2017

Interventions for neurocognitive dysfunction

J Ellero

M Lubomski
The University of Notre Dame Australia, michal.lubomski@nd.edu.au

B Brew
The University of Notre Dame Australia, bruce.brew@nd.edu.au

This article was originally published as:
Ellero, J., Lubomski, M., & Brew, B. (2017). Interventions for neurocognitive dysfunction. *Current HIV/AIDS Reports, 14* (1), 8-16.

Original article available here:
http://dx.doi.org/10.1007/s11904-017-0346-z

This is the accepted manuscript version of the article published as:

Ellero, J., Lubomski, M., and Brew, B. (2017). Interventions for neurocognitive dysfunction. *Current HIV/AIDS Reports, 14*(1), 8-16. doi: 10.1007/s11904-017-0346-z

This article has been published in final form at http://dx.doi.org/10.1007/s11904-017-0346-z

MANUSCRIPT TITLE PAGE

Title: Interventions for neurocognitive dysfunction.

Journal: Current HIV/AIDS Reports.

Author Names and Affiliations:

Jacqueline Ellero[1], Michal Lubomski[2], Bruce Brew[3]

[1]B. MedSci (Hons), MD

Department of Neurology, St Vincent's Hospital, 390 Victoria St, Darlinghurst. NSW, 2010. Sydney. Australia.

Email: Jacqueline.ellero@hotmail.com

[2]B.PharmSci, MBBS (Hons), MMed/Surg.

Department of Neurology, St Vincent's Hospital, 390 Victoria St, Darlinghurst. NSW, 2010. Sydney.

The University of Notre Dame Australia, School of Medicine, Sydney. 160 Oxford St, Darlinghurst. NSW, 2010. Sydney. Australia.

Email: michal.lubomski@nd.edu.au

[3]MBBS (Hons), MD, FRACP, FAAN

Departments of Neurology and Immunology, St Vincent's Hospital, 390 Victoria St and Peter Duncan Neurosciences Unit, St Vincent's Centre for Applied Medical Research. Darlinghurst. NSW, 2010. Sydney, Australia.

University of New South Wales, School of Medicine, Sydney, NSW. 2052, Australia

Email:B.Brew@UNSW.edu.au

Corresponding Author – Professor Bruce Brew

Email: B.Brew@UNSW.edu.au

(Phone) +612 8382 4100. (Fax) +612 8382 4101.

Postal Address: St Vincent's Hospital. Department of Neurology. Level 4 Xavier Building. 390 Victoria St, Darlinghurst. NSW, 2010. Sydney. Australia

Word Counts: Abstract: 144 Manuscript: 3848 References: 100

Sources of support / disclosures: Research not industry sponsored. No disclosures. All authors disclose no conflicts of interest.
This article does not contain any studies with human or animal subjects performed by any of the authors.

Title: Interventions for Neurocognitive Dysfunction

Abstract

Purpose of review: To evaluate current barriers to HIV cure strategies and interventions for neurocognitive dysfunction with a particular focus on recent advancements over the last three years.
Recent findings: Optimal anti-retroviral therapy (ART) poses challenges to minimise neurotoxicity, whilst ensuring blood brain barrier penetration and minimising the risk of cerebrovascular disease. CSF biomarkers, BCL11B and neurofilament light chain may be implicated with a neuroinflammatory cascade leading to cognitive impairment. Diagnostic imaging with diffusion tensor imaging as well as resting-state fMRI show promise in future diagnosis and monitoring of HAND.
Summary: The introduction of ART has resulted in a dramatic decline in HIV-associated dementia. Despite this reduction, milder forms of HIV-associated neurocognitive disorder (HAND) are still prevalent and are clinically significant. The central nervous system (CNS) has been recognised as a probable reservoir and sanctuary for HIV, representing a significant barrier to management interventions.

Key words

HIV, Neurocognitive Dysfunction, HAND, Dementia, CNS Reservoir, Neurotoxicity, Neuroimaging, Cerebrovascular disease.

Introduction

The number of people worldwide living with HIV is over 35 million (WHO 2015). HIV has devastating effects on the immune system, resulting in acquired immunodeficiency syndrome (AIDS). It also contributes to a range of neurocognitive dysfunctions, collectively referred to as HIV-associated neurocognitive disorder (HAND) [1]. HAND incorporates a spectrum of cognitive impairment (categorised by the Frascati criteria) ranging from asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) to HIV-associated dementia (HAD). Manifestations of HAND include impaired attention, memory, executive function, information processing speed and decision-making. Both ANI and MND are characterised by impaired cognition in two or more areas on neuropsychological testing, but while patients with MND have mild interference with functioning, patients with ANI are clinically asymptomatic. Alternatively, HAD is defined by marked cognitive impairment significantly affecting daily functioning [2].

The largest study to examine cognitive impairment in HIV is the Central Nervous System (CNS) HIV Antiretroviral Therapy Effects Research (CHARTER) cross sectional cohort study which found 52% (814/1555) of HIV positive patients suffered cognitive impairment [3]. The prevalence of HAD has declined significantly since the introduction of anti-retroviral therapy (ART) in the 1990s [3, 4]. However, less severe forms of HAND (ANI and MND) are still prominent with estimates ranging 20-50% [3, 5, 6]. Despite being asymptomatic, ANI is associated with increased risk of symptomatic decline (when compared to patients without neurocognitive impairment) [7], poorer quality of life and higher mortality [4] and is therefore important to address.

Existence of HIV Reservoirs: is the Central Nervous System Reservoir Real and is it Significant?

Despite suppression of viral replication in the plasma, replication of HIV persists in multiple reservoirs throughout the body including resting memory CD4 T cells in the blood, lymph nodes, gut associated lymphoid tissue, genital tract, bone marrow, lungs, kidneys and most likely, the CNS [8]. The majority of research effort to date has been focused towards the largest HIV reservoir located within the CD4 T cells. The CNS reservoir however, is less well studied. Debate in the literature exists regarding the presence of the CNS reservoir and indeed its importance in HIV cure strategies.

