]. The boosting of HIV specific T-cell responses in the peripheral tissues with vaccines may be effective but if these immune cells are not able to effectively cross the BBB this strategy would have limited efficacy in the CNS.

Immune modulators: check point inhibitors, CTL4 antibodies

There have been a number of monoclonal antibodies developed targeting checkpoint proteins over the last decade. Inhibitors of immune exhaustion receptors, such as program cell death −1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) enhance tumor cell apoptosis resulting in improved survival both in melanoma and non-small cell lung cancer (NSCLC) [63]. There has also been clinical success in treating malignancies involving the CNS with monoclonal antibodies against the PD-1 and it’s receptor, PDL-1 [64]. A recent study demonstrated success in treating metastatic brain disease in patients with NSCLC [65]. Data on the efficacy of these drugs in the setting of HIV is limited to several case reports that have shown improvement in CD4 cell counts and depletion of HIV viral reservoirs as a secondary outcome when administered to patients living with HIV, who were undergoing treatment for malignancy [65,66].

Little is known about the impact of checkpoint inhibitors on the CNS in the setting of HIV infection [67]. There is some emerging data examining the role of pembrolizumab in the treatment of progressive multifocal leukoencephalopathy (PML) [68]. Discussion on this will be covered in a separate manuscript in this issue. The efficacy of blocking PD-1 pathways as a mechanism of addressing T-cell exhaustion has been demonstrated in both non-human primates and humanized mice models. Studies with rhesus macaques showed PD-1 blockade had the effect of rapidly expanding CD8 T-cell populations and reduced the

viral load in CNS [69]. More recent mice model data has also demonstrated that PD-1 blockade can contribute to immune restoration, improving the CD8 reservoir, in addition to producing a two log reduction in viral loads[70].

Though promising, neurologic toxicity has emerged as a salient complication of checkpoint inhibitor therapy. The neurologic complications are heterogenous including myelitis, neuropathy, aseptic meningitis, encephalitis, Guillain-Barré syndrome and myasthenia gravis [71]. A pharmacovigilance study estimated the rates of these complications in patieints to be approximately 1–5% [72]. Fortunately, most of these adverse effects can be mitigated with the use of steroids or drug discontinuation. Lastly, immune reconstitution inflammatory syndrome (IRIS) remains a challenge in the application of these agents of particularly in the anatomically restricted space such as the CNS. The restoration of T-cell function can precipitate IRIS and this has been documented in cases where PML was treated with checkpoint inhibitors [68].

Conclusions

Although advances in ART over the last decade have significantly prolonged the lives of people living with HIV, many challenges in the treatment of HIV remain. The limited efficacy of ART in penetrating immune sanctuary sites has driven a critical need to identify immunotherapies that can potentially eradicate CNS viremia but also latently infected cells. In this review we have taken a practical approach to assessing the evidence, applications, and challenges in applying emerging immunotherapeutics to the treatment of CNS HIV infection.

We have summarized five emerging immunotherapeutic categories including broadly neutralizing antibodies, multi-affinity antibodies, CAR-T cell therapy, checkpoint inhibitors and therapeutic vaccines. These immunotherapeutic strategies hold tremendous potential in managing CNS disease in HIV infected patients and present unique mechanisms by which CNS viremia and latency may be addressed. However, we have also highlighted the many challenges that remain in applying immunotherapies to target HIV in the CNS. These include penetration of the blood brain barrier, immune compartmentalization, viral escape, neurotoxicity, and issues of potency and durable viral suppression.

Studying HIV-1 infection in the CNS has been historically challenging for a number of reasons. A major barrier has been the inability to directly sample CNS tissue until the post-mortem period. As a consequence, the CSF has largely been used as a surrogate. However, the CSF is not brain parenchyma and cannot accurately represent the CNS reservoir, trafficking mechanisms, or mechanisms of toxicity which may be helpful in guiding therapeutic development. In addition, much of the HIV research in the CNS to date has been carried out in non-human primate models using SIV. Though significant advances in our understanding of HIV immunology have come from non-human primate models, there remain differences. SIV has a reduced infectivity compared to HIV-1 and modifications to generate more neuro virulent strains of SIV may limit their applicability to studies in humans.

Despite these barriers there is already evidence within each of these therapeutic classes that the challenges can be overcome and an increasing number of human trials are underway. Each class of immunotherapeutics reviewed here has seen an evolution over the past decade with many now entering their second or third generations. A clear example of this has been the rapid development and evolution of CAR-T cell therapy. It has emerged as a promising area of immunotherapy with the ability to penetrate the CNS and target latent cells with high specificity. Applications in oncology have shown remarkable efficacy, including in CNS malignancy, and new third generation CAR-T cells are under development. This new generation of duo CAR-T cell therapy holds potential for increasing the specificity of HIV specific CAR-T by allowing cells to recognize multiple epitopes on infected CD4 cells thereby minimizing viral escape [39]. Although these therapies are promising, their limited use in the human trials to treat HIV infection still leaves unanswered questions about their long-term toxicity, off target effects, and impact on viral escape.

Advancements in bNAbs leading to the development of multi-affinity antibodies have also offered ways to overcome challenges faced by viral escape and the penetration of the BBB. Strategies to overcome the BBB have shown early success, and combining antibodies into multi-affinity complexes capable of binding BBB receptors, such as the transferrin receptor, to facilitate entry have proven effective. Concurrently, the engineering and linking, of various bNAbs has allowed them to target multiple conserved epitopes on the HIV-1 envelope increasing their breadth and potency. However, due to many of the limitations described above in studying HIV-1 in the CNS, it is not yet well-known which cells are able to be targeted by bNAbs in the CNS and what level of antigen presentation is required for the detection of latently infected cells. Unknowns also exist in determining if the entirety of the latent CNS reservoir is accessible to circulating bNAbs once they enter the CNS compartment.

Potential novel options have also emerged with advancements in the use of gene editing and human stem cells. A recent study has shown the use of CRISPER-Cas19 technology in addressing the latent viral reservoir. It demonstrated viral clearance of latently infected HIV cells in a humanized mouse model using gene editing to remove pro viral DNA from infected cells [73]. Though it must be emphasized that these studies are in mice models only, it lends support to the idea that gene editing may be a promising additional therapeutic option worthy of further research. It is not yet known what off target effects such treatments may have, how they translate to non-human primate models, and what clinical efficacy they may have in humans.

Ultimately targeting HIV in the CNS may require the combination of several immunotherapeutic strategies outlined here. But there remains a paucity of literature in this area and few clinical studies in humans looking at how immunotherapeutics impact HIV infection in the CNS. New therapeutic modalities are currently under investigation including gene editing and hematopoietic CAR-T stem cells which also may hold promise in the treatment of viral latency. However, if we are to harness the promise of immunotherapy in the treatment of HIV infection more research must be done to understand the impact of these therapies on HIV in the CNS.

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Key Points

- Immunotherapies are needed to address the shortcomings of traditional ART in treating HIV infection in the CNS
- These immunotherapeutic strategies hold tremendous potential and present unique mechanisms by which CNS viremia and latency may be addressed
- CAR-T cell therapy and multi-affinity antibodies represent promising areas of immunotherapy with the ability to penetrate the CNS and target latent cells with high specificity
- More human studies are needed to better understand the potential clinical applications and off target effects these therapies may have specifically in the CNS