Review

Discovery Medicine 2024; 36(185): 1091–1108
https://doi.org/10.24976/Discov.Med.202436185.101

Dysregulation of Gamma Delta T-Cells, CD8+ T Cells, CD4+ T Cells, and Natural Killer Cells in Brain Pathology: Understanding HIV-Induced Impairment and Exploring Targeted GSH Therapy

John Dawi[1], Scarlet Affa[2], Yura Misakyan[1], Samuel Kades[1], Syed Asim[1], Sumaiya Olia[1], Alexander Abdou[1], Vishwanath Venketaraman[1,*]

[1]College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA 91766, USA
[2]Department of Chemistry, Physics, and Engineering, Los Angeles Valley College, Valley Glen, CA 91401, USA
*Correspondence: vvenketaraman@westernu.edu (Vishwanath Venketaraman)

Published: 20 June 2024

This review comprehensively explores the dysregulation of Gamma Delta T-cells, CD8+ T Cells, and Natural Killer T Cells in the context of Human Immunodeficiency Virus (HIV) infection and its implications for brain pathology. It encompasses an overview of the HIV disease process, immune cell dysregulation, association with neurological diseases, and the critical role of Glutathione (GSH) in T-cell function. The alterations in Gamma Delta T-cells during chronic infection, the intricate dynamics of Vδ1 and Vδ2 subsets, and the potential of Vγ9Vδ2 T cells in inhibiting HIV replication are discussed. Additionally, the review addresses the exhaustion, impaired cytotoxicity, and premature senescence of CD8+ T cells, as well as the dysregulation of Natural Killer Cells (NKCs) and their impact on overall immune system activity. Furthermore, it examines the role of Gamma Delta ($\gamma\delta$) T-cells in brain injuries, infections, and tumors and highlights the therapeutic implications of elevated GSH levels in promoting a T helper 1 (Th1) immune response. However, HIV-infected patients with decreased GSH exhibit a T helper 2 (Th2) bias, compromising protection against intracellular pathogens. Finally, the review discusses studies in murine models demonstrating the impact of GSH levels on immune responses and underscores the therapeutic potential of targeting GSH to enhance immunity in HIV patients. Overall, this review provides valuable insights into the complex interplay between immune dysregulation, GSH levels, and HIV-associated brain pathology, offering insights into potential therapeutic avenues for mitigating immune compromise and neurological impairments in HIV patients.

Keywords: HIV; CD4+ T cell; Gamma Delta T-cell; Natural Killer Cell; GSH; CD3+ T cell

---

Introduction

The public emergence of Human Immunodeficiency Virus (HIV) in the United States can be traced back to 1981 when a peculiar spike in malignancies and opportunistic infections, particularly *Pneumocystis carinii* pneumonia and Kaposi's sarcoma, was observed [1]. The common denominator among the initial cluster of patients was a severe immune deficiency in individuals who were previously healthy. Since then, HIV has become a global health challenge, with an estimated 1.2 million individuals in the United States and approximately 39 million globally living with the virus [2]. In 2021, around 36,000 individuals in the US received a new HIV diagnosis, and there were nearly 20,000 HIV-related deaths [3].

In the initial stages of HIV-1 infection, the virus gains entry into host cells without causing immediate lethal damage (Fig. 1). However, this entry process can trigger intracellular signal cascades, potentially facilitating viral replication [4]. The HIV-1 envelope comprises two essential components, namely the external glycoprotein (gp120) and the transmembrane protein (gp41), which protrude from the surface of the virion. These components facilitate the entry of the virus into host cells. Initially, gp120 binds to the CD4+ receptor on the host cell membrane, followed by interactions with chemokine co-receptors such as C-C chemokine receptor 5 (CCR5) and C-X-C chemokine receptor 4 (CXCR4). These interactions trigger irreversible changes in the conformation of the viral envelope [4,5]. Subsequently, a fusion event occurs, leading to the formation of pores within minutes, allowing the release of the viral core into the host cell cytoplasm [4,5]. Post-core disassembly, the viral genome undergoes reverse transcription into DNA facilitated by the virus's reverse transcriptase enzyme. This process, prone to errors due to the enzyme's lack of proofreading activity, can generate related yet distinct viral variants [4,6]. During the middle stage of infection, the viral protein integrase collaborates with

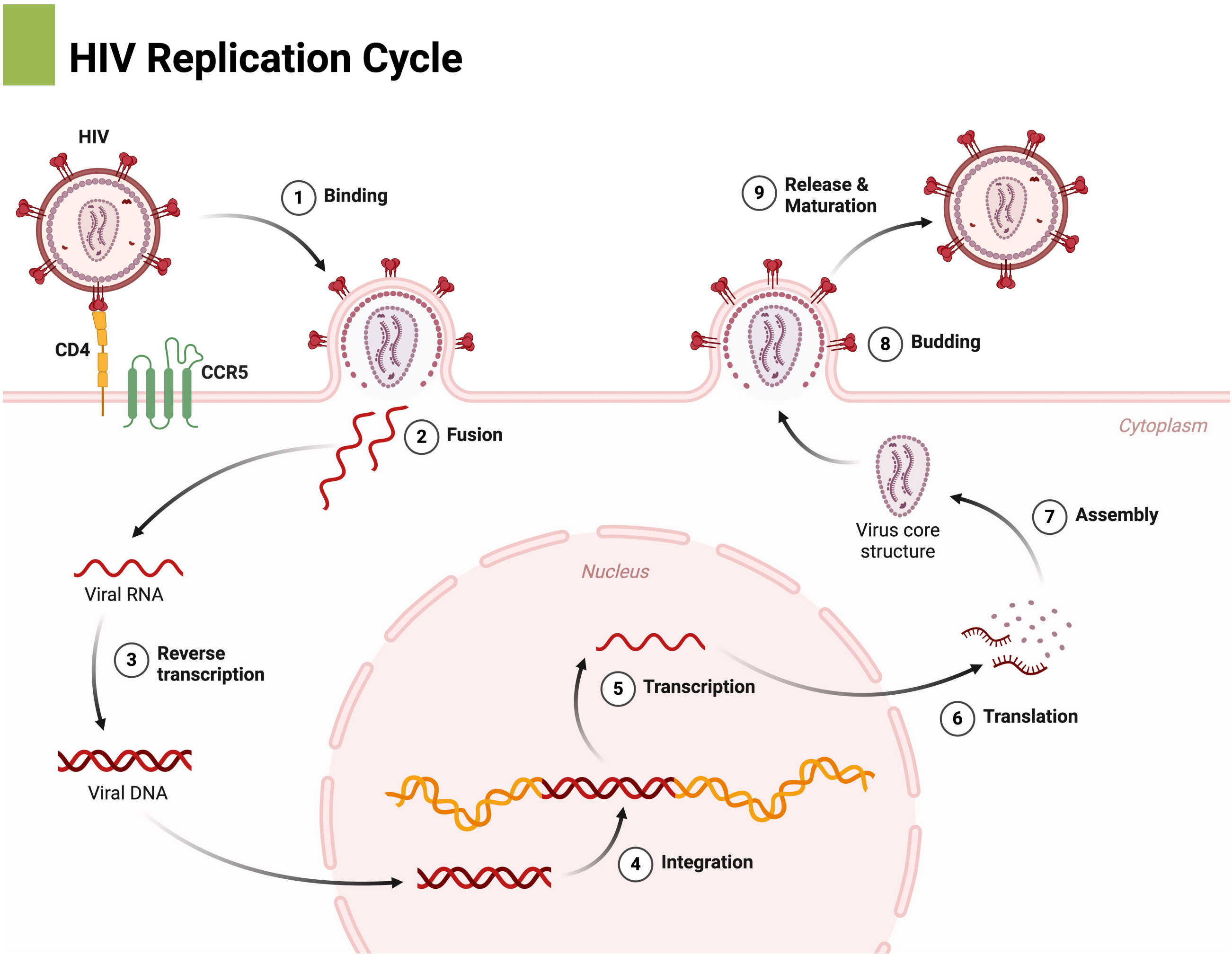

Fig. 1. Human Immunodeficiency Virus (HIV) life cycle. The figure shows the various steps in the life cycle of HIV from infection to intracellular reproduction to the release of new progeny. Created using Biorenders. https://www.biorender.com/. CCR5, C-C chemokine receptor 5.

enzymes involved in DNA repair from the host organism to incorporate the viral genome into regions of the host's chromosomal DNA that are rich in genes and actively transcribed [5,6]. This integration process, which is assisted by a host factor known as lens epithelium-derived growth factor (LEDGF/p75), represents a critical juncture as it permanently alters the host cell, rendering it capable of producing viruses [6]. In the later stages of infection, the synthesis of viral particles entails a combination of host-driven and virus-driven transcription processes. Viral proteins are transported to the vicinity of the cell membrane, where they assemble. The release of viral particles from the cell involves the vesicular sorting pathway, particularly through the mediation of endosomal sorting complexes required for transport (ESCRT) I, II, and III, which facilitate the budding of endosomes into multivesicular bodies [5]. Through its late domain, a concise sequence motif found in p6 of Gag, HIV-1 engages with TSG101, thereby exploiting this protein-sorting pathway [6]. The viral protease-mediated cleavage of the Gag-Pol polyprotein results in the generation of mature infectious virions [4,6,7]. Exploration into the initial events following HIV-1 penetration of the mucosal barrier suggests the presence of a window period wherein viral proliferation is not yet established, potentially allowing host defenses to exert control over viral expansion [6]. Crucial co-receptors for HIV-1 infection are the chemokine receptors CCR5 and CXCR4. Regardless of the transmission route, the majority of new infections involve viral variants dependent on CCR5 utilization. CXCR4-tropic viruses, which typically emerge during later stages of infection, have been associated with heightened pathogenicity and disease progression [6,7]. HIV infection typically commences asymptomatically, accompanied by subtle changes in the immune system. This initial stage persists for up to three months, culminating in seroconversion, the point at which HIV-specific antibodies become detectable in individuals recently exposed to the virus. The progression of infection and the onset of clinical symptoms can vary widely among individuals, often exhibiting a relatively slow trajectory. The duration from primary infection to the manifestation of symptoms indicative of advanced HIV diseases and immunosuppression spans several years [7]. Despite outward appearances of health during the primary infection, the virus actively replicates in the lymph nodes and bloodstream, causing gradual damage to the immune system [7]. The symptomatic stage marks the late phase of HIV disease, commonly referred to as Acquired Immunodeficiency Syndrome (AIDS), wherein individuals become susceptible to various opportunistic infections (OIs) [7]. These infections can encompass diseases induced by *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Pneumocystis carinii*, *cytomegalovirus* (CMV), toxoplasmosis, and candidiasis. It is widely acknowledged that individuals transition to an AIDS status when their plasma HIV load increases, coupled with a decline in CD4+ T cell count to below 200 mm^3 [7].

During the progression of HIV infection, a complex array of immune dysregulations unfolds, significantly impacting various components of the immune system. One of the primary hallmarks is the progressive depletion of CD4+ T cells, which are crucial for orchestrating immune responses [8]. Concurrently, CD8+ T cells experience dysfunction, characterized by exhaustion and impaired cytotoxicity, further compromising the immune response [9]. Additionally, alterations in Natural Killer Cells (NKCs) function have been observed, including changes in subset distribution and functional impairment [10]. Understanding these immunological alterations is paramount, particularly in the context of HIV-associated brain pathology and neurocognitive disorders. Significantly, HIV has the ability to breach the central nervous system (CNS), resulting in a range of neurological complications grouped together under the term HIV-associated neurocognitive disorders (HAND) [11]. These disorders range from mild neurocognitive impairment to severe HIV-associated dementia and are exacerbated by dysregulated immune responses within the CNS [12]. Persistent inflammation driven by immune activation and viral replication contributes to neuronal injury, synaptic dysfunction, and neurodegeneration, highlighting the critical role of immune dysregulation in the pathogenesis of HAND [13].

Despite the challenges posed by HIV, significant strides have been made in improving patient outcomes through the use of therapies such as antiretroviral drugs that target nucleosides and reverse transcriptase to induce viral suppression [14]. These advancements have transformed HIV from a once-debilitating and often fatal condition into a manageable chronic disease.

While the global impact of HIV is well-documented, its intricate interactions with the immune system, especially concerning Gamma Delta ($\gamma\delta$) T-cells, have significant implications for brain pathology [15]. Early in HIV infection, the virus initiates a cascade of immune dysregulation, directly impacting the functionality of $\gamma\delta$ T-cells, a crucial subset of the immune system known for their role in both innate and adaptive immunity. These cells are pivotal in the body's defense against pathogens and in modulating inflammatory responses within the CNS [15]. Research indicates that HIV-associated immune activation leads to alterations in $\gamma\delta$ T-cell populations, which is consequential for neurological health. For instance, the depletion of Vδ2 T-cells, a subset of $\gamma\delta$ T-cells, in HIV-infected individuals correlates with an increased susceptibility to opportunistic infections and may exacerbate neuroinflammatory conditions [16].

