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CNS Neurotoxicity of Antiretrovirals

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Abstract

The development of novel antiretroviral treatments has led to a significant turning point in the fight against HIV. Although therapy leads to virologic suppression and prolonged life expectancies, HIV-associated neurocognitive disorder (HAND) remains prevalent. While various hypotheses have been proposed to explain this phenomenon, a growing body of literature explores the neurotoxic effects of antiretroviral therapy. Research to date brings into question the potential role of such medications in neurocognitive and neuropsychiatric impairment seen in HIV-positive patients. This review highlights recent findings and controversies in cellular, molecular, and clinical neurotoxicity of antiretrovirals. It explores the pathogenesis of such toxicity and relates it to clinical manifestations in each medication class. The concept of accelerated aging in persons living with HIV (PLWH) as well as potential treatments for HAND are also discussed. Ultimately, this article hopes to educate clinicians and basic scientists about the neurotoxic effects of antiretrovirals and spur future scientific investigation into this important topic.

Graphical Abstract

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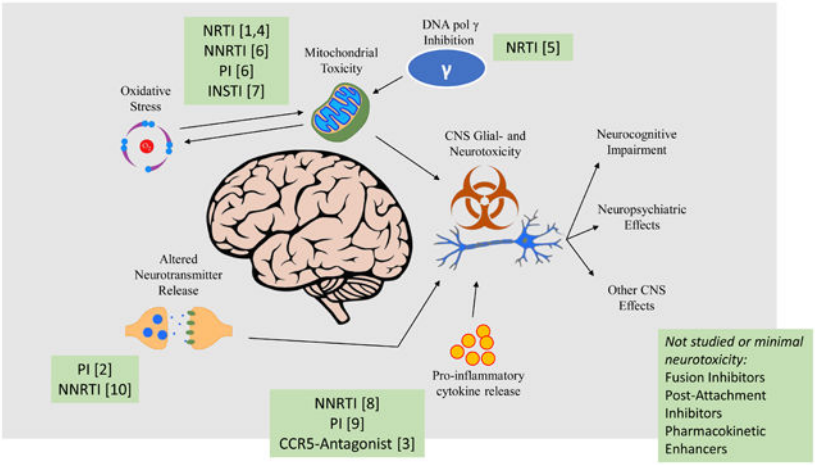

Introduction

The HIV epidemic led to the development of a myriad of antiretroviral therapies. First discovered was azidothymidine (AZT), and after patterns of AZT-resistance emerged, other nucleoside reverse transcriptase inhibitors (NRTIs) were developed. Next came non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Later came integrase inhibitors, fusion inhibitors, and entry inhibitors. A pharmacokinetic enhancer class (cobicistat) was recently introduced designed to improve the pharmacokinetics and increase effectiveness of HIV medications. Today, a regimen combining two NRTIs and one integrase inhibitor is typically recommended, though a multitude of other options exist based on individual circumstances such as genotypic resistance, prior exposure and demonstrated medication intolerance (Saag, Benson et al. 2018). With the advent of combination antiretroviral therapy (cART; sometimes referred to as highly active antiretroviral therapy or HAART), a once fatal disease has become indefinitely controllable, leading to drastically increased life expectancies in affected patients (Marcus, Chao et al. 2016). Since a definitive cure is not yet available, patients require life-long therapy, and with such a prolonged exposure to medications (in addition to long-term toxicity from the first-generation medications), a careful consideration of neurological adverse effects is warranted.

In particular, antiretroviral use has been associated with a range of neurological toxicity, from peripheral neuropathy to neuropsychiatric and neurocognitive deficits in the central nervous system (CNS) (Meeker, Robertson et al. 2014). However, it is often difficult to distinguish certain adverse effects caused by HIV medications from direct and indirect deleterious effects from the virus itself (Treisman and Soudry 2016). One such instance is HIV-associated neurocognitive disorder (HAND), a term which describes several disorders based on severity of neurocognitive impairment. They are asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD), a progressive and life-threatening form of dementia (Antinori, Arendt et al. 2007, Letendre 2011). To date, no specific treatment exists for HAND nor is a diagnostic biomarker available (Saylor, Dickens et al. 2016). Although other non-neurological

conditions have declined in prevalence due to the efficacy of cART, HAND remains common in the cART era. It is estimated that about one third of HIV+ patients have a HAND diagnosis and over half have neuropsychological impairment (Heaton, Clifford et al. 2010, Sacktor, Skolasky et al. 2016). Interestingly, the compositional prevalence of its subgroups has changed in the cART era. HAD has become increasingly uncommon (2%) while rates of ANI and MND actually increased (Heaton, Franklin et al. 2011, Singer and Nemanim 2017). This suggests that either cART is unable to adequately suppress HIV in the nervous system or that cART use is contributing to the development of HAND (Etherton, Lyons et al. 2015).

