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Biotypes of HIV-associated neurocognitive disorders based on viral and immune pathogenesis

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Abstract

Purpose of the review: Human Immunodeficiency Virus (HIV)-associated neurocognitive disorders (HAND) continues to be prevalent in people living with HIV despite antiretroviral therapy. However, understanding disease mechanisms and identifying therapeutic avenues has been challenging. One of the challenges is that HAND is a heterogeneous disease and that patients identified with similar impairments phenotypically may have very different underlying disease processes. As the NeuroAIDS field is re-evaluating the approaches used to identify patients with HIV-associated neurological impairments we propose the subtyping of patients into biotypes based on viral and immune pathogenesis.

Recent findings: Here we review the evidence supporting subtyping patients with HIV-associated neurological complications into four biotypes: (1) Macrophage-mediated HIV encephalitis, (2) CNS viral escape, (3), T cell-mediated HIV encephalitis, and (4) HIV protein-associated encephalopathy.

Summary: Subtyping patients into subgroups based on biotypes has emerged as a useful approach for studying heterogeneous diseases. Understanding biotypes of HIV-associated neurocognitive impairments may therefore enable better understanding of disease mechanisms, allow for the development of prognostic and diagnostic markers, and could ultimately guide therapeutic decisions.

Keywords

HIV; HIV-associated neurological disorders; biotypes; NeuroAIDS; encephalitis; immune reconstitution inflammatory syndrome

Introduction

Subtyping patients into groups based on biological disease features, or biotypes, has emerged as a useful approach for studying heterogeneous diseases. Biotypes based on immune specificities have long been established in rheumatic diseases and are reliable predictors of prognosis and treatment response [1, 2]. Biotypes are also being applied to

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neurologic diseases including cancer related cognitive impairment [3] and autism spectrum disorder, where outcomes are improved when biotype-specific therapies are implemented [4]. Further, biotypes identified by imaging studies in depression were shown to predict response to treatment [5]. Understanding biotypes of neurocognitive impairments may therefore enable better disease trajectory prediction and could ultimately guide therapeutic decisions.

Human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND), is a heterogeneous disease which occurs in a subset of people living with HIV, even those well controlled on antiretroviral therapy (ART) [6]. Patients with HAND have neurocognitive and motor function deficits which are classified as Asymptomatic Neurocognitive Impairment (ANI), HIV-associated Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD) [7]. These impairments represent a major quality of life issue for patients, however understanding disease mechanisms and identifying therapeutic avenues has been challenging. One reason for this is that the defined phenotypes (ANI, MND, and HAD) are themselves heterogeneous. The bulk of patients with HAND have ANI may be functionally cognitively normal. The large number of patients categorized as having ANI is likely due to outdated criteria resulting in an over-estimation of the true burden of neurocognitive deficits in people living with HIV [8**, 9*]. Including patients with ANI within the umbrella of HAND may therefore mask important biological findings as these patients may not be impaired. Further, patients classified as having MND or HAD have very different diseases, disease trajectory, and disease manifestations and can be subtyped into profiles based on types of deficits [10-14]. Therefore, defining disease mechanisms within MND or HAD may be obscured by disease heterogeneity. This is further complicated by the fact that not all patients are treated with antiretroviral drugs and when treatment is initiated, it may be at different stages of the illness which would further contribute to the heterogeneity of the disease. The choice of antiretroviral drugs and their variable penetration into the brain can further impact the neuropathogenesis of the infection. As in other diseases, clarity may be found by further sub-setting patients into biotypes.

Biotypes of HIV-Associated Cognitive Impairments

Although multiple approaches to subtyping patients with HAND are possible, including clinical assessment and presence of symptoms [8] or imaging findings [15], in this manuscript we focus on the biotypes of HIV-associated cognitive impairments based on viral and immune pathogenesis. Specifically, we propose four distinct biotypes of HAND that may have some overlap: (1) Macrophage-mediated HIV encephalitis, (2) CNS viral escape, (3) T cell-mediated HIV encephalitis, and (4) HIV protein-associated encephalopathy (Table 1). Subtyping patients into these categories may facilitate a better understanding of disease mechanisms that underlie each phenotype, ultimately leading to interventions that target the virologic or immunologic process driving the neurologic damage and impairments.