Formation of the CNS reservoir is believed to occur early during the course of infection. HIV enters the CNS by means of peripherally infected leukocytes (mainly monocytes), entering the Cerebral Spinal Fluid (CSF) as early as 2 weeks [9]. These monocytes and probably other cells act as "Trojan horses", facilitating entry of HIV into the CSF [10]. Once in the CSF, infection of neighbouring cells (predominately perivascular macrophages and microglial cells) occurs via direct contact with monocytes. Neuropathological studies of the brain suggest that infection of these cells is highest around the perivascular areas [11].

Blankson et al defined five specific characteristics that cells must meet in order to be considered biologically significant reservoirs of HIV-1. The cells must [1] contain integrated provirus, capable of replication, [2] be long-lived, allowing the virus to escape immune processes, [3] be significant in number, [4] require mechanisms to suppress the replication of HIV-1 and establish dormant infection, and finally [5] have the potential to be activated to produce new viral particles [12]. A review of the literature by Gray et al in 2014 established that the CNS fulfils most of these criteria to be considered as a reservoir [13].

Integrated HIV-1 provirus has been found in perivascular macrophages, microglia and astrocytes using fluorescence in-situ hybridisation and laser capture microdissection coupled with PCR [14, 15]. These cells are long-lived with half lives ranging from three months in macrophages [16], months to years in astrocytes [17] and years to lifetime in microglia [18]. The frequency of CNS cell infection has been demonstrated in several studies [15, 19]. Research by Eden et al found that up to 10% of patients with known HIV infection and undetectable HIV RNA plasma levels had raised HIV RNA in the CSF [20]. Gray et al have also established that HIV-1 within the CNS possess unique long terminal repeat sequences which allow the virus to remain dormant [21]. In-vitro studies have shown that astrocytes can be induced with interferon gamma, granulocyte macrophage colony stimulating factor and TNF alpha to artificially produce viral particles [22, 23]. What remains to be discovered is whether the integrated virus is capable of replication and whether or not the virus can be reactivated in vivo [24]. Finally, research by Gama et al has recently showed that the CNS harbors latent Simian Immunodeficiency Virus in macaques after lengthy ART suppression, further implicating the brain as a potential viral reservoir [25].

The Role of Astrocytes in the CNS HIV Reservoir

The understanding of the role of astrocytes in HIV reservoirs is evolving. While astrocytes appear to be less involved with viral replication than perivascular macrophages and microglial cells, recent studies have shown that up to 19% of astrocytes can be infected in HAD, therefore representing a potentially significant viral reservoir [19]. Churchill et al found that astrocytes were more frequently

infected with HIV in HAD and this was associated with the severity of HAND [19]. More recent research by Eugenin et al suggests that infected astrocytes may disturb the blood brain barrier (BBB) by triggering endothelial apoptosis [26]. A follow-up report from their research proposed that this astrocyte related disruption of the BBB may contribute to the formation of the CNS viral reservoir [27].

Identifying the Central Nervous System Reservoir: Biomarkers

The detection of biomarkers in the CNS is essential to evaluate the extent of the viral reservoir for HIV treatment monitoring. To date, no such markers have been validated. Researchers have proposed different CSF biomarkers including neurofilament light chain, neopterin and newer markers such as BCL11B. Neurofilament light chain (NFL) is one of the main components of the neuronal cytoskeleton and its CSF concentration is a sensitive marker of neuronal injury [28]. NFL CSF levels increase significantly in patients with HIV dementia and decrease with the commencement of ART. There is an approximate 42% reduction after 15 weeks of ART in some patients with elevated baseline CSF NFL levels [29]. CSF neopterin, a marker of CNS immune activation, is raised in nearly all patients with HAND on ART and in some patients without HAND. Its use as a biomarker is based on the concept that HIV in the CNS is not fully latent but instead shows periodic activity of replication with CNS damage, which may be subclinical. With cART CSF neopterin typically falls over several months, however often remains mildly elevated. BCL11B is a transcription factor which inhibits transcription of HIV-1. Desplats et al have found increased levels of BCL11B in patients with latent HIV infection in the CNS, defined as cases displaying proviral DNA in the brain with no productive infection. It has been proposed that BCL11B may trigger a neuroinflammatory cascade leading to cognitive impairment. BCL11B may represent an important potential biomarker of latent disease, although it usefulness in monitoring response to ART is not well understood [30]. The sample size of this study was small and larger studies are required to further assess the potential of BCL11B. The number of studies assessing CNS reservoir biomarkers is limited and it is therefore difficult to monitor disease activity in the CNS. Furthermore, CNS disease has been shown to occur in the absence of CSF viral load by current techniques [30], creating another hurdle to finding an ideal biomarker of the CNS reservoir.

Antiretroviral Strategies to Treat HAND: Penetrating the Blood Brain Barrier

The CNS reservoir poses a number of challenges with regards to HAND treatment strategies as there is good evidence that it is a sanctuary site. Firstly, can drugs commonly used to treat HIV (ARV) penetrate the BBB? Can drug treatments adequately target HIV infected cells? Is the CNS immune system then able to clear the virus?

The BBB is a dynamic interface between the CNS and blood, formed by tight junctions between capillary endothelial cells which regulate the transport of molecules and cells. Increasing evidence suggests that ARVs differ in their ability to cross the BBB (as measured by their CSF concentrations). The ability of ARVs to penetrate the CNS depends on multiple favourable factors including low molecular weight, high lipid solubility, low degree of ionization, high affinity for transmembrane receptors and low protein binding [31]. To consolidate these characteristics, a CNS penetration effectiveness (CPE) score was introduced by Letendre et al [32].