The dysregulation of $\gamma\delta$ T-cells in HIV patients extends beyond peripheral immune compromise, influencing their neuroprotective roles. These cells can infiltrate the CNS, responding to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), thereby playing a critical role in the immunosurveillance of the brain [16]. However, HIV-induced impairments in $\gamma\delta$ T-cell functions can disrupt this delicate balance, leading to increased vulnerability to neuroinvasive pathogens and contributing to the pathogenesis of HAND. The situation stresses on how important it is to understand the link between HIV-associated immunological disturbance and brain health, which is especially essential from a clinical standpoint when it comes to the role that $\gamma\delta$ T-cells play [15,16].

The implications arising from the immune dysregulation and the direct effect of HIV on the brain are indicators for further research on the development of therapeutic strategies targeting $\gamma\delta$ T-cell populations for maintenance or repair of their integrity [15]. This strategy may help in the neuroprotection, as well as in the dual treatment of HIV and its resultant neuropsychiatric manifestations [16]. The combination of immunology, neuropathology, and virology leads to a crucial way for the proper interpretation of the systemic outcomes of HIV and the development of more powerful treatment strategies for people with HIV [15,16].

Prevalent challenges like viral resistance and strict adherence to drug regimens persist, highlighting the ongoing urgent need for in-depth research and innovation to enhance the quality of care for individuals living with HIV [17]. The dysregulation of Gamma Delta T-cells and CD8+ T cells in the rich context of HIV infection unfolds intricate immunological alterations with profound implications. Gamma Delta T-cells, which are always distinct in their γ and δ chains, exhibit responsiveness to various cytokines, notably implicated in the immune response against HIV [18]. The Vδ1 and Vδ2 subsets undergo distinct changes, with potential implications for disease progression. Parallelly, CD8+ T cells, essential in recognizing and eliminating virus-infected cells, face dysfunction induced by chronic exposure to high viral antigen levels [18]. Exhaustion markers, like CTLA-4, give rise to impaired cytotoxicity and reduced effector molecule production, hindering their ability to control viral replication. Chronic HIV

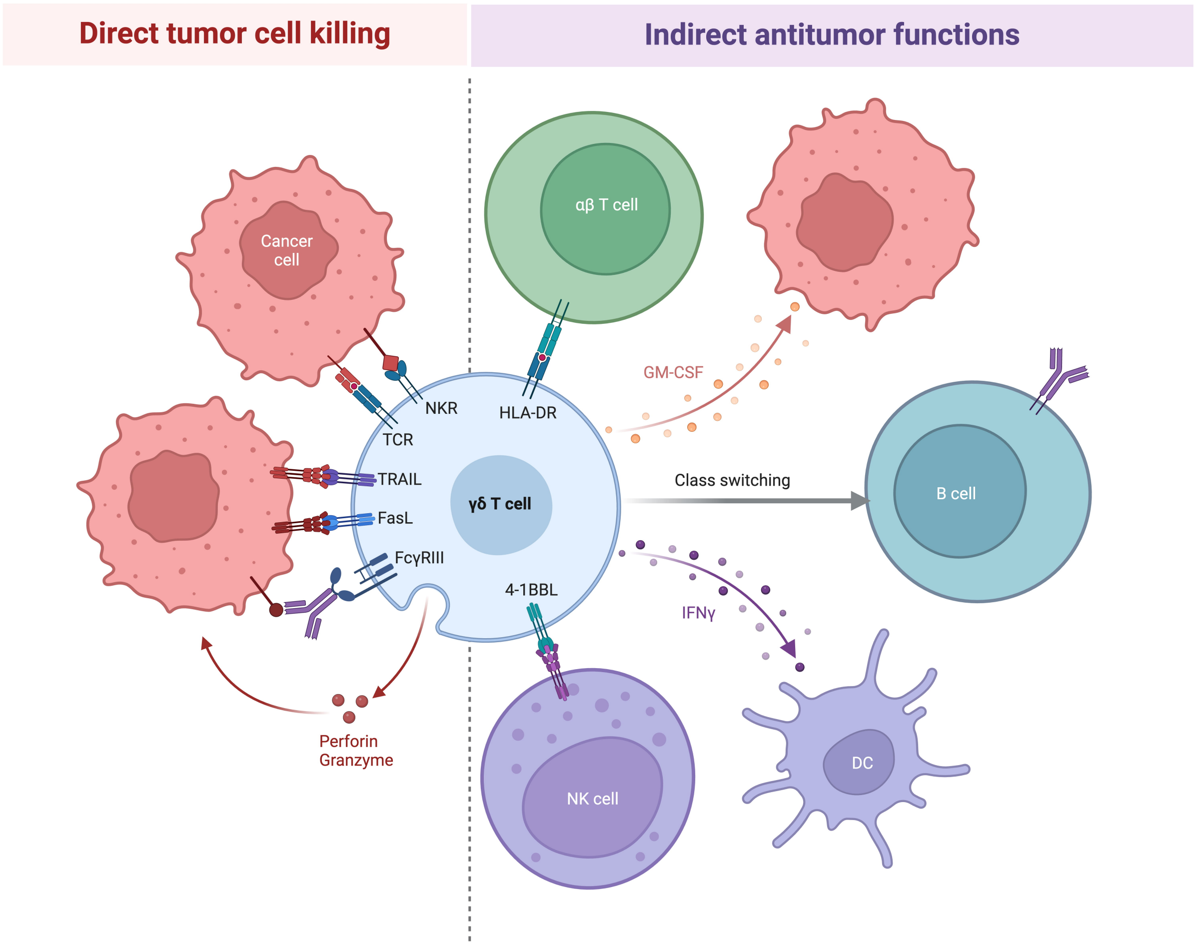

Fig. 2. Gamma Delta ($\gamma\delta$) T-cells anti-tumor effect. $\gamma\delta$ T-cells recognize tumor cells through T-cell receptors (TCRs) and Natural Killer Cell receptors (NKRs), enabling direct killing via TNF-Related Apoptosis-Inducing Ligand (TRAIL), Fas Cell Surface Death Receptor (FAS), or granule exocytosis pathways. The targeting of tumor cells is enabled by $\gamma\delta$ T-cells through antibody-dependent cellular cytotoxicity when they are treated with tumor-specific antibodies. Furthermore, $\gamma\delta$ T-cells facilitate antitumor immune responses by producing interferon-γ (IFN-γ) and exhibiting antigen-presenting cell functions. This activation subsequently triggers $\alpha\beta$ T cells and stimulates NK cells through the expression of 4-1BB ligand (4-1BBL). $\gamma\delta$ T-cells promote dendritic cell (DC) growth and activation through the action of IFN-γ. Interleukin-15 (IL-15) and IL-2 potentiate the antitumor features of $\gamma\delta$ T-cells, while PD-1 expression, Soluble Molecules of Major Histocompatibility Complex Class I Chain-related Molecule A (sMICA) presence, or treatment with decitabine and Histone Deacetylases (HDAC) inhibitors can dampen their killing capacity. Immune cell subsets like Treg cells and neutrophils may inhibit antitumor $\gamma\delta$ T-cell functions through the production of IL-10, Transforming Growth Factor Beta (TGFβ), Arginase-1, and reactive oxygen species (ROS). Created using Biorenders. https://www.biorender.com/.

infection further induces premature senescence of CD8+ T cells, fostering inflammation and immune compromise [18]. NKCs, modulated by inhibitory and activating receptors, exhibit dynamic changes in numbers and phenotypes during HIV progression. Dysfunctional NKCs impact immune responses by inhibiting the maturation of dendritic cells, crucial for orchestrating effective immune responses.

Gamma Delta T-cells reveal multifaceted roles in brain regulatory processes, brain infections, brain injury, autoimmune diseases, and brain tumors [18]. Here we highlight the intricate interplay of various T-cell subsets and NKCs in the context of HIV, emphasizing the need for targeted therapeutic approaches to preserve immune function [18].

Dysregulation of Gamma Delta T-Cells and CD8+ T cells

Part of what is allowing this HIV pandemic to persist is its pathogenesis since the aggressive retrovirus intricately impacts various lymphocyte subsets, with notable attention to the dysregulation of Gamma Delta T-cells and CD8+ T cells in its pathogenesis [19].

Gamma Delta T-cells, constituting a small fraction of CD3+ T cells in peripheral blood, stand out by their distinctive γ and δ-chains, in stark contrast to CD4+ helper T-cells and CD8+ cytotoxic T cells expressing $\alpha\beta$ T-cell receptors (TCRs) [19]. This unique characteristic enables rapid responses to nonpeptide antigens, circumventing the need for major histocompatibility complex (MHC) presentation or antigen-presenting cells. Notably, these cells exhibit responsiveness to cytokines like interleukin-12 (IL-12), IL-23, IL-17, and IL-18 [19]. Additionally, $\gamma\delta$ T-cells exhibit a complex anti-tumor immune response (Fig. 2).

Comprising two primary subsets, Vδ1 T cells and Vδ2 cells, Gamma Delta T-cells undergo alterations in chronic HIV infection, albeit in distinct ways. Research reveals an increase in Vδ1 T cells and an inverted Vδ2:Vδ1 ratio, marking a substantial effect on CD3+ T cells [20]. The significance of increased Vδ1 T cell levels in HIV progression is currently under investigation. In contrast, Vδ2 cells are frequently depleted, and their numbers do not fully recover even with antiretroviral therapy (ART). Noteworthy correlations exist between the immunodeficiency stage and Vδ2 cell depletion, especially in patients with opportunistic infections or CD4+ count below 200 cells/mm^3 of blood. Importantly, those patients lacking detectable Vγ9 chain demonstrate a preferential reduction of Vδ2 cells containing the Vγ9 chain in HIV infection [20]. Key research efforts connected HIV investigations with the developing comprehension of phosphoantigens and their influence on $\gamma\delta$ T-cell biology [21]. Poccia's team [21] affirmed previous findings regarding Vδ2 cell reduction in HIV-infected individuals and identified a disease-related "functional anergy", marked by reduced proliferation and cytokine reactions subsequent to mycobacterial antigen exposure [21]. Their analysis of Vγ9Vδ2 TCR chains in HIV+ individuals revealed preserved diversity in the Vδ2 cell chain repertoire. Contrary to expectations, spontaneous apoptosis did not differ between HIV patients and uninfected controls after *in vitro* phosphoantigen stimulation. Concurrently, Malkovsky and colleagues validated the existence of functional anergy in Vδ2 T cells sourced from individuals with HIV. They showcased diminished reactions to phosphoantigen or the typical cell target, Daudi B cells [22]. Both studies highlighted a significant reduction, but not elimination, of Vδ2 T cells in HIV disease. These cells exhibited substantial deficiencies in phosphoantigen response, suggesting anergy possibly induced by inappropriate *in vivo* activation. A separate investigation documented modified responses of $\gamma\delta$ T-cells to *Salmonella typhimurium* or *Candida albicans* in HIV-positive individuals compared to control subjects. Notably, intact responses of Vδ2 cells to *Mycobacteria* were observed solely in patients with CD4+ T cell counts surpassing 500/mm^3. Furthermore, Vδ2 cells were found to be diminished in the bloodstream but elevated in the liver in both HIV-positive and HIV-negative patients afflicted with disseminated *Mycobacterium avium* complex [20]. Furthermore, Vδ1 cells showed an increase in tissue sites among HIV patients, particularly in the liver or bone marrow [23,24]. These distinct alterations in $\gamma\delta$ T-cell subsets, both Vδ2 and Vδ1 cells, emerged as characteristic features of HIV disease.

The literature explores the pivotal role of Vγ9Vδ2 T cells in responding to phosphoantigens produced by various pathogens, both in peripheral blood and lymphatics, operating in an MHC-independent fashion [25]. These cells contribute significantly to NK cell function and activation through interaction with CD137+ expressed on Gamma Delta T-cells. Additionally, Vγ9Vδ2 T cells produce chemokines (Macrophage inflammatory protein-1 alpha (MIP-1α), MIP-1β, and Regulated on Activation, Normal T Expressed and Secreted (RANTES)) proven to inhibit HIV replication *in vitro* by blocking the CCR5 co-receptor crucial for HIV entry [26]. Moreover, Vδ2 T cells can be recruited to HIV-infected dendritic cells, controlling viral replication and reducing HIV transmission through Chemokine Ligand 4 (CCL4) production. However, during HIV, Vδ2 cells exhibit a significant reduction in interferon-γ (IFN-γ) production, suggesting a potential mechanism of Vγ9Vδ2 T cell anergy, an ongoing area of investigation [27].