Macrophage-mediated HIV encephalitis

In individuals who have not been treated with antiretroviral drugs, macrophage infiltration and the presence of multinucleated giant cells is considered the hallmark of HIV infection

in the brain [16]. These cells are predominantly in the perivascular region and some but not all are productively infected with HIV. In some individuals, perivascular astrocytes also contain the virus, however these cells have a restricted or latent viral infection [17]. There is also evidence of microglial cell activation, compromise of the blood brain barrier as indicated by leakage of serum proteins, and neuronal injury. Macrophage activation markers such CCL-2, tumor necrosis factor (TNF)-α, and neopterin can be detected in the cerebrospinal fluid, the dynamics of which change over the course of disease [18*]. MRI scans show atrophy of the brain with periventricular diffuse hyperintensities on T2 weighted images or FLAIR sequences (Figure 1 and reviewed in [19, 20]). These individuals often have severe cognitive impairment and bradykinesia or Parkinsonism and present with a subcortical dementia. They are usually severely immunosuppressed (CD4 cell counts <200 cells/mm^3) with high viral loads. If they remain untreated, they may die within a few months from the onset of the dementing illness. This syndrome develops in nearly 20-30% of untreated immunosuppressed individuals. It has been termed HIV encephalitis, AIDS dementia complex or HIV-associated dementia (HAD) in the literature [16, 21]. However, we propose that the term, macrophage-mediated viral encephalitis may be more appropriate to distinguish it from other forms of encephalitis seen in individuals treated with antiretroviral drugs.

CNS viral escape

CNS viral escape is characterized by high viral load in the CNS despite low serum viral loads and has been defined as asymptomatic, secondary, and symptomatic [22]. Asymptomatic viral escape has no evidence of brain injury or inflammation and may be a transitory finding [22, 23]. Both secondary and symptomatic viral escape phenotypes are associated with CSF pleocytosis [22] although etiology of the inflammation may be driven by different processes. Secondary CSF escape occurs during a CNS co-infection, such as syphilis or herpes viruses which may result in increased trafficking of CD4+ T cells into the CNS, some of which may be latently infected with HIV [22, 24]. The inflammation associated with symptomatic viral escape likely occurs due to the presence of HIV itself [22, 25-27]. CSF viral escape is an important contributor to the development of HIV-associated CD8+ T cell encephalitis, accounting for 68% of patients in a recently examined cohort [28**], suggesting that this process is mediated by immune responses directed towards HIV. Elevated WBC counts in the CSF may even predict viral escape and cognitive decline [22].

HIV viral escape in symptomatic patients can occur due to low penetration of ART into the CNS, poor adherence or compliance to ART, or mutations that confer resistance [22, 25]. Drug resistant mutations may arise more frequently in the CNS as there might be enhanced viral replication in this compartment. Recent studies documented elevated levels of soluble CD30, a marker of ongoing HIV-1 transcriptional activity, in the CSF despite ART [29*]. This contrasts sharply with ART induced decreases in soluble CD30 in the serum, suggesting that there may be ongoing viral replication in the CNS compartment despite ART. Which cells produce the virus detected in the CSF is an area of ongoing investigation. HIV establishes CNS infection early in disease [30] and has been documented primarily in microglia [31, 32], but also in astrocytes [17]. Some emerging evidence suggests that virus detected in the CSF during viral escape contains CD26, a marker

expressed on activated T cells, and therefore may be from CD4+ T cells [33*]. However, it is unknown if the T cells are trafficking in from the periphery or are brain-resident. Further, CD26 is expressed in regions of the human CNS with high levels in the meningeal endothelial cells [34] and is present in neurons and activated glia in rodent models [35].