In this article, we evaluate each of the classes of HIV therapy, reviewing the latest concepts and controversies regarding the clinical manifestations and cellular mechanisms of ART-induced CNS neurotoxicity. Where applicable, we include antiretroviral routes of administration in *in vivo* studies (intraperitoneal, CSF, etc.), and mention when medications used in studies are clinically relevant. However, note that estimating clinically-relevant concentrations is difficult, given lack of data on antiretroviral CSF:plasma area under the curve, predictions that parenchymal concentrations can reach greater levels than in the CSF, and the fact that HIV disrupts the blood brain barrier (BBB), allowing for increased antiretroviral CSF accessibility (Decloedt, Rosenkranz et al. 2015, Jensen, Monnerie et al. 2015). We discuss how CNS penetrance by ART may affect neurotoxicity, explore the concept of accelerated aging in PLWH (persons living with HIV), and highlight recent advancements in the possible treatment of HAND. Peripheral nervous system toxicity is beyond the scope of this review and only briefly covered.

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs, the first class of HIV medications discovered, work by blocking reverse transcriptase, thereby preventing the virus from generating functional cDNA via premature DNA strand termination (Shah, Gangwani et al. 2016). In ascending order of approval date, the NRTIs are azidothymidine/zidovudine (AZT), didanosine (ddI), stavudine (d4T), lamivudine (3TC), abacavir (ABC), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and tenofovir alafenamide fumarate (TAF). Older NRTIs such as AZT were found to have more off-target effects, limiting their clinical use relative to newer agents (Schweinsburg, Taylor et al. 2005).

Although potent inhibitors of reverse transcriptase, NRTIs also cause off-target inhibition of mitochondrial polymerase γ, the enzyme responsible for normal mitochondrial DNA replication (Kakuda 2000). Through this inhibition, the primary mechanism of NRTI toxicity appears to be mitochondrial toxicity, energy depletion, and oxidative stress, which have been demonstrated both *in vitro* and *in vivo* (Lewis, Day et al. 2003, Kohler and Lewis 2007, Nooka and Ghorpade 2018). The extent of mitochondrial polymerase γ inhibition among NRTIs is ddI > d4T >> 3TC > TDF ≥ FTC ≥ AZT ≥ ABC (Bienstock and Copeland 2004). This type of mitochondrial toxicity is considerably cell/tissue-dependent. Stavudine impairs mitochondria in axons and Schwann cells causing peripheral neuropathy, AZT impairs mitochondria in skeletal muscles and causes myopathy, and others can cause lipoatrophy and lactic acidosis (White 2001, Abers, Shandera et al. 2014, Margolis, Heverling et al. 2014).

Mitochondrial DNA (mtDNA) depletion from NRTI exposure is also persistent, dependent on cumulative exposure, and can cause long-term effects even after discontinuation (Poirier, Divi et al. 2003, Underwood, Robertson et al. 2015). TAF, a prodrug of tenofovir and a component of the vast majority of modern regimens, produces greater intracellular concentrations than TDF, which might lead to worse neurotoxicity.

It was previously thought that NRTI neurotoxicity was limited to the periphery, but emerging evidence has called this into question. From a clinical standpoint, AZT is known to cause insomnia, nausea, and severe headaches, and in high doses can cause seizures (Richman, Fischl et al. 1987, Saracchini, Vaccher et al. 1989). Other NRTIs have been linked to retinal atrophy, and dose-dependent psychiatric disturbances (Turjanski and Lloyd 2005, Gabrielian, MacCumber et al. 2013). One study used magnetic resonance spectroscopy in patients as a proxy for brain mitochondrial integrity and their results suggested that didanosine and/or stavudine may cause depleted brain mitochondria (Schweinsburg, Taylor et al. 2005). On a cellular level too, NRTIs have been implicated in CNS toxicity. Abacavir induced endoplasmic reticulum (ER) stress in human astrocytes at therapeutic doses, activating all three unfolded protein response (UPR) pathways *in vitro* (Nooka and Ghorpade 2017, Nooka and Ghorpade 2018). Oligodendrocyte dysfunction (both *in vitro* and *in vivo* with intravenous administration) seen with other ART drugs (such as ritonavir and lopinavir) was not observed in NRTIs (Jensen, Monnerie et al. 2015). In mice, long-term intraperitoneal NRTI administration at clinically relevant concentrations led to mtDNA deletion and mitochondrial toxicity in cortical neurons (Zhang, Song et al. 2014, Hung, Chen et al. 2017). Additionally, TDF has been associated with increased risk of developing chronic kidney disease (Scherzer and Shlipak 2015) (presumably through mitochondrial nephrotoxicity (Rodriguez-Nóvoa, Alvarez et al. 2010)) which, in itself, is known to cause cognitive decline (Etgen, Chonchol et al. 2012). Overall, given the link between mitochondrial dysfunction and cognitive impairment (Finsterer 2012), researchers have suggested that although no direct clinical association has been found, NRTI-related mitochondrial toxicity may directly or indirectly contribute to the development of HAND (Hung, Chen et al. 2017).