Beyond Gamma Delta T-cells, CD8+ T cells, or cytotoxic T lymphocytes (CTLs), play a pivotal role in HIV infection by recognizing and eliminating virus-infected cells through MHC class 1 molecules [28]. Nevertheless, HIV has evolved strategies to evade the immune system, inducing dysfunction in CD8+ T cells. Chronic exposure to high viral antigen levels leads to CD8+ T cell exhaustion, marked by upregulated inhibitory receptors like Cytotoxic T-lymphocyte-associated Antigen 4 (CTLA-4), Programmed Cell Death Protein 1 (PD-1), and Tim-3, inhibiting T-cell proliferation and contributing to a state of exhaustion where cells are less responsive to antigen presentation [28]. Literature underscores that CD8+ T cells in HIV infection often lose polyfunctionality, diminishing their capacity to produce multiple effector molecules simultaneously, significantly impacting their ability to control viral replication [29]. Furthermore, HIV infection causes these cells to exhibit impaired cytotoxicity, associated with reduced granzyme B and perforin expression [30].

Finally, Sauce *et al*. [29] illustrate that chronic HIV infection contributes to premature senescence of CD8+ T cells, leading to dysfunctional cells that do not multiply but do not die as expected. This phenomenon results in significant inflammation and immune compromise, further facilitating opportunistic infections later in the disease course of HIV [29].

A comprehensive understanding of the dysregulation of CD8+ T cells and Gamma Delta T-cells is imperative for developing targeted therapeutic approaches aimed at preserving immune function and improving outcomes for HIV-infected patients [19,28,29].

By manipulating the isoprenoid metabolism within cancer cells, the predominant Vγ9Vδ2 T cell subset found in human peripheral blood, which responds to prenyl pyrophosphates, is strategically redirected towards tumors [30]. This redirection is achieved through the use of aminobisphosphonates such as zoledronate, pamidronate, and risedronate, which serve as structural analogues of prenyl pyrophosphates containing an amino moiety. As a result, aminobisphosphonates indirectly inhibit the activity of farnesyl pyrophosphate synthase (FPPS) within the mevalonate pathway, resulting in the buildup of prenyl pyrophosphate substrates [31].

Neurological diseases have a strong association with HIV infection and the CNS effect of this virus, which is marked by conditions like HAND documented in references [32]. In this case the reason why the dysregulation of CD8+ T cells $\kappa\alpha\iota$ $\gamma\delta$ T-cells is significant is that these immune cells are important for maintaining the balance between the viral infections in the central nervous system [32]. $\gamma\delta$ T-cells is a necessary part of the immunosurveillance of the brain due to their unique function in ability to cross the blood-brain barrier and their capacity to react to pathogens irrespective of MHC [32]. This defense system may be hindered by their dysregulation during HIV infection, increasing susceptibility to opportunistic infections and neuroinflammation [32]. Similarly, the exhaustion and dysfunction of CD8+ T cells, exacerbated by chronic HIV exposure, impair their ability to eliminate virus-infected cells effectively, further facilitating the progression of neurological damage [32]. This complex interaction between HIV-induced immune dysregulation and CNS pathology shows the urgent need for therapeutic strategies that target both viral control and immune restoration to mitigate the neurological impact of HIV.

Over the past decade, endeavors to harness $\gamma\delta$ T-cells for cancer immunotherapy have unfolded, demonstrating varying degrees of efficacy alongside an overall commendable safety profile. Recent trials investigating the anti-cancer potential of zoledronate combined with low-dose IL-2 yielded diverse outcomes. In renal cell carcinoma, the combined treatment resulted in a slight increase in Vδ2pos cells initially, but this expansion diminished with repeated cycles, ultimately failing to produce the desired response [33]. Conversely, a separate study noted no discernible response in patients with solid tumors (melanoma and renal cell carcinoma). However, they observed a partial response in acute myeloid leukemia patients, alongside an unexpected rise in vascular endothelial growth factor levels [34]. Notably, aside from grade 4 fever, no severe side effects were observed. In a recent phase IV clinical trial involving cancer-free subjects, it was found that the degree of transient inflammation-related side effects triggered by zoledronate treatment could be anticipated through *ex vivo* assessments of IFN-γ production by zoledronate-activated peripheral blood cells [35]. Furthermore, repeated administration of zoledronate led to the diminishment of the central memory subset of Vγ9Vδ2 T cells in the blood, along with a sustained decrease in their absolute count. This depletion is attributed to peripheral blood neutrophils, which ingest zoledronate and hinder T cell proliferation by generating hydrogen peroxide [36]. Additionally, recurrent exposure to phosphoantigens (PAgs), whether accumulated in response to aminobisphosphonates or stemming from an accelerated mevalonate pathway, has the potential to induce a differentiation shift in Vγ9Vδ2 T cells, ultimately resulting in functional exhaustion [37]. Consequently, zoledronate alone appears inadequate to mount an effective anti-tumor response. Nevertheless, combining zoledronate with chemotherapy has been demonstrated to enhance the survival of breast cancer and multiple myeloma patients in multicenter studies [38,39].

Exploring the potential of $\gamma\delta$ T-cells in neuro-oncology, particularly for glioblastoma and other brain cancers, could revolutionize treatment paradigms. Adoptive cell transfer (ACT) of these cells, tailored for the CNS, offers a promising avenue for targeted, immunotherapy-based strategies to combat neurologically focused malignancies.

The adoption of ACT, involving *ex vivo* expanded $\gamma\delta$ T-cells, emerges as a more promising therapeutic strategy compared to utilizing zoledronate as a standalone treatment. Two distinct research groups documented the re-infusion of autologous phosphoantigen (PAg)-expanded Vδ2pos T cells in metastatic renal cell carcinoma cases [40]. Notably, when T cells were infused with IL-2 alone, disease stabilization was observed in 6 out of 10 patients, whereas infusion with both IL-2 and zoledronate led to disease stabilization in 5 out of 10 cases and 1 complete response. However, due to the limited number of patients in both studies, the apparent superior efficacy of combining IL-2 and zoledronate may have been coincidental. Moreover, in cases where cells expanded with IL-2 and zoledronate were infused without further exogenous stimulation, a partial response was observed in 3 out of 10 patients with diverse solid tumors [41]. Given that these patients underwent chemotherapy alongside adoptive cell transfer (ACT), the noted response could potentially be attributed to the additive or synergistic effect of the combined therapy.

Similar effects were also observed by Nicol *et al.* [42], with complete and partial responses seen in patients receiving both cell infusion and chemo/hormone therapy. Nonetheless, the limited and heterogeneous patient cohorts in these studies, encompassing variations in cancer type, additional therapy, and T cell infusion composition, pose challenges in accurately delineating the clinical impact of $\gamma\delta$ T-cells.

The utilization of ACT involving $\gamma\delta$ T-cells, in conjunction with other cytotoxic cell types, has demonstrated enhanced efficacy when combined with radiofrequency ablation [43]. While these trials primarily utilized patients' autologous peripheral blood T cells for ACT, the functional capacity of autologous T cells may be substantially compromised in certain instances [44]. A recent investigation by Wilhelm *et al.* [44] demonstrated significant clinical efficacy by infusing patients with a $\gamma\delta$ T-cell product obtained from haploidentical donors, resulting in complete regression observed in 3 out of 4 patients with advanced hematological malignancies [45]. The donor-derived $\gamma\delta$ T-cells persisted for 28 days and underwent *in vivo* expansion in response to exogenous IL-2 and zoledronate. Additionally, it has been shown that infused $\gamma\delta$ T-cells can persist for an extended duration without IL-2 supplementation, possibly relying on endogenous IL-15, while exogenous IL-18 can act as a potent co-stimulator of $\gamma\delta$ T-cell proliferation [46–48].

Despite boasting a commendable safety profile, the clinical performance of $\gamma\delta$ T-cell therapy has been modest thus far [49]. The anticipated discoveries related to the diverse ligands recognized on tumor cells by the Vδ2neg T cell subset are expected to advance our comprehension of the mechanisms underlying these cells. This, in turn, is projected to broaden our capacity to effectively utilize these mechanisms for immunotherapy.

When it comes to AIDS, the dysregulation of $\gamma\delta$ T-cells gains particular significance given their potential duty in combating CNS tumors, such as primary CNS lymphoma, a common AIDS-related malignancy [50]. As a result, the unique immunological challenges posed by HIV could impair $\gamma\delta$ T-cells' anti-tumor efficacy within the CNS, underscoring the urgent need for research into enhancing their function to provide a dual benefit of managing HIV and its oncogenic manifestations in the brain [51].

Dysregulation of Natural Killer Cells and Dendritic Cells

Moreover, NKCs play crucial roles in both adaptive and innate immunity, contributing to protection against tumors and viral infections in an antigen-nonspecific manner [52]. The two predominant NKC subtypes, CD56bright/CD16- and CD56dim/CD16+, exhibit distinct functions. The former is associated with regulatory functions, releasing tumor necrosis factor-alpha (TNF-α) and interferon-γ, while the latter, being more abundant, is primarily responsible for cytotoxic activity and interferon-γ secretion upon activation [53]. The cytotoxic function of NKCs involves the destruction of cells lacking major histocompatibility complex class I (MHC-I) molecules on their surface [54]. NKC function is modulated by Natural Killer Cell receptors (NKRs), acting as inhibitory (iNKRs) or activating (aNKRs) stimuli. iNKRs prevent the killing of normal healthy cells, whereas aNKRs stimulate apoptosis in infected cells by detecting the absence of MHC-I expression [55].

In the context of HIV-1 infection, NKC homeostasis undergoes dynamic changes with disease progression. Initially, there is a reported increase in NKC numbers to compensate for the viral load, with a specific rise in the CD56dim/CD16+ subset and a decrease in CD56bright/CD16-, potentially aiding in the clearance of infected cells [55]. However, during chronic stages, NKC numbers and frequency normalize while the phenotypes of the cells undergo marked alterations. There is an overall increase in the reportedly dysfunctional CD56–/CD16+ subtype and a decrease in the CD56dim/CD16+ subset. The CD56–/CD16+ cells express high levels of iNKRs and low levels of aNKRs, contributing to the dysregulation of NKC activity [54].

Furthermore, there is a documented decrease in several activating NKC receptors, including Natural Killer Protein 30 (NKp30), NKp44, NKp46, and Natural Killer Group 2D (NKG2D), responsible for mediating the natural killer response to viral infection. The loss of receptor expression is suggested as one of several mechanisms leading to a compromised clearance of HIV-1 infected cells [56].

Beyond direct effects on NKCs, dysregulated NKC activity extends to inhibit other immune cells, thereby hindering overall immune system activity. CD56–/CD16+ NKCs fail to secrete crucial cytokines, such as interferon-γ, tumor necrosis factor-alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor. This failure disrupts the induction of dendritic cell maturation, a subset of antigen-presenting cells responsible for mobilizing immune responses. Consequently, there is an increase in immature dendritic cells, unable to secrete regulatory cytokines such as interferon-alpha, leading to an inability to clear HIV-infected CD4+ T cells and allowing the disease to progress to chronic stages [53].

NKCs exhibit unique functions in the context of HIV, and their dysregulation poses challenges for the immune system in clearing infected cells. Consequently, NKCs remain a potential target for antiviral and targeted therapies, with potential strategies ranging from leveraging the memory response possessed by NKCs to enhancing their cytotoxic activity [57,58].

In 2022, a study by Kim *et al.* [58] illustrated how allogeneic human peripheral blood NK cells effectively prolonged the delay of viral rebound after ART interruption in HIV-infected humanized mice. Their approach involved a "kick and kill" strategy, where a single administration of the Protein Kinase C (PKC) modulator SUW133 served as the kick, while NK cells acted as the killing agent [58]. This approach not only delayed viral rebound but also reduced the diversity of rebounding viral clones and eradicated infected cells harboring productive virus from the splenocytes of a subset of HIV-1-infected humanized mice [58]. Allogeneic NK cells, renowned for their robust alloreactivity against leukemic cells, have been safely utilized in patients, with ongoing exploration of their potential against infectious diseases, including COVID-19, through clinical trials [59,60]. While allogeneic NK cells have yet to be clinically employed against HIV infection, studies indicate their promise, supported by Killer Cell Immunoglobulin-like Receptors (KIR) and Human Leukocyte Antigen (HLA) mismatches correlating with protection against HIV transmission and *in vitro* inhibition of HIV infection by allogeneic

NK cells [61]. Kim *et al.* (2022) [58] emphasized the effectiveness of allogeneic NK cells from human peripheral blood, particularly when combined with the latency-reversing agent (LRA) SUW133 in a kick and kill approach targeting the HIV reservoir. The selection of SUW133 as the LRA in the study builds on previous evidence showcasing its ability to activate CD4+ T cells and reverse latency *in vivo* [62]. The synthetic analog SUW133, a viable alternative to bryostatin with scalable Guanosine Monophosphate (GMP) synthesis, induced increased CD69+ expression on CD4+ T cells *in vivo*, as observed in mice treated with SUW133 alone or in combination with NK cells [63,64]. Monitoring viral loads post-ART interruption revealed that SUW133 alone delayed rebound viremia for two to four weeks, albeit eventual rebound occurred, underscoring the necessity for a killing agent such as NK cells in a sustained kick and kill approach [63]. The timing of NK cell injections proved crucial, with NK cells demonstrating efficacy when administered after ART interruption, hindering or eradicating reactivating latently infected T cells before viral dissemination to new target cells could occur [58]. This stands in contrast to NK cells alone, administered during ART suppression, which failed to significantly delay viral rebound, indicating their role as a kick in augmenting HIV-expressing target cells *in vivo* [58]. Additionally, the reduced basal immune activation state observed in TKO-BLT mice could influence NK cell recognition of spontaneously activating latently infected cells during ART [58]. Kim *et al.* (2022) [58] highlighted the potential of allogeneic NK cells and SUW133 in a strategic kick and kill approach to tackle the challenges posed by HIV reservoirs and viral rebound following ART interruption.

