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Neurotoxicity in the Post-HAART Era: Caution for the Antiretroviral Therapeutics

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Abstract

Despite the advent of highly active antiretroviral therapy (HAART), HIV-associated neurological disorders (HAND) remain a major challenge in human immunodeficiency virus (HIV) treatment. The early implementation of HAART in the infected individuals helps suppress the viral replication in the plasma and other compartments. Several studies also report the beneficial effect of drugs that successfully penetrate central nervous system (CNS). However, recent data in both clinical setup and in in vitro studies indicate CNS toxicity of the antiretrovirals (ARVs). Although the evidence is limited, correlation between prolonged use of ARVs and neurotoxicity strongly suggests that it is essential to study the underlying mechanisms responsible for such toxicity. Furthermore, closer attention toward clinical outcomes is required to screen various ARV regimens for their association with HAND and other comorbidities. A growing body of literature also indicates a possible role of accelerated aging in the antiretroviral therapy-associated neurotoxicity. Lastly, owing to high pill burden, multiple drugs in the HIV treatment also invite a possible role of drug–drug interaction via various cytochrome P450 enzymes. The particular emphasis of this review is to highlight the need to identify alternative approaches in reducing the CNS toxicity of the ARV drugs in HIV-infected individuals.

Keywords

HIV; Antiretroviral therapy; Neurotoxicity; Brain; HIV-associated neurocognitive disorder; CYP450

Introduction

According to World Health Organization (WHO), there are 36.9 million individuals currently living with human immunodeficiency virus (HIV) worldwide (AIDS by the numbers 2015 2015). Although a majority of these individuals belong to sub-Saharan Africa, the prevalence of HIV in North America is also significantly high. In recent years, the

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occurrence rate of new HIV infections has declined, particularly in developed countries, where the anti-HIV treatment is both affordable and easily accessible. Once considered a death sentence, it is now generally accepted that HIV can be classified as a chronic condition, which can be managed by the effective use of ARV drugs. The advent of antiretroviral therapy (ART) has been a blessing for the individuals, suffering from this dreadful virus. In spite of the fact that there is no cure for HIV infection, the virus replication can be suppressed with the proper use of ARV drugs, allowing the infected individuals to have longer life span. However, due to a variety of factors, complications associated with HIV and its treatment significantly affect the quality of life of those on ARV medications, in spite of cautious use of antiretrovirals (ARVs).

In addition to affecting the immune system of the host, HIV can also affect the central nervous system (CNS). The infiltration of the virus into CNS occurs rapidly after the infection; therefore, the function of the resident cells in the brain such as microglia and astrocytes is compromised, leading to various CNS complications. Neurons are refractory to viral infection, but HIV proteins secreted by virus-infected cells are known to induce neuronal toxicity (Kaul 2008; Rumbaugh and Nath 2006), and therefore, cognitive and executive functions of infected individual are affected (Watkins and Treisman 2015). It has been reported that almost half of the HIV-infected individuals also develop various forms of HIV-associated neurological disorders (HAND) (Heaton et al. 2010). Clinical use of the term HAND refers to a series of disorders that comprise asymptomatic neurocognitive impairment (ANI), minor cognitive motor disorder (MCMD), or the most severe form, HIV-associated dementia (HAD) (Antinori et al. 2007). Thus, despite the success of highly active antiretroviral therapy (HAART), the neurotoxicity associated with HIV still presents a challenge in the treatment of HIV-infected individuals.

In general, the use of HAART has been beneficial to suppress the HIV-1 viral loads in the periphery and in the CNS. However, the use of HAART does not prevent the occurrence of HAND. On the contrary, studies have reported that mild to moderate neurocognitive manifestations of HIV infection persist in about 40 % of patients who are already on treatment (Heaton et al. 2010; Sacktor et al. 2002; Simioni et al. 2010; Villa et al. 1996). As a result, several efforts have been redirected to improve the bioavailability of the ARVs across the blood–brain barrier (BBB) (Bressani et al. 2011; Mahajan et al. 2010).

Although the brain acts mostly as a reservoir for HIV-1, the astrocytes and microglia demonstrate a low level of HIV-1 replication in the presence of combination antiretroviral therapy (cART) (Palmer et al. 2008). This warrants more attention toward the management of HIV replication in the brain. In addition, peripheral toxicity of several ARVs has been reported (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2016), which implies a possibility that antiretroviral drugs themselves contribute to the CNS toxicity. The continuous use of these drugs for a prolonged time may contribute to the persistence of HAND in the post-HAART era. The underlying mechanisms of HAND could involve the combined effect of multiple factors such as drugs of abuse, HIV proteins and ARV drugs. In this review, we will focus primarily on the neurotoxicity associated with antiretroviral drugs and their implications in the HAND.

Classes of Antiretroviral Drugs: CNS Toxicity

The treatment of HIV infection is effectively approached from various directions by targeting key steps in the viral replication cycle. In general, the life cycle of HIV can be divided into 5 steps: (1) attachment and entry, (2) reverse transcription, (3) integration, (4) proteolytic processing and (5) release. Due to the frequent occurrence of drug resistance in the ARV therapy, HIV-infected individuals are typically prescribed multiple drugs that target more than one of these aforementioned steps. While this approach has been effective in hampering viral replication leading to reduced mortality and morbidity rates, the use of multiple drugs also invites a myriad of toxicity. Moreover, the neurotoxicity of these drugs is highly variable depending on the class of the drug and individual drugs within each class. Since the basic pharmacology and clinical therapeutics of these drugs have been extensively discussed in the past, we will focus on the toxicity aspects for the purpose of this review. In addition, a few reviews are available that highlight the side effects of ARV drugs (Abers et al. 2013) and their impact on neuropsychological function (Cysique and Brew 2009). The following section covers overview of CNS toxicity associated with various classes, which are further discussed in the different sections. In this review, we refer to antiretroviral drugs as ARVs and combination of ARV therapy regimens as cART, which is often interchangeably addressed as HAART.

Viral Entry Inhibitors

There are two entry inhibitors that are approved by FDA for HIV treatment: (1) maraviroc, which prevents the attachment of the virus to the host cell by preventing the binding of the HIV-1 gp120 with C–C chemokine co-receptor type 5 (CCR5), and (2) enfuvirtide, which prevents the fusion of the virus with the host cell by preventing conformational changes in gp41. There is no evidence so far indicating maraviroc-associated neurotoxicity. However, some early reports indicated that enfuvirtide could be associated with sensory neuropathy. As per T-20 (enfuvirtide) versus optimized regimen only (TORO1) study, a small number of patients (11 %) on enfuvirtide demonstrated a higher prevalence of neuropathy (Fung and Guo 2004; Lalezari et al. 2003), whereas the follow-up TORO2 study did not report similar observations (Fung and Guo 2004; Lazzarin et al. 2003). Another study carried out using 14 patients, supported the observations of TORO2 study and concluded that enfuvirtide did not induce any sensory neuropathy (Cherry et al. 2008). Despite a few early reports, there is currently no conclusive evidence for neurotoxicity of the entry inhibitors maraviroc or enfuvirtide. Of note, so far all tested C-X-C chemokine receptor type 4 (CXCR4) inhibitors have failed clinical trials due to toxicity in the periphery.

