Human Immunodeficiency Virus in the Brain—Culprit or Facilitator?

Luminita Ene

HIV Department, "Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania.

ABSTRACT

INTRODUCTION: Human immunodeficiency virus (HIV) enters the brain early, where it can persist, evolve, and become compartmentalized. Central nervous system (CNS) disease can be attributed to HIV alone or to the complex interplay between the virus and other neurotropic pathogens.

AIM: The current review aims to describe the direct impact of HIV on the brain as well as its relationship with other pathogens from a practitioner's perspective, to provide a general clinical overview, brief workup, and, whenever possible, treatment guidance.

METHODS: A review of PubMed was conducted to identify studies on neuropathogenesis of HIV in relation to host responses. Furthermore, the interaction between the CNS pathogens and the host damage responses were revised in the setting of advanced and also well-controlled HIV infection.

RESULTS: Similar to other pathogens, HIV leads to CNS immune activation, inflammation, and viral persistence. Therefore, almost half of the infected individuals present with neurocognitive disorders, albeit mild. Compartmentalized HIV in the CNS can be responsible in a minority of cases for the dramatic presentation of symptomatic HIV escape. Disruption of the immune system secondary to HIV may reactivate latent infections or allow new pathogens to enter the CNS. Opportunistic infections with an inflammatory component are associated with elevated HIV loads in the cerebrospinal fluid and also with greater cognitive impairment. The inflammatory immune reconstitution syndrome associated with CNS opportunistic infections can be a life-threatening condition, which needs to be recognized and managed by efficiently controlling the pathogen burden and timely balanced combination antiretroviral therapy. Latent neurotropic pathogens can reactivate in the brain and mimic HIV-associated severe neurological diseases or contribute to neurocognitive impairment in the setting of stable HIV infection.

CONCLUSIONS: As HIV can be responsible for considerable brain damage directly or by facilitating other pathogens, more effort is needed to recognize and manage HIV-associated CNS disorders and to eventually target HIV eradication from the brain.

KEYWORDS: HIV, brain, opportunistic infections, latent infections, cognitive impairment

Introduction

Even if universal access to combination antiretroviral therapy (cART) has dramatically changed the face of human immunodeficiency virus (HIV) infection,[1] HIV-associated central nervous system (CNS) complications are still challenging bedside clinical HIV practice and benchside NeuroAIDS research.[2] The repertoire of HIV-associated CNS disorders includes opportunistic infections (OIs), immune reconstitution inflammatory syndrome (IRIS), HIV-associated neurocognitive disorders (HAND), collateral damage of cART on the brain (including toxicity or inadequate penetration), associated effect of cerebrovascular diseases,[3] and accelerated aging.[4]

The classification of HIV-associated cognitive dysfunction underwent several nosological changes over time.[5,6] In the past decade, the refined definition of HAND added to the classic entity HIV-associated dementia (HAD) less severe forms such as mild neurocognitive disorder and asymptomatic neurocognitive impairment (ANI).[6] This later raised a lot of controversy because it does not involve a patent impairment of patients' functionality and is therefore difficult to diagnose in clinical settings, leading to overestimation of the rates of cognitive impairment.[7–10] However, ANI is not a benign condition, as it is associated with an altered CNS biomarker profile[11,12] and progression to symptomatic forms.[13,14] A further challenge is to disentangle HAND from age-related and inflammation-related diseases in the context of HIV.[15]

Central nervous system complications in the setting of HIV infection result both from a direct pathogenic effect of the virus and from the induced immune suppression, which facilitate new infections or promote reactivation of latent infections in the brain.

The current review aims to describe the direct impact of HIV on the brain as well as its relationship with other pathogens (bacteria, viruses, or parasites) from a practitioner's perspective, to provide a general clinical overview, brief workup,

and, whenever possible, treatment guidance. A review of PubMed original and review articles was conducted to decipher the interplay between HIV, other pathogens, and host responses in the brain, their clinical relevance, and to identify therapeutic approaches.

The first part of the review will summarize HIV neuroinvasion, compartmentalization of HIV infection in the brain, and immune responses. Cerebrospinal fluid (CSF) viral escape and its clinical impact will be also discussed.

The second part will describe the current concepts in brain acute and latent infections in the setting of chronic HIV infection focusing on interactions between pathogens and host immune responses.

HIV Entry and Persistence in the Brain

There is evidence that HIV enters the brain early after acute infection.[16] The mechanism of HIV entry is similar to that of other viruses, i.e., migration across the blood-brain barrier (BBB) via infected monocytes or blood lymphocytes using the "Trojan horse" model[17] or through endothelial cells, as free virions.[18] Infected monocytes will differentiate into perivascular macrophages after crossing the BBB. The macrophage lineage is the substrate for productive HIV infection within the CNS. Astrocytes can harbor HIV but do not support productive HIV replication; they may contribute to HIV-related brain damage through astrogliosis.[19] Astrocyte activation triggered by HIV neurotoxic proteins induces production of high levels of glutamate. Neurons are not infected directly by HIV, but elevated extracellular glutamate levels are able to cause neuronal bioenergetic disturbances and subsequent neuronal injury.[20] Local production of chemokines and cytokines as result of HIV replication together with systemic inflammation and microbial translocation can also contribute to neuronal injury.[21]

There is clear evidence that HIV seeds in the brain and is able to evolve independently from the systemic compartment. Immune activation is evident in the brain soon after initial systemic infection, even in settings with relatively reduced CSF HIV load and inflammation.[22] The HIV compartmentalization in CSF during primary infection, defined as independent HIV replication, was shown in 20% of HIV-infected patients using single genome amplification and phylogenetic analysis.[23] In the same study, sequestration of transmitted lineages within the CNS shortly after infection can serve as source for early CNS replication. It is uncertain if the source of compartmentalized HIV is the virus population seeded early in the brain or later during chronic infection.[24,25] In terms of cell types associated with HIV compartmentalization, CCR5 viruses infecting macrophages and related cells (M-tropic) show more sequence diversity compared with viruses infecting T cells (T-tropic)[26–28] and are mainly found in patients with HAD.[29] Human immunodeficiency virus from the brain appears to represent a robust reservoir, able to replicate in the CNS, and rebound after interruption of cART.[30]

Persistence of HAND in the Era of Antiretroviral Therapy

Almost half of the HIV-positive individuals have a certain degree of neurocognitive impairment (NCI),[31] a proportion which is similar for young adults infected with HIV in early childhood.[32] This proportion was not changed by the advent of cART.[31] However, cART significantly reduced the proportion of HAD, whereas ANI accounts nowadays for most of the NCI cases.[31,33]