Patients with symptomatic viral escape have a wide spectrum of symptoms including headache, tremors, cognitive impairment, confusion, focal neurologic deficits, and seizures [25, 36, 37]. These symptoms most often occur months to years after being stable on ART [22, 25]. Brain atrophy in viral escape is rare and neuroimaging in patients most commonly demonstrate white matter hyperintensities (Figure 1) with deep brain nuclei involvement and enhancement in some patients [22, 25]. Patients with symptomatic viral escape benefit from changes to ART regimens that provide better CNS penetration or to compensate for viral mutations [22, 25, 38]. Although similar clinical manifestations can occur in patients with secondary viral escape, these patients may benefit from therapies targeting the co-infection or steroids that help to control inflammation [39].

T cell mediated HIV encephalitis

T cell mediated HIV encephalitis is characterized by a CD4+ or CD8+ immune infiltrate that can be perivascular and diffuse into the parenchyma [40, 41]. This biotype encompasses both immune reconstitution inflammatory syndrome (IRIS), which can be driven by CD4+ or CD8+ T cells, and CD8+ T cell encephalitis. Patients with T cell mediated HIV encephalitis present with a wide range of clinical symptoms and signs including headache, confusion, cognitive impairment, and seizures [42]. This clinical syndrome overlaps with symptomatic viral escape described above. Neuroimaging can show diffuse white matter hyperintensities with mild edema (Figure 1 and reviewed in [43]). IRIS specifically occurs after ART initiation (reviewed in [44-46]) whereas HIV associated CD8 encephalitis can occur at any time and has been observed in patients who are well controlled on ART, treatment naïve, or as an IRIS event [28, 47, 48].

Risk factors for this biotype include low CD4+ T cell nadir (<100 cells/μL), the presence of opportunistic infections, and a rapid immune restoration after initiation of ART [45, 46]. The immune pathogenesis of this biotype is underscored by the increased risk of development of IRIS in patients treated with integrase inhibitors, which cause a rapid decline in viral loads [49-51]. This viral load decrease is accompanied by a sustained, hyperactive, and dysregulated immune response most often directed at opportunistic pathogens, residual HIV, or less frequently to self-antigens [52-56]. Metabolic alterations, including increased glycolysis and altered amino acid and lipid metabolism, which are correlated with immune activation, have been noted in patients that develop IRIS prior to the initiation of ART and during the IRIS event [57, 58]. Overactivation of both the innate and adaptive immune responses have been noted with particular activation of monocytes [59] and antigen specific CD4+ T-cells [52, 53, 60, 61] which results in an over production of proinflammatory cytokines and chemokines, further driving inflammation.

In patients with opportunistic infections, antigen specific T cells can infiltrate the CNS [54]. In contrast, little is known about the antigen specificity of the T cells that infiltrate the brain in the absence of an opportunistic infection. In four patients where T cell

receptor sequencing from the CNS was performed there was no evidence of a dominant clone [28]. Even in the absence of HIV CSF escape it may be that there is an influx of HIV-specific CD8+ T cells, as well as non-specific T cells, into the CNS as has been reported in acute infections [62] and IRIS [53]. Although not specifically examined in the context of T cell mediated viral encephalitis, brain resident T cells may also influence the disease process. In murine models, brain resident viral specific T cells have been shown to induce reactive gliosis during antigen restimulation [63*] and a recent cohort study of neuropathological findings in patients with HIV-associated CD8 encephalitis revealed that in addition to T-cell infiltration microglial activation is a common feature of this disease [28]. Microglial activation, in turn, can recruit additional T cells into the brain, driving widespread inflammation.