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Once the virus enters into the host cell, the genomic RNA of the virus is converted into cDNA with the help of a viral enzyme, reverse transcriptase. The drugs acting on reverse transcriptase are classified into two subcategories depending on whether or not they are analogs of nucleoside/nucleotides. The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are mainly associated with peripheral neuropathy to variable extents. The primary underlying mechanism for peripheral neuropathy involves inhibition of mitochondrial DNA (mtDNA), polymerase γ, which results in depletion of mtDNA in axons, and Schwann cells

(Dalakas et al. 2001). High occurrence of peripheral neuropathy is observed with didanosine, stavudine and zalcitabine as compared to other drugs in this class (Dragovic and Jevtovic 2003; Venhoff et al. 2010). In contrast, zidovudine, emtricitabine, lamivudine, tenofovir and abacavir are considered non-neurotoxic drugs. A few studies have reported that zidovudine produced serious psychiatric symptoms including mania, hallucinations and psychosis (Cespedes and Aberg 2006; Maxwell et al. 1988; Schaerf et al. 1988; Venhoff et al. 2010), but the underlying mechanisms are unclear and may need further investigations. More recently, various NRTIs were shown to be neurotoxic in human dorsal root ganglia (DRG) (Robinson et al. 2007). Overall, the neurotoxicity of NRTIs is highly tissue/cell specific and CNS toxicity other than peripheral neuropathy is rather rare.

Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)

An alternative class of drugs that targets HIV reverse transcriptase is non-nucleoside reverse transcriptase inhibitors (NNRTIs). As the name suggests, the NNRTIs do not resemble the nucleosides/nucleotides and therefore their mechanism of action is significantly different from that of the NRTIs. Among various drugs of this class, nevirapine and efavirenz have been mainly known to cause neuropsychiatric adverse effects. In spite of being one of the safest antiretroviral drugs, patients taking nevirapine develop symptoms such as hallucinations, delusion, mood changes, vivid dreams and depression (Morlese et al. 2002; Schaerf et al. 1988; Wise et al. 2002). A recent study reported that switching to nevirapine from drug regimens that cause neuropsychiatric symptoms (i.e., efavirenz primarily) effectively reduced the occurrence of the psychiatric episodes (Pedrol et al. 2015), suggesting that neurotoxicity of nevirapine may be less severe as compared to other drugs used in the study.

Several studies have demonstrated CNS toxicity associated with efavirenz, which includes psychiatric symptoms among more than 50 % of the patients. Among various symptoms, vivid dreams and hallucinations are classical side effects associated with efavirenz. The CNS toxicity of efavirenz has been studied in various systems, which suggest that an increase in proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β or attenuated creatine kinase levels in the brain could be underlying mechanisms (O'Mahony et al. 2005; Streck et al. 2008). It is likely that CYP2B6 genotype may affect the concentrations of efavirenz in the brain, which could produce CNS toxicity (Gatanaga et al. 2007). Another study demonstrated a possible role for mitochondrial toxicity, autophagy and endoplasmic reticulum (ER) stress in efavirenz-mediated CNS toxicity (Blas-Garcia et al. 2014). Unlike nevirapine and efavirenz, the other NNRTIs such as etravirine, rilpivirine and delavirdine do not demonstrate significant CNS toxicity. However, a recent study indicated that etravirine reduced microtubule-associated protein 2 (MAP-2) intensity in cultured rat neurons suggesting moderate neurotoxicity of etravirine (Robertson et al. 2012).

Protease Inhibitors (PI)

HIV protease serves as an essential enzyme in the processing and maturation of various viral proteins. The drugs falling into PIs category serve an important approach in circumventing HIV viral replication and thereby rendering the virus non-functional. Boosted monotherapy with only protease inhibitors has been suggested to carry more advantages over cART for

viral suppression (Perez-Valero et al. 2011). The current guidelines for ARV regimen recommend PI-based therapy as a first-line approach (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2016). However, patients on PIs also demonstrate various neurotoxicities that demand close attention toward the underlying mechanisms. Almost all of the PI drugs are metabolized via CYP450 enzymes, which increases the risk of drug–drug interactions. Several studies have indicated that PIs could potentiate neuropathy associated with NRTIs (Ellis et al. 2008; Pettersen et al. 2006). Since drug availability is highly variable, neurotoxicity associated with PIs is mostly pronounced in combination treatments as compared to individual PIs. For example, ritonavir shows the highest neurotoxicity as compared to other PIs (Bonfanti et al. 2000). Similarly, a lopinavir–ritonavir combination has been shown to impair neurocognitive behavior in mice (Gupta et al. 2012). Other studies demonstrate neurotoxicity with indinavir, amprenavir and atazanavir (James et al. 2002; Pettersen et al. 2006; Robertson et al. 2012; Vivithanaporn et al. 2016).

Integrase Strand Transfer Inhibitors (INSTI)

Ever since the first Food and Drug Administration (FDA)-approved drug in 2007, integrase inhibitors have been clinically proven to be effective ARV drugs, which have placed the integrase-based ARV regimen as the first-line approach. However, several reports have recently emerged indicating CNS toxicity associated with drugs belonging to this class. For example, raltegravir was found to produce neuropsychiatric symptoms such as psychosis, insomnia and nightmares (Harris et al. 2008; Teppler et al. 2011). Another integrase inhibitor, elvitegravir, was reported to induce adverse psychiatric symptoms in a few patients in a randomized trial study (Cohen et al. 2011).

Considering the recent advancement in the antiretroviral therapeutics and their side effects, it is plausible to conclude that cART may be involved in producing impairments in cognitive function and neurodeficiency. Therefore, their efficacy in the CNS should be closely monitored to reduce the incidents of HAND among patients who are treated with HAART for a long time.

CNS Penetration Effectiveness (CPE) and HAND

In the recent years, the knowledge on pharmacokinetics of various ARVs in the cerebrospinal fluid (CSF) has greatly increased. Based on the concentrations of various ARVs in plasma and CSF, CPE rankings are assigned to each drug, which represents the ratios of drug concentration in the CNS to that in the plasma (Letendre 2011; Letendre et al. 2010). The CPE score of a combination therapy is calculated by adding individual CPE scores, which provides estimated effectiveness of the cART. It is generally assumed that cART with a higher CPE score shows greater viral suppression as indicated by viral RNA copies in CSF. A comprehensive review by Eisfeld and colleagues summarized these findings to discuss the effect of CPE in regard to their clinical outcomes (Eisfeld et al. 2012). Therefore, patients on cART with higher CPE scores could benefit from higher bioavailability of these drugs in brain, which can control HIV replication. A few studies support the above notion, and HIV-1-infected individuals with HAND clearly exhibit better

neurocognitive performance if they are on cART regimen with higher combined CPE scores (Carvalhal et al. 2015; Eisfeld et al. 2013; Smurzynski et al. 2011). However, contrasting observations were reported in another study, which suggested that patients on a higher CPE regimen demonstrated poorer neurocognitive outcomes (Marra et al. 2009). The positive correlation between higher CPE and HAND has been established in yet another study by Caniglia and colleagues, which demonstrated a risk assessment profile in antiretroviral therapy naïve individuals receiving high, medium or low CPE regimens. The study reported that regimen with a high CPE score increased the risk of HIV dementia by more than 50 % as compared to a low CPE score regimen (Caniglia et al. 2014), whereas other neuroAIDS comorbidities such as toxoplasmosis, cryptococcal meningitis and progressive multifocal leukoencephalopathy were unaffected (Caniglia et al. 2014). Moreover, cessation of cART improved neuropsychological test scores in a longitudinal study (Robertson et al. 2010). These contrasting observations indicate that further studies are required to safely prescribe cART and the present regimens with higher CPE scores should be carefully assessed for risk–benefit outcomes in neuropsychiatric performance. It is well established that HIV disrupts the blood–brain barrier (BBB) integrity, which may contribute to higher CNS penetration of the drugs with high CPE scores and produce various neurotoxic effects. Therefore, apart from CPE scores, concentration of individual ARV drugs in the CNS should be closely monitored to understand the cognitive decline in HIV-infected individuals.