Dysregulation of T Cells and Neurological Disease Process

The Rule of Gamma Delta T-Cells in Brain Regulatory Processes

Another subset of cells, $\gamma\delta$ T-cells, which are part of the innate immune system, are significantly involved in the neurological disease process. Numerous studies have elucidated the role of $\gamma\delta$ T-cells, particularly focusing on their function as receptors for heat shock protein 70 (HSP70) in the context of human multiple sclerosis (MS) [65]. Notably, these cells have shown potential cytotoxicity towards brain cells, as indicated by the expression of HSP70 in oligodendrocytes, post-ischemic neurons, and microglia following heat exposure [66]. Different types of $\gamma\delta$TCRs (Gamma Delta T-cells Receptors) are expressed in various brain regions, and while healthy normal CNS tissue contains $\gamma\delta$ T-cells, their expression of low CD45RB levels suggests a potential role as meningeal IL-17A-producing cells [67].

Given the virus's documented impacts on neurological function and structure, the complex regulatory activities of $\gamma\delta$ T-cells within the CNS provide a fascinating intersection with HIV/AIDS neurology [68]. HIV/AIDS may cause significant changes to the neuroprotective and regulatory roles of $\gamma\delta$ T-cells, which could worsen the development of HAND [69]. The immune system's regular monitoring and protective processes of $\gamma\delta$ T-cells in the brain may be disrupted by the virus, making the brain more vulnerable to opportunistic infections and neuroinflammation—two characteristics of hand—and increasing the risk of developing other infections [70]. Furthermore, $\gamma\delta$ T-cells' ability to regulate neuroinflammatory responses indicates their potential as therapeutic targets to lessen HIV's neurodegenerative repercussions. Further study at that connection is necessary to uncover innovative techniques for maintaining neurological health in HIV-positive persons by understanding how HIV modulates $\gamma\delta$ T-cell activities inside the CNS [71].

Contrary to the belief that $\gamma\delta$ T-cells do not exist in the normal healthy CNS parenchyma, a significant number is found in the meninges, particularly IL-17A-producing cells, influencing anxiety-like behaviors in mice [72]. The meningeal $\gamma\delta$ T-cells, although non-proliferative and not self-renewing, produce IL-17 under steady conditions, possibly reliant on TCR signaling and signals from commensal microbes. Although the mechanism by which cytokines from the meninges reach the brain parenchyma remains uncertain, IL-17A directly affects excitatory neurons in the medial prefrontal cortex [73].

Regarding memory-related functions, the deficiency of $\gamma\delta$ T-cells does not affect certain behaviors but results in impaired short-term spatial working memory, which is dependent on IL-17A [74]. IL-17A then signals to glial cells, triggering the production of brain-derived neurotrophic factor (BDNF), which may have implications for long-term potentiation during the formation of short-term memory. The sensitive interaction between immune signaling and neuroplasticity is highlighted by the BDNF modulation mediated by IL-17A [75]. Additionally, it implies that $\gamma\delta$ T-cells are crucial for the cognitive functions of the brain. For instance, increasing $\gamma\delta$ T-cell activity and their IL-17A production may help reduce symptoms in Alzheimer's disease models where cognitive loss is evident by increasing BDNF levels and maintaining neuronal health [76]. Therefore, focusing on the $\gamma\delta$ T-cell-IL-17A-BDNF axis offers a novel approach to preventing memory impairments and preserving cognitive skills, making it a prospective therapeutic intervention route in neurodegenerative illnesses [77].

Maternal IL-17A plays a pivotal role in progeny behavior, as evidenced by observations in a poly I:C-induced maternal immune activation (MIA) model, which leads to autism-like behavior in offspring [78]. Despite the absence of IL-17A expression in the fetal brain, CD4+ T cells are identified as significant IL-17A producers, influenced by factors such as maternal microbiota and dietary salt intake [79,80]. Maternal salt intake induces abnormal behaviors in offspring, underscoring the impact of maternal CD4+ T cell-derived IL-17A on cognitive functions. The potential involvement of $\gamma\delta$ T cells in MIA-induced behaviors and cognitive dysfunction amid environmental changes remains a topic warranting further investigation.

Role of Gamma Delta T-Cells in Brain Infections

Microbial infections, such as toxoplasma and malaria, can induce neuroinflammation and impact neurological symptoms. In toxoplasma infection, IL-6 deficiency correlates with increased brain cysts and necrosis, with IL-6 knockout mice displaying altered T cell populations, suggesting a potential role for $\gamma\delta$ T-cells in inflammation [81]. Similarly, *Plasmodium yoelii* infection induces brain inflammation, and $\gamma\delta$ T-cells, particularly IL-2-mediated infiltration, play a critical role in susceptibility to infection [82]. $\gamma\delta$ T-cell deficiency is also linked to reduced pathology in intracranial mesocestoides corti-mediated neurocysticercosis [83].

Given that $\gamma\delta$ T-cells are involved in immune control and brain infections, investigating the relationship between these cells and HIV/AIDS in the context of neurology is crucial [84]. Because HIV might disrupt immune system functions, such as $\gamma\delta$ T-cell activity, there is a chance that neuroinflammation will worsen, and the central nervous system will become more susceptible to opportunistic infections [84]. This underscores a distinct facet of HIV's influence on neurological well-being, indicating that $\gamma\delta$ T-cell dysregulation may heighten the intensity of HAND [84]. Gaining further insight into this connection may open the door for tailored treatments meant to reduce HIV's neurological effects by improving or regaining $\gamma\delta$ T-cell activity in the central nervous system.

Following West Nile virus (WNV) infection, $\gamma\delta$ T-cell infiltration occurs, with Vγ1+ and Vγ4+ cells being predominant producers of IFN-γ and TNF-α, respectively. Aging increases Vγ4+ cells but reduces Vγ1+ cells, and Vγ4+ cells also produce IL-17A post-WNV infection [85,86]. In oral herpes simplex virus type 1 (HSV-1) infection, $\gamma\delta$ T-cells are crucial in limiting viral spreading in the trigeminal ganglia, particularly in susceptible BALB/c mice [87].

The Epstein-Barr virus (EBV), often linked to MS, demonstrates a notable prevalence in longitudinal analyses. Antibodies derived from clonally expanded B cells in MS have been discovered to target EBV Epstein-Barr nuclear antigen 1 (EBNA1) and CNS-derived GlialCAM protein [76]. The presence of EBNA1/GlialCAM antibodies is linked to severe MS. Moreover, $\gamma\delta$ T-cells have exhibited cytotoxicity against EBV-infected cells *in vitro*, indicating a potential role in EBV-mediated MS [88–90]. Additionally, $\gamma\delta$ T-cells exhibit a strong association with cytomegalovirus (CMV) infection. Considering the connection between herpesviruses and neurodegenerative diseases, $\gamma\delta$ T-cells may play a pivotal role in preventing neurological disorders associated with CNS viral infections [91–94].

$\gamma\delta$ T-cells play an integral part in the defense against brain infections, as shown by their response to the Zika virus (ZIKV), which also involves fighting viral encephalitis [95]. Studies reveal that $\gamma\delta$ T lymphocytes have a vital function in managing ZIKV infection and reducing related brain impairment, including microcephaly in infants and Guillain-Barré syndrome in adults [95]. These cells identify neural progenitor cells that are infected and release IFN-γ to prevent viral multiplication in the central nervous system. This activity demonstrates the wider ramifications of the antiviral properties of $\gamma\delta$ T-cells, emphasizing their significance in protecting the nervous system against many infections [95]. The ability of $\gamma\delta$ T-cells to navigate between immune surveillance and neuroprotection illustrates their potential as therapeutic targets for enhancing the CNS's resilience to infections, including those exacerbated by HIV-induced immune compromise [95].

Gamma Delta T-Cells and Brain Injury

Following ischemic injury, $\gamma\delta$ T-cells infiltrate the brain parenchyma, playing distinct roles in inflammation. CD4+ T cells stimulate TNF-α production by means of IFN-γ, whereas $\gamma\delta$ T-cells, via IL-17A, foster neutrophil infiltration. The combined action of IL-17A and TNF-α synergistically triggers astrocyte-mediated C-X-C Motif Chemokine Ligand 1 (CXCL1) expression, thereby amplifying neutrophil infiltration [96,97]. Microbiota, influencing $\gamma\delta$ T-cell activation, regulates outcomes of ischemic stroke. IL-17A from $\gamma\delta$ T-cells exacerbates stroke pathology, while antibiotic-induced reduction of $\gamma\delta$ T-cells leads to better outcomes [98]. Notably, infiltrating Vγ4+ or Vγ6+ cells express IL-17A, and CCR6 appears crucial for their migration [99,100].

In a $NaIO_3$-mediated retinal pigment epithelium injury model, $\gamma\delta$ T-cells demonstrate a regulatory role by producing IL-4 and IL-10 in an AhR-dependent manner, mitigating injury [101]. Perinatal brain injury, impacting neurophysiological maturation, is associated with increased $\gamma\delta$ T-cells expressing IL-17A and VEGF-A due to the presence of gut microbiota, Klebsiella [102].

Research conducted by Cugurra A *et al.* [102] indicates that the skull bone marrow contributes myeloid cells and B cells to the meninges and parenchyma, which may potentially influence the progression of brain injuries [103,104]. Although T cells are considered peripheral blood-derived, experimental exploration is needed to clarify potential *de novo* development of $\gamma\delta$ T-cells in skull bone marrow or meninges [102]. Furthermore, $\gamma\delta$ T-cells play a role in bone regeneration after injury via IL-17, suggesting a potential regulatory role in skull regeneration following brain injury [105].

The dysregulation of $\gamma\delta$ T-cells in HIV/AIDS is critically relevant to neurological outcomes, as these cells play a vital role in the CNS's immune surveillance and response to infections [68]. In HIV-infected individuals, compromised $\gamma\delta$ T-cell function could exacerbate susceptibility to CNS opportunistic infections and contribute to the development of HAND [68]. This highlights the intersection between HIV-induced immune dysregulation and neurologic complications, underscoring the importance of understanding and targeting $\gamma\delta$ T-cell function within the CNS to mitigate the neurologic impact of HIV/AIDS.

HIV's invasion of the brain represents a critical aspect of its pathology, leading to HAND. The virus's ability to cross the blood-brain barrier and infect microglial cells results in chronic inflammation and neuronal damage [68]. $\gamma\delta$ T-cells, key players in the immune response to brain injuries, could potentially influence the progression of HAND by modulating the inflammatory milieu within the CNS. Their role in neuroinflammation suggests that dysregulation or impairment in HIV could exacerbate neuronal damage [68]. Understanding the dynamics of $\gamma\delta$ T-cells in the context of HIV brain infection could unveil novel therapeutic targets to alleviate or halt the progression of HAND, emphasizing the need for comprehensive research into their specific functions and mechanisms of action within the HIV-infected brain.

Gamma Delta T-Cells and Autoimmune Disease in CNS

$\gamma\delta$ T-cells derived from human peripheral blood have demonstrated the ability to *ex vivo* eliminate freshly derived human brain oligodendrocytes, indicating a potential role in the progression of MS [106]. These cells have been detected in plaques and cerebrospinal fluid (CSF) of individuals with MS, further suggesting their involvement in the disease [107]. Moreover, in patients with recent-onset MS, highly activated oligoclonal $\gamma\delta$ T-cells have been observed, suggesting their expansion due to MS antigens and their role in initiating MS pathology [107].

Utilizing a murine experimental autoimmune encephalomyelitis (EAE) model, the administration of anti-$\gamma\delta$TCR (UC7-13D5) exacerbated EAE pathology, emphasizing the regulatory role of $\gamma\delta$ T-cells in disease progression through TCR signaling inhibition [108,109]. Some other murine EAE studies associated $\gamma\delta$ T-cells with IFN-γ levels, while early IL-17A production from $\gamma\delta$ T-cells influenced later T helper 17 (Th17) cell activation, indicating heterogeneity in their role in MS or EAE [110,111].