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

NNRTIs include, in order of approval, nevirapine, delavirdine, efavirenz, etravirine, rilpivirine and doravirine. Unlike NRTIs, these drugs do not resemble nucleotides/nucleosides and act on reverse transcriptase noncompetitively to impair cDNA synthesis. Although this class is generally better tolerated than NRTIs, resistant HIV strains became problematic, necessitating that NNRTIs be used in combination with other antiretrovirals (hence cART) (Margolis, Heverling et al. 2014). As a class, the most common adverse event is rash, though individual drugs in this class have their own specific side effect profiles (Drake 2000).

Of the NNRTIs, the most infamous for CNS toxicity is efavirenz, which in the past was also one of the most commonly prescribed cART components due to its efficacy and favorable pharmacokinetics (Shah, Gangwani et al. 2016). Efavirenz has been associated with both neurological (dizziness, insomnia, vivid dreams, headache, and impaired concentration) and

psychiatric (paranoia, hallucinations, anxiety, mania, and depression) adverse effects (Apostolova, Funes et al. 2015). These adverse effects occur in upwards of half of patients taking efavirenz and although they typically resolve after several weeks, some can be more persistent (Arendt, de Nocker et al. 2007). The adverse effect most classically associated with efavirenz is vivid dreams. An ambulatory electroencephalogram (EEG) study found that patients taking efavirenz (in a dose-dependent manner) had longer sleep latencies and shorter duration of rapid eye movement (REM) sleep, which was theorized to result in more intense REM periods (i.e. vivid dreams) (Gallego, Barreiro et al. 2004). This lack of sleep efficacy (which typically persists for over 3 months of therapy) also would explain the daytime fatigue and somnolence experienced by patients on the medication (Moyle, Fletcher et al. 2006). Psychiatric symptoms caused by efavirenz exposure can be even more disabling for certain patients. The population of PLWH already have higher rates of psychiatric disorders than the general population (with nearly half of PLWH screening positive) (Bing, Burnam et al. 2001). Clinicians therefore need to carefully screen and monitor their patients when prescribing efavirenz, especially since it may cause increased rates of suicidality (Mollan, Smurzynski et al. 2014), although this remains controversial (Kenedi and Goforth 2011). However, when mental illness contraindicates this drug, using alternative regimens which have less convenient dosing schedules could lead to decreased ART adherence (Kenedi and Goforth 2011).

The mechanisms responsible for efavirenz neurotoxicity (or more relevantly, its main metabolite, 8-hydroxy-efavirenz, a more potent neurotoxin than the parent drug) are currently not well elucidated (Apostolova, Funes et al. 2015, Grilo, Joao Correia et al. 2017). Recently, there has been considerable scientific interest in understanding how pharmacogenetics impacts its CNS side effects. Research suggests that, similar to NRTIs, the toxicity of efavirenz is mediated by oxidative stress and consequent mitochondrial dysfunction (in addition to elevating intracellular pro-inflammatory factors) (Shah, Gangwani et al. 2016, Ciavatta, Bichler et al. 2017). Furthermore, efavirenz is consistently found to be more neurotoxic than other ART drugs tested, consistent with its clinical side effect profile. In one experiment of four antiretrovirals in primary rat neurons, efavirenz was the only one to cause ER stress and mitochondrial toxicity at clinically-relevant concentrations (Blas-García, Polo et al. 2014). In an *in vitro* study, efavirenz elicited a dose-dependent (encompassing the range of clinical concentrations) impairment in striatal nerve terminal mitochondrial respiration, leading to depleted ATP levels at the synapse (Stauch, Emanuel et al. 2017). In a recent *in vitro* and *ex vivo* study, efavirenz was the only NNRTI (and more potently than ART drugs in other classes) that demonstrated detrimental effects on neuronal viability, morphology, respiration, and excitability when exposed to rat cortical neurons at target plasma concentrations (Ciavatta, Bichler et al. 2017).

Given the well-characterized CNS side effect profile of efavirenz and the persistence of HAND in the cART era, researchers were interested in its effect on cognitive function. As expected, efavirenz is associated with long-term cognitive impairment. In a recent large cohort study, patients taking long-term efavirenz had significant neurocognitive impairment in many domains compared to those taking lopinavir-ritonavir. This effect was less among HCV seropositive individuals (Ma, Vaida et al. 2016). Another large study observed efavirenz use was associated with HAND, with higher education acting as a protective factor

(Ciccarelli, Fabbiani et al. 2011). Switching patients from efavirenz to an alternative regimen did not lead to improvement in neurocognitive measures after 10 weeks, suggesting that efavirenz likely leads to persistent neurocognitive dysfunction (Payne, Chadwick et al. 2017).

Other drugs in the NNRTI class in addition to efavirenz are known to have CNS toxicity, with nevirapine being more toxic than the remaining NNRTIs (Shah, Gangwani et al. 2016). However, compared to efavirenz, these drugs' CNS side effects are less studied, less frequent, and less significant in clinical practice (Abers, Shandera et al. 2014).