ARVs with greater CNS penetration have been associated with reduced rates of HAND in some trials. Studies have also suggested that regimens with higher CPE scores are associated with a higher chance of undetectable CSF HIV RNA [32, 33]. Consequently, it has been suggested that ARVs with high penetration be selected for use in patients with HAND. Other trials however present conflicting data. A randomised controlled trial by Ellis et al showed no significant difference in neurocognitive outcomes when comparing treatment with ART with an expected high BBB penetration versus low BBB penetration [34]. This study however had significant limitations including a short lead in time (of 8 weeks) for ARV stability prior to study entry, high drop-out rate, early termination of the study and a higher proportion of patients in the optimised CPE group with comorbidities possibly contributing to cognitive dysfunction including Hepatitis C. Further, no measure of the BBB was incorporated into the trial: it could be argued that participants with an impaired BBB from HIV may not require ARVs with good penetration.

Additionally, various studies have shown conflicting results as to whether or not HIV CSF levels correlate with changes in cognitive function [35]. Although often used as a surrogate marker of brain activity, CSF concentrations do not necessarily reflect those of brain tissue. Further criticisms of the CPE rank are that it does not take into account other important properties of ARV therapy including potential toxicity (both systemic, for example cardiovascular from Abacavir, and brain), compartmentalised resistance in the CNS and the possibility of pre-existing BBB impairment in some patients facilitating CNS entry of otherwise poorly penetrating ARVs. Furthermore, despite adequate concentrations in the CNS, some ARTs including the NRTIs zidovudine, lamivudine and stavudine, have demonstrated insufficient inhibitory activity in astrocytes, a potentially significant source of HIV-1 [36].

Of the ART drug classes, non-nucleoside reverse transcriptase inhibitors (NNRTIs) generally score most favourably in terms of BBB penetration [37]. However, when taking into consideration the toxicity profiles of drugs, the NRTIs (including zidovudine, abacavir, lamivudine and emtricitabine) are preferred [38]. Protease inhibitors are poor penetrators of the BBB [39] due to their high protein binding and large molecular size. They are however potent with a high genetic barrier to resistance and thus present a possible future target, for example with nanoparticles. Dolutegravir, a once daily novel integrase inhibitor achieves acceptable therapeutic CSF concentrations, with BBB transport governed mainly by passive diffusion. It demonstrates a high CPE score of 4 and is considered favourable for treatment of HAND [40]. Maraviroc, a chemokine receptor type 5 (CCR5) entry inhibitor has also recently been shown to improve global neurocognitive functioning in virally suppressed men with HAND [41]. Maraviroc has shown good antiretroviral efficacy in cells including those of monocyte/macrophage lineage and good CNS penetration and demonstrates anti-inflammatory properties. It has been recently supported as part of intensification regimes to treat HAND [41].

Clearing Targeted Cells: is the Central Nervous System Immune System Capable?

The CNS immune system is different to the rest of the body due its relative protection provided by the BBB. Immune recovery can paradoxically cause severe neurological disease. ART can indirectly cause neurotoxicity through immune reconstitution inflammatory syndrome (IRIS), caused by excessive response of the immune system to exposed antigens. Risk factors for developing IRIS include a very low CD4 count in addition to opportunistic infection (particularly JC virus, Cryptococcus and Mycobacterium Tuberculosis). HIV treatments therefore will likely require modulation of the CNS immune system [24].

There are two types of IRIS; the first type “unmasked” occurs in the context of an existing opportunistic infection and “paradoxic” where reactivation occurs without a previously diagnosed opportunistic pathogen [42]. The initiation of ART generates a prompt CNS immunological response to the pathogen, often associated with a significant inflammatory response. This is mediated by a pro-inflammatory cytokine cascade, including (interleukin [IL]-6, IL-12, TNF-α) which are elevated in the CSF [43]. It is via this accelerated neuroinflammatory mechanism, including BBB breakdown, where IRIS is believed to be implicated in the cognitive and behavioural changes seen at least in some patients with HAND [42, 44]. Although rare, approximately 1% of patients commencing ART may develop CNS-IRIS. The clinical consequences can be devastating [45].

The timing of ART commencement in the context of opportunistic infection is controversial due to the potential risk of IRIS. However, there is increasing support for the early introduction of ART in the hope of reducing the risk of AIDS-related morbidity and mortality via earlier immunologic recovery resulting in a faster clearance of the opportunistic infection [46, 47]. An exception to the above recommendation is Mycobacterium Tuberculosis infection in patients with a CD4 cell count below 100 cells/microL as well as Toxoplasmosis and cryptococcal meningitis, where ART delay by two weeks for Tuberculosis and Toxoplasmosis, and five weeks for Cryptococcus is recommended [48]. This strategy is considered to minimise risk of IRIS, other opportunistic infections and death [49, 50]. The use of corticosteroids in patients at risk of encephalitis, cerebral oedema and herniation is controversial. There is a lack of controlled trials and hence for the majority of patients, a conservative management option is preferred with close observation [51, 52]. IRIS mediated BBB inflammation may cause obstruction of CSF outflow leading to intracranial hypertension [53].

Progressive Multifocal Leukoencephalopathy (PML), caused by the JC virus, results in progressive demyelination of the CNS and is deleterious in potentiating cognitive impairment in HIV patients [54]. There are no proven efficacious treatments aside from ART and hence early treatment is recommended. In the setting of IRIS developing upon initiating ART, steroids may be required until memory T cell recovery is sufficient to arrest the JC virus [55]. Although evidence is lacking, early use of steroids may be beneficial in PML associated IRIS [55]. Ultimately, the ideal means of preventing IRIS is by “prophylactically” treating identified but subclinical or minimally clinical opportunistic infections with appropriate antimicrobial therapy (eg, Tuberculosis, Hepatitis B Virus, Pneumocystis and Cryptococcosis) for several months prior to initiation of ART [54, 56]. Patients who are receiving steroids for lengthy periods of time for IRIS should also receive prophylaxis for pneumocystis pneumonia and fungal infections, and for tuberculosis in endemic regions [42].