Importantly, patients with this biotype may benefit from immune modulatory therapies. While the immune response is important for containing the HIV or underlying opportunistic infections, the immune response during T cell encephalitis contributes to CNS damage and therefore dampening the response with corticosteroids can significantly reduce the incidence of death [28]. Other immune modulatory therapies, such as the use of maraviroc, a CCR5 inhibitor, have been suggested to have clinical utility. However, in a small study, IRIS associated with PML was not prevented nor was disease course influenced by CCR5 inhibition when compared to patients who received corticosteroids only [64].

HIV protein associated encephalopathy

HIV can also induce CNS damage through the production and release of toxic proteins and by driving proteinopathy processes. Once integrated, current ART does not impair translation of viral proteins, therefore proteins such as Tat, Nef, gp120, Vpr, and Gag, which modify CNS cell viability and functioning, are still produced, even from defective proviruses [56, 65, 66*]. Patients with viral protein associated encephalopathy are typically well controlled on ART with no detectable virus in the blood or CSF, but HIV proteins such as Tat can be detected in the CSF and the presence of this protein is associated with cognitive impairments [56, 65]. The production of viral proteins in the brain can directly and indirectly damage the CNS by several mechanisms including inducing apoptosis, causing synaptic loss, impairing metabolic pathways, driving inflammation, and inducing oxidative stress (Figure 2) [56, 67-73]. Further, the production of viral proteins in the periphery can result in endothelial dysfunction which contributes to the development of cardiovascular disease (reviewed in [74]) that can result in ischemic stress in the CNS.

In addition to inflammation and direct neurotoxicity, viral proteins can also induce proteinopathy. Amyloid beta (Aβ) [75, 76] and Tau [77, 78] deposits are present in the brains from patients with HIV and deposition of Aβ is correlated with HIV disease duration and not age [79], suggesting the virus contributes to the deposition of this protein. Viral proteins induce the production of Aβ and its secretion (Figure 2). Gag drives secretase-dependent cleavage of amyloid precursor protein (APP) which amplifies the production of Aβ in microglia [80] and Tat drives the enhanced expression of β-site cleaving enzyme, APP, and Aβ in astrocytes [81]. Both Tat [82] and Nef [83] stimulate the secretion of Aβ from neurons. Tat also inhibits neprilysin and thus prevents the degradation of Aβ [84, 85].

Tat may also stimulate the phosphorylation of Tau into its pathogenic isoforms [77]. Further, viral proteins can increase the toxicity of protein aggregates. For example, Tat can complex with Aβ forming multifibrillar structures which have increased toxicity as compared to Aβ alone [71]. Understanding the contribution and mechanisms behind proteinopathies driven by viral proteins is critical for therapeutic development. For example, in *in vitro* models, Aβ deposition and neurotoxicity induced by Gag could be prevented with gamma-secretase inhibitors [80]. Additionally, as the production of viral proteins from integrated virus is not targeted by ART, the development of adjunctive therapies inhibiting the expression or biological function of these proteins is needed.

Conclusion

Despite rigorous efforts and extensive research, little progress has been made in our ability to predict, prevent, or treat HIV-associated neurocognitive impairments except for optimization of ART. One large barrier to these advancements is that despite similar clinical phenotypes, patients with HAND may have highly divergent disease processes. In this review we suggest that classifying patients based on viral and immune pathogenesis may clarify important disease mechanisms and elucidate pathways for therapeutic targeting. It also helps identify some clinical phenotypes that are based on distinct underlying pathophysiological processes. Further deep phenotyping of these biotypes is necessary to understand the underlying mechanisms and clinical manifestations. This could provide clues for the proper diagnosis and treatment of these conditions.