Protease Inhibitors (PI)

In the HIV life cycle, once mRNA is translated into protein precursors, a virally-encoded protease is required to cleave these into mature proteins (Flexner 1998, Brik and Wong 2003). The protease enzyme as a therapeutic target led to the development of protease inhibitors, including saquinavir mesylate, ritonavir, indinavir, nelfinavir mesylate, lopinavir, atazanavir sulfate, fosamprenavir calcium, tipranavir, and darunavir. Of note, after discovering the cytochrome P450-inhibiting effects of ritonavir, it is now used mostly as a pharmacokinetic booster, allowing for less-frequent dosing of PI-containing regimens (Lv, Chu et al. 2015). In comparison to NNRTI-containing regimens, PI-based regimens were found to have lower rates of resistance (Riddler, Haubrich et al. 2008), though the use of PIs has been limited by their drug-drug interactions and off-target toxicities. In particular, they can cause lipodystrophy syndrome (due to homology between protease enzyme and two lipid metabolism enzymes) and insulin resistance (which in some cases, can lead to the development of diabetes), in addition to cardiovascular disease (Carr 2000, Brown, Cole et al. 2005, Lv, Chu et al. 2015). Newer PIs, such as darunavir, have been designed specifically to minimize these off-target effects (Pokorná, Machala et al. 2009).

Results from cell and animal studies of PI neurotoxicity have been mixed. In one *in vitro* study, darunavir did not cause mitochondrial toxicity in rat neurons at clinically relevant concentrations, unlike efavirenz (Blas-García, Polo et al. 2014). Lopinavir and to a lesser extent, amprenavir, caused disruption of astrocytic glutamate homeostasis *in vitro* and were associated with gliosis and neurobehavioral deficits in mice exposed to oral doses (Vivithanaporn, Asahchop et al. 2016). Lopinavir, but not darunavir, was neurotoxic to primary rat neuroglial cultures. This was thought to be mediated by oxidative stress (Stern, Lee et al. 2018). In another *in vitro* study, darunavir caused reactive oxygen species (ROS) production in astrocytes although not at clinically relevant concentrations (Latronico, Pati et al. 2018). Intravenous ritonavir and lopinavir (at doses based on human plasma and CSF levels) had detrimental effects on mice oligodendrocyte maturation *in vivo* which was reversed with drug cessation (Jensen, Monnerie et al. 2015). Investigators studying the effects of ART on neurotransmitter release found that indinavir reduced *in vitro* synaptic acetylcholine transmission at plasma-level concentrations (Ekins, Mathews et al. 2017).

PIs also appear to cause certain CNS effects on a clinical level. Ritonavir was shown to be more neurotoxic than other PIs and can cause nausea, dizziness, and circumoral paresthesia (Markowitz, Saag et al. 1995). However, using ritonavir as an pharmacokinetic enhancer

allows for lower doses, which reduces the frequency of adverse events (Hill, van der Lugt et al. 2009). Several studies (Bacellar, Muñoz et al. 1994, Pettersen, Jones et al. 2006) have found increased risk of peripheral neuropathy with PI use (although a recent analysis found the independent risk from PIs is small (Ellis, Marquie-Beck et al. 2008)). Based on results from aforementioned cell and animal studies, it is feasible that PI use could contribute to neurocognitive dysfunction. HAND has been associated with myelin disruption (with reduced levels of myelin basic protein) and structural white matter deterioration on imaging (ritonavir and lopinavir have oligodendrocyte toxicity (Jensen, Monnerie et al. 2015)). Furthermore, since neurotransmitter system dysfunction could help explain ART CNS toxicity, the authors who found impaired synaptic acetylcholine transmission with indinavir suggested that this may contribute to cognitive dysfunction (Ekins, Mathews et al. 2017). An autopsy study found that PI exposure increased the risk of cerebral small vessel disease, which was, in turn, associated with neurocognitive impairment (Soontornniyomkij, Umlauf et al. 2014). A large study did not find differences in neurocognitive performance with PI use, in comparison to triple therapy, after several years (Arenas-Pinto, Stöhr et al. 2016). Another study found that CSF viral escape (when HIV is detectable in CSF but not in the serum) is associated with PI use, but did not lead to worse neurocognitive performance (Pérez-Valero, Ellis et al. 2019). PI use is associated with hyperbilirubinemia, but this was not shown to affect neurocognitive function (Barber, Moyle et al. 2016). Despite the link between PIs and certain neurologic adverse effects, there is little, if any, clinical or preclinical evidence of a link between their use and HAND.