Antiretroviral Toxicity and CNS

The CNS is comprised of three major types of cells—neurons, microglia and astrocytes. In addition, epithelial cells, which make the BBB, and oligodendrocytes also provide essential meshwork in the formation of the brain. HIV penetration into the CNS is largely dependent on the peripheral monocytes, which then infiltrate into the CNS via the “Trojan horse” mechanism (Kaul 2008). The infected monocytes can further release virus, which can lead to infection of the microglial cells and limited infection of the astrocytes (Eugenin et al. 2011; Kaul 2008; Kaul et al. 2001; Kramer-Hammerle et al. 2005). Although neurons remain uninfected, the HIV-infected patients demonstrate neuronal damage, which could be due to the indirect toxicity (Kaul 2008; Rumbaugh and Nath 2006; Watkins and Treisman 2015). The HIV-associated neurotoxicity has been extensively discussed, and therefore, in this review we have summarized the effect of cART-mediated toxicity on different types of cells in the brain.

Neurons

Although cART regimens used in the clinical setting are able to reach the CNS and suppress viral replication, very few candidate drugs can successfully penetrate BBB with adequate bioavailability of the drugs. It is also not very clear whether these concentrations of the drugs could have any deleterious effects on the neuronal cells. Recent evidence suggests that ARV drugs might be playing a more prominent role in the development of HAND than it was thought earlier. Despite the effective viral suppression, progressive loss of neurons is reported in HIV-infected individuals on HAART (Gongvatana et al. 2013). It is also unclear whether the drugs with high CPE scores effectively preserve the neurocognitive functions or accelerate HAND. An important finding by Robertson group demonstrated neurotoxicity of 15 different ARVs from different classes in an in vitro study (Robertson et al. 2012). The

ARV drugs have been reported to develop adverse effects in neurons as observed in both, human and animal tissues. In a study performed in macaques, rodent model and cultured rat neurons, ARVs induced oxidative stress and neurotoxicity, which was ameliorated by the use of monomethylfumarate (Akay et al. 2014). NRTIs such as didanosine, zalcitabine, stavudine and zidovudine were shown to reduce axonal length in human DRG (Liu et al. 2008; Robinson et al. 2007). Similar findings were observed in rat DRG, where stavudine or didanosine treatment resulted in shortening of neurite length (Cherry et al. 2010). The increase in peripheral neuropathy was shown to involve upregulation of TNF-α and BDNF when assessed for allodynia associated with zalcitabine and stavudine, respectively (Renn et al. 2011; Zheng et al. 2011). Another study demonstrated that efavirenz (EFV) could induce ER stress in the brain endothelial cells via upregulation and activation of protein kinase-like ER kinase (PERK) and inositol-requiring kinase 1α (IRE1α) and inhibited autophagosome formation by preventing the synthesis of phosphatidylinositol 3-phosphate (Bertrand and Toborek 2015). EFV has also been shown to induce protein expression of β-secretase and promote amyloid beta (Aβ) production in vitro and in vivo with reduced microglial phagocytic clearance of Aβ (Brown et al. 2014). The alteration in mitochondrial dynamics via EFV is attributed to increased nitric oxide (NO), autophagy, mitochondrial depolarization, decreased ATP production and alteration in mitochondrial respiratory function (Apostolova et al. 2015; Funes et al. 2015; Purnell and Fox 2014). More recently, EFV was shown to abrogate cell proliferation in neural stem cells in C57BL/6 mice, which was attributed to depleted ATP stores and depleted mitochondrial membrane potential (Jin et al. 2016).

Various NRTIs have been shown to affect mtDNA in mouse cortical neurons. All the NRTIs (stavudine, zidovudine, lamivudine and didanosine) tested in this study significantly reduced mtDNA copy number in cultured mouse cortical neurons. However, the authors did not find any reduction in mtDNA in mice treated with above drugs for either 1 or 4 months (Zhang et al. 2014b). Another study performed in patas monkey demonstrated significantly lower copies of mtDNA in the group that was exposed to NRTIs at birth or before birth as opposed to the control cohort (Divi et al. 2010).

Monocyte-Derived Macrophage/Microglia

Monocyte-derived macrophages (MDM) play an important role in CNS penetration of HIV. Monocytes continuously migrate through the endothelial cells and perform immune surveillance and thereby carry the perivascular HIV into the CNS. Similarly, macrophage/microglia serve as primary immune cells in the CNS and therefore are major targets of HIV in the brain. Once infected with HIV, microglia can support active replication of HIV and release a myriad of inflammatory cytokines/chemokines to overcome HIV infection in the CNS. The indirect toxicity of these neuroinflammatory molecules plays an important role in the development of HAND. Due to their role in the active HIV replication, macrophage/microglia also serve as the primary target for the cART making them prone to cART-associated toxicity. In a study conducted over 7 days, stavudine decreased mtRNA in U937 monocytes (Galluzzi et al. 2005). Similarly, raltegravir increased levels of IL-8 in brain macrophages, which remained higher in the presence of HIV suggesting neuroinflammatory effects of raltegravir (Tatro et al. 2014). A combination therapy with didanosine/stavudine

and lamivudine/zidovudine was shown to reduce mtDNA in the MDMs, which was further reduced in HIV-1. These drugs also reduced complement-mediated phagocytosis in MDMs either alone or in combination, whereas indinavir increased complement-mediated phagocytosis (Azzam et al. 2006). Another study reported that combination of ARV drugs, particularly PIs and NRTIs, reduced clearance of Aβ in murine microglia by inhibiting phagocytosis (Giunta et al. 2011). A similar study reported reductions in microglial Aβ clearance with the use of efavirenz (Brown et al. 2014). Zhang and colleagues demonstrated increased oxidative stress, ER stress and inflammatory cytokines such as IL-6 and TNF-α in response to protease inhibitors such as lopinavir, ritonavir and lopinavir/ritonavir combination in macrophages (Zhang et al. 2014a).

Astrocytes

Astrocytes are the most abundant cell type in the brain and play a multifaceted role in the homeostasis of brain microenvironment. Although they are not productively infected with HIV-1, the infection can become productive in the presence of supportive inflammatory environment (Carroll-Anzinger and Al-Harthi 2006). The literature on the effects of ARV drugs on the astrocytes is very limited. Considering the importance of astrocytes in maintaining neuronal functions, astrocytic toxicity may directly correlate with neurodegeneration. A recent study demonstrated that PIs could reduce excitatory amino acid transporter-2 (EAAT-2) in the astrocytes, which regulates recycling of excitatory neurotransmitter, glutamate. Disruption of EAAT-2 via PIs may lead to glutamate accumulation and thereby neuronal excitotoxicity (Vivithanaporn et al. 2016). We have also observed an increase in proinflammatory cytokines and oxidative stress in astrocytes by PIs (unpublished data). Further research is needed to determine the extent to which astrocytes are affected with the ARV treatment and the molecular mechanism(s) responsible for the same.

Oligodendrocytes

One of the classic markers of HAND is abnormalities in the white matter of the brain, which directly correlates with the neurocognitive functions of the brain. Surprisingly, patients with HAND demonstrate more pronounced white matter volume loss and myelin disruption when they are on cART (Kelly et al. 2014; Ragin et al. 2004; Wright et al. 2015). These cART-treated patients also demonstrate significant alterations in the genes associated with myelination such as myelin basic protein (MBP) and myelin-associated oligodendrocyte basic protein (Borjabad et al. 2011). Therefore, it is possible that cART contributes to the development of white matter dysfunction in the HIV-infected individuals. A study performed in the oligodendrocytes demonstrated that PIs significantly reduced MBP, disrupted oligodendrocyte maturation and increased oxidative stress (Jensen et al. 2015). Given the paramount significance of oligodendrocyte-mediated myelination in the normal brain function, it is important to study the effect of cART regimen on myelination and to identify underlying mechanism to reassess the therapeutic strategy.

