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## Beneficial and Adverse Effects of cART Affect Neurocognitive Function in HIV-1 Infection: Balancing Viral Suppression against Neuronal Stress and Injury

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### Abstract

HIV-associated neurocognitive disorders (HAND) persist despite the successful introduction of combination antiretroviral therapy (cART). While insufficient concentration of certain antiretrovirals (ARV) may lead to incomplete viral suppression in the brain, many ARVs are found to cause neuropsychiatric adverse effects, indicating their penetration into the central nervous system (CNS). Several lines of evidence suggest shared critical roles of oxidative and endoplasmic reticulum stress, compromised neuronal energy homeostasis, and autophagy in the promotion of neuronal dysfunction associated with both HIV-1 infection and long-term cART or ARV use. As the lifespans of HIV patients are increased, unique challenges have surfaced. Longer lives convey prolonged exposure of the CNS to viral toxins, neurotoxic ARVs, polypharmacy with prescribed or illicit drug use, and age-related diseases. All of these factors can contribute to increased risks for the development of neuropsychiatric conditions and cognitive impairment, which can significantly impact patient well-being, cART adherence, and overall health outcome. Strategies to increase the penetration of cART into the brain to lower viral toxicity may detrimentally increase ARV neurotoxicity and neuropsychiatric adverse effects. As clinicians attempt to control peripheral viremia in an aging population of HIV-infected patients, they must navigate an increasingly complex myriad of comorbidities, pharmacogenetics, drug-drug interactions, and psychiatric and cognitive dysfunction. Here we review in comparison to the neuropathological effects of HIV-1; the available information on neuropsychiatric adverse effects and neurotoxicity of clinically used ARV and cART. It appears altogether that future cART aiming at controlling

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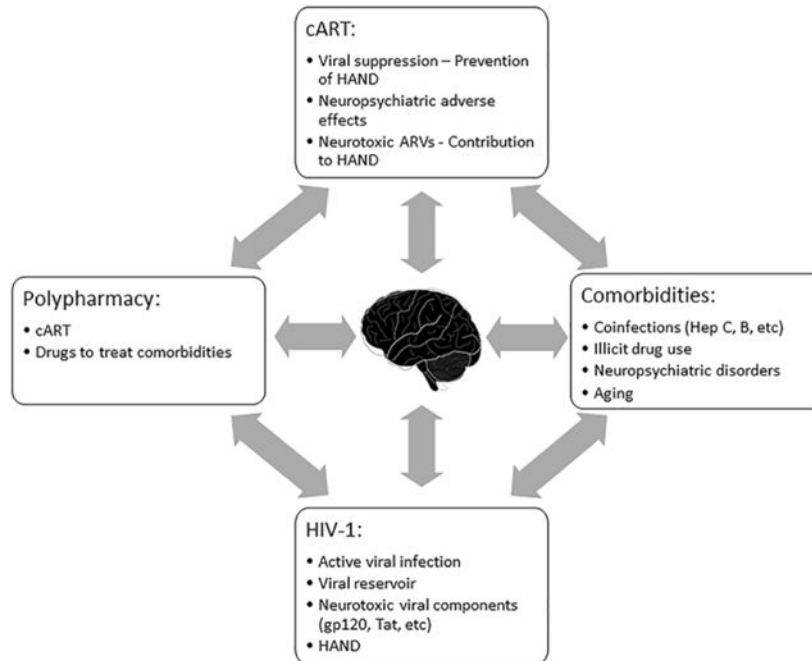
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HIV-1 in the CNS and preventing HAND will require an intricate balancing act of suppressing viral replication while minimizing neurotoxicity, impairment of neurocognition, and neuropsychiatric adverse effects.