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Key points

- HIV-associated neurocognitive disorders is a heterogenous disease
- Biotypes of HIV-associated neurocognitive impairments based on pathogenesis may elucidate key disease mechanisms
- There are four distinct pathological biotypes driven in part by the choice, timing of initiation, and duration of treatment with antiretroviral drugs
- Each of these biotypes have overlapping yet distinct clinical and neuro-radiological features, prognostic features and require unique modes of intervention

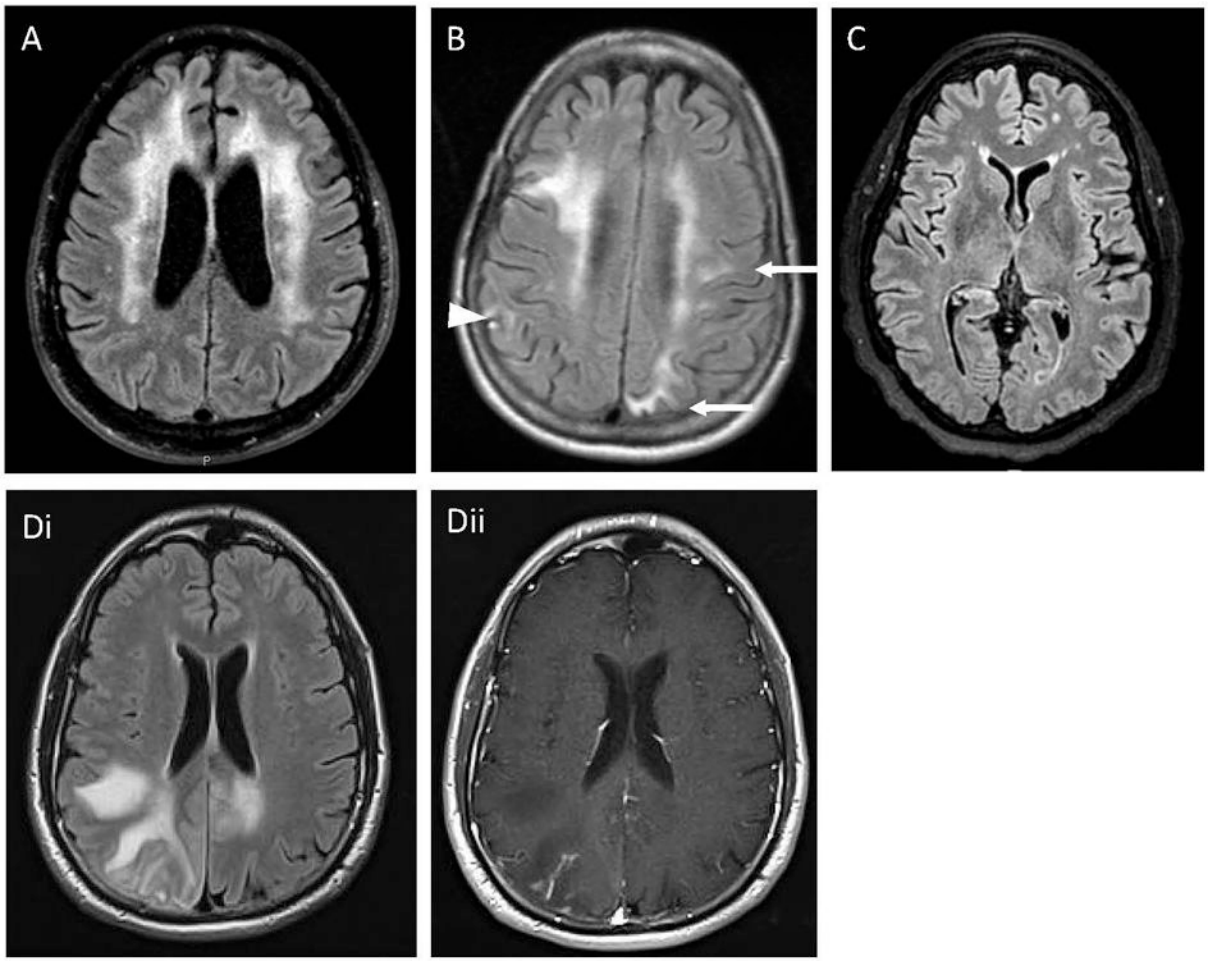

Figure 1.