Tight Junction Proteins (TJPs) and Blood–Brain Barrier (BBB) Disruption in ARV Neurotoxicity

The BBB is a highly regulated neuroanatomical interface separating peripheral circulation from the CNS, which serves as a protective barrier to prevent pathogen attacks on the brain. Apart from acting as a selective permeable barrier, BBB also acts as a regulator of several ion channels and drug transporters. The structural and functional role of BBB in brain homeostasis is well documented (Abbott et al. 2010; Banks and Erickson 2010; Nag et al. 2011), and it mainly consists of cerebral microvascular endothelium along with astrocytes, pericytes, neurons and extracellular matrix (Zlokovic 2008). In addition, various TJPs such as occludin, claudins and scaffolding proteins such as junctional adhesion molecule (JAM) and zona occludens (ZO)-1, -2 and -3 create molecular exchange channels (Ballabh et al. 2004; Bazzoni and Dejana 2004; Persidsky et al. 2006). Altered expression and arrangement of tight junction proteins lead to disruption of BBB, which is a characteristic feature of many CNS pathologies including HIV-1 infection (Kanmogne et al. 2007). Several studies have demonstrated the roles of different HIV-1 proteins such as gp120, Tat, Nef, Vpr in alteration of BBB integrity, which primarily affects the structure and function of claudin-1, claudin-5, JAM-A and ZO-2 (András et al. 2003; András and Toborek 2011; Atluri et al. 2015; Huang et al. 2009) without changing the protein expressions of occludin and ZO-1 (András et al. 2003; Toborek et al. 2005). Activation of various transcription factors and receptors such as mitogen-activated protein kinase (MAPK) 1/2, vascular endothelial growth factor receptor type 2 (VEGFR2), phosphatidylinositol-3-kinase (PI3 K) and nuclear factor-kappa B (NF-kB) has been implicated in HIV-1-mediated TJP alterations (András et al. 2005; Chaudhuri et al. 2008). Despite the extensive understanding of how HIV-1 disrupts BBB integrity, very limited knowledge is available about how ART could affect BBB. The use of ARV drugs significantly diminishes systemic HIV burden, but these drugs fail to restore the BBB integrity. In current therapeutic interventions, various strategies are being employed to increase the CNS penetration of ARV drugs; however, this carries an increased risk of neurotoxicity (Gomes et al. 2014; Sharma and Garg 2010). Thus, efforts to target ARV drugs to CNS must balance neurotoxic risks with potential gains. The lack of sufficient understanding of the above mechanisms presents a unique challenge to develop therapeutically safe and effective drugs as they have narrow therapeutic index.

As indicated earlier, despite some reports that a low concentration of ARV drugs may have deleterious effects (Robertson et al. 2010), very little data are available on the role of ARV drugs in BBB disruption. Majority of the studies on TJPs are performed in the endothelial cells from non-CNS compartments (Table 1). However, these studies provide an important lead toward our understanding of ARV-mediated damage to BBB. An in vitro report showed that pharmacological levels of saquinavir and indinavir significantly reduce Notch-4 expression through oxidative stress mechanism (Grigorian et al. 2008), which may directly affect endothelial viability via regulation of CBF-1, Su(H), Lag-1 (CSL) transcription factors (Lai 2002), p21 (Noseda et al. 2004) and vascular endothelial growth factor (VEGF) (Liu et al. 2003). Another study along the similar lines showed that saquinavir and indinavir reduced the expression of Notch-4 and ZO-1 in vivo causing BBB disruption (Manda et al. 2010). Ritonavir was found to increase the permeability of human dermal microvascular

endothelial cells by reducing the protein expression levels of ZO-1, occludin and claudin-1 (Chen et al. 2005). In this study, the authors demonstrated that ritonavir increased oxidative stress by production of superoxide anions and ERK1/2 activation to reduce the expressions of TJPs (Chen et al. 2005). Similarly, efavirenz was found to increase endothelial cell permeability by decreasing expressions of claudin-1, occludin, ZO-1 and JAM-1 via oxidative stress and JNK/NF-kB activation (Jamaluddin et al. 2010). Zidovudine and indinavir have also been reported to increase BBB permeability by creating intercellular gaps in blood microvascular endothelial cells, which leads to lowered transendothelial electrical resistance (Fiala et al. 2004).

In summary, the above studies point to the neurotoxic implications of ARV drugs that lead to disruption of BBB via loss of endothelial TJPs. In the presence of HIV-1 proteins, these effects could be further worsened because both ARV drugs and HIV-1 proteins induce oxidative stress, disrupt normal mitochondrial function, alter gene expression and activate various cell signaling cascades (Kline and Sutliff 2008). As summarized in Tables 1 and 2, several reports demonstrate that many of the currently approved ARV drugs induce cytotoxicity in the endothelial cells of the CNS origin as well as that of non-CNS origin. By understanding the mechanisms underlying ARV-induced BBB disruption, it might be possible to improve the quality of life of HIV-1-infected patients through better drug design.

Drug Transporters in ARV Neurotoxicity

A variety of drug transporters such as ATP-binding cassette (ABC) and solute lipid carrier (SLC) families of drug transporters are involved in the disposition of ARV drugs across the brain (Kis et al. 2010). While ABC and SLC transporters are necessary for the influx and efflux of various molecules that maintain cellular homeostasis, it has been widely known that these transporters contribute to several drug–drug interactions of clinical importance (Shugarts and Benet 2009). ARV drugs are both, substrates and inhibitors of these transporters, which invites the aforementioned risk of drug–drug interactions (Kis et al. 2010). While inhibition of efflux proteins by ARV drugs can increase bioavailability and efficacy of other ARV drugs, it can also lead to increased toxicity. Similarly, induction of efflux proteins by ARV drugs can lead to decreased plasma concentration, resulting in decreased efficacy. In this review, we will focus on ARV drug interactions, which can lead to increased bioavailability in the brain, and therefore increased neurotoxicity.

The treatment of HIV-1 infection in the brain presents a great challenge because of lower CNS penetration of ARV drugs. A variety of ABC transporters such as P-gp, multidrug resistance proteins (MRPs) and breast cancer resistance proteins (BCRPs) and SLC transporters such as ENT1, ENT2, OAT-1, -2 and -3 and CNT2 are expressed in the brain (Kis et al. 2010; Mahringer and Fricker 2016). While ABC transporters can hamper CNS drug penetration, expression of SLC transporters can facilitate the uptake of drugs with low CNS penetration. The overall drug concentration in the brain depends on the net effect on ABC and SLC transporters. Since PIs and NRTIs are front-line agents in the cART, drug–drug interactions between these two classes are of clinical importance. However, NRTIs are not metabolized by CYPs, so it is likely that drug transporters may play an important role in these interactions. PIs such as nelfinavir, ritonavir and nevirapine have been reported to

increase accumulation of integrase inhibitor, raltegravir, via a P-gp-dependent mechanism (Hashiguchi et al. 2013). Lopinavir/ritonavir has been shown to increase plasma concentration of atazanavir and saquinavir suggesting a possible action on P-gp (Vishnuvardhan et al. 2003). Administration of PIs with tenofovir results in 25–37 % increase in the exposure of tenofovir (Kis et al. 2010). A clinical study has also shown that co-administration of ritonavir with indinavir results in higher concentration of indinavir in CSF (van Praag et al. 2000). Clearly, these interactions indicate toward the possible role of ABC transporters in ARV-mediated toxicity.

Drug uptake transporters have also been shown to facilitate ARV-induced toxicity. For example, these transporters could concentrate NRTIs inside mitochondria and allow inhibition of mitochondrial-specific polymerase γ (Lee et al. 2003; Lewis 2003), which is known to increase psychological side effects of various NRTIs. Both, ENT1 and ENT3, have been found to be present on the mitochondrial surface (Govindarajan et al. 2009; Lai et al. 2004), which may lead to increased intake of several NRTIs including lamivudine, zalcitabine, didanosine, stavudine and azidothymidine, thereby leading to increased toxicity of these drugs (Govindarajan et al. 2009).

Increasing amount of literature indicates that drug transporters can significantly increase the possible drug–drug interaction with ARV drugs, and therefore, further studies should be redirected toward understanding how ARVs may induce or inhibit the expression of these transporters. This may add a vital piece of information to solve the puzzling question of ARV toxicity.