## Graphical Abstract



## Keywords

HIV-1; infection; AIDS; NeuroHIV; HAND; antiretroviral; cART; brain; behavior; neurocognition; stress; toxicity

## Introduction

In the early 1980s, infection with human immunodeficiency virus (HIV-1) and acquired immunodeficiency syndrome (AIDS) developed into an acute epidemic (Fauci, 1999; Piot et al., 2001). The first drug for treatment of HIV-1 infection, azidothymidine (AZT)/zidovudine (ZDV) was reported in 1985 and approved by the Food and Drug Administration (FDA) in the United States in 1987. The discovery of additional, new classes of antiretrovirals and the introduction of combination antiretroviral therapy (cART), also known as highly active antiretroviral therapy (HAART), in the mid-1990s eventually changed the course of HIV-1 infection into a chronic but manageable disease, if treatment is available (Vella et al., 2012) (<http://www.unaids.org/en/resources/fact-sheet>). Nevertheless, 2.1 million people become newly infected by HIV-1 each year and more than 1 million people die from AIDS-related causes. As of 2017, UNAIDS estimates that the number of people living with HIV has grown globally to 36.9 million with 21.7 million receiving cART (UNAIDS, 2018). More than 1.2 million people live with HIV in the USA alone (<http://www.cdc.gov/hiv/>) (UNAIDS, 2013, 2015). HIV affects all organs that are infiltrated by permissive cells and

thus enable the formation of viral reservoirs (Folks et al., 1988; Rothenberger et al., 2015; Sung and Margolis, 2018). HIV-infection of the central nervous system (CNS) frequently causes neurological problems, including neuropathic pain, and in about 50% of patients it leads to HIV-associated neurocognitive disorder (HAND) (Tozzi et al., 2001; Simpson et al., 2002; Cysique et al., 2004; Antinori et al., 2007; Heaton et al., 2010a; Saylor et al., 2016). Despite the use of antiretrovirals (ARVs) and effective virological control, HAND persists and the contributing neuropathological mechanisms remain to be fully elucidated (Kaul et al., 2001; Antinori et al., 2007; Kaul, 2008; Heaton et al., 2010a; McArthur et al., 2010; Simioni et al., 2010; Saylor et al., 2016).

The advent and availability of cART together with early intervention has lengthened patient lifespans to near normal ages (Antiretroviral Therapy Cohort, 2017) and reduced the incidence of HIV-associated dementia (HAD), the most severe form of HAND (Eisfeld et al., 2013; Heaton et al., 2015). However, it has become evident over time that most ARVs have neuropsychiatric adverse effects (DHHS, 2018), and the prevalence of cognitive impairment milder than dementia remains high in individuals living with HIV and receiving cART (McArthur et al., 2010; Heaton et al., 2011; Saylor et al., 2016). Moreover, recent studies found that a temporary interruption of cART in virologically controlled HIV patients gave rise to significant improvements of neurocognitive function (Robertson et al., 2010; Evans et al., 2011; Evans et al., 2012; Underwood et al., 2014). Meanwhile, several lines of experimental evidence suggest that at least some ARV compounds can themselves exert neurotoxicity (Lewin et al., 1995; Carr, 2003; Keswani et al., 2003; Robertson et al., 2012a; Akay et al., 2014; Sanchez et al., 2016; Sanchez and Kaul, 2017). All these observations suggest that HIV patients are at risk of exposure to a combination of potential contributors to neurotoxicity and HAND: namely HIV and its components and certain ARVs and their combinations. In this review we will discuss current information on HIV-1 and ARV effects on the CNS, the combination of which is encountered in the clinical setting as a chronic situation. The neurotoxic and neuropsychiatric effects of both the treatment and the disease itself requires a better understanding of the pathological and pharmacological mechanisms at the organismal and cellular level.

### HIV-1 Infection

HIV-1 infection can be transmitted through certain body fluids including blood, semen, pre-seminal fluids, rectal fluids, vaginal fluids, and breast milk. Consequently, HIV-1 can be contracted through sexual contact, blood transfusion, needle-sharing, and from an infected mother to a child. Human CD4 and coreceptors, in particular chemokine receptors CXCR4 (CD184) and CCR5 (CD195), are the sites of host-virus interaction that mediate infection. The envelope protein of HIV-1, gp120, binds to CD4 receptors exclusively expressed on specific immune cells, to engage chemokine coreceptors. This action initiates infection of the virus' primary target cells: macrophages and T-lymphocytes (Alkhatib et al., 1996; Bleul et al., 1996; Dragic et al., 1996; Oberlin et al., 1996; Trkola et al., 1996). Presumably within hours of infection in the periphery, the virus arrives in the brain where CCR3, besides CCR5, seems to facilitate HIV infection of microglia (He et al., 1997; Kaul et al., 2001; Gonzalez-Scarano and Martin-Garcia, 2005). Although CCR5-preferring (R5) HIV-1 are generally considered as being macrophage-tropic (M-tropic) and CXCR4-preferring virus