Integrase Inhibitors

Integrase is an HIV-encoded protein necessary for integration of viral cDNA into host DNA and after 12 years of development, the first agent in the integrase inhibitor class, raltegravir, was introduced in 2007 (Pommier, Johnson et al. 2005), followed by dolutegravir, elvitegravir, and most recently approved, bictegravir in 2018. In general, these drugs are some of the most efficacious among antiretrovirals, have low rates of resistance, and are relatively tolerable in the clinical setting (Patel P. 2018). The most common side effects of this class include diarrhea, nausea, and headache (del Mar Gutierrez, Mateo et al. 2014). In clinical trials, raltegravir had lower rates of CNS adverse events than efavirenz and similar rates of severe adverse effects relative to placebo (Lennox, DeJesus et al. 2010, Steigbigel, Cooper et al. 2010, Nguyen, Isaacs et al. 2011). Subsequent studies found higher rates of myalgia in patients taking raltegravir although this was rarely a cause for discontinuation (Lee, Amin et al. 2013). A large study in Botswana found evidence for neural tube defects associated with dolutegravir use during pregnancy (Zash, Jacobson et al. 2017, Zash, Makhema et al. 2018). The most common neuropsychiatric effect reported with raltegravir and dolutegravir is insomnia which was reversible after drug cessation and can be improved by switching to morning dosing schedules (Gray and Young 2009, Capetti, Di Giambenedetto et al. 2017). Other neuropsychiatric effects linked to integrase inhibitors include depression and anxiety and have been found to have higher rates than initially suggested by clinical trials (Harris, Larsen et al. 2008, Curtis, Nichols et al. 2014, Fettiplace, Stainsby et al. 2017, Harris 2018). A large clinical study found that the discontinuation rates due to adverse events for raltegravir, dolutegravir, and elvitegravir were 3.6, 3.8, and 5.0%

(Penafiel, de Lazzari et al. 2017). Dolutegravir had higher rates of discontinuation due to neuropsychiatric effects compared to raltegravir and elvitegravir. These results were consistent with findings from a previous cohort study which additionally showed an almost three-fold increase in discontinuation rate in female patients and older patients (Hoffmann, Welz et al. 2017). When bictegravir was introduced, trials found rates of neuropsychiatric effects comparable to dolutegravir, suggesting a class effect of integrase inhibitors (Gallant, Lazzarin et al. 2017, Sax, Pozniak et al. 2017).

Although reports of neuropsychiatric effects from integrase inhibitors suggest neurotoxicity, underlying mechanisms for such toxicity are not fully understood. In one *in vitro* study, raltegravir did not cause mitochondrial toxicity in rat neurons at clinically-relevant concentrations, unlike efavirenz (Blas-García, Polo et al. 2014). In another, raltegravir caused ROS production in astrocytes, although not at clinically relevant concentrations (Latronico, Pati et al. 2018). However, an *in vitro* study found that elvitegravir but not raltegravir nor dolutegravir was neurotoxic to primary rat neuroglial cultures at clinically relevant plasma level concentrations. This effect was thought to be mediated by the integrated stress response (ISR) rather than strictly oxidative stress (Stern, Lee et al. 2018). The ISR is normally an adaptive response to cellular stressors which restores homeostasis but with prolonged exposure to certain insults, this response activates pathways that lead to cell death (Pakos-Zebrucka, Koryga et al. 2016).

A clinical study of dolutegravir-containing ART found high dolutegravir concentrations in the CSF, suggesting a possible mechanism by which concentration-dependent neurotoxicity causes CNS adverse effects (Letendre, Mills et al. 2014). Other than neuropsychiatric effects, integrase inhibitors do not appear to cause significant neurocognitive impairment. On the contrary, dolutegravir is being studied as a possible treatment for HAND, as discussed later.

Entry Inhibitors

To infect a host cell, the HIV envelope proteins gp41 and gp120 bind to host CD4 and then to a co-receptor, typically CCR5 or CXCR4. In 2003, enfuvirtide, a gp41 inhibitor was approved and later maraviroc, a CCR5 antagonist, gained FDA approval. Very recently, ibalizumab, a monoclonal antibody against CD4, gained approval in 2018. These drugs prevent viral entry into host cells. Of note, HIV-2 uses different chemokine receptors and therefore this class is only effective with HIV-1 (Saraiya, Kanagala et al. 2018).

Enfuvirtide use in ART is limited by its requirement of twice-daily parenteral administration due to poor solubility and rapid removal from circulation (although research shows that conjugating it with polyethylene glycol may help with this problem) (Cheng, Wang et al. 2016). However, it remains an effective therapy for drug-resistant HIV when other regimens have been exhausted (Lalezari, Henry et al. 2003. Enfuvirtide was initially thought to have increased rates of peripheral neuropathy (Fung and Guo 2004, yet subsequent studies found no clear evidence of this link (Cherry, Duncan et al. 2008). To date, there have been no significant reports of CNS toxicity in enfuvirtide, and in general, it has a favorable safety profile with adverse events mostly limited to injection-site reactions (LaBonte, Lebbos et al.

2003, Oldfield, Keating et al. 2005, Manfredi and Sabbatani 2006, Treisman and Soudry 2016).