Antiretroviral Toxicity and Aging

Ever since the advent of ARV therapies, the life span of HIV-infected individuals has significantly prolonged. Consequently, the proportion of these individuals who are 45 and older is reaching 50 % in the USA and other developed nations (Antiretroviral Therapy Cohort 2008). Advanced age is one of the demographic factors associated with increased risk of neurocognitive decline and susceptibility to HAND in HIV-infected individuals (Becker et al. 2004; Wendelken and Valcour 2012). It has been shown that older people with HIV show significant cognitive decline in 1 year as compared to younger people with HIV or in seronegative controls. This suggests that HIV is associated with accelerated cognitive aging and HIV-infected individuals in their 50 s have cognitive function of a 70–80 year old (Seider et al. 2014). Interestingly, these effects still persist in the post-HAART era (Sacktor et al. 2002). A study was conducted on 251 HIV-seropositive subjects from a Northeastern AIDS Dementia Consortium (NEAD) cohort recruited between April 1998 and August 1999. The authors subdivided these 251 subjects into those taking HAART and not taking HAART. The authors found no significant differences in the patients on HAART as compared to patients not on HAART in neuropsychological assessments (Sacktor et al. 2002). A metabolomics study by Cassol et al. was conducted in the CSF from the HIV-infected individuals, which revealed increased levels of several metabolites suggesting accelerated aging in the HIV-infected patients. Particularly, neurotransmitters (glutamate, N-acetylaspartate), markers of glial activation (myo-inositol) and ketone bodies (beta-hydroxybutyric acid, 1,2-propanediol) were higher in the CSF (Cassol et al. 2014). In

addition, plasma inflammatory biomarkers [interferon (IFN)-αa, IFN-γ, IL-8, IL-1β, IL-6, IL-2Ra] and intrathecal IFN responses (IFN-γ and kynurenine: tryptophan ratio) directly correlated with increased CSF metabolomics profile (Cassol et al. 2014). Another commonly observed phenomenon in age-related cognitive decline is the similarity between the pathophysiology of Alzheimer's disease (AD) and HIV with respect to abnormal accumulation of Aβ. Both, AD and HIV, differ in that the Aβ plaques are diffuse and tend to occur in neuronal soma and along axonal tracks in HIV, whereas in AD, they tend to be predominantly present in neurites (Green et al. 2005). Evidence suggests that long-term cART might be associated with Aβ accumulation (Brew et al. 2009; Green et al. 2005). In the study by Green and coworkers, 162 AIDS autopsies from University of California San Diego and University of California Los Angles between 1983 and 2001 were assessed for the Aβ deposition, wherein they found substantially increased Aβ deposition in post-HAART patients as compared to pre-HAART patients (Green et al. 2005). Neurofibrillary tangles composed of hyperphosphorylated tau (pTau), which is common in AD, were also found in HIV. Although occurrence of elevated pTau is seen at very early age in the brains of people infected with HIV than in normal controls, the elevation of pTau predominantly occurs in older individuals with AD (Anthony et al. 2006). Surprisingly, the levels of pTau did not correlate with the HIV viral load in the brain (Smith et al. 2014), but higher levels were found to be associated with ARV treatment (Anthony et al. 2006). The occurrence and the pattern of spread of pTau in HIV also resemble the pattern seen in normal aging and AD (Anthony et al. 2006; Price et al. 1991). Collectively, these studies strongly suggest a link between the use of ARVs to treat HIV infection and the occurrence of an aging phenotype in the brain. More research is needed to establish the direct impact of ARV drugs on the induction of aging-associated markers in the brain and to differentiate between the relative contribution of the virus itself and ARVs.

Role of Cytochrome P450 in Antiretroviral-Mediated CNS Toxicity

Cytochrome P450 (CYP) enzymes are known to be involved in the metabolism/activation/inactivation of majority of pharmaceutical drugs (Ingelman-Sundberg 2004). Particularly, CYP1, CYP2 and CYP3 classes of the CYPs contribute to the activation/inactivation of various ARVs, especially NNRTIs, PIs, maraviroc and elvitegravir (Michaud et al. 2012). Since most of the ARVs are both, the substrate and inhibitors of various CYPs (Table 3), they offer higher rates of drug–drug interactions. Therefore, the expression and activity of CYPs play a major role in the bioavailability of ARVs in various tissues including the brain (Meyer et al. 2007). With appropriate dose adjustments and taking drug–drug interaction into account, the bioavailability of several antiretroviral drugs can be improved, which also can improve drug treatment at lower concentrations. In fact, CYP3A4 inhibition via ritonavir has been successfully employed in clinical use for treatments with other protease inhibitors (Kumar et al. 1999; van Heeswijk et al. 2001). More recently, cobicistat, a pharmacokinetic booster, was clinically approved for its use in combination therapy with integrase inhibitor-based or PI-based regimen due to its CYP3A4 inhibitor property (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2016). Although, with cautious clinical oversight, the toxic drug–drug interactions could be prevented, the role of CYPs in direct toxicity of the drugs must be evaluated. Since the ARVs are mainly

metabolized by CYP2B6, 2C19 or 3A4, it is plausible to predict that the toxicity could be attributed to these three enzymes.

CYP2B6

CYP2B6 is the only enzyme from CYP2B family that is expressed in the brain in addition to liver and other extra hepatic tissues (Ding and Kaminsky 2003; Gervot et al. 1999). Among various ARVs, nevirapine and efavirenz are metabolized by CYP2B6 (Gatanaga et al. 2007; Wang and Tompkins 2008). A study by Haughey group demonstrated that efavirenz and its metabolite, 8-hydroxy efavirenz, increased dendritic spine injury (Tovar-y-Romo et al. 2012). Moreover, the metabolism of efavirenz into 8-hydroxy efavirenz is mediated via CYP2B6 (Bumpus et al. 2006), which suggests the implication of CYP2B6 in efavirenz-mediated neurotoxicity. Since the CYP2B6 gene is highly polymorphic, its expression is highly variable among individuals. Altogether, there are 28 alleles and more than 100 single nucleotide polymorphisms (SNPs) reported with CYP2B6. Particularly, CYP2B6*6 haplotype variant has been found to affect the metabolism profile of efavirenz. Since efavirenz is both, inducer and substrate of CYP2B6 (Robertson et al. 2008; Ward et al. 2003), individuals with CYP2B6*6/*6 variants achieve higher plasma concentrations of efavirenz (Tsuchiya et al. 2004). Rotger et al. demonstrated increased neuropsychological toxicity of efavirenz due to CYP2B6 516G>T mutation (Rotger et al. 2005). Similarly, Sanchez Martin et al. (2013) demonstrated CNS toxicity with CYP2B6 785A>G mutation. CYP2B6 mutations are also associated with plasma concentrations of nevirapine, which may elicit CNS toxicity as described earlier.

CYP2C19

The CYP2C19 is expressed in various brain regions (Persson et al. 2014), and among various drugs, nelfinavir and etravirine are metabolized via CYP2C19. Both of them moderately inhibit CYP2C19 enzyme activity (Kakuda et al. 2010; Lillibridge et al. 1998). Since polymorphism of CYP2C19 reduces its metabolic potential, variants such as CYP2C19*2 and CYP2C19*17 could lead to increased concentrations of these drugs. Both etravirine and nelfinavir are scored as 2 and 1, respectively, as per CPE index; therefore, their CNS toxicity is almost non-existent if any. Individuals with mutant CYP2C19 could increase the overall toxicity in the periphery. As mentioned earlier, both etravirine and nevirapine are not associated with significant CNS toxicity other than a single report by Robertson et al. (2012) for etravirine-mediated neurotoxicity.