Further inquiry is necessary into the complex function of $\gamma\delta$ T-cells in the context of HIV and its neurological manifestations, especially considering the virus's tendency to impact the CNS and cause HAND [112]. Research into the immunomodulatory properties of $\gamma\delta$ T-cells, their participation in viral infection management, and their possible neuroprotective activities is essential to comprehending and reducing the consequences of HIV on the brain [112]. This investigation may provide new targets for treatment that use the special capacities of $\gamma\delta$ T-cells to improve CNS immunity and stop or lessen the severity of HAND, filling in a significant knowledge vacuum on how HIV affects brain function.

Analysis of human samples has revealed the presence of Vδ1+ cells in both the blood and CSF of patients with MS, while Vδ2+ T cells have exhibited potent cytotoxicity against oligodendrocytes [113]. Long-term treatment with IFN-β in MS patients has been associated with the expansion of Vδ1-Vδ2-Vγ9-$\gamma\delta$ T-cells, a phenomenon correlated with improved outcomes in MS [114]. In a murine model of EAE, $\gamma\delta$ T-cells have been observed infiltrating the brain parenchyma via integrin beta 2, with a subsequent reduction in expression following infiltration [115]. Furthermore, gut-derived Lactobacillus acidipiscis has been found to influence Vγ4+ and Vγ1+ cells, potentially exerting opposing effects that impact the outcomes of EAE [116].

Opposing roles have been identified for IFN-γ-producing and IL-17A-producing $\gamma\delta$ T-cells, as evidenced by the exacerbation of EAE in mice deficient in IFN-γ or its receptor [117,118]. Investigating the contribution of meninges-derived IL-17A or Vγ6+ cells in murine EAE models would be an intriguing avenue of research. Additionally, $\gamma\delta$ T-cells have been implicated in the pathology of Rasmussen's encephalitis (RE), with clonal expansion of Vδ1+ cells observed in the parenchyma of RE patients. Microglial activation via Toll-like receptors (TLRs) may trigger multiple CNS inflammations by enhancing IL-17A-producing $\gamma\delta$ T-cells through the action of IL-1 and IL-23 [119,120]. In HIV infection, the brain becomes a critical battleground where the virus and immune response intersect, leading to complex neurological outcomes. The unique role of $\gamma\delta$ T-cells in brain infections underscores their potential impact on HAND [121]. Given their ability to penetrate the blood-brain barrier and mediate immune responses, dysregulation of $\gamma\delta$ T-cells in HIV could contribute significantly to the pathogenesis and progression of HAND [112]. Understanding how HIV affects $\gamma\delta$ T-cell function within the CNS is essential for developing targeted therapies aimed at mitigating the neurocognitive decline associated with HIV, highlighting the need for research focused on the interplay between HIV, $\gamma\delta$ T-cells, and brain health.

It is typical of HIV and the CNS interaction to present a labyrinthine entanglement with autoimmune diseases, where the immune system's response to the virus unintentionally causes neurological damage [121]. $\gamma\delta$ T-cells, being an immune system's unique actor, are suggested to mediate both neuroprotection and neuroinflammation. Here, in the context of HIV, the cells show a response that is quite similar to autoimmune disorders such as MS, which means that they target brain-originated cells primarily [121]. Identifying the complete impact of HIV on the $\gamma\delta$ subset of T cells and its performance in CNS can add real value to the understanding of the mechanism involved in the appearance of HAND which highlights common grounds in viral-induced and autoimmune responses in the brain [121].

The dysregulation of $\gamma\delta$ T-cells in HIV-infected individuals might mirror the pathological processes seen in autoimmune diseases of the CNS, offering a novel perspective on HAND's pathogenesis [121]. The virus's unchallenged ability to trigger inflammatory cascades and alter the CNS's immunological environment could lead to an imbalance in $\gamma\delta$ T-cell activities, exacerbating neurodegenerative processes [121]. Exploring the parallels between HIV-induced CNS changes and autoimmune CNS diseases could unveil new therapeutic targets aimed at modulating $\gamma\delta$ T-cell responses to mitigate the detrimental effects of HIV within the brain, ultimately improving outcomes for individuals suffering from HIV-related neurological complications.

Gamma Delta T-Cells and Brain Tumor

$\gamma\delta$ T-cells are increasingly recognized for their significant role in various tumors, displaying a correlation with improved prognosis among tumor-infiltrating immune cells [122]. Within the tumor microenvironment, distinct subsets of $\gamma\delta$ T-cells, classified into IL-17A-producing and IFN-γ-producing cells, exhibit diverse functions [123]. IFN-γ-producing cells generally possess cytotoxic properties, while IL-17A-producing cells tend to promote a protumor environment, as evidenced in murine tumor models [124]. Research findings have unveiled a correlation between $\gamma\delta$ T-cells and prolonged survival in patients with brain tumors, particularly high-grade glioma (HGG), which contrasts with the inverse relationship observed in $\alpha\beta$ T cells [125]. In a murine model of HGG, the depletion of NK cells, $\gamma\delta$ T-cells, CD8+ T cells, or CD4+ T cells did not affect the survival of mice bearing HGG [126]. Hypoxia has been identified as a factor positively correlated with increased glioma grade and negatively impacting the infiltration of $\gamma\delta$ T-cells [126]. Metformin, known for inhibiting tumor cell respiration, has been shown to alleviate hypoxia-induced suppression of $\gamma\delta$ T-cells, thereby restoring their anti-tumor functions. While IL-17A and IL-17F did not exhibit a correlation with HGG survival, the essential role of NKG2D expression on IFN-γ-producing $\gamma\delta$ T-cells in anti-HGG immunity has been established [126]. NKG2D-expressing $\gamma\delta$ T-cells have been recognized as critical immune cells in the HGG microenvironment [126]. Furthermore, administration of anti-$\gamma\delta$TCR antibodies has been found to neutralize the antitumor functions mediated by $\gamma\delta$ T-cells, suggesting the involvement of $\gamma\delta$TCR in anti-HGG immunity [127]. The simultaneous engagement of $\gamma\delta$TCR and NKG2D is crucial, potentially elucidating why other NKG2D-expressing cells, such as NK cells, did not respond to metformin treatment [128].

Considering their potential, $\gamma\delta$ T-cells are considered promising targets for next-generation anti-brain tumor therapy [129].

Glioblastoma (GBM), recognized as the most prevalent and aggressive malignant brain tumor, presents a formidable challenge to conventional therapies, with patients typically facing a median overall survival of 1–2 years [129]. Despite the emergence of immunotherapy options such as anti-PD-1 therapy, clinical trials investigating GBM treatments have yielded discouraging outcomes [130]. The immune landscape of the GBM microenvironment, often described as a "cold tumor" due to reduced neoantigen presence and immune cell infiltration compared to "hot tumors", may account for these setbacks [131]. $\gamma\delta$ T-cells have emerged as a promising alternative target for anti-GBM therapy [131]. The preferential infiltration of Vγ9Vδ2 T cells observed in GBM patient tissues further emphasizes their potential [132]. There has been a surge of interest in adoptive cell therapy; however, the efficacy of *in vitro* expanded conventional T cells remains limited, possibly due to factors such as the low mutational and neoantigen burden, as well as downregulated antigen processing, which contributes to GBM immune evasion [133,134]. *In vitro* studies have spotlighted the cytotoxic prowess of $\gamma\delta$ T-cells against various GBM cells while sparing normal brain cells [135]. Notably, Vγ9Vδ2 T cells have demonstrated an ability to target glioma stem cells, effectively managing Glioma Stem Cell (GSC)-derived brain tumors in animal models. However, injections of splenocyte-derived $\gamma\delta$ T-cells failed to extend the survival period of immunocompetent GL261-bearing mice, and $\gamma\delta$ T-cell deficiency did not impact mouse survival [126]. When it comes to HIV infection, the immune system's compromise can lead to an increased susceptibility to various cancers, including CNS tumors such as primary CNS lymphoma, which is notably more prevalent among HIV-positive individuals. The unique properties of $\gamma\delta$ T-cells, including their potential to infiltrate tumor microenvironments and exert cytotoxic effects, could be particularly relevant for targeting such HIV-associated brain tumors. Given their role in modulating immune responses within the CNS, enhancing the function or presence of $\gamma\delta$ T-cells could offer a novel therapeutic strategy for managing or even preventing the development of brain tumors in HIV-infected patients. This approach could be especially beneficial considering the challenges posed by the immunosuppressed status of these individuals, highlighting the need for innovative treatments that leverage the anti-tumor capabilities of $\gamma\delta$ T-cells within the context of HIV-related immunodeficiency. These findings indicate a high rate of apoptosis among $\gamma\delta$ T-cells within the GBM microenvironment, which corresponds to the concept that tumor hypoxia plays a role in inducing apoptosis in these cells [131]. Integrating $\gamma\delta$ T-cell therapy with strategies aimed at counteracting hypoxia or employing supplementary approaches such as metformin and Hypoxia Inducible Factor 1 Subunit Alpha (HIF1A) inhibitor pretreatment substantially enhances the survival rates of mice bearing tumors [136]. In addressing cell death induced by chemotherapy, the utilization of engineered $\gamma\delta$ T-cells resistant to chemo/radiotherapy presents a viable alternative approach [137]. Allogenic $\gamma\delta$ T-cell therapy, not relying on MHC-mediated antigen presentation, holds distinct advantages and is anticipated to be a "game changer" in tumor therapy, including GBM [138].

GSH Depletion Related HIV Progression and T Cell Dysfunction

Preventing said tumors also depends on inhibiting HIV progression, and achieving this heavily relies on a tripeptide known as Glutathione (GSH). The AIDS model induced by the Lymphoproliferative-Bone Marrow 5 (LP-BM5) murine leukemia virus serves as a valuable tool for researchers investigating the immunopathogenesis of HIV, shedding light on various cellular factors and agents that contribute to prolonging host immunocompetence [139]. Among the endogenous tripeptide agents, GSH, consisting of gamma-glutamyl-cysteinyl-glycine, emerges as a crucial player, demonstrating efficacy in innate cell-mediated defense and detoxification against oxidative stressors [140]. The expression of GSH significantly influences the development of T helper cells, leading to a delicate balance between Th1 and Th2 cell subtypes, ultimately impacting host immunocompetence.

Research by Dobashi *et al.* [141] reveals that elevated GSH levels contribute to an increase in interleukin-12 (IL-12), a cytokine crucial for differentiating progenitor T-cells into the Th1 subtype. This Th1 cell dominance results in elevated interferon-γ (IFN-γ) production, essential for macrophage activation, and increased IL-2 production [141]. This inhibits Th2 production, thus promoting Th1 cell proliferation and enhancing macrophage-mediated pathogen phagocytosis [141]. HIV-infected patients with decreased GSH levels exhibit diminished IL-12 levels, leading to preferential Th2 cell activation, potentially compromising the host's protection against intracellular pathogen invasion. This Th2 bias triggers an adaptive immunoglobulin response mediated by IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 [141]. This suppressed Th1 immune response is observed in various immunocompromising infections, including HIV, Leishmania, and *Mycobacterium tuberculosis* [142].

Brundu *et al.* [143] found that injection of LP-BM5 murine leukemia virus into mice induces AIDS and reduces GSH quantities in lymphoid organs, spleen, lymph nodes, pancreas, and brain acutely 5 weeks post-infection. This decrease correlates with a pronounced Th2 immune response, as indicated by cytokine responses. Treatment with N-(N-acetyl-l-cysteinyl)-S-acetylcysteamine (I-152), a supplier of N-acetyl-cysteine, replenishes cysteine levels and restores GSH levels in organs. This restoration enhances Th1-mediated interferon-γ production and decreases Th2-mediated IL-4 and IL-5 cytokines, rebalancing the Th1/Th2 response to infection [143].

Furthermore, Herzenberg *et al.* [144] demonstrate a marked reduction in GSH levels in CD4+ T cells of HIV patients, suggesting a potential association with reduced patient survival rates by 2–3 years. Their research underscores GSH deficiency as a determinant of survival, as oral administration of the GSH pro-drug N-acetylcysteine leads to improved clinical outcomes [144]. This highlights the therapeutic potential of targeting GSH levels to enhance immune responses and improve clinical outcomes in HIV patients.