Neuroprotective Agents

Several drugs have been trialled as adjunctive therapy in an attempt to reduce the inflammatory response and its consequence that persists despite suppressive ART. Agents trialled include N-methyl-D-aspartate agonists, calcium channel blockers and antioxidants, which have shown minimal to no effect. Selegiline (a monoamine oxidase B inhibitor) is thought to provide neuroprotection by decreasing oxygen free radicals and increasing the production of neurotrophic factors. Previous studies with selegiline showed improvements in verbal memory and motor performance [57] however more recent studies have found no benefit [58].

Minocycline is believed to have CNS protective effects through a number of mechanisms including inhibition of apoptosis, the production of nitric oxide and subsequent oxygen free radicals. However, trials have not shown differences in markers of oxidative stress [59]. Memantine, an NMDA antagonist, has also unfortunately shown no improvement in cognitive function in a 48-week follow up study [60]. Small trials using nimodipine suggested some benefit; however, these results were inconclusive [61]. Unfortunately, no large RCTs have been performed and consequently no specific therapies with the exclusion of ART have been recommended for the routine treatment of HAND [4].

ART neurotoxicity

The significant decrease in HAD since the introduction of ART has raised little doubt that ART has been beneficial in reducing the more severe forms of HAND. However, the suggestion of poorer cognitive outcomes in some studies of high CPE regimens has prompted concerns of ART neurotoxicity [62]. There has been a relatively small focus on the potential neurotoxicity of ART to date.

Increasing evidence suggests that ART causes toxicity to neurons via depletion of mitochondrial function and production of reactive oxygen species. This notion has been supported by a small autopsy study in which HIV infected individuals with HAND were more likely to display evidence of depletion of mitochondrial DNA in the frontal cortex with subsequent oxidative damage [63]. Furthermore, chronic administration of NRTIs in mice studies has shown to decrease the mitochondrial DNA in neurons of the frontal cortex [64].

Data regarding neurotoxicity of specific first line ART agents are emerging. Of particular note is the toxicity associated with efavirenz, one of the most commonly prescribed agents. Early toxicity has been well described [65]. Additionally, long-term use has recently been associated with reduced cognitive function [66]. Antiretroviral switch studies have also shown improvement in general CNS symptoms when efavirenz is replaced with an alternative drug [67, 68]. Most other evidence regarding first line agents has come from case reports or series (see Table 1).

Neuroimaging and HAND

Several novel non-invasive magnetic resonance imaging (MRI) techniques have recently been evaluated. These extend beyond older findings on MRI T2 weighted sequences of generalised cerebral atrophy and white matter hyperintensities. They include more extensive MR spectroscopy (MRS), diffusion tensor imaging (DTI) and functional MRI (fMRI) with the more recent resting-state fMRI (RS-fMRI). Some of these imaging techniques may reflect early HIV subcortical changes over several months.

MRS detects signal amplitude of specific cerebral metabolites within defined volumes of the brain. Frequently assessed metabolites include N-acetyl aspartate (a neuronal marker), choline (marker of cellular proliferation and inflammatory response), creatine (brain energy metabolism), myoinsitol (a putative marker of gliosis) and glutamine (measures neurotoxicity due to excess NMDA receptor activation). MRS studies of HAND have found decreased N-acetyl aspartate and raised choline and myoinositol levels. These changes have been found predominantly in the frontal white matter and basal ganglia [69]. More recent MRS studies have emphasised the importance of cardiovascular risk

factors and duration of HIV infection as independent factors for neuronal injury and inflammation in HAND. Cysique et al found that cardiovascular disease risk factors were associated with lower N-acetyl aspartate in the posterior cingulate cortex and the caudate. Also noted was that an increased duration of HIV infection was associated with lower caudate N-acetyl aspartate. Greater CNS penetration of cART was associated with lower myo-inositol levels in the posterior cingulated cortex [70].

DTI provides information about the movement of water molecules along fibre tracts. Recent studies have found DTI to be superior to conventional MRI in detecting white matter abnormalities in HAND [71, 72]. DTI may also be able to predict the severity of HAND [73-75]. Abnormalities in DTI have also shown to be reversible following ART, with improvement in the mean, axial and radial diffusivity of the corpus callosum and centrum semiovale of 21 patients over a six month period. These findings further support a potential future role of DTI in the diagnosis and monitoring of HAND [76].

Functional MRI has shown to be sensitive in detecting mild cognitive abnormalities [77]. Recent research has found decreased blood flow and volume in patients with HAND, correlating with the severity of disease [78]. The more recent technique, RS-fMRI, measures low frequency fluctuations in the blood oxygenation level dependent signal at resting state (as opposed to task driven changes) to explore the functional architecture of the brain. RS-fMRI has identified various spatially distinct but functionally related areas of the brain. A recent cross-sectional study by Ann et al found significant differences in the fMRI patterns of HIV patients with HAND compared to HIV patients without HAND. Specifically, these changes were identified between the precuneus and prefrontal cortex [79]. The study however was limited by its small sample size and use of only male participants. Further studies are required to evaluate the potential role of RS-fMRI in HAND.

Cerebrovascular Disease

Since the introduction of ART there has been a significant reduction in HAD but not in the milder forms of HAND. This apparent therapeutic paradox has prompted investigation into other potential underlying causes. Recent research has looked towards vascular disease as a possible explanation. Specific ART regimens have been found to increase the risk of cerebrovascular disease (CVD) both directly, and indirectly, through increasing CVD risk factors including diabetes, hypertension and hyperlipidaemia [80-82]. This risk is particularly increased in those treated for long periods [83, 84]. In HIV un-infected patients, MRI detected white matter hyperintensities are believed to reflect ischaemia and have been associated with cognitive impairment (85). A recent study by Su et al found that periventricular MRI white matter hyperintensities were more extensive in HIV-infected men compared to un-infected controls and the extent of white matter hyperintensities correlated with the degree of cognitive impairment [86]. These findings are consistent with other research of HAND in the ART era [87] and provide support for the optimisation of cardiovascular risk factors in HIV infected patients. The conclusions of Su et al however were made through inference that white matter hyperintensities accurately reflect the burden of CVD. Further studies are warranted to further elucidate the role of CVD in HAND.