CYP3A4/5

CYP3A4 (and its close isoform, CYP3A5) contributes to the metabolism of majority of the antiretroviral drugs. In addition to hepatocytes, CYP3A4 is expressed in various brain regions and the catalytic activity is reported as high as 80 % of that observed in the hepatocytes (Meyer et al. 2007; Yadav et al. 2006). Since majority of the drug–drug interactions are known to involve CYP3A4, the HIV-infected patients are in general at higher risk of the drug-associated toxicity owing to the presence of CYP3A4. To aid this process further, the HIV patients are typically prescribed a multidrug regimen, which compounds the toxicity of the drugs. For example, concomitant administration of entry inhibitor maraviroc (CYP3A4 substrate) and NNRTI efavirenz (CYP3A4 inducer) is

contraindicated since it affects the bioavailability of maraviroc. The CYP3A4 inhibitor activity of ritonavir is potentially beneficial to improve the drug availability of other protease inhibitors (Abel et al. 2008). To further complicate the process, some protease inhibitors act as both inducers and inhibitors of CYP3A4 activity depending on the co-administration of the other drugs with them. CYP3A4-associated toxicity needs closer attention vis-a-vis neurotoxic potential of various cART drugs. Similar to other CYPs mentioned earlier, CYP3A4/5 is also known to have multiple isoforms and polymorphism that affect the drug metabolism profile of ARV. Since ritonavir is known to be associated with neurotoxicity of several other drugs (Bonfanti et al. 2000; Gupta et al. 2012), it is reasonable to consider the possible role of CYP3A4.

Although there is very limited information about the role of CYP450 in ARV-associated neurotoxicity, the possible drug–drug interaction clearly warrants further attention.

Possible Association with Chronic Use of Antiretroviral Drugs

The advent of antiretroviral drugs has clearly kept the viral replication in check. However, there is growing body of literature which suggests that chronic use of antiretroviral drugs could be responsible for the prevalence of milder forms of HAND. The neurotoxicity potential of the antiretroviral drugs is also linked with the CPE score. A study performed using 79 patients demonstrated improved suppression of CSF HIV RNA with cART with higher CPE, but the neurocognitive performance was poorer than those who were on lower CPE drugs (Marra et al. 2009). In addition to the CPE score, this study also suggested that multiple drug regimens and poor adherence also contributed to the neurological complications among the patients. A study by Robertson et al. (2012) demonstrated that different antiretroviral drugs have a wide range of neurotoxicity at therapeutic concentrations as demonstrated by the MAP-2 density. Another multicentered study demonstrated beneficial outcomes upon discontinuation of ARV on cognitive impairment (Robertson et al. 2010). This study was conducted on a cohort of people on HAART for 6 months, followed by discontinuation of the drug, which showed improvement in neuropsychological score over 96 weeks. This is the first study demonstrating CNS toxicity associated with chronic treatment with ARV. A similar study in the randomized Strategies for Management of Anti-Retroviral Therapy (SMART) trial in HIV-infected patients demonstrated that continuous antiretroviral therapy was associated with cardiovascular risk factors, which could also lead to neurocognitive impairment. The study further correlated the CD4 counts with the ARV-associated neurocognitive impairment (Wright et al. 2010). Another SMART study demonstrated no significant difference in the neurocognitive performance regardless of continuous or intermittent ARV treatment (Grund et al. 2013). Although the explanation for contradicting observations between the 2010 Robertson study and SMART study is not obvious, a possible explanation could be the legacy effect prior to the ARV introduction to those HIV-infected patients. A similar study in chronic HIV infection was conducted for over 2 years in 226 HIV-infected patients (Gongvatana et al. 2013). This study focused on measuring various brain metabolite concentrations to correlate HIV infection and ARV treatment with neurocognitive impairment. The neurological damage was assessed with neuroimaging and various neuropsychological assessments. As reported in this study, the neurocognitive decline was associated with a decrease in the brain

metabolites in various regions regardless of viral suppression (Gongvatana et al. 2013). Although this study does not provide clear evidence for the underlying mechanism, the possibility of the legacy effect of pre-CART condition could explain the outcome. A study by Fumaz et al. (2012) demonstrated the role of IL-6 in neurocognitive performance, which revealed that HIV-infected individuals on cART were at a higher risk of developing psychological stress if their plasma IL-6 levels were high. Assuming the inverse correlation between plasma cytokine levels and neurocognitive performance, it is logical to expect that neuroinflammation due to cART and comorbid disorders in the CNS may affect the neurobehavioral outcomes in the HIV-infected individuals.

Prolonged use of ARV has been suggested as one of the major contributors to neurological complications. A more recent study demonstrated that chronic efavirenz treatment could lead to worse neurocognitive functioning among HIV-infected patients (Ma et al. 2016). This study, conducted in 445 patients from CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort, demonstrated that patients on efavirenz showed a worse neurocognitive impairment as compared to those who were on ritonavir-boosted lopinavir regimen. Furthermore, hepatitis C virus (HCV) coinfection was found as an additional cofactor. Efavirenz-treated cohort showed worse neurocognitive impairment in the HCV-negative patients, and lopinavir-treated patients showed increased damage in HCV-positive patients. A more comprehensive longitudinal study in CHARTER cohort by Heaton et al. demonstrated no observational evidence for ARV-associated neurotoxicity (Heaton et al. 2015). This study rather suggested educational background and cognitive reserve as a possible link between neurocognitive improvement and ARV treatment. In fact, this study suggested that the subset with neurocognitive impairment might have comorbid condition, nadir CD4 count and possible history of drug abuse.

Altogether, the link between chronic use of ARV and neurocognitive impairment is still not conclusive and further studies are necessary to understand neurotoxicity associated with ARVs. Several studies support the ideology of cautious and early use of ARVs followed by close monitoring of neurological profile of HIV-infected patients despite successful suppression of the virus. Rigorous attempts to identify possible mechanisms for the ARVs-associated neurotoxicity could provide novel insight toward more efficient therapeutic approaches.

Concluding Remarks and Future Suggestions

The use of cART has been undoubtedly beneficial in the suppression of HIV and has increased the life span of the HIV-infected individuals. In addition, one cannot argue against the effectiveness of cART in reducing the prevalence of HAD. However, the emergence of milder forms of HAND has drawn the attention of researchers and clinicians toward possibility of toxicity and CSF viral escape associated with prolonged use of the cART. As summarized in Table 4, growing body of research has demonstrated neurotoxic potential of various ARV drugs. Another theory favors the possibility of inadequate concentrations of cART drugs beyond the BBB, and therefore, research is redirected toward strategies to improve the drug availability in CNS. Although CPE scores do not provide conclusive

information on the neurocognitive outcomes, it warrants cautious use of drugs that may achieve higher concentrations in the brain.

Although the current review only focuses on the neurotoxicity of ARV drugs, the contribution of ARVs to the HAND is further complicated with the pre-existing toxicity of various viral proteins. It is very likely that the underlying mechanisms for toxicity of both, ARVs and HIV, could share some common targets. The use of substances of abuse also adds another variable toward this complex issue, since they also invite various drug–drug interactions due to their cross-talk with CYP enzymes. For example, a recent study assessed neurotoxicity of ARV from four different pharmacological classes in the context of methamphetamine, a frequently abused stimulant drug and comorbidity factor for HIV patients (Sanchez et al. 2016). This study also tested an integrase inhibitor and found, in part, independent effects of ARVs on presynaptic terminals, neurites, autophagy and neuronal ATP levels. Similarly, alcohol was shown to exacerbate mechanical hyperalgesia induced via zalcitabine (Ferrari and Levine 2010). At present, the knowledge of the neurotoxic potential of ARV is very limited, which has been documented in recent years. It is important to pay closer attention toward the role of ARV in HAND. A combined study of ARV with or without HIV as a whole, or the role of viral proteins in association with ARV, may provide novel insights into underlying mechanisms. The outcomes from these studies are quintessential to develop a better approach in HIV treatment strategies. Possible future directions for novel strategies could be to minimize ARV complications by developing drugs with better metabolic profile and simplification of drug regimens by combining multiple drugs with the least drug–drug interaction. New treatment strategies to combat HIV-associated neurotoxicity or by using drugs targeting alternative gene targets could also present an opportunity to personalize the regimens based on individual genetic profile.