Early cART rapidly reduces the HIV burden in the CSF at a similar rate to plasma. Still, reduction or control of HIV replication in the brain by cART does not manage to eliminate the milder forms of NCI. This can be due to several factors such as ongoing low-grade viral replication and inflammation within the CNS,[34] cumulative exposure and possible toxicity of antiretroviral and other medications,[35–37] and the effects of comorbidities and neurodegeneration that occur with aging.[38,39] The decay of HIV from CSF in chronically infected patients is slow because of compartmentalized infection and accounts for severe forms of cognitive impairment.[25] Persistent inflammation and immune activation in the setting of chronic HIV infection seems to be one of the mechanisms behind NCI. Central nervous system immune activation occurs with acute infection, escalates thereafter, and then decreases but is not entirely managed with cART.[40] New and more subtle contributors to NCI were recently identified: disruption of bioenergetic brain homeostasis, which could be an early event preceding functional deficits,[41] and transport of infected cells between the CNS and the systemic lymph nodes by the subdural lymphatic drainage system,[42] thus maintaining immune activation.[43]

As access to cART is currently available worldwide and treatment guidelines now recommend early treatment, would there be any additional risks for HIV-associated neurological problems? Will milder forms of HAND persist with early treatment[44] or will neurocognitive functioning of early-treated, well-managed individuals be similar to the performance of HIV-uninfected persons?[45]

HIV in the Brain of Patients on Stable Antiretroviral Therapy

Cerebrospinal fluid HIV escape is the term used to designate the instances when HIV is detected in the CSF of patients on stable cART, despite suppression of plasma viruses below the limits of detection or CSF HIV load is at least 0.5 log higher than plasma HIV load.[46–48] Three types of CSF escape have been defined[49]: (1) asymptomatic CSF escape, which is similar to plasma blips; (2) neurosymptomatic CSF escape, usually associated with virologic failure in CSF compartment and neurocognitive worsening; and (3) secondary CSF escape. In this last situation, CNS viral replication occurs in the context of another infection or inflammatory process that causes an entry of inflammatory cells susceptible to HIV infection into the CSF.

Asymptomatic CSF viral escape was diagnosed by screening in well-established cohorts or as part of other research studies. Its prevalence was estimated at 5% to 10% of cART recipients and was associated with immune activation.[40,47] Although it was defined as asymptomatic, the persistence of detectable HIV CSF loads was associated with increased risk for depression.[50] So far, asymptomatic CSF escape requires monitoring but not cART modification. Symptomatic viral escape earned more attention because of its dramatic presentation with new neurocognitive worsening in patients with good CD4 count and stable cART with undetectable or low-level plasma HIV load.[51–53] Symptomatic CSF viral escape appears to question the strategy of protease inhibitor monotherapy.[54–57] In this scenario, there is clear evidence of compartmentalization of HIV in CNS, with viruses harboring resistance mutations.[52,58] Even if the neurocognitive signs are very vivid, similar to HIV encephalitis, the CSF viral load remains moderate, suggesting the contribution of other mechanisms such as inflammation and immune dysregulation.[48,59,60] In most patients, neurocognitive symptoms subside after changing antiretroviral therapy but diffuse leukoencephalopathy may persist after clinical improvement.[48] From a pharmacologic point of view, antiretroviral drug distribution and toxicity in the CNS needs to be considered in assessing the causes of symptomatic viral escape.[61] Nevertheless, because HIV CSF escape demonstrates the ability of HIV to independently evolve in the CNS despite cART, targeting the CNS reservoir through additional strategies will be highly important for HIV eradication and cure.[62]

CD8 T-cell encephalitis is a clinical entity that reflects a paradoxical response driven by immune activation reacting to low-level CNS HIV replication.[43] Although the clinical neurological symptoms are similar to those of CSF escape, the hallmark of CD8 encephalitis is the pathologic finding of diffuse microglial hyperplasia and massive and diffuse perivascular and intraparenchymal infiltration by CD8 lymphocytes.[63] The pathogenic mechanism behind this entity is the exaggerated CD8 cytotoxic response that was initially linked not only to IRIS[64] but also to other conditions such as concomitant minor infection, interruption of cART, or virologic escape.[65] CD8 encephalitis has been described through case reports and case series in recent years.[65,66] As the confirmatory diagnosis is mainly histologic, a presumptive diagnosis of CD8 encephalitis is based on the following: (1) magnetic resonance imaging (MRI) findings of diffuse T2 and fluid-attenuated inversion recovery high signal intensities localized in both white and gray matter and unusual multiple linear gadolinium-enhanced perivascular lesions, (2) CSF findings of mildly elevated protein and pleocytosis (with >90% lymphocytes, predominantly CD8+) in a patient with stable antiretroviral treatment and neurocognitive worsening.[65] The recommended treatment for this disease consists of glucocorticosteroids to counteract the vigorous inflammatory process, in addition to the adjustment of the antiretroviral regimen.[65]

General Concept: HIV is Not Lonely in the Brain

The nervous system is immunoprivileged because it benefits from a robust immunosurveillance system.[67] Infections of the brain are less common than of other organs and occur when pathogens break down the BBB or cross it via immune cells using a Trojan horse model. Some neurotropic pathogens, such as herpes viruses, *Toxoplasma gondii*, and even *Mycobacterium tuberculosis*, once entered, are able to persist in the human nervous system for their entire life span. Immune suppression induced by HIV can alter the fragile balance between the pathogens and the host's immune responses and leave the individual at risk for subsequent reactivation of latent infections and disease.

Moreover, HIV and its proteins facilitate the entry and/or reactivation of several pathogens in the brain by both enhancing adhesion to and invasion of the brain microvascular endothelial cells, as is the case for *Cryptococcus neoformans*,[68] or by Tat-mediated activation of transcription, in the case of John Cunningham virus (JCV).[69]

Thus, HIV itself or the subsequent alteration of immune responses can favor reactivation of or new infections of the brain. But, conversely, OIs generate inflammation that can increase the passage of HIV across the BBB or sustain the local production of HIV, sometimes despite systemic antiretroviral control.[70] A pertinent question is how much HIV would be expected to be found in the CSF of a patient with various OIs and what is the degree of NCI in HIV-infected patients with brain OIs?