Future Directions

A major barrier to HAND cure is the persistence of latently infected cells within the CNS. Recent studies have focused attention on latency reversing agents (LRAs) including histone deacetylase inhibitors, which aim to eliminate the obstacle of latency by stimulating transcription of dormant cells. The long terminal repeat sequences of CNS virus are believed to contain specific mutations, which allow the virus to remain latent. This has opened the door to potential targeted therapies [21]. However, eradication through a "shock and kill" strategy has the potential to induce robust inflammation with consequent brain damage [11]. Future studies will need to employ other techniques.

In recent years, attention has been directed towards nanotechnology, including nanoparticles, as a technique to deliver ARVs across the BBB. Nanoparticles offer a number of desirable properties including versatility, small controllable size, large surface area to volume ratio and hydrophobicity [88]. Nanoparticles may ameliorate some of the limitations of cART, through improved toxicity profiles, selective drug delivery, increased drug stability and optimised drug distribution [89]. Although many novel nanotherapeutic techniques have been proposed, very few have reached clinical trials and it will likely take some time before the full potential of nanotechnology in HIV is realised.

Conclusion

This review has highlighted current barriers to HIV cure strategies and interventions for neurocognitive dysfunction. Recent studies continue to provide an improved understanding of the complex interaction of the CNS as a viral reservoir and its implications in HIV eradication. Developments in diagnostic imaging with diffusion tensor imaging as well as resting-state fMRI show promise in future diagnosis and monitoring of HAND. Improved HIV disease control due to cART has rendered neurocognitive management with a promising yet challenging outlook, balancing the effects of ART related neurotoxicity, optimising BBB penetration and CNS activity as well as managing the evolving risk of cerebrovascular disease. Future research in HAND is advancing with the development of LRAs as well as potential nanotechnology, improving CNS ART delivery.

Table 1: Neurotoxicity of Individual Anti-Retroviral Therapy

Drug class	Drug name	CPE score	CNS adverse effects
NNRTIs	Efavirenz	3	Neuropsychiatric symptoms including hallucinations, mood changes and delusions. Neurocognitive impairment [65]
	Rilpivirine	3	No reports to date
	Nevirapine	4	Behavioural and mood changes. Vivid dreams [90]
	Etravirine	2	Headache. Also associated with peripheral neuropathy [91]
NRTIs	Tenofovir	1	Neuropsychiatric symptoms [92]
	Abacavir	3	Neuropsychiatric symptoms, headache [93]
	Emtricitabine	3	Neuropsychiatric symptoms, headache [94]
	Lamivudine	2	No reports to date
	Zidovudine	4	Headache, mood disturbance, dizziness [95]
Protease inhibitors (with ritonavir)	Darunavir	3	Headache [96]
	Indinavir	3	Headache, insomnia, dizziness, mood disturbance [96]
	Atazanavir	2	Headache and mood disturbance [97]
Integrase inhibitors	Raltegravir	3	Headache and neuropsychiatric symptoms including psychosis, nightmares, insomnia [98]
	Dolutegravir	4	Altered mood and insomnia [99]
	Elvitegravir	2	No reports to date
Entry inhibitors	Maraviroc	3	No reports to date
Fusion inhibitors	Enfuviritide	1	Headache, dizziness, taste disturbance. Also associated with peripheral neuropathy [100]

References

1. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69(18):1789-99.
2. Gisslen M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? BMC infectious diseases. 2011;11:356.
3. 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(23):2087-96.
4. Lescure FX, Omland LH, Engsig FN, Roed C, Gerstoft J, Pialoux G, et al. Incidence and impact on mortality of severe neurocognitive disorders in persons with and without HIV infection: a Danish nationwide cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52(2):235-43.
5. Cysique LA, Brew BJ. Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. Journal of neurovirology. 2011;17(2):176-83.
6. Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. Aids. 2010;24(9):1243-50.
7. Grant I, Franklin DR, Jr., Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014;82(23):2055-62.
8. Eisele E, Siliciano RF. Redefining the viral reservoirs that prevent HIV-1 eradication. Immunity. 2012;37(3):377-88.
9. Davis LE, Hjelle BL, Miller VE, Palmer DL, Llewellyn AL, Merlin TL, et al. Early viral brain invasion in iatrogenic human immunodeficiency virus infection. Neurology. 1992;42(9):1736-9.
10. Liu NQ, Lossinsky AS, Popik W, Li X, Gujuluva C, Kriederman B, et al. Human immunodeficiency virus type 1 enters brain microvascular endothelia by macropinocytosis dependent on lipid rafts and the mitogen-activated protein kinase signaling pathway. Journal of virology. 2002;76(13):6689-700.
11. Brew BJ, Gray L, Lewin S, Churchill M. Is specific HIV eradication from the brain possible or needed? Expert opinion on biological therapy. 2013;13(3):403-9.
12. Blankson JN, Persaud D, Siliciano RF. The challenge of viral reservoirs in HIV-1 infection. Annual review of medicine. 2002;53:557-93.
13. Gray LR, Roche M, Flynn JK, Wesselingh SL, Gorry PR, Churchill MJ. Is the central nervous system a reservoir of HIV-1? Current opinion in HIV and AIDS. 2014;9(6):552-8.
14. Churchill MJ, Gorry PR, Cowley D, Lal L, Sonza S, Purcell DF, et al. Use of laser capture microdissection to detect integrated HIV-1 DNA in macrophages and astrocytes from autopsy brain tissues. Journal of neurovirology. 2006;12(2):146-52.
15. Thompson KA, Cherry CL, Bell JE, McLean CA. Brain cell reservoirs of latent virus in presymptomatic HIV-infected individuals. The American journal of pathology. 2011;179(4):1623-9.
16. Koppensteiner H, Brack-Werner R, Schindler M. Macrophages and their relevance in Human Immunodeficiency Virus Type I infection. Retrovirology. 2012;9:82.
17. Colodner KJ, Montana RA, Anthony DC, Folkerth RD, De Girolami U, Feany MB. Proliferative potential of human astrocytes. Journal of neuropathology and experimental neurology. 2005;64(2):163-9.
18. Soulet D, Rivest S. Bone-marrow-derived microglia: myth or reality? Current opinion in pharmacology. 2008;8(4):508-18.