Maraviroc is a slowly reversible, noncompetitive CCR5 antagonist. Similar to enfuvirtide, maraviroc has favorable tolerability, a limited resistance pattern, and is a potent agent in virologic failure cases (Emmelkamp and Rockstroh 2007, Emmelkamp and Rockstroh 2008). In clinical trials, maraviroc monotherapy achieved rapid viral load reduction in a matter of days (Fatkenheuer, Pozniak et al. 2005), and the most common side effects were similar between maraviroc and placebo (Yost, Pasquale et al. 2009). However, maraviroc is only effective in patients with CCR5-tropic HIV-1, a feature that limits its use and requires tropism testing prior to use (Emmelkamp and Rockstroh 2008). Unfortunately, all trials on CXCR4 inhibitors have failed due to peripheral toxicity (Shah, Gangwani et al. 2016). In *in vitro* toxicology studies, maraviroc was the least toxic to astrocytes compared to a number of ART drugs from other classes, with a TC_{50} 10,000-fold higher than CSF concentrations (Latronico, Pati et al. 2018). One *in vitro* study showed that it may cause pro-inflammatory activation of microglia cells in rats (Lisi, Tramutola et al. 2012). However, a subsequent study provided evidence against this claim, showing that by blocking CCR5 in the CNS, maraviroc could ameliorate neuropathic pain (when administered intrathecally in rats) by restoring the balance of pro- and antinociceptive factors in astrocytes and microglia (Piotrowska, Kwiatkowski et al. 2016). There have been no substantial clinical reports of neurocognitive impairment with maraviroc. Rather, maraviroc and a similar investigational drug, cenicriviroc, are being studied as potential treatment options for HAND, as discussed below.

Ibalizumab, the most recent entry inhibitor, has advantages over others in the class. Its weekly dosing could improve adherence and its unique mechanism of action could prevent cross-resistance of HIV. Although data on neurotoxicity screening in this medication is sparse, it has also been fairly well-tolerated with no significant neurological effects reported (Jacobson, Kuritzkes et al. 2009, Bruno and Jacobson 2010).

Pharmacokinetic Enhancers

When ritonavir was initially approved at a 600mg twice daily dose, toxicity (nausea, vomiting, diarrhea, etc.) led to discontinuation in up to a third of patients (Rublein, Eron Jr et al. 1999, Monforte, Lepri et al. 2000). Additionally, it led to many drug-drug interactions due to its cytochrome P450 inhibiting effects (predominantly CYP3A4 but also CYP2D6) (Kumar, Rodrigues et al. 1996, Rathbun and Rossi 2002). In humans, ritonavir increased the area under the curve (AUC) of CYP3A-metabolized drugs by up to 20-fold in humans and increased AUC of CYP2D6-metabolized drugs by 145% (Hsu, Granneman et al. 1998). Given that most PIs undergo metabolism through the CYP3A pathway, researchers quickly realized the potential of using ritonavir to “boost” levels of these drugs. Trials comparing ritonavir to dual protease inhibition with ritonavir and another drug led to substantial improvements in viral suppression and allowed ritonavir to be used at less toxic doses (Yu and Daar 2000, Michelet, Ruffault et al. 2001). With this discovery, the pharmacokinetic enhancer class was incidentally created. Adding an enhancer to an ART regimen allows for reduced pill burden, simpler regimens, and improved adherence, which all lead to increased

antiviral efficacy (Xu and Desai 2009). Ritonavir itself does not appear to have serious CNS effects although by boosting levels of other drugs, it theoretically has the potential to indirectly propagate such neurotoxic effects of antiretrovirals (Danner, Carr et al. 1995, Carr and Cooper 2000).

Cobicistat is a CYP3A inhibitor designed to enhance the activity of antiretrovirals similar to ritonavir, but holds several unique advantages such as an easier dosing schedule and a more favorable side effect profile (Xu, Liu et al. 2010, Larson, Wang et al. 2014, Marzolini, Gibbons et al. 2016, Tseng, Hughes et al. 2017). Similar to ritonavir, it is possible that it could promote potential neurotoxic effects of the medications it enhances. Although no evidence of neurotoxicity has been reported, it has not been extensively tested relative to other HIV medications.

Blood Brain Barrier (BBB)

HIV invasion of the CNS occurs early in disease progression, with the virus being detected in CSF as early as 8 days after initial exposure, leading to activation of pro-inflammatory responses in the CSF and brain parenchyma (Valcour, Chalermchai et al. 2012). In around 5-20% of HIV+ patients on ART, HIV is detected in the CSF despite elimination in the plasma below detectable limits, a term called CSF viral escape (Canestri, Lescure et al. 2010, Joseph, Cinque et al. 2016). This entity can be divided into three categories- asymptomatic, neuro-symptomatic (clinical and progressive CNS disease), and secondary (increased CSF virus resulting from a secondary infection) (Ferretti, Gisslen et al. 2015). The CSF reservoir created by this escape is associated with elevated CSF levels of neopterin (a marker of macrophage activation), and is thought to increase the risk of HAND (Chen, Gill et al. 2014, Gisslén and Hunt 2019). It was theorized that if antiretroviral drugs could penetrate the BBB, this HIV reservoir could be effectively reduced, leading to improvement in CNS insult. To estimate exposure to the CNS by antiretrovirals, researchers developed the CNS penetration effectiveness (CPE) scale. Each drug is ranked from one (lowest penetrance) to four (highest penetrance) based on factors such as CSF concentration and drug pharmacology (Letendre, Ellis et al. 2010). The CPE scale's negative correlation with viral RNA in the CNS (the higher the score, the lower the viral load) was validated in several studies (Letendre, Marquie-Beck et al. 2008, Marra, Zhao et al. 2009). CPE correlation with neurocognitive performance is less clear.