The HIV RNA is found more frequently in the CSF of patients with neurological diseases compared with those without neurological diseases,[71,72] usually at lower levels than in plasma.[73] However, higher CSF than plasma HIV RNA was detected in patients with brain infections involving macrophage activation: tuberculous meningitis (TBM), cryptococcal meningitis (CNM), and neurotoxoplasmosis.[71,74] In contrast, patients with progressive multifocal leukoencephalopathy (PML) have less local inflammation and a reduced HIV replication in CSF when compared with patients with HIV encephalopathy and patients with non-PML OIs.[75]

Whether HIV replication in the brain is independent of replication in plasma of patients with OI is still a matter of debate. The finding of high levels of divergent human immunodeficiency virus 1 (HIV-1) quasispecies, higher viral loads in opportunistic neurological infections that are independent of plasma viral load and CD4 count,[72,76] and different viral kinetics of HIV-1 in the CSF[77] implies that there is a local source of HIV in the brain that could influence both neurological disease occurrence and outcomes.

There are few data on cognitive impairment in patients with neurological OIs. An exploratory cross-sectional study of long-term neurocognitive outcomes following recovery from opportunistic brain infections in HIV-positive adults found that the *T gondii* encephalitis and PML survivors had the

highest cognitive deficits.[78] This is not unexpected considering the significant brain damage usually associated with these two neurological OIs. Tuberculous meningitis survivors were not part of this analysis. The most impaired cognitive domains were psychomotor, learning, and memory for neurotoxoplasmosis survivors and psychomotor and speed of information processing for PML survivors. Patients with OIs without significant brain destruction, such as CNM, may present a spontaneous decline in HIV CSF viral load[77] following acute infection and may also improve their cognitive function after an initial significant short-term decline.[79] Interestingly, a recent study described significant deficits in neurocognitive function in advanced HIV/AIDS individuals with positive *C neoformans* antigenemia in CSF but with no meningitis that improved after initiation of preemptive fluconazole treatment and cART.[80]

All these data, taken together, suggest that quantification of HIV RNA in CSF is clinically useful, particularly in patients with neurological disorders. Comprehensive workup in HIV-infected individuals with severe immune suppression should include screening of latent brain pathogens, diagnosis, and initial efficient treatment of the OIs. Also, antiretroviral regimens with good CSF penetration must be considered, primarily in patients with higher CSF viral loads, advanced HIV disease, and CNS disorders associated with significant macrophage activation.[81] However, timing of the antiretroviral treatment in the context of a neurological OI is problematic due to the risk of life-threatening IRIS.

IRIS—the Evil Side of cART

Immune reconstitution inflammatory syndrome in the CNS is emerging as an important neurological complication, particularly, as cART is becoming widely available. Currently, there are guidelines for prevention, diagnosis, or treatment of the CNS manifestations of IRIS,[82,83] and several excellent reviews provide an overview of clinical and epidemiologic features, pathophysiological mechanisms, available therapy, and preventive strategies.[84–86] Herein, the aim is to provide brief guidance in understanding, recognizing CNS-IRIS, and appropriately addressing it.

Severe immune suppression is typically an essential condition setting the scene for IRIS. Immune reconstitution inflammatory syndrome is usually related to a certain pathogen and therefore the clinical features of IRIS will reflect the underlying pathogen-related signs and symptoms. There are two instances of IRIS based on the two distinct temporal patterns of disease, namely, "unmasking IRIS" and "paradoxical IRIS." In unmasking IRIS, after cART initiation, a new OI is revealed with an important inflammatory component. In paradoxical IRIS, the OI was previously diagnosed and treated with good response, and there is a paradoxical clinical deterioration that also has a prominent inflammatory component. Paradoxical IRIS is a challenge because it has to be disentangled from other causes of clinical deterioration such as resistant strains, treatment toxicity, and nonadherence to treatment or a different medical condition.

The CNS-IRIS has a wide frequency ranging from 9% to 47% of individuals with a CNS OI who start antiretroviral therapy and is associated with a mortality rate of 13% to 75%.[86]

The conceptual model of IRIS pathophysiology is built on the interplay between the pathogen and the host immune responses.[85] The pathogen load is high in the setting of advanced HIV infection, especially if the OI is disseminated, untreated, or specific treatment is suboptimal or has just started. This scenario is typical for *M tuberculosis* IRIS and cryptococcal IRIS. Altered immune responses following cART might occur due to several mechanisms. Exuberant restoration of antigen-specific responses can occur as result of a rapid recovery of highly differentiated CD4 lymphocytes after cART initiation.[87] However, disruption of regulatory T-cell number or responses might lead to excessive inflammation.[88] The suppression of T-regulatory cells may activate compensatory activation of macrophages as part of the innate immune system with excessive inflammatory responses after immune restoration.[89]

Thus, both the high burden of microbial antigen and the globally disturbed immune responses could determine an excess of pro-inflammatory cytokines in blood and CSF[90–93] and subsequently extreme clinical manifestations.

The usual CNS-IRIS pathogens are *M tuberculosis, C neoformans*, and JCV but IRIS should be suspected in relation to other CNS infections, too. The CNS-IRIS caused due to *M tuberculosis* and *C neoformans* has been better studied especially because these conditions are associated with the highest mortality rate.[94,95] There seem to be premorbid scenarios for IRIS such as a paucity of cerebrospinal inflammation prior to antiretroviral therapy for cryptococcal IRIS and higher levels of inflammatory markers at baseline for TBM IRIS.[94] Progressive multifocal leukoencephalopathy IRIS, driven by accumulation of CD8 cytotoxic cells,[96] especially the paradoxical form, is hard to diagnose because it is difficult to distinguish PML IRIS from the natural course of PML. Some specific neuroimaging signs can support the PML IRIS diagnosis, namely, the presence of inflammatory signs and gadolinium enhancement on MRI and an elevated lactate to creatinine ratio by spectroscopy.[97] Toxoplasmic encephalitis IRIS has been reported seldom, mainly as unmasking form.[98,99]

Treating CNS-IRIS is as difficult as diagnosing it. A good approach would be to screen severely immune suppressed patients for CNS OI pathogens (eg, *C neoformans* antigen) with consecutive preemptive treatment to lower the probability of unmasking IRIS.[86,100] Despite particular aspects of CNS-IRIS determined by the causative agent, there are some common practical points for the management of paradoxical CNS-IRIS. (1) Remember that paradoxical IRIS is a diagnosis of exclusion.[101] (2) Ensure CSF pathogen load is reduced

before cART initiation. This can be achieved by prolonged induction therapy or higher dose initial consolidating therapy. In the particular case of *C neoformans*, cART should be started once the CSF cultures are sterile.[102] (3) Delay cART initiation if CNS-IRIS is a threat. The current recommendations are to start cART after at least 4 weeks for CNM[103] and after 8 weeks for TBM.[104] (4) The use of anti-inflammatory medication is beneficial. Systemic corticosteroids are recommended for severe forms of IRIS, in the absence of contraindications, and are more commonly indicated for mycobacterial-associated and fungal-associated IRIS than for viral-associated IRIS.[105] (5) Stop cART only under exceptional circumstances. A temporary discontinuation of cART might be considered if there is a persistent or severely depressed level of consciousness, severe neurological disability, and no improvement with corticosteroids.[86]

The Not So Usual Suspects

Occasionally, rather unexpected microorganisms are responsible for neurological conditions that clinically resemble those caused by more commonly encountered pathogens, especially in the setting of HIV infection. These events justify an extensive differential diagnosis workup. This can be difficult in a resource-limited setting, albeit more relevant because severe immune suppression is more common. In the current section, a few circumstances when the "usual suspects" behave differently or a "classical" clinical presentation unravels an uncommon pathogen will be discussed.