19. Churchill MJ, Wesselingh SL, Cowley D, Pardo CA, McArthur JC, Brew BJ, et al. Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. Annals of neurology. 2009;66(2):253-8.
20. Eden A, Fuchs D, Hagberg L, Nilsson S, Spudich S, Svennerholm B, et al. HIV-1 viral escape in cerebrospinal fluid of subjects on suppressive antiretroviral treatment. The Journal of infectious diseases. 2010;202(12):1819-25.
21. Gray LR, Cowley D, Welsh C, Lu HK, Brew BJ, Lewin SR, et al. CNS-specific regulatory elements in brain-derived HIV-1 strains affect responses to latency-reversing agents with implications for cure strategies. Molecular psychiatry. 2016;21(4):574-84.
22. Gorry PR, Ong C, Thorpe J, Bannwarth S, Thompson KA, Gatignol A, et al. Astrocyte infection by HIV-1: mechanisms of restricted virus replication, and role in the pathogenesis of HIV-1-associated dementia. Current HIV research. 2003;1(4):463-73.
23. Carroll-Anzinger D, Al-Harthi L. Gamma interferon primes productive human immunodeficiency virus infection in astrocytes. Journal of virology. 2006;80(1):541-4.
24. Gray LR, Brew BJ, Churchill MJ. Strategies to target HIV-1 in the central nervous system. Current opinion in HIV and AIDS. 2016;11(4):371-5.
25. Gama L, Abreu CM, Shirk EN, Price SL, Li M, Laird GM, et al. Reactivation of SIV reservoirs in the brain of virally suppressed macaques. Aids. 2016.
26. Eugenin EA, Clements JE, Zink MC, Berman JW. Human immunodeficiency virus infection of human astrocytes disrupts blood-brain barrier integrity by a gap junction-dependent mechanism. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011;31(26):9456-65.
27. Eugenin EA, Berman JW. Cytochrome C dysregulation induced by HIV infection of astrocytes results in bystander apoptosis of uninfected astrocytes by an IP3 and calcium-dependent mechanism. Journal of neurochemistry. 2013;127(5):644-51.
28. Norgren N, Rosengren L, Stigbrand T. Elevated neurofilament levels in neurological diseases. Brain research. 2003;987(1):25-31.
29. Jessen Krut J, Mellberg T, Price RW, Hagberg L, Fuchs D, Rosengren L, et al. Biomarker evidence of axonal injury in neuroasymptomatic HIV-1 patients. PloS one. 2014;9(2):e88591.
30. Desplats P, Dumaop W, Smith D, Adame A, Everall I, Letendre S, et al. Molecular and pathologic insights from latent HIV-1 infection in the human brain. Neurology. 2013;80(15):1415-23.
31. Nabha L, Duong L, Timpone J. HIV-associated neurocognitive disorders: perspective on management strategies. Drugs. 2013;73(9):893-905.
32. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Archives of neurology. 2008;65(1):65-70.
33. Cusini A, Vernazza PL, Yerly S, Decosterd LA, Ledergerber B, Fux CA, et al. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. Journal of acquired immune deficiency syndromes. 2013;62(1):28-35.
34. Ellis RJ, Letendre S, Vaida F, Haubrich R, Heaton RK, Sacktor N, et al. Randomized trial of central nervous system-targeted antiretrovirals for HIV-associated neurocognitive disorder. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;58(7):1015-22.
35. Brew BJ, Letendre SL. Biomarkers of HIV related central nervous system disease. International review of psychiatry. 2008;20(1):73-88.
36. Gray LR, Tachedjian G, Ellett AM, Roche MJ, Cheng WJ, Guillemin GJ, et al. The NRTIs lamivudine, stavudine and zidovudine have reduced HIV-1 inhibitory activity in astrocytes. PloS one. 2013;8(4):e62196.

37. Ene L, Duiculescu D, Ruta SM. How much do antiretroviral drugs penetrate into the central nervous system? Journal of medicine and life. 2011;4(4):432-9.
38. Chen LF, Hoy J, Lewin SR. Ten years of highly active antiretroviral therapy for HIV infection. The Medical journal of Australia. 2007;186(3):146-51.
39. Gimenez F, Fernandez C, Mabondzo A. Transport of HIV protease inhibitors through the blood-brain barrier and interactions with the efflux proteins, P-glycoprotein and multidrug resistance proteins. Journal of acquired immune deficiency syndromes. 2004;36(2):649-58.
40. Letendre SL, Mills AM, Tashima KT, Thomas DA, Min SS, Chen S, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(7):1032-7.
41. Gates TM, Cysique LA, Siefried KJ, Chaganti J, Moffat KJ, Brew BJ. Maraviroc-intensified combined antiretroviral therapy improves cognition in virally suppressed HIV-associated neurocognitive disorder. Aids. 2016;30(4):591-600.
42. Nath A. Neurologic Complications of Human Immunodeficiency Virus Infection. Continuum. 2015;21(6 Neuroinfectious Disease):1557-76.
43. Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. Hiv/Aids. 2015;7:49-64.
44. Hong S, Banks WA. Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. Brain, behavior, and immunity. 2015;45:1-12.
45. McCombe JA, Auer RN, Maingat FG, Houston S, Gill MJ, Power C. Neurologic immune reconstitution inflammatory syndrome in HIV/AIDS: outcome and epidemiology. Neurology. 2009;72(9):835-41.
46. Grant PM, Komarow L, Andersen J, Sereti I, Pahwa S, Lederman MM, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. PloS one. 2010;5(7):e11416.
47. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PloS one. 2009;4(5):e5575.
48. Boulware DR, Meya DB, Muzoora C, Rolfes MA, Huppler Hullsiek K, Musubire A, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. The New England journal of medicine. 2014;370(26):2487-98.
49. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. The Journal of infectious diseases. 2004;190(9):1670-6.
50. Burman WJ. Issues in the management of HIV-related tuberculosis. Clinics in chest medicine. 2005;26(2):283-94, vi-vii.
51. Johnson T, Nath A. Immune reconstitution inflammatory syndrome and the central nervous system. Current opinion in neurology. 2011;24(3):284-90.
52. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. Aids. 2008;22(5):601-10.
53. Venkataramana A, Pardo CA, McArthur JC, Kerr DA, Irani DN, Griffin JW, et al. Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients. Neurology. 2006;67(3):383-8.
54. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukeoncephalopathy C. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Therapeutic advances in neurological disorders. 2015;8(6):255-73.
55. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. Neurology. 2009;72(17):1458-64.

56. Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;58(9):1308-11.
57. Sacktor N, Schifitto G, McDermott MP, Marder K, McArthur JC, Kieburtz K. Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study. Neurology. 2000;54(1):233-5.
58. Schifitto G, Yiannoutsos CT, Ernst T, Navia BA, Nath A, Sacktor N, et al. Selegiline and oxidative stress in HIV-associated cognitive impairment. Neurology. 2009;73(23):1975-81.
59. Sacktor N, Miyahara S, Evans S, Schifitto G, Cohen B, Haughey N, et al. Impact of minocycline on cerebrospinal fluid markers of oxidative stress, neuronal injury, and inflammation in HIV-seropositive individuals with cognitive impairment. Journal of neurovirology. 2014;20(6):620-6.
60. Zhao Y, Navia BA, Marra CM, Singer EJ, Chang L, Berger J, et al. Memantine for AIDS dementia complex: open-label report of ACTG 301. HIV clinical trials. 2010;11(1):59-67.
61. Navia BA, Dafni U, Simpson D, Tucker T, Singer E, McArthur JC, et al. A phase I/II trial of nimodipine for HIV-related neurologic complications. Neurology. 1998;51(1):221-8.
62. Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. Aids. 2009;23(11):1359-66.
63. Zhang Y, Wang M, Li H, Zhang H, Shi Y, Wei F, et al. Accumulation of nuclear and mitochondrial DNA damage in the frontal cortex cells of patients with HIV-associated neurocognitive disorders. Brain research. 2012;1458:1-11.
64. Zhang Y, Song F, Gao Z, Ding W, Qiao L, Yang S, et al. Long-term exposure of mice to nucleoside analogues disrupts mitochondrial DNA maintenance in cortical neurons. PloS one. 2014;9(1):e85637.
65. Decloedt EH, Maartens G. Neuronal toxicity of efavirenz: a systematic review. Expert opinion on drug safety. 2013;12(6):841-6.
66. Ma Q, Vaida F, Wong J, Sanders CA, Kao YT, Croteau D, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. Journal of neurovirology. 2016;22(2):170-8.
67. Waters L, Fisher M, Winston A, Higgs C, Hadley W, Garvey L, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. Aids. 2011;25(1):65-71.
68. Nguyen A, Calmy A, Delhumeau C, Mercier I, Cavassini M, Mello AF, et al. A randomized cross-over study to compare raltegravir and efavirenz (SWITCH-ER study). Aids. 2011;25(12):1481-7.
69. Brew BJ, Chan P. Update on HIV dementia and HIV-associated neurocognitive disorders. Current neurology and neuroscience reports. 2014;14(8):468.
70. Cysique LA, Moffat K, Moore DM, Lane TA, Davies NW, Carr A, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. PloS one. 2013;8(4):e61738.
71. Filippi CG, Ulug AM, Ryan E, Ferrando SJ, van Gorp W. Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. AJNR American journal of neuroradiology. 2001;22(2):277-83.
72. Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Kemper CA, Deresinski S, Sullivan EV. Frontostriatal fiber bundle compromise in HIV infection without dementia. Aids. 2009;23(15):1977-85.