Several studies found that regimens with higher CPE were associated with better neurocognitive function in addition to lower CNS levels of TNF-α, a prominent inflammatory marker (Cysique, Waters et al. 2011, Smurzynski, Wu et al. 2011, Tiraboschi, Muñoz-Moreno et al. 2015, Carvalhal, Gill et al. 2016). In contrast, other studies found either no effect or the opposite effect with higher CPE scores correlating with lower neurocognitive performance or higher risk of dementia (Marra, Zhao et al. 2009, Cross, Combrinck et al. 2013, Caniglia, Cain et al. 2014). Some found that ART intensification with high-CPE medications did not a translate to reduced intrathecal immunoactivation (Yilmaz, Verhofstede et al. 2010, Dahl, Lee et al. 2011). Furthermore, one study found that interrupting ART is associated with improved neurocognitive performance (Robertson, Su et al. 2010). Participants in this study took older, more toxic regimens, so the relevance of this

finding for newer ART is unclear. Another study found that placing patients on higher CPE regimens only improved neurocognition in patients who were impaired at baseline (Tozzi, Balestra et al. 2009). Authors of these studies suggest that although highly-penetrating regimens are effective at reducing the CNS viral reservoir, they also have higher potential to exert neurotoxicity. Future investigation is required to determine which regimens can optimally suppress HIV in the CNS while simultaneously minimizing neurotoxicity, in the hopes of stabilizing or improving neurocognition.

Aging and Antiretrovirals

With the advent of ART, HIV+ patients have been living longer, and while this is a step in the right direction, the graying of this population brings with it certain clinical ramifications (Kirk and Goetz 2009). For instance, age-related multimorbidity in PLWH (including metabolic syndrome and vascular disease) may also contribute to neurotoxicity, with the resulting polypharmacy increasing the risk of drug-drug interactions that could cause CNS injury (Alonso-Villaverde, Aragonès et al. 2010, Tarr and Telenti 2010). Although the underlying mechanisms remain largely unclear, HIV and aging appear to independently contribute to neurocognitive decline and HAND development (Cañizares, Cherner et al. 2014, Seider, Luo et al. 2014, Coban, Robertson et al. 2017). This suggests that HIV patients experience premature and accelerated aging, although some researchers question whether the root cause is HIV itself or rather the deleterious effects from therapy (Smith, de Boer et al. 2012).

A working hypothesis to explain the accelerated aging phenomenon is that age-related CNS injury resulting from toxicity of ART and concomitant drugs enhance vulnerability to CNS complications, even in those with virologic control. Aging-related changes in drug distribution, binding proteins, metabolism and elimination can lead to greater ART drug exposure in the elderly (Mangoni and Jackson 2004, Klotz 2009, Winston, Jose et al. 2013). Aging causes structural and functional changes in the BBB, such as decreased endothelial cell counts, choroid plexus epithelium flattening and calcification, as well as thickening of basement and arachnoid membranes. These changes result in increased BBB permeability which may likely affect ART CNS pharmacokinetics (Erdő, Denes et al. 2017). PI distribution in the CNS seems to be particularly affected by age, with studies showing that elderly HIV+ patients have decreased clearance of lopinavir and darunavir, longer half-life of indinavir, and higher total exposure of atazanavir (Zhou, Havlir et al. 2000, Crawford, Spritzler et al. 2010, Avihingsanon, Kerr et al. 2013, Winston, Jose et al. 2013, Calza, Colangeli et al. 2017).

Current research is investigating ways to mitigate accelerated cognitive aging in PLWH. One trial (NCT02936401) is currently assessing the use of Mindfulness Based Stress Reduction as a method to improve function in patients older than 60 with HAND. Another (NCT03483740) is testing cognitive remediation group therapy in a similar cohort of older individuals with HAND. A comprehensive review of potential HAND treatment is discussed below.

Experimental HAND Treatment

Given the persistence of HAND in the cART era and the possible contribution from antiretroviral neurotoxicity, a number of previous and current trials have investigated possible therapeutic options to combat HAND (Cross and Kolson 2017). These include drugs already approved for treating other neurodegenerative diseases (selegiline and memantine) (Schifitto, Navia et al. 2007, Schifitto, Zhang et al. 2007), drugs predominantly used for nonneurologic conditions (minocycline, fluconazole, intranasal insulin [NCT03277222], and statins [NCT01600170]) (Rezaie-Majd, Maca et al. 2002, Sacktor, Miyahara et al. 2011, Gerena, Skolasky et al. 2012, Nakasujja, Miyahara et al. 2013, Meulendyke, Queen et al. 2014, Sacktor, Skolasky et al. 2018), and antioxidants (Coenzyme Q_{10}, heme oxygenase-1, and dimethyl fumarate) (Cross, Cook et al. 2011, Louboutin and Strayer 2018, Velichkovska, Surnar et al. 2018).