Toxoplasma gondii is a parasite that may reactivate in the brain of individuals with advanced HIV and generate brain abscesses. Therefore, empiric treatment for *Toxoplasma* infection should be considered in HIV-infected patients with focal neurological signs and brain abscesses on neuroimaging even before an extensive differential diagnosis workup. Nonfocal presentation of brain toxoplasmosis is rare. A diffuse form of toxoplasmic encephalitis might resemble HIV-related dementia with acute[106] or subacute presentation.[107] Another interesting presentation of *T gondii* infection in severe immune suppressed patients was subacute meningitis in a cohort study from Indonesia.[108] The authors tested retrospectively for *T gondii* (serology and polymerase chain reaction) all archived samples from a well-characterized cohort of 64 HIV-infected patients presenting with subacute meningitis in a referral hospital in Indonesia and found CSF *T gondii* DNA in 32.8% of the tested samples. The mortality rates were highest in the DNA *T gondii*–positive group that did not receive treatment for toxoplasmosis. Therefore, the authors recommend including toxoplasmosis in the differential diagnosis of HIV-infected patients with subacute meningitis and potentially administering empiric treatment for toxoplasmosis.

Several neurological presentations can be caused by neurological opportunistic diseases that occur concomitantly. Such is the case of a patient with HIV and well-diagnosed Kaposi sarcoma, disseminated cytomegalovirus (CMV), and neurotoxoplasmosis, who presented with encephalitis secondary to compartmentalized CMV infection in the CSF.[109]

Epstein-Barr virus (EBV) in the brain of HIV-infected patients is mainly associated with primary brain lymphoma—a diffuse, large-cell non-Hodgkin lymphoma of B-cell origin. An atypical case of progressive neurocognitive worsening, periodic seizures, and psychiatric symptoms lead to an initial diagnosis of HIV encephalitis but was later found to be an HIV-associated lymphoproliferative disorder with unusual morphologic features.[110] Another interesting case report was that of a patient with HIV symptomatic viral escape presentation that turned out to be EBV encephalitis.[111] The patient had gradual NCI; while on stable cART with excellent CD4 count, HIV RNA in plasma was 700 copies/mL and in CSF 7000 copies/mL. The EBV DNA in CSF was positive and EBV encephalitis was confirmed also by brain biopsy. The patient improved after adjusting the cART regimen and 6 months of valganciclovir treatment. This case emphasizes the need to search for additional causes of brain disorders, even with typical diagnosis scenarios.

Measles subacute encephalitis is an example of an unusual neurological complication of measles that was reported by our group and occurred as clusters during two consecutive measles epidemics in Romania in parenterally HIV-infected children and adolescents with severe immune suppression (1997-1998 and 2006-2007).[112] Myoclonus was the characteristic symptom, followed by rapidly progressing motor deficits, cognitive decline, coma, and exitus. The presence of measles virus was confirmed by immunocytochemistry. Interestingly, the HIV RNA levels in CSF were strikingly low compared with plasma, in the absence of antiretroviral treatment (2.31 ± 0.23 vs 4.22 ± 1.31), possibly due to the inhibitory effect of measles virus on HIV.[113] This effect was previously reported[114] but not in the CSF. The mechanism of HIV suppression is, in addition to severe lymphopenia, an increased production of molecules that are able to suppress HIV replication, such as β-chemokines,[115] especially for CCR5-tropic HIV.[116]

Latent Pathogens Still Suspect for NCI

So far, we discussed neurological conditions with clinical vivid symptoms, mostly in individuals with advanced HIV and the role of HIV as culprit or facilitator for these conditions. As cART is becoming widely available and early treatment will hopefully be offered in the future to most of the HIV-infected individuals, will latent infections be a threat for their neurocognitive functioning?

An interesting study on HIV-infected individuals from the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) cohort found that patients with serologic evidence of past syphilis (but not neurosyphilis) without any other confounding medical conditions to be more cognitively impaired (with a greater number of impaired domains and a higher

global deficit score), compared with a matched HIV group without evidence of syphilis.[117] Moreover, patients with prior neurosyphilis had higher CSF HIV RNA indicating secondary CSF HIV escape probably through persistent immune activation after syphilis treatment.[118] A more recent study among HIV-infected individuals with early syphilis found a high proportion of neurosyphilis that was correlated with HIV RNA levels and cART.[119] Therefore, the authors stressed the need for CSF-penetrating cART regimens in all patients with early syphilis.

Another fascinating multifaceted pathogen with brain tropism is *T gondii*, which is also associated, in its latent form, with behavioral changes[120] and psychiatric conditions.[121] The underlying mechanism is alteration of the dopaminergic neuromodulation system with increased dopamine release.[122] Our group described increased cognitive deficits in HIV and/or *Toxoplasma* coinfected individuals.[123] Interestingly, we found that latent toxoplasmosis contributes to NCI in young adults, regardless of their HIV status. Another study found an association between latent *Toxoplasma* and NCI, with increased risk for coinfected individuals with higher CD4+ T-cell counts.[124]

Cytomegalovirus latent infection has been linked to immune dysregulation, inflammation, and senescence.[125,126] Cytomegalovirus affects the CNS in multiple ways, such as replication-mediated cell injury[127] and brain vascular endothelium disease,[128,129] that could be associated with adverse neurocognitive outcomes. In chronic HIV-infected individuals on stable cART, the levels of CMV antibodies were associated with cardiovascular risk and neurocognitive performances, and these findings were moderated by age.[130]

Herpes viruses and other latent pathogens are more likely to reactivate in HIV-infected adults than in the general population. Therefore, even with excellent control of HIV replication and restoration of immune responses, inflammation and immune activation associated with latent pathogens might contribute directly to NCI or by associated secondary HIV escape. There is so far no effective strategy to control these latent infections and to reduce their impact on cognition.