Staal *et al.* (1992) [145] previous work established the crucial role of intracellular GSH in modulating HIV transcription and replication *in vitro*, emphasizing its influence on signal transduction by inflammatory cytokines. Further elaborating on this, detailed multiparameter fluorescence-activated cell sorting (FACS) investigations highlight a significant reduction in relative GSH levels within CD4+ and CD8+ T cells among HIV-positive individuals in comparison to uninfected counterparts [145]. This study, encompassing 134 HIV-infected subjects and 31 uninfected controls, sheds light on distinct intracellular GSH concentrations across various immune cell subsets, including CD4+ T cells, CD8+ T cells, B cells, and monocytes. Particularly noteworthy is the marked decline in intracellular GSH levels observed within T cell populations, particularly among individuals in advanced stages of HIV infection. In patients with AIDS, GSH levels decrease to 63% of normal levels in CD4+ T cells and 62% in CD8+ T cells Similarly, those with AIDS-related complex (ARC) exhibit GSH levels at 66% of normal in CD4+ T cells and 69% in CD8+ T cells [145]. These findings underscore the potential significance of low intracellular GSH levels as a contributing factor to HIV infection and ensuing immunodeficiency.

The critical role of GSH depletion in the progression of HIV and its impact on T-cell dysfunction bridges a vital gap in understanding HIV-associated immunodeficiency and its systemic effects, particularly in the CNS [146]. GSH, a potent antioxidant, is instrumental in maintaining immune cell function and preventing oxidative stress, which is exacerbated by HIV infection [146]. The reduction of GSH levels in HIV-infected individuals compromises the immune system's ability to combat the virus and contributes to the deterioration of neurological functions, highlighting a direct link between systemic immunodeficiency and neurocognitive disorders such as HAND [146]. By targeting GSH replenishment, therapeutic strategies could not only improve immune competence but also potentially mitigate the neurodegenerative impact of HIV, offering a dual approach to managing the disease. This underscores the importance of GSH in the broader context of HIV pathogenesis, emphasizing the need for interventions that address both the systemic and neurological manifestations of HIV [146].

Discussion

This project presents a holistic exploration of the HIV disease process and the dysregulation of immune cell subsets, specifically Gamma Delta T-cells, CD8+ T cells, and NKCs. Advancements in antiretroviral therapies have transformed HIV into a manageable chronic disease; however, challenges persist, necessitating ongoing research and innovation. Examining the dysregulation of Gamma Delta T-cells and CD8+ T-cells reveals alterations in subsets like Vδ1 and Vδ2 cells, highlighting challenges in maintaining effective immune responses during chronic HIV infection. The study emphasizes the need for targeted therapeutic approaches to preserve immune function and enhance outcomes for HIV-infected individuals. Simultaneously, the investigation into the multifaceted roles of $\gamma\delta$ T-cells in neurological processes provides novel insights, challenging conventional beliefs about their presence in the CNS parenchyma. The study underscores the pivotal involvement of $\gamma\delta$ T-cells in neuroinflammation, infection responses, autoimmune diseases, and brain tumors, positioning them as promising anti-tumor agents, particularly in glioblastoma. Moreover, the exploration of GSH depletion in HIV progression emphasizes its impact on T-cell dysfunction. Targeting GSH levels presents a promising strategy to enhance immune responses in HIV patients.

Emerging research suggests the potential of leveraging the microbiome to modulate immune responses, including $\gamma\delta$ T-cell activity, in HIV-infected individuals. This novel approach could offer dual benefits: enhancing gut barrier integrity to reduce systemic inflammation and directly influencing CNS health to mitigate neurocognitive impairments associated with HIV. By targeting the gut microbiome, researchers aim to restore microbial balance and strengthen the intestinal barrier, thereby reducing microbial translocation and systemic immune activation. Additionally, modulating the microbiome may have direct effects on the CNS, as growing evidence indicates bidirectional communication between the gut and the brain through the gut-brain axis. By influencing microbial composition and metabolite production, microbiome modulation could potentially attenuate neuroinflammation and neurocognitive dysfunction observed in HAND.

This strategy represents a promising frontier in the holistic management of HIV, integrating immunology, neurology, and microbiome science to unveil innovative therapeutic pathways. By considering the interconnectedness of the immune system, gut microbiome, and CNS function, researchers aim to develop targeted interventions that not only control viral replication and preserve immune function but also address the complex neurocognitive sequelae of HIV infection. Furthermore, understanding the role of the microbiome in HIV pathogenesis opens new avenues for personalized medicine approaches, where interventions could be tailored to individual microbial profiles and disease states, ultimately improving treatment outcomes and quality of life for individuals living with HIV.

Conclusion

In conclusion, this comprehensive review elucidates the complex immunological dynamics associated with HIV infection and its neurological implications, thereby laying the groundwork for precise therapeutic strategies aimed at enhancing the prognosis and life quality of individuals affected by HIV. It is imperative that future investigations delve into these therapeutic potentials to refine treatment modalities and tackle the multifaceted nature of HIV pathogenesis.

Availability of Data and Materials

Not applicable.

Author Contributions

JD, SAf, SK, YM, SAs, SO, AA, and VV collected and analyzed the literature. JD and VV provided help and advice on the structure and content of the paper. JD, SAf, SK, YM, SAs, SO, and AA wrote the manuscript. JD and SAf edited the final version of the manuscript. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

We appreciate the funding support from the NIH-NHLBI (2R15HL143545-02).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] MHAF. Timeline of the HIV and AIDS epidemic. HIV.gov. 2023. Available at: https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline/#year-1981 (Accessed: 9 October 2023).

[2] UNAIDS. Latest global and regional statistics on the status of the AIDS epidemic. 2023. Available at: https://www.unaids.org/s

ites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (Accessed: 9 October 2023).

[3] MHAF. HIV & AIDS Trends and U.S. Statistics Overview. 2023. Available at: https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics (Accessed: 9 October 2023).

[4] Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet. 2006; 368: 489–504.

[5] Eckert DM, Kim PS. Mechanisms of viral membrane fusion and its inhibition. Annual Review of Biochemistry. 2001; 70: 777–810.

[6] Martin-Serrano J, Zang T, Bieniasz PD. Role of ESCRT-I in retroviral budding. Journal of Virology. 2003; 77: 4794–4804.

[7] Naif HM. Pathogenesis of HIV Infection. Infectious Disease Reports. 2013; 5: e6.

[8] Douek DC, Roederer M, Koup RA. Emerging concepts in the immunopathogenesis of AIDS. Annual Review of Medicine. 2009; 60: 471–484.

[9] Im SJ, Hashimoto M, Gerner MY, Kao C, Pavlova NN, Shih HY, *et al*. The Role of Exhausted CD8+ T Cells in Chronic Viral Infections. Current Opinion in Virology. 2019; 37: 1–6.

[10] Titanji K, De Milito A, Cagigi A, Thorstensson R, Grützmeier S, Atlas A, *et al*. Loss of memory B cells impairs maintenance of long-term serologic memory during HIV-1 infection. Blood. 2006; 108: 1580–1587.

[11] Anthony IC, Bell JE. The Neuropathology of HIV/AIDS. International Review of Psychiatry. 2008; 20: 15–24.

[12] Heaton RK, Clifford DB, Franklin DR, Jr, Woods SP, Ake C, Vaida F, *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75: 2087–2096.

[13] Vivithanaporn P, Nelles K, DeBlock L, Newman SC, Gill MJ, Power C. Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. Journal of the Neurological Sciences. 2012; 312: 45–51.

[14] Jolayemi O, Bogart LM, Storholm ED, Goodman-Meza D, Rosenberg-Carlson E, Cohen R, *et al*. Perspectives on preparing for long-acting injecod treatment for HIV among consumer, clinical and nonclinical stakeholders: A qualitative study exploring the anticipated challenges and opportunities for implementation in Los Angeles County. PLoS ONE. 2022; 17: e0262926.

[15] Laurent C, Dorothée G, Hunot S, Martin E, Monnet Y, Duchamp M, *et al*. Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. Brain. 2017; 140: 184–200.

[16] Williams GP, Schonhoff AM, Jurkuvenaite A, Gallups NJ, Standaert DG, Harms AS. CD4 T cells mediate brain inflammation and neurodegeneration in a mouse model of Parkinson's disease. Brain. 2021; 144: 2047–2059.

[17] Larijani MS, Ramezani A, Sadat SM. Updated Studies on the Development of HIV Therapeutic Vaccine. Current HIV Research. 2019; 17: 75–84.

[18] Richard Z. Toll-like receptor (TLR)7 and TLR8 stimulation of mucosal-associated invariant T cells and gamma delta T cells: a role in HIV susceptibility. 2023. Available at: https://mspace.lib.umanitoba.ca/items/2e2fb2d0-a19e-4198-be49-cdbeaedf54f9 (Accessed: 20 October 2023).

[19] Juno JA, Eriksson EM. $\gamma\delta$ T-cell responses during HIV infection and antiretroviral therapy. Clinical & Translational Immunology. 2019; 8: e01069.

[20] Pauza CD, Poonia B, Li H, Cairo C, Chaudhry S. $\gamma\delta$ T Cells in HIV Disease: Past, Present, and Future. Frontiers in Immunology. 2015; 5: 687.

[21] Poccia F, Boullier S, Lecoeur H, Cochet M, Poquet Y, Colizzi V, *et al*. Peripheral V gamma 9/V delta 2 T cell deletion and anergy to nonpeptidic mycobacterial antigens in asymptomatic HIV-1-infected persons. Journal of Immunology. 1996; 157: 449–461.

[22] Wallace M, Scharko AM, Pauza CD, Fisch P, Imaoka K, Kawabata S, *et al*. Functional gamma delta T-lymphocyte defect associated with human immunodeficiency virus infections. Molecular Medicine. 1997; 3: 60–71.

[23] Agrati C, D'Offizi G, Narciso P, Selva C, Pucillo LP, Ippolito G, *et al*. Gammadelta T cell activation by chronic HIV infection may contribute to intrahepatic vdelta1 compartmentalization and hepatitis C virus disease progression independent of highly active antiretroviral therapy. AIDS Research and Human Retroviruses. 2001; 17: 1357–1363.

[24] Rossol R, Dobmeyer JM, Dobmeyer TS, Klein SA, Rossol S, Wesch D, *et al*. Increase in Vdelta1+ gammadelta T cells in the peripheral blood and bone marrow as a selective feature of HIV-1 but not other virus infections. British Journal of Haematology. 1998; 100: 728–734.

[25] Dhar S, Chiplunkar SV. Harnessing the Power of Vγ9Vδ2 T Cells. Trends in Immunology. 2018; 39: 948–961.

[26] Cocchi F, DeVico AL, Garzino-Demo A, Cara A, Arya ML, Gallo RC, *et al*. Chemokines in HIV-1 Infection: From Viral Entry to AIDS Pathogenesis. The Journal of Experimental Medicine. 1996; 184: 61–72.

[27] Martini F, Urso R, Gioia C, De Felici A, Narciso P, Amendola A, *et al*. gammadelta T-cell anergy in human immunodeficiency virus-infected persons with opportunistic infections and recovery after highly active antiretroviral therapy. Immunology. 2000; 100: 481–486.

[28] Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nature Reviews Immunology. 2015; 15: 486–499.

[29] Sauce D, Larsen M, Fastenackels S, Pauchard M, Ait-Mohand H, Schneider L, *et al*. HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. Blood. 2011; 117: 5142–5151.

[30] Legut M, Cole DK, Sewell AK. The promise of $\gamma\delta$ T cells and the $\gamma\delta$ T cell receptor for cancer immunotherapy. Cellular & Molecular Immunology. 2015; 12: 656–668.

[31] Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. Clinical and Experimental Immunology. 2005; 139: 101–111.

[32] Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Gill H, Attali M, Asher I. HIV-associated neurocognitive disorders (HAND). The Israel Medical Association Journal. 2015; 17: 54–59.

[33] Lang JM, Kaikobad MR, Wallace M, Staab MJ, Horvath DL, Wilding G, *et al*. Pilot trial of interleukin-2 and zoledronic acid to augment $\gamma\delta$ T cells as treatment for patients with refractory renal cell carcinoma. Cancer Immunology, Immunotherapy. 2011; 60: 1447–1460.

[34] Kunzmann V, Smetak M, Kimmel B, Weigang-Koehler K, Goebeler M, Birkmann J, *et al*. Tumor-promoting versus tumor-antagonizing roles of $\gamma\delta$ T cells in cancer immunotherapy: results from a prospective phase I/II trial. Journal of Immunotherapy. 2012; 35: 205–213.

[35] Welton JL, Morgan MP, Martí S, Stone MD, Moser B, Sewell AK, *et al*. Monocytes and $\gamma\delta$ T cells control the acute-phase response to intravenous zoledronate: insights from a phase IV safety trial. Journal of Bone and Mineral Research. 2013; 28: 464–471.

[36] Rossini M, Adami S, Viapiana O, Fracassi E, Ortolani R, Vella A, *et al*. Long-term effects of amino-bisphosphonates on circulating $\gamma\delta$ T cells. Calcified Tissue International. 2012; 91: 395–399.