Although some ART drugs are associated with neurotoxicity, several ongoing trials are testing treatment intensification approach for cognitive improvement. One trial (NCT01448486) investigated the effects of raltegravir intensification on neurocognitive performance but was unfortunately stopped prematurely due to insufficient patient recruitment. Maraviroc intensification in humans caused an improvement in neuropsychiatric performance, hypothesized to result from reducing the HIV burden in monocytes, leading to two current clinical trials (NCT02159027 and NCT02519777) (Burdo, Weiffenbach et al. 2013, Ndhlovu, Umaki et al. 2014). Cenicriviroc, when given to HAND patients, led to decreased inflammatory monocyte activation and subtle improvement in cognitive performance (D'Antoni, Paul et al. 2018).

Apart from a few mild successes in trials listed above, we still have not discovered a consistent and efficacious treatment or prevention of HAND. The explanation for this lack of effectiveness is multifactorial. Inherently, clinical trials frequently fail despite promising preclinical results, due to inadequate patient recruitment/retention, fundamental differences between animal models and human subjects, unforeseen adverse effects, etc. More specifically, the underlying epidemiology, natural progression, and pathogenesis behind HAND still eludes us. Does persistent HAND despite virologic suppression result from incomplete antiretroviral CSF penetration, direct or indirect neurotoxicity from antiretrovirals, or something else entirely? Without a clear pathological target, developing specific treatment modalities becomes exceptionally challenging. This is why the impetus for the aforementioned clinical trials came either from medications that showed neuroprotection in other diseases or simply came from incidental findings in the clinic. As such, it is unlikely that these therapies could actually reverse ART-induced specific neurotoxicities rather than simply imparting general neuroprotection. In order to properly confront this disease entity, more research to provide answers to preclinical questions about HAND is essential.

Conclusions

Antiretroviral neurotoxicity is a growing body of research, with novel molecular, cellular, and animal studies uncovering the pathogenesis of such toxicity and relating it to clinical

manifestations seen in patients. Each medication has a unique side effect profile, but understanding their long-term effects is becoming increasingly relevant, as the development of new therapy extends the average lifespan of PLWH. New challenges are being uncovered with this aging population, given that they experience longer cumulative ART exposure, have more comorbidities, and develop changes in their pharmacokinetic responses to such drugs (Erdő, Denes et al. 2017). Although HIV exerts neurotoxic effects on the brain and can use the CNS as a reservoir for replication, the fact that regimens with higher CPE do not necessarily lead to cognitive improvement has led researchers to hypothesize that ART itself may, in part, contribute to neurotoxicity (Caniglia, Cain et al. 2014). This theory is supported by the persistence of HAND in the cART era (Heaton, Clifford et al. 2010).

Despite the potential for ART-induced neurotoxicity, viral load reduction in the plasma and CNS should remain the principal objective of antiretroviral treatment. Moving forward, we advocate for the following: 1) clinicians maintain a high level of suspicion of HAND (even when sufficiently treated), 2) scientists continue to unravel the epidemiology and pathogenesis of ART-induced neurotoxicity with rigorous studies, and 3) researchers develop and assess novel treatment options for such neurotoxicity, including HAND.

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Table 1

Antiretroviral medications by class, including year of approval and CNS penetration effectiveness (CPE) score, a measurement of how well medications penetrate the CNS

	Abbreviation	Approval Year	CPE Score
NRTI			
azidothymidine/zidovudine	AZT/ZDV	1987	4
didanosine	ddI	1991	2
stavudine	d4T	1994	2
lamivudine	3TC	1995	2
abacavir	ABC	1998	3
tenofovir disoproxil fumarate	TDF	2001	1
emtricitabine	FTC	2003	3
tenofovir alafenamide	TAF	2015	1
NNRTI			
nevirapine	NVP	1996	4
delavirdine	DLV	1997	3
efavirenz	EFV	1998	3
etravirine	ETR	2008	2
rilpivirine	RPV	2011	-
doravirine	DOR	2018	-
Protease Inhibitors			
saquinavir mesylate	SQV	1995	1
ritonavir *	RTV	1996	1
indinavir	IDV	1996	3
nelfinavir mesylate	NFV	1997	1
lopinavir	LPV	2000	3
atazanavir sulfate	ATV	2003	2
fosamprenavir calcium	FOS	2003	2
tipranavir	TPV	2005	1
darunavir	DRV	2006	3
Fusion Inhibitors			
enfuvirtide	T-20	2003	1
CCR5 Co-receptor Antagonists			
maraviroc	MVC	2007	3
Integrase Inhibitors			
raltegravir	RAL	2007	3
dolutegravir	DTG	2013	-
elvitegravir	EVG	2014	-
bictegravir	BIC	2018	-

	Abbreviation	Approval Year	CPE Score
Post-Attachment Inhibitors			
ibalizumab	IBA	2018	-
Pharmacokinetic Enhancers			
ritonavir *	RTV	1996	1
cobicistat	COBI	2014	-

* Ritonavir is used clinically as a PK enhancer rather than an antiretroviral.