Hepatitis C virus (HCV) has not only been associated with numerous symptoms affecting everyday functioning (fatigue, depression) but also with NCI even in subjects without evidence of hepatic decompensation. Hepatitis C virus can be present in brain[131] and determine immune activation that was hypothesized to be the underlying mechanism of NCI.[132] In HIV/HCV coinfected individuals, the added contribution of HCV to NCI is debated. Some studies found HCV as independent contributor to NCI[133–135] and also to increased risk for death.[136] Other studies that carefully excluded other confounding conditions did not find an added effect of HCV to NCI.[137] However, effective treatment of HCV was associated with improved outcomes[138] and is therefore critical for decreasing HIV-associated neurological morbidity.

Conclusions

Human immunodeficiency virus enters the brain and is able to alter the CNS immune environment allowing reactivation of latent or entry of new pathogens. Neurocognitive impairment can be associated with HIV directly or through other uncontrolled or latent infections. The approach to CNS infections in the setting of chronic HIV infection has to address the balance between opportunistic pathogens, host immune responses, and HIV burden. There is a need for a holistic approach as HIV can be both the culprit and the facilitator for brain damage. Some practical points from a practitioner's perspective in a patient with CNS symptoms are as follows: search for HIV in the CSF and treat, search for other pathogens irrespective of finding high burden of HIV in CSF, and appropriately plan the management of coexisting infections with respect to HIV treatment. Latent brain infections can contribute to NCI. If neither HIV nor other pathogens explain the neurological problem, search for toxic, metabolic, vascular, or aging-related factors.

Author Contributions

The author contributed to the conception and design, literature review, drafting the manuscript, revising it critically for important intellectual content and give approval for the final version.

REFERENCES

1. Fauci AS, Marston HD. Ending the HIV-AIDS pandemic—follow the science. *N Engl J Med*. 2015;373:2197–2199.
2. Kranick SM, Nath A. Neurologic complications of HIV-1 infection and its treatment in the era of antiretroviral therapy. *Continuum (Minneap Minn)*. 2012;18:1319–1337.
3. Clifford DB. HIV-associated neurocognitive disorder. *Curr Opin Infect Dis*. 2017;30:117–122.
4. Cohen RA, Seider TR, Navia B. HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimers Res Ther*. 2015;7:37.
5. Singh D. What's in a name? AIDS dementia complex, HIV-associated dementia, HIV-associated neurocognitive disorder or HIV encephalopathy. *Afr J Psychiatry (Johannesbg)*. 2012;15:172–175.
6. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789–1799.
7. Foley JM, Wright MJ, Gooding AL, et al. Operationalization of the updated diagnostic algorithm for classifying HIV-related cognitive impairment and dementia. *Int Psychogeriatr*. 2011;23:835–843.
8. Gisslen M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *BMC Infect Dis*. 2011;11:356.
9. Torti C, Foca E, Cesana BM, Lescure FX. Asymptomatic neurocognitive disorders in patients infected by HIV: fact or fiction? *BMC Med*. 2011;9:138.
10. Valcour VG. HIV, aging, and cognition: emerging issues. *Top Antivir Med*. 2013;21:119–123.

11. Bonnet F, Amieva H, Marquant F, et al. Cognitive disorders in HIV-infected patients: are they HIV-related? *AIDS*. 2013;27:391–400.

12. Garvey LJ, Pavese N, Politis M, et al. Increased microglia activation in neurologically asymptomatic HIV-infected patients receiving effective CART. *AIDS*. 2014;28:67–72.

13. Grant I, Franklin DR Jr, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*. 2014;82:2055–2062.

14. Sacktor N, Robertson K. Evolving clinical phenotypes in HIV-associated neurocognitive disorders. *Curr Opin HIV AIDS*. 2014;9:517–520.

15. Valdez AN, Rubin LH, Neigh GN. Untangling the Gordian knot of HIV, stress, and cognitive impairment. *Neurobiol Stress*. 2016;4:44–54.

16. Joseph SB, Arrildt KT, Sturdevant CB, Swanstrom R. HIV-1 target cells in the CNS. *J Neurovirol*. 2015;21:276–289.

17. Kramer-Hammerle S, Rothenaigner I, Wolff H, Bell JE, Brack-Werner R. Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. *Virus Res*. 2005;111:194–213.

18. Spudich S, Gonzalez-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. *Cold Spring Harb Perspect Med*. 2012;2:a007120.

19. Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol*. 2005;5:69–81.

20. Williams DW, Veenstra M, Gaskill PJ, Morgello S, Calderon TM, Berman JW. Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders. *Curr HIV Res*. 2014;12:85–96.

21. Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS ONE*. 2008;3:e2516.

22. Spudich S, Gisslen M, Hagberg L, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. *J Infect Dis*. 2011;204:753–760.

23. Sturdevant CB, Joseph SB, Schnell G, Price RW, Swanstrom R, Spudich S. Compartmentalized replication of R5 T cell-tropic HIV-1 in the central nervous system early in the course of infection. *PLoS Pathog*. 2015;11:e1004720.

24. Harrington PR, Schnell G, Letendre SL, et al. Cross-sectional characterization of HIV-1 env compartmentalization in cerebrospinal fluid over the full disease course. *AIDS*. 2009;23:907–915.

25. Ellis RJ, Gamst AC, Capparelli E, et al. Cerebrospinal fluid HIV RNA originates from both local CNS and systemic sources. *Neurology*. 2000;54:927–936.

26. Schnell G, Joseph S, Spudich S, Price RW, Swanstrom R. HIV-1 replication in the central nervous system occurs in two distinct cell types. *PLoS Pathog*. 2011;7:e1002286.

27. Spudich SS, Huang W, Nilsson AC, et al. HIV-1 chemokine coreceptor utilization in paired cerebrospinal fluid and plasma samples: a survey of subjects with viremia. *J Infect Dis*. 2005;191:890–898.

28. Soulie C, Tubiana R, Simon A, et al. Presence of HIV-1 R5 viruses in cerebrospinal fluid even in patients harboring R5X4/X4 viruses in plasma. *J Acquir Immune Defic Syndr*. 2009;51:60–64.

29. Koenig S, Gendelman HE, Orenstein JM, et al. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. *Science*. 1986;233:1089–1093.

30. Gianella S, Kosakovsky Pond SL, Oliveira MF, et al. Compartmentalized HIV rebound in the central nervous system after interruption of antiretroviral therapy. *Virus Evol*. 2016;2:vew020.

31. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75:2087–2096.

32. Ene L, Franklin DR, Burlacu R, et al. Neurocognitive functioning in a Romanian cohort of young adults with parenterally-acquired HIV-infection during childhood. *J Neurovirol*. 2014;20:496–504.

33. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. *Ann Neurol*. 2010;67:699–714.

34. Schibler M, Calmy A, Cavassini M, Du Pasquier R. Intracerebral HIV replication despite an efficient antiretroviral treatment: clinical impact and management. *Rev Med Suisse*. 2014;10:908, 910–902.

35. Rozzi SJ, Avdoshina V, Fields JA, et al. Human immunodeficiency virus promotes mitochondrial toxicity. *Neurotox Res*. 2017;32:723–733.

36. Shah A, Gangwani MR, Chaudhari NS, Glazyrin A, Bhat HK, Kumar A. Neurotoxicity in the post-HAART era: caution for the antiretroviral therapeutics. *Neurotox Res*. 2016;30:677–697.

37. Underwood J, Robertson KR, Winston A. Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? *AIDS*. 2015;29:253–261.

38. Thomas JB, Brier MR, Snyder AZ, Vaida FF, Ances BM. Pathways to neurodegeneration: effects of HIV and aging on resting-state functional connectivity. *Neurology*. 2013;80:1186–1193.

39. Jahanshad N, Valcour VG, Nir TM, et al. Disrupted brain networks in the aging HIV+ population. *Brain Connect*. 2012;2:335–344.

40. Dahl V, Peterson J, Fuchs D, Gisslen M, Palmer S, Price RW. Low levels of HIV-1 RNA detected in the cerebrospinal fluid after up to 10 years of suppressive therapy are associated with local immune activation. *AIDS*. 2014;28:2251–2258.

41. Borjabad A, Morgello S, Chao W, et al. Significant effects of antiretroviral therapy on global gene expression in brain tissues of patients with HIV-1-associated neurocognitive disorders. *PLoS Pathog*. 2011;7:e1002213.

42. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med*. 2015;212:991–999.

43. Spudich SS. Immune activation in the central nervous system throughout the course of HIV infection. *Curr Opin HIV AIDS*. 2016;11:226–233.

44. Spudich SS, Ances BM. CROI 2017: neurologic complications of HIV infection. *Top Antivir Med*. 2017;25:69–76.

45. Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. *Neurology*. 2013;80:371–379.

46. Rawson T, Muir D, Mackie NE, Garvey LJ, Everitt A, Winston A. Factors associated with cerebrospinal fluid HIV RNA in HIV infected subjects undergoing lumbar puncture examination in a clinical setting. *J Infect*. 2012;65:239–245.

47. Eden A, Fuchs D, Hagberg L, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. *J Infect Dis*. 2010;202:1819–1825.

48. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS*. 2012;26:1765–1774.

49. Ferretti F, Gisslen M, Cinque P, Price RW. Cerebrospinal fluid HIV escape from antiretroviral therapy. *Curr HIV/AIDS Rep*. 2015;12:280–288.

50. Hammond ER, Crum RM, Treisman GJ, et al. Persistent CSF but not plasma HIV RNA is associated with increased risk of new-onset moderate-to-severe depressive symptoms; a prospective cohort study. *J Neurovirol*. 2016;22:479–487.

51. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. *Clin Infect Dis*. 2003;37:1107–1111.

52. Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis*. 2010;50:773–778.

53. Bingham R, Ahmed N, Rangi P, Johnson M, Tyrer M, Green J. HIV encephalitis despite suppressed viraemia: a case of compartmentalized viral escape. *Int J STD AIDS*. 2011;22:608–609.

54. Ferretti F, Gianotti N, Lazzarin A, Cinque P. Central nervous system HIV infection in "less-drug regimen" antiretroviral therapy simplification strategies. *Semin Neurol*. 2014;34:78–88.

55. Imaz A, Cayuela N, Niubo J, et al. Short communication: focal encephalitis related to viral escape and resistance emergence in cerebrospinal fluid in a patient on lopinavir/ritonavir monotherapy with plasma HIV-1 RNA suppression. *AIDS Res Hum Retroviruses*. 2014;30:984–987.

56. Donath M, Wolf T, Sturmer M, et al; Frankfurt HIV Cohort Study. HIV-1 replication in central nervous system increases over time on only protease inhibitor therapy. *Med Microbiol Immunol*. 2016;205:575–583.

57. Ferretti F, Bigoloni A, Passeri L, et al. Cerebrospinal fluid analysis for HIV replication and biomarkers of immune activation and neurodegeneration in long-term atazanavir/ritonavir monotherapy treated patients. *Medicine (Baltimore)*. 2016;95:e4144.

58. Mukerji SS, Misra V, Lorenz D, et al. Temporal patterns and drug resistance in CSF viral escape among CART-experienced HIV-1 infected adults. *J Acquir Immune Defic Syndr*. 2017;75:246–255.

59. Calcagno A, Atzori C, Romito A, et al. Cerebrospinal fluid biomarkers in patients with plasma HIV RNA below 20 copies/mL. *J Int AIDS Soc*. 2014;17:19719.

60. de Almeida SM, Rotta I, Ribeiro CE, et al. Dynamic of CSF and serum biomarkers in HIV-1 subtype C encephalitis with CNS genetic compartmentalization-case study. *J Neurovirol*. 2017;23:460–473.

61. Nightingale S, Winston A, Letendre S, et al. Controversies in HIV-associated neurocognitive disorders. *Lancet Neurol*. 2014;13:1139–1151.

62. Joseph J, Cinque P, Colosi D, et al. Highlights of the Global HIV-1 CSF Escape Consortium Meeting, 9 June 2016, Bethesda, MD, USA. *J Virus Erad*. 2016;2:243–250.

63. Miller RF, Isaacson PG, Hall-Craggs M, et al. Cerebral CD8+ lymphocytosis in HIV-1 infected patients with immune restoration induced by HAART. *Acta Neuropathol*. 2004;108:17–23.

64. Gray F, Bazille C, Adle-Biassette H, Mikol J, Moulignier A, Scaravilli F. Central nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral treatment. *J Neurovirol*. 2005;11:16–22.

65. Lescure FX, Moulignier A, Savatovsky J, et al. CD8 encephalitis in HIV-infected patients receiving cART: a treatable entity. *Clin Infect Dis*. 2013;57:101–108.

66. Gray F, Lescure FX, Adle-Biassette H, et al. Encephalitis with infiltration by CD8+ lymphocytes in HIV patients receiving combination antiretroviral treatment. *Brain Pathol*. 2013;23:525–533.

67. Lafon M. Latent viral infections of the nervous system: role of the host immune response. *Rev Neurol (Paris)*. 2009;165:1039–1044.