73. Wu Y, Storey P, Cohen BA, Epstein LG, Edelman RR, Ragin AB. Diffusion alterations in corpus callosum of patients with HIV. AJNR American journal of neuroradiology. 2006;27(3):656-60.
74. Chen Y, An H, Zhu H, Stone T, Smith JK, Hall C, et al. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. NeuroImage. 2009;47(4):1154-62.
75. Zhu T, Zhong J, Hu R, Tivarus M, Ekholm S, Harezlak J, et al. Patterns of white matter injury in HIV infection after partial immune reconstitution: a DTI tract-based spatial statistics study. Journal of neurovirology. 2013;19(1):10-23.
76. Wright PW, Heaps JM, Shimony JS, Thomas JB, Ances BM. The effects of HIV and combination antiretroviral therapy on white matter integrity. Aids. 2012;26(12):1501-8.
77. Melrose RJ, Tinaz S, Castelo JM, Courtney MG, Stern CE. Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. Behavioural brain research. 2008;188(2):337-47.
78. Ances BM, Roc AC, Wang J, Korczykowski M, Okawa J, Stern J, et al. Caudate blood flow and volume are reduced in HIV+ neurocognitively impaired patients. Neurology. 2006;66(6):862-6.
79. Ann HW, Jun S, Shin NY, Han S, Ahn JY, Ahn MY, et al. Characteristics of Resting-State Functional Connectivity in HIV-Associated Neurocognitive Disorder. PloS one. 2016;11(4):e0153493.
80. Erratum: Incidence, morbidity, mortality, and prevalence of diabetes in Denmark, 2000-2011: results from the Diabetes Impact Study 2013 [Corrigendum]. Clinical epidemiology. 2016;8:7.
81. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. The Journal of infectious diseases. 2010;201(3):318-30.
82. Grunfeld C. Dyslipidemia and its Treatment in HIV Infection. Topics in HIV medicine : a publication of the International AIDS Society, USA. 2010;18(3):112-8.
83. Zanni MV, Schouten J, Grinspoon SK, Reiss P. Risk of coronary heart disease in patients with HIV infection. Nature reviews Cardiology. 2014;11(12):728-41.
84. Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;59(12):1787-97.
85. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology. 2010;9(7):689-701.
86. Su T, Wit FW, Caan MW, Schouten J, Prins M, Geurtsen GJ, et al. White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy. Aids. 2016;30(15):2329-39.
87. Wright EJ, Grund B, Robertson K, Brew BJ, Roediger M, Bain MP, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. Neurology. 2010;75(10):864-73.
88. Edagwa BJ, Zhou T, McMillan JM, Liu XM, Gendelman HE. Development of HIV reservoir targeted long acting nanoformulated antiretroviral therapies. Current medicinal chemistry. 2014;21(36):4186-98.
89. Roy U, Rodriguez J, Barber P, das Neves J, Sarmento B, Nair M. The potential of HIV-1 nanotherapeutics: from in vitro studies to clinical trials. Nanomedicine. 2015;10(24):3597-609.
90. Morlese JF, Qazi NA, Gazzard BG, Nelson MR. Nevirapine-induced neuropsychiatric complications, a class effect of non-nucleoside reverse transcriptase inhibitors? Aids. 2002;16(13):1840-1.

91. Katlama C, Clotet B, Mills A, Trottier B, Molina JM, Grinsztejn B, et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. Antiviral therapy. 2010;15(7):1045-52.
92. Allavena C, Le Moal G, Michau C, Chiffoleau A, Raffi F. Neuropsychiatric adverse events after switching from an antiretroviral regimen containing efavirenz without tenofovir to an efavirenz regimen containing tenofovir: a report of nine cases. Antiviral therapy. 2006;11(2):263-5.
93. Foster R, Taylor C, Everall IP. More on abacavir-induced neuropsychiatric reactions. Aids. 2004;18(18):2449.
94. Benson CA, van der Horst C, Lamarca A, Haas DW, McDonald CK, Steinhart CR, et al. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. Aids. 2004;18(17):2269-76.
95. Fischl MA, Richman DD, Hansen N, Collier AC, Carey JT, Para MF, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. A double-blind, placebo-controlled trial. The AIDS Clinical Trials Group. Annals of internal medicine. 1990;112(10):727-37.
96. Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet. 2007;370(9581):49-58.
97. Rutstein RM, Samson P, Fenton T, Fletcher CV, Kiser JJ, Mofenson LM, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the Pediatric AIDS Clinical Trials Group Protocol 1020A. The Pediatric infectious disease journal. 2015;34(2):162-7.
98. Steigbigel RT, Cooper DA, Teppler H, Eron JJ, Gatell JM, Kumar PN, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50(4):605-12.
99. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381(9868):735-43.
100. Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. The New England journal of medicine. 2003;348(22):2175-85.

Special Mention References

**Gray 2014. Is the CNS a reservoir of HIV?

This review summarised the evidence supporting the CNS as a reservoir of HIV

**Gray LR, Cowley D, Welsh C, Lu HK, Brew BJ, Lewin SR, et al. CNS-specific regulatory elements in brain-derived HIV-1 strains affect responses to latency-reversing agents with implications for cure strategies. Molecular psychiatry. 2016;21(4):574-84.

This article demonstrated the unique transcriptional regulatory mechanisms of CNS HIV and the implications of latency reversing agents for HIV cure.

**Gray LR, Tachedjian G, Ellett AM, Roche MJ, Cheng WJ, Guillemin GJ, et al. The NRTIs lamivudine, stavudine and zidovudine have reduced HIV-1 inhibitory activity in astrocytes. PloS one. 2013;8(4):e62196.

This article showed that lamivudine, stavudine and zidovudine had insufficent inhibiotr activity against HIV in astrocytes.

**Eugenin EA, Berman JW. Cytochrome C dysregulation induced by HIV infection of astrocytes results in bystander apoptosis of uninfected astrocytes by an IP3 and calcium-dependent mechanism. Journal of neurochemistry. 2013;127(5):644-51.

This article proposed that astrocyte related disruption of the BBB may contribute to the formation of the CNS viral reservoir.

*Jessen Krut J, Mellberg T, Price RW, Hagberg L, Fuchs D, Rosengren L, et al. Biomarker evidence of axonal injury in neuroasymptomatic HIV-1 patients. PloS one. 2014;9(2):e88591.

This article showed that CSF levels of NFL are significantly increased in HIV dementia patients and decrease with the commencement of ART.

**Desplats P, Dumaop W, Smith D, Adame A, Everall I, Letendre S, et al. Molecular and pathologic insights from latent HIV-1 infection in the human brain. Neurology. 2013;80(15):1415-23.

This article revealed the potential of BCL11B as a biomarker of latent disease.

*Brew BJ, Chan P. Update on HIV dementia and HIV-associated neurocognitive disorders. Current neurology and neuroscience reports. 2014;14(8):468.

This review article discussed the potential of MRS studies in diagnosing HAND.

**Cysique LA, Moffat K, Moore DM, Lane TA, Davies NW, Carr A, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. PloS one. 2013;8(4):e61738.

This article demonstrated the significance of cardiovascular risk factors and age as independent factors for neuronal injury.

*Su T, Wit FW, Caan MW, Schouten J, Prins M, Geurtsen GJ, et al. White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy. Aids. 2016;30(15):2329-39.

This study found that the degree of periventricular MRI white matter hyperintensities correlated with degree of cognitive impairment.