Magnetic resonance imaging of brain showing distinct biotypes of HAND: (A) Periventricular high signal intensities in the white matter that spares the U fibers and the juxta cortical fibers. The ventricles are enlarged. This is representative of a patient with HIV associated dementia which would correspond to macrophage-mediated HIV encephalitis. (B) Periventricular high signal intensities that extend to the juxta cortical fibers (arrows) and the cortex (arrowhead). This represents a patient with HIV associated immune reconstitution inflammatory syndrome which corresponds to a T cell mediated HIV-encephalitis. (C) Diffuse cortical atrophy with preservation of the subcortical structures which was progressive over several years. This represents a patient well controlled on long-term antiretroviral therapy and corresponds to HIV-protein associated encephalopathy. (D) Patient with HIV infection and progressive multifocal leukoencephalopathy. (Di) Focal areas of high signal intensity lesions that extend to the U fibers and juxta cortical regions. (Dii) enhancement with gadolinium in the center of the lesion which corresponds to T cell encephalitis in the setting of an opportunistic infection.

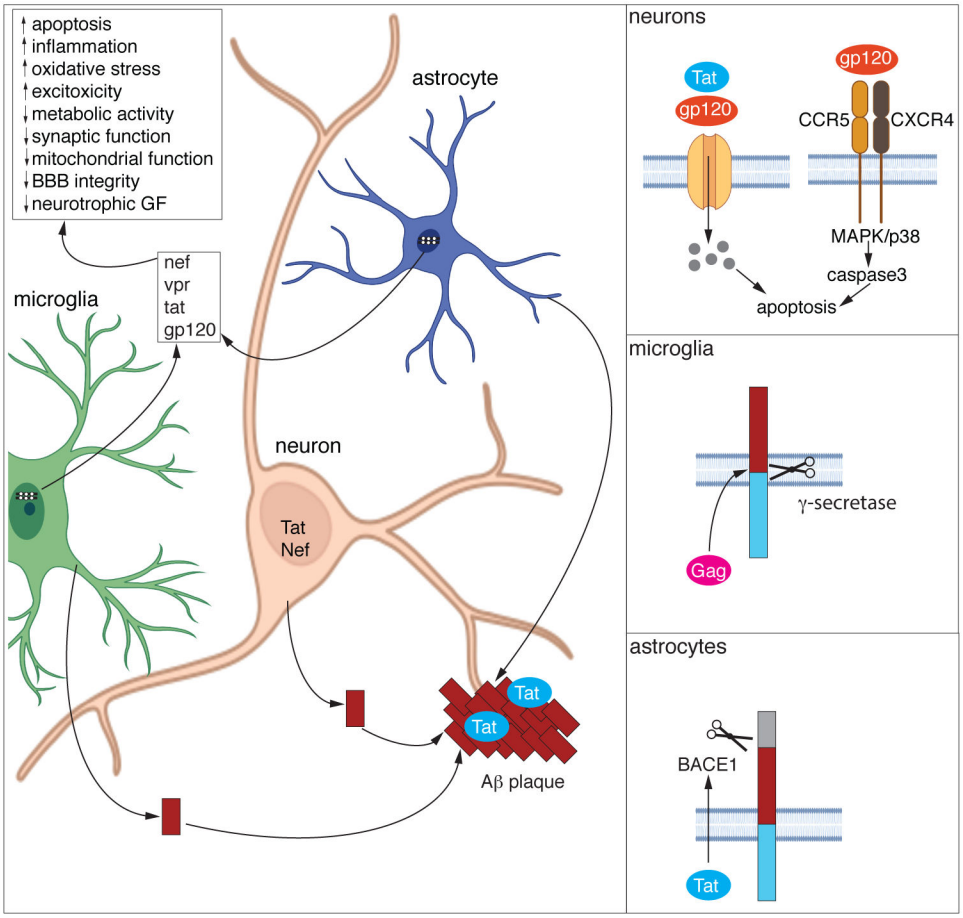

Figure 2. Viral protein mediated neurotoxicity and proteinopathy.