68. He X, Shi X, Puthiyakunnon S, et al. CD44-mediated monocyte transmigration across *Cryptococcus neoformans*-infected brain microvascular endothelial cells is enhanced by HIV-1 gp41-I90 ectodomain. *J Biomed Sci*. 2016;23:28.

69. Bonwetsch R, Croul S, Richardson MW, et al. Role of HIV-1 Tat and CC chemokine MIP-1alpha in the pathogenesis of HIV associated central nervous system disorders. *J Neurovirol*. 1999;5:685–694.

70. Antinori A, Giancola ML, Grisetti S, et al. Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS*. 2002;16:1867–1876.

71. Christo PP, Greco DB, Aleixo AW, Livramento JA. Factors influencing cerebrospinal fluid and plasma HIV-1 RNA detection rate in patients with and without opportunistic neurological disease during the HAART era. *BMC Infect Dis*. 2007;7:147.

72. Zhang Y, Wei F, Liang Q, et al. High levels of divergent HIV-1 quasispecies in patients with neurological opportunistic infections in China. *J Neurovirol*. 2013;19:359–366.

73. Garcia F, Niebla G, Romeu J, et al. Cerebrospinal fluid HIV-1 RNA levels in asymptomatic patients with early stage chronic HIV-1 infection: support for the hypothesis of local virus replication. *AIDS*. 1999;13:1491–1496.

74. Marais S, Meintjes G, Lesosky M, Wilkinson KA, Wilkinson RJ. Interleukin-17 mediated differences in the pathogenesis of HIV-1-associated tuberculous and cryptococcal meningitis. *AIDS*. 2016;30:395–404.

75. Monno L, Zimatore GB, Di Stefano M, Appice A, Livrea P, Angarano G. Reduced concentrations of HIV-RNA and TNF-alpha coexist in CSF of AIDS patients with progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 1999;67:369–373.

76. Christo PP, Greco DB, Aleixo AW, Livramento JA. HIV-1 RNA levels in cerebrospinal fluid and plasma and their correlation with opportunistic neurological diseases in a Brazilian AIDS reference hospital. *Arq Neuropsiquiatr*. 2005;63:907–913.

77. Cecchini DM, Canizal AM, Rojas H, et al. Kinetics of HIV-1 in cerebrospinal fluid and plasma in cryptococcal meningitis. *Infect Dis Rep*. 2012;4:e30.

78. Levine AJ, Hinkin CH, Ando K, et al. An exploratory study of long-term neurocognitive outcomes following recovery from opportunistic brain infections in HIV+ adults. *J Clin Exp Neuropsychol*. 2008;30:836–843.

79. Carlson RD, Rolfes MA, Birkenkamp KE, et al. Predictors of neurocognitive outcomes on antiretroviral therapy after cryptococcal meningitis: a prospective cohort study. *Metab Brain Dis*. 2014;29:269–279.

80. Montgomery MP, Nakasujja N, Morawski BM, et al; COAT and ORCAS Trial Teams. Neurocognitive function in HIV-infected persons with asymptomatic cryptococcal antigenemia: a comparison of three prospective cohorts. *BMC Neurol*. 2017;17:110.

81. De Luca A, Ciancio BC, Larussa D, et al. Correlates of independent HIV-1 replication in the CNS and of its control by antiretrovirals. *Neurology*. 2002;59:342–347.

82. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.

83. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. 2010;10:791–802.

84. Riedel DJ, Pardo CA, McArthur J, Nath A. Therapy insight: CNS manifestations of HIV-associated immune reconstitution inflammatory syndrome. *Nat Clin Pract Neurol*. 2006;2:557–565.

85. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV AIDS (Auckl)*. 2015;7:49–64.

86. Bahr N, Boulware DR, Marais S, Scriven J, Wilkinson RJ, Meintjes G. Central nervous system immune reconstitution inflammatory syndrome. *Curr Infect Dis Rep*. 2013;15:583–593.

87. Mahnke YD, Greenwald JH, DerSimonian R, et al. Selective expansion of polyfunctional pathogen-specific CD4(+) T cells in HIV-1-infected patients with immune reconstitution inflammatory syndrome. *Blood*. 2012;119:3105–3112.

88. Lim A, D'Orsogna L, Price P, French MA. Imbalanced effector and regulatory cytokine responses may underlie mycobacterial immune restoration disease. *AIDS Res Ther*. 2008;5:9.

89. Barber DL, Andrade BB, Sereti I, Sher A. Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none. *Nat Rev Microbiol*. 2012;10:150–156.

90. Jarvis JN, Meintjes G, Bicanic T, et al. Cerebrospinal fluid cytokine profiles predict risk of early mortality and immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis. *PLoS Pathog*. 2015;11: e1004754.

91. Johnson TP, Patel K, Johnson KR, et al. Induction of IL-17 and nonclassical T-cell activation by HIV-Tat protein. *Proc Natl Acad Sci U S A*. 2013; 110:13588–13593.

92. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS ONE*. 2013;8:e63541.

93. Boulware DR, Meya DB, Bergemann TL, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS Med*. 2010;7:e1000384.

94. Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2013;56:450–460.

95. Agarwal U, Kumar A, Behera D, French MA, Price P. Tuberculosis associated immune reconstitution inflammatory syndrome in patients infected with HIV: meningitis a potentially life threatening manifestation. *AIDS Res Ther*. 2012;9:17.

96. Martin-Blondel G, Bauer J, Cuvinciuc V, et al. In situ evidence of JC virus control by CD8+ T cells in PML-IRIS during HIV infection. *Neurology*. 2013;81:964–970.

97. Gheuens S, Ngo L, Wang X, Alsop DC, Lenkinski RE, Koralnik IJ. Metabolic profile of PML lesions in patients with and without IRIS: an observational study. *Neurology*. 2012;79:1041–1048.

98. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. 2011;82:691–693.

99. Atreya AR, Arora S, Gadiraju VT, Martagon-Villamil J, Skiest DJ. Toxoplasma encephalitis in an HIV-infected patient on highly active antiretroviral therapy despite sustained immune response. *Int J STD AIDS*. 2014;25:383–386.

100. Longley N, Harrison TS, Jarvis JN. Cryptococcal immune reconstitution inflammatory syndrome. *Curr Opin Infect Dis*. 2013;26:26–34.

101. Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*. 2009;48:667–676.

102. Wiesner DL, Boulware DR. *Cryptococcus*-related immune reconstitution inflammatory syndrome (IRIS): pathogenesis and its clinical implications. *Curr Fungal Infect Rep*. 2011;5:252–261.

103. Abassi M, Boulware DR, Rhein J. Cryptococcal meningitis: diagnosis and management update. *Curr Trop Med Rep*. 2015;2:90–99.