[37] Coscia M, Vitale C, Peola S, Foglietta M, Rigoni M, Griggio

V, *et al*. Dysfunctional Vγ9Vδ2 T cells are negative prognosticators and markers of dysregulated mevalonate pathway activity in chronic lymphocytic leukemia cells. Blood. 2012; 120: 3271–3279.

[38] Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, *et al*. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. The Lancet. Oncology. 2011; 12: 631–641.

[39] Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, *et al*. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet. 2010; 376: 1989–1999.

[40] Kobayashi H, Tanaka Y, Yagi J, Minato N, Tanabe K. Phase I/II study of adoptive transfer of $\gamma\delta$ T cells in combination with zoledronic acid and IL-2 to patients with advanced renal cell carcinoma. Cancer Immunology, Immunotherapy. 2011; 60: 1075–1084.

[41] Noguchi A, Kaneko T, Kamigaki T, Fujimoto K, Ozawa M, Saito M, *et al*. Zoledronate-activated Vγ9$\gamma\delta$ T cell-based immunotherapy is feasible and restores the impairment of $\gamma\delta$ T cells in patients with solid tumors. Cytotherapy. 2011; 13: 92–97.

[42] Nicol AJ, Tokuyama H, Mattarollo SR, Hagi T, Suzuki K, Yokokawa K, *et al*. Clinical evaluation of autologous gamma delta T cell-based immunotherapy for metastatic solid tumours. British Journal of Cancer. 2011; 105: 778–786.

[43] Cui J, Wang N, Zhao H, Jin H, Wang G, Niu C, *et al*. Combination of radiofrequency ablation and sequential cellular immunotherapy improves progression-free survival for patients with hepatocellular carcinoma. International Journal of Cancer. 2014; 134: 342–351.

[44] Wilhelm M, Smetak M, Schaefer-Eckart K, Kimmel B, Birkmann J, Einsele H, *et al*. Successful adoptive transfer and in vivo expansion of haploidentical $\gamma\delta$ T cells. Journal of Translational Medicine. 2014; 12: 45.

[45] Izumi T, Kondo M, Takahashi T, Fujieda N, Kondo A, Tamura N, *et al*. Ex vivo characterization of $\gamma\delta$ T-cell repertoire in patients after adoptive transfer of Vγ9Vδ2 T cells expressing the interleukin-2 receptor β-chain and the common γ-chain. Cytotherapy. 2013; 15: 481–491.

[46] Caccamo N, Battistini L, Bonneville M. $\gamma\delta$ T Cells: First Line of Defense and Beyond. Annual Review of Immunology. 2021; 39: 161–201.

[47] Sugie T, Murata-Hirai K, Iwasaki M, Morita CT, Li W, Okamura H, *et al*. Zoledronic acid-induced expansion of $\gamma\delta$ T cells from early-stage breast cancer patients: effect of IL-18 on helper NK cells. Cancer Immunology, Immunotherapy. 2013; 62: 677–687.

[48] Wada I, Matsushita H, Noji S, Mori K, Yamashita H, Nomura S, *et al*. Intraperitoneal injection of in vitro expanded Vγ9Vδ2 T cells together with zoledronate for the treatment of malignant ascites due to gastric cancer. Cancer Medicine. 2014; 3: 362–375.

[49] Pahl J, Cerwenka A. Tricking the balance: NK cells in anti-cancer immunity. Immunobiology. 2017; 222: 11–20.

[50] Bouza E, Giannella M, Torres MV, Catalán P, Sánchez-Carrillo C, Hernández-Cruz B, *et al*. Is primary central nervous system lymphoma still an AIDS defining condition? A descriptive study at a tertiary hospital in the era of highly active antiretroviral therapy. BMC Infectious Diseases. 2018; 18: 1–7.

[51] Torrano V, Valcarcel-Jimenez L, Cortazar AR, Liu X, Urosevic J, Castillo-Martin M, *et al*. The metabolic co-regulator PGC1α suppresses prostate cancer metastasis. Nature Cell Biology. 2016; 18: 645–656.

[52] Scully E, Alter G. NK Cells in HIV Disease. Current HIV/AIDS Reports. 2016; 13: 85–94.

[53] Mikulak J, Oriolo F, Zaghi E, Di Vito C, Mavilio D. Natural killer cells in HIV-1 infection and therapy. AIDS. 2017; 31: 2317–2330.

[54] Long EO, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. Annual Review of Immunology. 2013; 31: 227–258.

[55] Alter G, Teigen N, Davis BT, Addo MM, Suscovich TJ, Waring MT, *et al*. Sequential deregulation of NK cell subset distribution and function starting in acute HIV-1 infection. Blood. 2005; 106: 3366–3369.

[56] Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, *et al*. HIV-1 Entry into CD4+ Cells Is Mediated by the Chemokine Receptor CC-CKR-5. Nature. 1996; 381: 661–666.

[57] Vivier E, Tomasello E, Baratin M, Walzer A, Ugolini S, Vivier D. Targeting Natural Killer Cells in Cancer Immunotherapy. Nature Reviews Immunology. 2018; 18: 295–307.

[58] Kim JT, Zhang TH, Carmona C, Lee B, Seet CS, Kostelny M, *et al*. Latency reversal plus natural killer cells diminish HIV reservoir in vivo. Nature Communications. 2022; 13: 121.

[59] Fennessey CM, Pinkevych M, Immonen TT, Reynaldi A, Venturi V, Nadella P, *et al*. Genetically-barcoded SIV facilitates enumeration of rebound variants and estimation of reactivation rates in nonhuman primates following interruption of suppressive antiretroviral therapy. PLoS Pathogens. 2017; 13: e1006359.

[60] Jeyaraman M, Muthu S, Bapat A, Jain R, Sushmitha ES, Gulati A, *et al*. Bracing NK cell based therapy to relegate pulmonary inflammation in COVID-19. Heliyon. 2021; 7: e07635.

[61] Nagler A, Lanier LL, Cwirla S, Phillips JH. Comparative studies of human FcRIII-positive and negative natural killer cells. Journal of Immunology. 1989; 143: 3183–3191.

[62] Marsden MD, Zhang TH, Du Y, Dimapasoc M, Soliman MSA, Wu X, *et al*. Tracking HIV Rebound following Latency Reversal Using Barcoded HIV. Cell Reports. Medicine. 2020; 1: 100162.

[63] Schaufelberger DE, Koleck MP, Beutler JA, Vatakis AM, Alvarado AB, Andrews P, *et al*. The large-scale isolation of bryostatin 1 from Bugula neritina following current good manufacturing practices. Journal of Natural Products. 1991; 54: 1265–1270.

[64] Wender PA, Hardman CT, Ho S, Jeffreys MS, Maclaren JK, Quiroz RV, *et al*. Scalable synthesis of bryostatin 1 and analogs, adjuvant leads against latent HIV. Science. 2017; 358: 218–223.

[65] Müller N, Frenzel KH, Schwarz M, Würl D, Hampel H, Penning R, *et al*. Expression of human heat-shock protein 70 antigens and gamma/delta T-cell receptor antigens in human central nervous tissue. Annals of the New York Academy of Sciences. 1994; 741: 305–315.

[66] Szymanska B, Rajan AJ, Gao YL, Tronczynska E, Brosnan CF, Selmaj K. Evidence for gammadelta T cells with a restricted Vgamma6 junctional region in the normal mouse central nervous system. Journal of Neuroimmunology. 1999; 100: 260–265.

[67] Alves de Lima K, Rustenhoven J, Da Mesquita S, Wall M, Salvador AF, Smirnov I, *et al*. Meningeal $\gamma\delta$ T cells regulate anxiety-like behavior via IL-17a signaling in neurons. Nature Immunology. 2020; 21: 1421–1429.

[68] Biradar S, Lotze MT, Mailliard RB. The Unknown Unknowns: Recovering Gamma-Delta T Cells for Control of Human Immunodeficiency Virus (HIV). Viruses. 2020; 12: 1455.

[69] McGuire JL, Gill AJ, Douglas SD, Kolson DL. Central and peripheral markers of neurodegeneration and monocyte activation in HIV-associated neurocognitive disorders. Journal of Neurovirology. 2015; 21: 439–448.

[70] Krebs SJ, Slike BM, Sithinamsuwan P, Allen IE, Chalermchai T, Tipsuk S, *et al*. Sex differences in soluble markers vary before and after the initiation of antiretroviral therapy in chronically

HIV-infected individuals. AIDS. 2016; 30: 1533–1542.

[71] Al-Attas OS, Al-Daghri NM, Al-Rubeaan K, da Silva NF, Sabico SL, Kumar S, *et al.* Changes in endotoxin levels in T2DM subjects on anti-diabetic therapies. Cardiovascular Diabetology. 2009; 8: 20.

[72] Derecki NC, Cardani AN, Yang CH, Quinnies KM, Crihfield A, Lynch KR, *et al.* Regulation of learning and memory by meningeal immunity: a key role for IL-4. The Journal of Experimental Medicine. 2010; 207: 1067–1080.

[73] Ribeiro M, Brigas HC, Temido-Ferreira M, Pousinha PA, Regen T, Santa C, *et al.* Meningeal $\gamma\delta$ T cell-derived IL-17 controls synaptic plasticity and short-term memory. Science Immunology. 2019; 4: eaay5199.

[74] Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, *et al.* The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science. 2016; 351: 933–939.

[75] Dong Y, Benveniste EN. Immune function of astrocytes. Glia. 2001; 36: 180–190.

[76] Hohman TJ, Alzheimer's Disease Neuroimaging Initiative. An obesity-associated gut microbiome with increased capacity for energy harvest is associated with cognitive decline in Alzheimer's disease. Alzheimer's & Dementia. 2017; 13: 1019–1020.

[77] Tsai VWW, Macia L, Johnen H, Kuffner T, Manadhar R, Jørgensen SB, *et al.* TGF-b superfamily cytokine MIC-1/GDF15 is a physiological appetite and body weight regulator. PLoS ONE. 2013; 8: e55174.

[78] Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, *et al.* Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. Nature. 2017; 549: 528–532.

[79] Wu C, Yosef N, Thalhamer T, Zhu C, Xiao S, Kishi Y, *et al.* Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature. 2013; 496: 513–517.

[80] Suzuki Y, Rani S, Liesenfeld O, Kojima T, Lim S, Nguyen TA, *et al.* Impaired resistance to the development of toxoplasmic encephalitis in interleukin-6-deficient mice. Infection and Immunity. 1997; 65: 2339–2345.

[81] Haque A, Echchannaoui H, Seguin R, Schwartzman J, Kasper LH, Haque S. Cerebral malaria in mice: interleukin-2 treatment induces accumulation of gammadelta T cells in the brain and alters resistant mice to susceptible-like phenotype. The American Journal of Pathology. 2001; 158: 163–172.

[82] Cardona AE, Teale JM. Gamma/delta T cell-deficient mice exhibit reduced disease severity and decreased inflammatory response in the brain in murine neurocysticercosis. Journal of Immunology. 2002; 169: 3163–3171.

[83] Welte T, Lamb J, Anderson JF, Born WK, O'Brien RL, Wang T. Role of two distinct gammadelta T cell subsets during West Nile virus infection. FEMS Immunology and Medical Microbiology. 2008; 53: 275–283.

[84] Chevalier MF, Bhatnagar N, Didier C, Lopez-Gonzalez M, Pavie J, Bollens D, *et al.* $\gamma\delta$ T-cell subsets in HIV controllers: potential role of T$\gamma\delta$17 cells in the regulation of chronic immune activation. AIDS. 2019; 33: 1283–1292.

[85] Welte T, Aronson J, Gong B, Rachamallu A, Mendell N, Tesh R, *et al.* Vγ4+ T cells regulate host immune response to West Nile virus infection. FEMS Immunology and Medical Microbiology. 2011; 63: 183–192.

[86] Kastrukoff LF, Lau AS, Takei F, Smyth MJ, Jones CM, Clarke SRM, *et al.* Redundancy in the immune system restricts the spread of HSV-1 in the central nervous system (CNS) of C57BL/6 mice. Virology. 2010; 400: 248–258.

[87] Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, *et al.* Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022; 375: 296–301.

[88] Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, *et al.* Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. Nature. 2022; 603: 321–327.

[89] Liu J, Bian Z, Wang X, Xu LP, Fu Q, Wang C, *et al.* Inverse correlation of V$\delta2^+$ T-cell recovery with EBV reactivation after haematopoietic stem cell transplantation. British Journal of Haematology. 2018; 180: 276–285.

[90] Khairallah C, Déchanet-Merville J, Capone M. $\gamma\delta$ T Cell-Mediated Immunity to Cytomegalovirus Infection. Frontiers in Immunology. 2017; 8: 105.

[91] Seaks CE, Wilcock DM. Infectious hypothesis of Alzheimer disease. PLoS Pathogens. 2020; 16: e1008596.

[92] Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, Haroutunian V, *et al.* Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus. Neuron. 2018; 99: 64–82.e7.