Once integrated, provirus from microglia and astrocytes continue to produce viral proteins, some of which are secreted into the extracellular environment or released in exosomes. These proteins can cause neurotoxicity by direct and indirect mechanisms. Extensive investigations have found numerous mechanisms by which viral proteins indirectly damage the CNS (summarized in the main panel) and broadly include excitotoxicity, metabolic alterations, proinflammatory processes, and blood brain barrier impairments. Direct neuronal toxicity has been demonstrated for both Tat and gp120 (top inset). These proteins can induce neuronal apoptosis by engaging with the NMDA receptor and allowing for calcium flux into the cell leading to apoptosis. Additionally, gp120 can bind to CXCR4 and CCR5 resulting in activation of p38 mitogen-activated protein kinase (MAPK) resulting in apoptosis.

Viral proteins can also drive proteinopathies including amyloid-beta (Aβ) accumulation. Aβ can be produced from microglia, astrocytes, and neurons and viral proteins increase the synthesis and secretion of Aβ from all these cell types. In neurons, both Tat and Nef stimulate the secretion of Aβ (main figure). In microglia, Gag increases APP cleavage by γ-secretase resulting in an increase in secretion of Aβ from microglia (middle inset). Tat drives the expression of APP and beta-secretase 1 (BACE1) in astrocytes which results in increased release of Aβ from these cells (bottom inset). The released Aβ from all these

cell types can form protein aggregates that are stabilized in a complex with Tat and exert enhanced neurotoxicity as compared to Aβ alone (main panel).

Table 1.

Key immune, viral, and pathology features of proposed biotypes of HIV-associated neurologic impairments.

Biotype	Macrophage-mediated HIV encephalitis	CNS viral escape	T cell-mediated HIV encephalitis	HIV protein-associated encephalopathy
Clinical features	Subacute subcortical dementia	Headache, tremors, cognitive impairment, confusion, focal neurologic deficits, and seizures	Diverse symptoms. Can include sensory and visual changes, headache, confusion, cognitive impairment, seizures and coma	Slowly progressive cognitive and psychomotor impairments
ART status	Untreated.	Treated. Associated with low CNS drug penetration, poor drug compliance, and drug resistant viral mutations	Treated.	Treated.
Immune profile	CD4 T cells <200/mm^3; elevated markers of macrophage activation in CSF	Asymptomatic: none; secondary and symptomatic: lymphocytic pleocytosis	Low CD4+ T cell nadir (<100 cells/μL) prior to ART, rapid immune restoration after initiation of ART; Lymphocytic pleocytosis(CD4+ or CD8+); microglial activation	Neuroinflammation, lymphocytic infiltration is possible. Microglial and astrocyte activation.
Viral profile	Viral load elevated in blood and CSF	Viral load elevated in CSF; ART resistant mutations	Often associated with opportunistic infections; HIV can be present in CSF or brain	Undetectable viral loads, but viral proteins (Tat, Nef, gp120, Vpr, and Gag) detectable in CSF
Pathology	Macrophage infiltration; multinucleated giant cells infected with HIV; astrocyte infection, neurodegeneration	Lymphocytic infiltrate into the CNS.	CD4+ or CD8+ immune infiltrate that can be both perivascular and diffuse into the parenchyma	Neuronal loss, Aβ and Tau deposits
Neuroimaging	Diffuse periventricular hyperintensities in white matter	White matter hyperintensities with deep brain nuclei involvement and enhancement	diffuse white matter hyperintensities with mild edema	Brain atrophy
Treatment	ART with CNS penetration	Changes to ART to enhance CNS penetration or overcome viral mutations. Treatment of secondary infection.	Treatment of opportunistic infection and corticosteroids.	None currently available.

Aβ - Amyloid beta, ART – Antiretroviral therapy, CSF - Cerebrospinal fluid, CNS – Central nervous system