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Table 1

Cytotoxic effect of ART drugs on endothelial cells of brain origin

Class	Drug	Effect on TJPs	Effect on endothelium	Endothelial cell studied	References
NRTIs	Zidovudine	–	↑ Oxidative stress ↑ Mitochondrial dysfunction ↑ Cell death	hCMEC/D3	Manda et al. (2011)
NNRTIs	Efavirenz	–	↑ Oxidative stress ↑ ER Stress ↓ Autophagy ↑ Permeability	hCMEC/D3	Bertrand and Toborek (2015) and Jamaluddin et al. (2010)
PIs	Indinavir	–	↑ Oxidative stress ↑ Cell death ↑ Mitochondrial dysfunction	BMVECs	Wang et al. (2007)
	Saquinavir	↓ ZO-1	↑ Cell death ↓ Notch-4 ↑ Oxidative stress	RBMECs	Baliga et al. (2004) and Manda et al. (2010)

hCMEC/D3 human cerebral microvascular endothelial cell line, *BMVECs* brain microvascular endothelial cells, *RBMECs* rat brain microvascular endothelial cells

Table 2

Cytotoxic effect of ART drugs on endothelial cells of non-CNS origin

Class	Drug	Effect on TJPs	Effect on endothelium	Endothelial cell type studied	References
NRTIs	Zidovudine	–	↑ Oxidative stress ↑ Mitochondrial dysfunction ↑ Cell death	HAECs	Glover et al. (2014), Manda et al. (2011) and Kline et al. (2009)
	Stavudine	–	↑ Oxidative stress	BAECs	Sutliff et al. (2002)
	Abacavir	–	↑ Oxidative stress ↓ eNOS	HPAECs	Wang et al. (2009)
	Lamivudine	–	↑ Oxidative stress ↓ eNOS	HPAECs	Wang et al. (2009)
NNRTIs	Efavirenz	↓ Claudin-1, occludin, ZO-1, JAM-1	↑ Permeability ↑ Oxidative stress ↑ ER stress ↓ Autophagy	HCAECs	Bertrand and Toborek (2015 and Jamaluddin et al. (2010)
PIs	Ritonavir	↓ Claudin-1, occludin, ZO-1	↑ Permeability ↑ Oxidative stress ↑ Cell death ↓ eNOS	HMECs, HCAECs	Chen et al. (2005), Fu et al. (2005) and Zhong et al. (2002)
	Atazanavir, atazanavir + ritonavir	–	↑ Oxidative stress ↑ Inflammation ↑ Cell death ↓ eNOS	HCAECs	Auclair et al. (2014)
	Amprenavir	–	↑ Oxidative stress ↓ eNOS	HCAECs	Wang et al. (2007)
	Indinavir	–	↑ Permeability ↑ Oxidative stress ↑ Cell death ↓ Notch-4 expression ↑ Mitochondrial dysfunction ↓ eNOS ↓ TEER	HCAECs	Wang et al. (2007), Fiala et al. (2004), Grigorian et al. (2008) and Manda et al. (2011)
	Nelfinavir	–	↑ Oxidative stress ↓ eNOS ↑ Cell death ↓ Notch-4	HCAECs	Mondal et al. (2004) and Wang et al. (2007)
	Lopinavir, lopinavir + ritonavir	–	↑ Oxidative stress ↑ Inflammation ↓ eNOS	HCAECs	Auclair et al. (2014)

eNOS endothelial nitric oxide synthase, *TEER* transendothelial electrical resistance, *HAECs* human arterial endothelial cells, *BAECs* bovine aortic endothelial cells, *HPAECs* human pulmonary artery endothelial cells, *HMECs* human mammary endothelial cells, *HCAECs* human coronary artery endothelial cells

Table 3

Interaction of different classes of ARV drugs with CYP450

Class	Antiretroviral	Metabolism	CYP induction/inhibition	References
NRTIs	Efavirenz	CYP2B6, CYP2A6, CYP3A, CYP1A2	↓↑ CYP3A4, ↑ CYP2B6, ↑ CYP2C19	Brown et al. (2009), Fan-Havard et al. (2013) and Xu and Desta (2013)
	Etravirine	CYP2C9, CYP2C19, CYP3A4/5	↓↑ CYP3A4, ↓ CYP2C9, ↓ CYP2C19	
	Nevirapine	CYP2D6, CYP2B6, CYP3A4/5	↑ CYP3A4	
PIs	Atazanavir Darunavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	CYP3A4/5 CYP3A4/5 CYP3A4/5 CYP3A4/5 CYP3A4/5, CYP2C19 CYP3A4/5 CYP3A4/5 CYP3A4/5	↓↑ CYP3A4	Eagling et al. (1997, 2002), Granfors et al. (2006), Kempf et al. (1997), Kumar et al. (1996), Malaty and Kuper (1999), Saitoh et al. (2010), Vourvahis and Kashuba (2007) and Yeh et al. (2006)
CCR5 co-receptor inhibitor	Maraviroc	CYP3A4/5	–	Hyland et al. (2008)
Integrase inhibitor	Elvitegravir	CYP3A4/5	↓↑ CYP3A4	Ramanathan et al. (2011)

Table 4

Summary of current understanding of the ARV-associated neurotoxicity

Class of drugs	Drug	Major findings	References
Entry inhibitor	Enfuvirtide	Higher prevalence of neuropathy in 11 % patients	Lalezari et al. (2003)
		Higher prevalence of peripheral neuropathy	Fung and Guo (2004)
		Worsening of neuropathy symptoms in 21 % patients	Cherry et al. (2008)
	Maraviroc	↑ Microglial activation via proinflammatory modulators over chronic use	Lisi et al. (2012)
INSTI	Raltegravir	Exacerbation of depression	Harris et al. (2008)
		↑ IL-8 in brain macrophages	Tatro et al. (2014)
NNRTI	Efavirenz	↑ TNF-α and ↑ IL-1β, spatial memory deficits	O'Mahony et al. (2005)
		↓ Creatine levels in brain	
		Role of CYP2B6 in metabolite formation leading to ↑ dendritic spine injury	Bumpus et al. (2006) and Tovar-y-Romo et al. (2012)
		↑ Autophagy, ↓ ATP production, ↑ mitochondrial depolarization and altered mitochondrial morphology in neurons	Purnell and Fox (2014)
		↑ LC3-II, ↑ CHOP and ↓ mitochondrial membrane potential in primary rat neurons	Blas-Garcia et al. (2014)
		↑ β-Secretase expression, ↑ amyloid beta, ↑ ROS, ↑ mitochondrial stress	Brown et al. (2014)
		Altered mitochondrial respiratory function in cultured neuronal and glial cells.	Funes et al. (2015)
		↑ NO in mitochondria	Apostolova et al. (2015)
		Induction ER stress via stimulation of IRE1α and PERK. Decreased autophagy by affecting Beclin1/Atg14/PI3KIII complex, ↑ cytotoxicity	Bertrand and Toborek (2015)
		↓ ATP stores, ↓ mitochondrial membrane potential ↓ neural stem cell proliferation in culture and C57BL/6 mice	Jin et al. (2016)
	Etravirine	↓ MAP-2 density in rat neurons	Robertson et al. (2012)
	Nevirapine	Neuropsychiatric symptoms	Morlese et al. (2002)
		Neuropsychiatric symptoms	Wise et al. (2002)
NRTI	Didanosine	Neurite degeneration in DRG	Liu et al. (2008)
	Didanosine/stavudine, lamivudine/zidovudine	↓ mtDNA content in MDMs	Azzam et al. (2006)
	Stavudine	↓ mtRNA in U937, HUT78 and CEM cells	Galluzzi et al. (2005)
		↑ BDNF in spinal dorsal horn contributed to neuropathic pain in C57BL/6 mice	Renn et al. (2011)
	Stavudine, didanosine	↑ Peripheral neuropathy in HIV patients	Dragovic and Jevtovic (2003)
		Impaired neurite growth in fetal rat DRG	Cherry et al. (2010)
	Zalcitabine	↓ Mitochondrial DNA and peripheral neuropathy	Dalakas et al. (2001)
		↑ TNF-α associated with neuropathic pain in DRG	Zheng et al. (2011)
	Zidovudine	Lethal neurotoxicity in AIDS patient	Hagler and Frame (1986)