[93] Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, *et al.* Alzheimer's Disease-Associated β-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection. Neuron. 2018; 100: 1527–1532.

[94] Gelderblom M, Arunachalam P, Magnus T. $\gamma\delta$ T cells as early sensors of tissue damage and mediators of secondary neurodegeneration. Frontiers in Cellular Neuroscience. 2014; 8: 368.

[95] Papotto PH, Ribot JC, Silva-Santos B. IL-17$^+$ $\gamma\delta$ T cells as kick-starters of inflammation. Nature Immunology. 2017; 18: 604–611.

[96] Gelderblom M, Weymar A, Bernreuther C, Velden J, Arunachalam P, Steinbach K, *et al.* Neutralization of the IL-17 axis diminishes neutrophil invasion and protects from ischemic stroke. Blood. 2012; 120: 3793–3802.

[97] Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, *et al.* Commensal microbiota affects ischemic stroke outcome by regulating intestinal $\gamma\delta$ T cells. Nature Medicine. 2016; 22: 516–523.

[98] Arunachalam P, Ludewig P, Melich P, Arumugam TV, Gerloff C, Prinz I, *et al.* CCR6 (CC Chemokine Receptor 6) Is Essential for the Migration of Detrimental Natural Interleukin-17-Producing $\gamma\delta$ T Cells in Stroke. Stroke. 2017; 48: 1957–1965.

[99] Lu L, Wang Y, Zhou L, Li Y, Zhang X, Hu X, *et al.* Vγ4 T cell-derived IL-17A is essential for amplification of inflammatory cascades in ischemic brain tissue after stroke. International Immunopharmacology. 2021; 96: 107678.

[100] Zhao Z, Liang Y, Liu Y, Xu P, Flamme-Wiese MJ, Sun D, *et al.* Choroidal $\gamma\delta$ T cells in protection against retinal pigment epithelium and retinal injury. FASEB Journal. 2017; 31: 4903–4916.

[101] Seki D, Mayer M, Hausmann B, Pjevac P, Giordano V, Goeral K, *et al.* Aberrant gut-microbiota-immune-brain axis development in premature neonates with brain damage. Cell Host & Microbe. 2021; 29: 1558–1572.e6.

[102] Cugurra A, Mamuladze T, Rustenhoven J, Dykstra T, Beroshvili G, Greenberg ZJ, *et al.* Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. Science. 2021; 373: eabf7844.

[103] Brioschi S, Wang WL, Peng V, Wang M, Shchukina I, Greenberg ZJ, *et al.* Heterogeneity of meningeal B cells reveals a lymphopoietic niche at the CNS borders. Science. 2021; 373: eabf9277.

[104] Ono T, Okamoto K, Nakashima T, Nitta T, Hori S, Iwakura Y, *et al.* IL-17-producing $\gamma\delta$ T cells enhance bone regeneration. Nature Communications. 2016; 7: 10928.

[105] Freedman MS, Ruijs TC, Selin LK, Antel JP. Peripheral blood gamma-delta T cells lyse fresh human brain-derived oligodendrocytes. Annals of Neurology. 1991; 30: 794–800.

[106] Shimonkevitz R, Colburn C, Burnham JA, Murray RS, Kotzin

BL. Clonal expansions of activated gamma/delta T cells in recent-onset multiple sclerosis. Proceedings of the National Academy of Sciences of the United States of America. 1993; 90: 923–927.

[107] Kobayashi Y, Kawai K, Ito K, Honda H, Sobue G, Yoshikai Y. Aggravation of murine experimental allergic encephalomyelitis by administration of T-cell receptor gammadelta-specific antibody. Journal of Neuroimmunology. 1997; 73: 169–174.

[108] Koenecke C, Chennupati V, Schmitz S, Malissen B, Förster R, Prinz I. In vivo application of mAb directed against the gammadelta TCR does not deplete but generates “invisible” gammadelta T cells. European Journal of Immunology. 2009; 39: 372–379.

[109] Ponomarev ED, Novikova M, Yassai M, Szczepanik M, Gorski J, Dittel BN. Gamma delta T cell regulation of IFN-gamma production by central nervous system-infiltrating encephalitogenic T cells: correlation with recovery from experimental autoimmune encephalomyelitis. Journal of Immunology. 2004; 173: 1587–1595.

[110] Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KHG. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. Immunity. 2009; 31: 331–341.

[111] Zeine R, Pon R, Ladiwala U, Antel JP, Filion LG, Freedman MS. Mechanism of gammadelta T cell-induced human oligodendrocyte cytotoxicity: relevance to multiple sclerosis. Journal of Neuroimmunology. 1998; 87: 49–61.

[112] Amor S, Peferoen LAN, Vogel DYS, Breur M, van der Valk P, Baker D, *et al*. Inflammation in neurodegenerative diseases–an update. Immunology. 2014; 142: 151–166.

[113] Maimaitijiang G, Watanabe M, Shinoda K, Isobe N, Nakamura Y, Masaki K, *et al*. Long-term use of interferon-β in multiple sclerosis increases Vδ1$^-$Vδ2$^-$Vγ9$^-$ $\gamma\delta$ T cells that are associated with a better outcome. Journal of Neuroinflammation. 2019; 16: 179.

[114] Wohler JE, Smith SS, Zinn KR, Bullard DC, Barnum SR. Gammadelta T cells in EAE: early trafficking events and cytokine requirements. European Journal of Immunology. 2009; 39: 1516–1526.

[115] Ren S, Zhang X, Guan H, Wu L, Yu M, Hou D, *et al*. *Lactobacillus acidipiscis* Induced Regulatory Gamma Delta T Cells and Attenuated Experimental Autoimmune Encephalomyelitis. Frontiers in Immunology. 2021; 12: 623451.

[116] Ferber IA, Brocke S, Taylor-Edwards C, Ridgway W, Dinisco C, Steinman L, *et al*. Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). Journal of Immunology. 1996; 156: 5–7.

[117] Willenborg DO, Fordham S, Bernard CC, Cowden WB, Ramshaw IA. IFN-gamma plays a critical down-regulatory role in the induction and effector phase of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. Journal of Immunology. 1996; 157: 3223–3227.

[118] Owens GC, Erickson KL, Malone CC, Pan C, Huynh MN, Chang JW, *et al*. Evidence for the involvement of gamma delta T cells in the immune response in Rasmussen encephalitis. Journal of Neuroinflammation. 2015; 12: 134.

[119] Derkow K, Krüger C, Dembny P, Lehnardt S. Microglia Induce Neurotoxic IL-17+ $\gamma\delta$ T Cells Dependent on TLR2, TLR4, and TLR9 Activation. PLoS ONE. 2015; 10: e0135898.

[120] Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, *et al*. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nature Medicine. 2015; 21: 938–945.

[121] Rojas-Celis V, Valiente-Echeverría F, Soto-Rifo R, Toro-Ascuy D. New Challenges of HIV-1 Infection: How HIV-1 Attacks and Resides in the Central Nervous System. Cells. 2019; 8: 1245.

[122] Park JH, Lee HK. Function of $\gamma\delta$ T cells in tumor immunology and their application to cancer therapy. Experimental & Molecular Medicine. 2021; 53: 318–327.

[123] Lopes N, McIntyre C, Martin S, Raverdeau M, Sumaria N, Kohlgruber AC, *et al*. Distinct metabolic programs established in the thymus control effector functions of $\gamma\delta$ T cell subsets in tumor microenvironments. Nature Immunology. 2021; 22: 179–192.

[124] Park JH, Kim HJ, Kim CW, Kim HC, Jung Y, Lee HS, *et al*. Tumor hypoxia represses $\gamma\delta$ T cell-mediated antitumor immunity against brain tumors. Nature Immunology. 2021; 22: 336–346.

[125] Yazdanifar M, Barbarito G, Bertaina A, Airoldi I. $\gamma\delta$ T Cells: The Ideal Tool for Cancer Immunotherapy. Cells. 2020; 9: 1305.

[126] Park JH, Kang I, Lee HK. $\gamma\delta$ T Cells in Brain Homeostasis and Diseases. Frontiers in Immunology. 2022; 13: 886397.

[127] Fisher JP, Heuijerjans J, Yan M, Gustafsson K, Anderson J. $\gamma\delta$ T cells for cancer immunotherapy: A systematic review of clinical trials. Oncoimmunology. 2014; 3: e27572.

[128] Meraviglia S, Lo Presti E, Tosolini M, La Mendola C, Orlando V, Todaro M, *et al*. Distinctive features of tumor-infiltrating $\gamma\delta$ T lymphocytes in human colorectal cancer. Oncoimmunology. 2017; 6: e1347742.

[129] Lakomy R, Kazda T, Selingerova I, Poprach A, Pospisil P, Belanova R, *et al*. Real-World Evidence in Glioblastoma: Stupp’s Regimen After a Decade. Frontiers in Oncology. 2020; 10: 840.

[130] Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, *et al*. Effect of Nivolumab vs Bevacizumab in Patients with Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial. JAMA Oncology. 2020; 6: 1003–1010.

[131] Sampson JH, Gunn MD, Fecci PE, Ashley DM. Brain immunology and immunotherapy in brain tumours. Nature Reviews. Cancer. 2020; 20: 12–25.

[132] Lee M, Park C, Woo J, Kim J, Kho I, Nam DH, *et al*. Preferential Infiltration of Unique Vγ9Jγ2-Vδ2 T Cells into Glioblastoma Multiforme. Frontiers in Immunology. 2019; 10: 555.

[133] Garg AD, Vandenberk L, Van Woensel M, Belmans J, Schaaf M, Boon L, *et al*. Preclinical efficacy of immune-checkpoint monotherapy does not recapitulate corresponding biomarkers-based clinical predictions in glioblastoma. Oncoimmunology. 2017; 6: e1295903.

[134] Brown MC, Ashley DM, Khasraw M. Low tumor mutational burden and immunotherapy in gliomas. Trends in Cancer. 2022; 8: 345–346.

[135] Bryant NL, Suarez-Cuervo C, Gillespie GY, Markert JM, Nabors LB, Meleth S, *et al*. Characterization and immunotherapeutic potential of gammadelta T-cells in patients with glioblastoma. Neuro-Oncology. 2009; 11: 357–367.

[136] O’Brien SM, Klampatsa A. Novel therapies in the treatment of glioblastoma multiforme. Journal of the National Comprehensive Cancer Network. 2019; 17: 952–955.

[137] Lamb LS, Jr, Bowersock J, Dasgupta A, Gillespie GY, Su Y, Johnson A, *et al*. Engineered drug resistant $\gamma\delta$ T cells kill glioblastoma cell lines during a chemotherapy challenge: a strategy for combining chemo- and immunotherapy. PLoS ONE. 2013; 8: e51805.

[138] Lusczek ER, Vincent BG, Berezovskaya A. The Role of Allogeneic $\gamma\delta$ T Cell Therapies in Cancer Immunotherapy. Frontiers in Immunology. 2021; 12: 701052.

[139] Mosier DE. Animal models for retrovirus-induced immunodeficiency disease. Immunological Investigations. 1986; 15: 233–261.

[140] Shan XQ, Aw TY, Jones DP. Glutathione-dependent protection against oxidative injury. Pharmacology & Therapeutics. 1990; 47: 61–71.

[141] Dobashi K, Aihara M, Araki T, Shimizu Y, Utsugi M, Iizuka

K, *et al*. Regulation of LPS induced IL-12 production by IFN-gamma and IL-4 through intracellular glutathione status in human alveolar macrophages. Clinical and Experimental Immunology. 2001; 124: 290–296.

[142] Morris D, Ly J, Chi PT, Daliva J, Nguyen T, Soofer C, *et al*. Glutathione synthesis is compromised in erythrocytes from individuals with HIV. Frontiers in Pharmacology. 2014; 5: 73.

[143] Brundu S, Palma L, Picceri GG, Ligi D, Orlandi C, Galluzzi L, *et al*. Glutathione Depletion Is Linked with Th2 Polarization in Mice with a Retrovirus-Induced Immunodeficiency Syndrome, Murine AIDS: Role of Proglutathione Molecules as Immunotherapeutics. Journal of Virology. 2016; 90: 7118–7130.

[144] Herzenberg LA, De Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, *et al*. Glutathione deficiency is associated with impaired survival in HIV disease. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94: 1967–1972.

[145] Staal FJ, Roederer M, Israelski DM, Bubp J, Mole LA, McShane D, *et al*. Intracellular glutathione levels in T cell subsets decrease in HIV-infected individuals. AIDS Research and Human Retroviruses. 1992; 8: 305–311.

[146] Djigma FW, Sorgho PA, Soubeiga ST, Yonli AT, Sombie HK, Kiendrebeogo IT, *et al*. Role of Glutathione S-Transferase (GSTM1 and GSTT1) Genes Deletion in Susceptibility to HIV-1 Disease Progression. Journal of Biosciences and Medicines. 2020; 8: 41–54.