104. Torok ME, Farrar JJ. When to start antiretroviral therapy in HIV-associated tuberculosis. *N Engl J Med*. 2011;365:1538–1540.

105. Pepper DJ, Marais S, Maartens G, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. 2009;48:e96–e107.

106. Davis C, Manteuffel J. Unusual presentation of *Toxoplasma gondii* encephalitis. *West J Emerg Med*. 2012;13:488–490.

107. Arendt G, Hefter H, Figge C, et al. Two cases of cerebral toxoplasmosis in AIDS patients mimicking HIV-related dementia. *J Neurol*. 1991;238: 439–442.

108. Ganiem AR, Dian S, Indriati A, et al. Cerebral toxoplasmosis mimicking subacute meningitis in HIV-infected patients; a cohort study from Indonesia. *PLoS Negl Trop Dis*. 2013;7:e1994.

109. Trentalange A, Calcagno A, Raviolo S, et al. Cytomegalovirus central nervous system compartmentalization in a patient presenting with AIDS. *Antivir Ther*. 2015;20:357–359.

110. Lloyd IE, Clement PW, Salzman KL, Jensen RL, Salama ME, Palmer CA. An unusual and challenging case of HIV-associated primary CNS lymphoma with Hodgkin-like morphology and HIV encephalitis. *Diagn Pathol*. 2015;10:152.

111. Trevillyan JM, Mahony AA, McLean C, Hoy JF. Successful treatment of Epstein-Barr virus encephalitis in the setting of HIV-associated neurocognitive disorder: a diagnostic and therapeutic challenge. *Antivir Ther*. 2013;18:257–261.

112. Duiculescu D, Ene L, Ungureanu E, et al. Unique features of measles encephalitis in Romanian HIV cohort. *J Neurovirol*. 2007;13:77.

113. Ene L, Ungureanu E, Oprea C, et al. Decreased CSF HIV load in patients with subacute myoclonic measles encephalitis. *J Neurovirol*. 2007;13:78.

114. Moss WJ, Ryon JJ, Monze M, Cutts F, Quinn TC, Griffin DE. Suppression of human immunodeficiency virus replication during acute measles. *J Infect Dis*. 2002;185:1035–1042.

115. Garcia M, Yu XF, Griffin DE, Moss WJ. In vitro suppression of human immunodeficiency virus type 1 replication by measles virus. *J Virol*. 2005;79:9197–9205.

116. Grivel JC, Garcia M, Moss WJ, Margolis LB. Inhibition of HIV-1 replication in human lymphoid tissues ex vivo by measles virus. *J Infect Dis*. 2005;192:71–78.

117. Marra CM, Deutsch R, Collier AC, et al. Neurocognitive impairment in HIV-infected individuals with previous syphilis. *Int J STD AIDS*. 2013;24: 351–355.

118. de Almeida SM, Bhatt A, Riggs PK, et al. Cerebrospinal fluid human immunodeficiency virus viral load in patients with neurosyphilis. *J Neurovirol*. 2010;16:6–12.

119. Firlag-Burkacka E, Swiecki P, Cielniak I, et al. High frequency of neurosyphilis in HIV-positive patients diagnosed with early syphilis. *HIV Med*. 2016;17:323–326.

120. Fekadu A, Shibre T, Cleare AJ. Toxoplasmosis as a cause for behaviour disorders—overview of evidence and mechanisms. *Folia Parasitol (Praha)*. 2010;57:105–113.

121. Nimgaonkar VL, Yolken RH. Neurotropic infectious agents and cognitive impairment in schizophrenia. *Schizophr Bull*. 2012;38:1135–1136.

122. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. *PLoS ONE*. 2011;6:e23866.

123. Ene L, Marcotte TD, Umlauf A, et al. Latent toxoplasmosis is associated with neurocognitive impairment in young adults with and without chronic HIV infection. *J Neuroimmunol*. 2016;299:1–7.

124. Bharti AR, McCutchan A, Deutsch R, et al. Latent toxoplasma infection and higher *Toxoplasma gondii* immunoglobulin G levels are associated with worse neurocognitive functioning in HIV-infected adults. *Clin Infect Dis*. 2016;63: 1655–1660.

125. Freeman ML, Lederman MM, Gianella S. Partners in crime: the role of CMV in immune dysregulation and clinical outcome during HIV infection. *Curr HIV/AIDS Rep*. 2016;13:10–19.

126. Gianella S, Letendre S. Cytomegalovirus and HIV: a dangerous Pas de Deux. *J Infect Dis*. 2016;214:S67–S74.

127. Zhang L, Li L, Wang B, Qian DM, Song XX, Hu M. HCMV induces dysregulation of glutamate uptake and transporter expression in human fetal astrocytes. *Neurochem Res*. 2014;39:2407–2418.

128. Alcendor DJ, Charest AM, Zhu WQ, Vigil HE, Knobel SM. Infection and upregulation of proinflammatory cytokines in human brain vascular pericytes by human cytomegalovirus. *J Neuroinflammation*. 2012;9:95.

129. Parrinello CM, Sinclair E, Landay AL, et al. Cytomegalovirus immunoglobulin G antibody is associated with subclinical carotid artery disease among HIV-infected women. *J Infect Dis*. 2012;205:1788–1796.

130. Brunt SJ, Cysique LA, Lee S, Burrows S, Brew BJ, Price P. Short communication: do cytomegalovirus antibody levels associate with age-related syndromes in HIV patients stable on antiretroviral therapy? *AIDS Res Hum Retroviruses*. 2016;32:567–572.

131. Forton DM, Allsop JM, Cox IJ, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. *AIDS*. 2005;19:S53–S63.

132. Forton DM, Hamilton G, Allsop JM, et al. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol*. 2008;49:316–322.

133. Cherner M, Letendre S, Heaton RK, et al. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*. 2005;64:1343–1347.

134. Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ. Neurocognition in individuals co-infected with HIV and hepatitis C. *J Addict Dis*. 2008;27:11–17.

135. Thiyagarajan A, Garvey LJ, Pflugrad H, et al. Cerebral function tests reveal differences in HIV-infected subjects with and without chronic HCV co-infection. *Clin Microbiol Infect*. 2010;16:1579–1584.

136. 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. *J Neurol Sci*. 2012;312:45–51.

137. Clifford DB, Vaida F, Kao YT, et al. Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people. *Neurology*. 2015;84:241–250.

138. Yarlott L, Heald E, Forton D. Hepatitis C virus infection, and neurological and psychiatric disorders: a review. *J Adv Res*. 2017;8:139–148.