Class of drugs	Drug	Major findings	References
		Causal relationship with manic syndrome	Maxwell et al. (1988)
		Lethal neurotoxicity in AIDS patient	Saracchini et al. (1989)
	Zidovudine, lamivudine, didanosine, stavudine	↓ mtDNA in infant brains exposed to NRTI in utero	Divi et al. (2010)
	Zidovudine, stavudine, didanosine, lamivudine	Long-term exposure reduces MtDNA in cortical neurons	Zhang et al. (2014b)
	Zidovudine, stavudine, didanosine, zalcitabine	Axonal injury in DRG	Robinson et al. (2007)
NRTI/PI	Lamivudine, indinavir, abacavir, zidovudine and their combinations	↑ Amyloid beta production, ↓ microglial phagocytosis of amyloid beta	Giunta et al. (2011)
	Lopinavir, ritonavir, zidovudine	↑ Oxidative stress in oligodendrocytes, ↓ MBP and ↑ CNPase in HIV-positive/ART-treated patients compared with the HIV-negative patients, ↓ oligodendrocyte differentiation with PI	Jensen et al. (2015)
	Zidovudine/indinavir	Increased cell death, increased oxidative stress (↑ ROS, ↑ MDA, ↓ GSH), loss of mitochondrial membrane	Manda et al. (2011)
PI	Amprenavir/lopinavir	Increased risk of sensory neuropathy	Ellis et al. (2008)
	Amprenavir/ritonavir	Increased behavioral deficit, ↓ EAAT2 and ↓ PCNA in astrocytes	Vivithanaporn et al. (2016)
	Indinavir	Significant neuronal atrophy, neurite retraction and process loss in HIV-infected DRG	Pettersen et al. (2006)
	Lopinavir, ritonavir	↓ Myelin basic protein, ↓ galactocerebroside in oligodendrocytes	Jensen et al. (2015)
	Lopinavir, ritonavir, lopinavir + ritonavir	↑ Oxidative stress, ↑ ER stress, ↑ IL-6 and ↑ TNF-α in macrophages	Zhang et al. (2014a)
	Lopinavir/ritonavir	Compromised cognitive and motor function, loss of tight junction proteins (↓ ZO-1, ↓ occludin), synaptic proteins (↓ phos-synapsin), activation of astrocytes (↑ GFAP) and microglia (↑ iba1) ↑ cytokines (TNF-α, IL-6, IL-1β), ↓ BDNF	Gupta et al. (2012)
		↑ Astrogliosis marker in CSF of HIV-infected patients	Du Pasquier et al. (2013)
		↓ EAAT2 and ↓ PCNA in astrocytes and ↓ L-glutamate, ↓ L-aspartate and ↓ L-serine in mouse cortex	Vivithanaporn et al. (2016)
	Ritonavir, saquinavir	Increased rate of neurological toxicity such as headache, peripheral neuropathy, perioral paresthesia and taste alteration	Bonfanti et al. (2000)
	Ritonavir, saquinavir, atazanavir	↑ NQO-1 and HO-1, ↑ calpain-cleaved spectrin, ↑ oxidative stress, ↓ MAP-2, ↓ synaptophysin, ↓ CaMKII	Akay et al. (2014)
	Saquinavir	Loss of blood-brain barrier permeability (↓ Notch-4), no effect on cell viability	Grigorian et al. (2008)
		Increased oxidative stress (↑ ROS), loss of tight junction protein (↓ ZO-1), loss of blood-brain barrier permeability (↓ Notch-4, ↑ brain distribution of [14C] sucrose)	Manda et al. (2010)
	Saquinavir, zidovudine, nevirapine	In combination with methamphetamine showed ↓ neuronal ATP, ↓ MAP-2 and ↓ pre-synaptic synaptophysin	Sanchez et al. (2016)
HAART		↑ Phospho-Tau in HAART patients as compared to untreated	Anthony et al. (2006)
		Poor neurocognitive outcomes among patients who were on drugs with higher CPE	Marra et al. (2009)

Class of drugs	Drug	Major findings	References
		CHARTER study: ARV-associated neurocognitive impairments correlated with CD4 counts.	Heaton et al. (2010)
		High prevalence of HAND (asymptomatic neurocognitive impairment 24 %, mild neurocognitive disorders 52 % and HIV-associated dementia 8 %) despite undetectable viral RNA	Simioni et al. (2010)
		Improved cognitive function due to ARV discontinuation	Robertson et al. (2010)
		HIV + individuals on ARV treatment with viral RNA <50 copies/mL and taking >3 ARVs with better CPE had better neurocognitive outcomes in ALLRT cohort	Smurzynski et al. (2011)
		↑ Frequency of CNS diseases with CPE scores ≤4 and ↓ frequency with CPE scores ≥10; however, these differences were nonsignificant.	Garvey et al. (2011)
		↑ Class II MHC, alteration in MBP	Borjabad et al. (2011)
		Progressive CNS complications, including neuronal injury observed in chronically HIV-infected persons despite stable ARV treatment and viral suppression, ↓ brain metabolites leading to neurocognitive decline	Gongvatana et al. (2013)
		The incidence of HIV dementia increased by more than 70 % after initiating an antiretroviral regimen with a high CPE score compared with a low score. No apparent change in any other neuroAIDS conditions	Caniglia et al. (2014)
		Acceleration of aging in HIV patients on ART, ↑ inflammatory markers, ↑ glutamate neurotoxicity and altered brain waste disposal systems demonstrated by CSF metabolomics	Cassol et al. (2014)
		HIV+ patients taking three-drug cART regimens with higher CPE demonstrated better neurocognitive performance in ontario HIV treatment network cohort in a cross-sectional study	Carvalhal et al. (2015)
		Poor cognitive abilities among patients on efavirenz	Ma et al. (2016)

IL interleukin, *TNF* tumor necrosis factors, *CYP* cytochrome P450, *ATP* adenosine triphosphate, *LC-3II* microtubule-associated protein 1A/1B-light chain 3, *CHOP* C/EBP homologous protein, *ROS* reactive oxygen species, *NO* nitric oxide, *IRE1α* inositol-requiring enzyme 1, *PERK* PKR-like endoplasmic reticulum kinase, *MAP-2* microtubule-associated protein 2, *DRG* dorsal root ganglion, *mtDNA* mitochondrial DNA, *BDNF* brain-derived neurotrophic factor, *MDA* malondialdehyde, *GSH* glutathione, *MBP* myelin basic protein, *CNPase* 2′,3′-cyclic-nucleotide 3′-phosphodiesterase, *EAAT-2* excitatory amino acid transporters, *PCNA* proliferating cell nuclear antigen, *ZO* zona occludens 1, *GFAP* glial fibrillary acidic protein, *iba1* induction of brown adipocytes 1, *CSF* cerebrospinal fluid, *NQO1* NAD(P)H dehydrogenase (quinone 1), *HO1* heme oxygenase1, *caMKII* Ca^{2+}/calmodulin-dependent protein kinase II, *CPE* CNS penetration effectiveness, *MHC* major histocompatibility complex, *PI* protease inhibitor, *NRTI* nucleoside/nucleotide reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *INSTI* integrase strand transfer inhibitors, *HAART* highly active antiretroviral therapy