strains (X4) as infecting T-lymphocytes (T-tropic), the reality appears less clear-cut. It has been discovered that syncytia-inducing viruses initially thought to be only X4-tropic can in fact be dual-tropic and infect via CXCR4 or CCR5 (Simmons et al., 1996). Additionally, M- and T-tropic SIV strains can enter target cells using CCR5 (Edinger et al., 1997). Overall, HIV-infected CD4<sup>+</sup> T-lymphocytes seem to be highly efficient propagators of the virus, but also rapidly succumb to apoptosis, with the exception of a distinct number of memory cells that form a quiescent, latent reservoir (Bukrinsky et al., 1991; Pantaleo and Fauci, 1995; Chun and Fauci, 1999; Alexaki et al., 2008). In contrast, HIV-1 infected macrophages, which appear to be less efficient virus producers, can be a comparably long-lived reservoir that presumably carries the virus into the brain and passes it on to local macrophages and microglia (Ho et al., 1985; Koenig et al., 1986; Kaul et al., 2001; Collman et al., 2003; Gonzalez-Scarano and Martin-Garcia, 2005). ARVs have variable penetration across the blood-brain barrier (BBB), let alone the ability to reach therapeutic drug concentrations in the CNS. Several studies have reported a discordance between HIV RNA levels found in the cerebral spinal fluid (CSF) versus the plasma. Patients receiving cART and achieving suppression of plasma viremia (<50 copies/mL) have presented with neurological symptoms and were found to have higher levels of HIV RNA in the CSF (>200 copies/mL). In some patients, genotyping revealed resistance-associated mutations toward ARVs in the CSF viral population; suggesting that treatment was failing specifically in the CNS (Canestri et al., 2010; Peluso et al., 2012). Consequently, the CNS constitutes an HIV-1 reservoir which poses a major challenge for viral eradication (Nath, 2015; Ellis and Letendre, 2016; Gray et al., 2016).

### **HIV-1 Associated Neurocognitive Disorders (HAND) and Neuropathology**

HIV-1 infected adults and children of all ages are at risk of developing neurological symptoms that comprise motor and cognitive dysfunction, termed HIV-associated neurocognitive disorders (HAND) (Navia et al., 1986; Price et al., 1988; Kaul et al., 2001; Antinori et al., 2007). Based on a panel of standardized measures, HAND is classified into three categories of disorders with increasing severity of dysfunction: i) asymptomatic neurocognitive impairment (ANI), ii) mild neurocognitive disorder (MND) and iii) HAD. The introduction of cART lowered the incidence of HAND's most severe form, dementia, indicating a beneficial effect on cognitive function (Sacktor et al., 2001; Eisele et al., 2013; Heaton et al., 2015). Nevertheless, HAND/HAD remains a significant independent risk factor for death due to AIDS, and the prevalence of milder cognitive impairment (ANI, MND) continues to be high in HIV patients on cART (McArthur et al., 1993; Ellis et al., 1997; Wright et al., 2008; Heaton et al., 2010b; McArthur et al., 2010; Heaton et al., 2011; Saylor et al., 2016). Improved control of viral replication in the periphery and efficient therapy of opportunistic infections succeed in prolonging survival, but current cART regimens largely fail to protect from HAND or to reverse the disease (Cunningham et al., 2000; McArthur et al., 2003; Cysique et al., 2006; Giancola et al., 2006; Nath and Sacktor, 2006; Brew et al., 2009; Saylor et al., 2016). More than 90% of a group of 669 HIV patients receiving the first iterations of cART and who passed away between 1996 and 2001, developed HAD in the last 12 months of life as an AIDS-defining condition (Welch and Morse, 2002). Also, the proportion of new HAND/HAD cases with a CD4<sup>+</sup> T cell count above 200  $\mu\text{l}^{-1}$  is growing (Sacktor et al., 2002; McArthur et al., 2003). Thus, as people live

longer with HIV-1 infection the prevalence of dementia could continue to rise despite cART (Lipton, 1997; Cunningham et al., 2000; Kaul et al., 2001; McArthur et al., 2003; Kaul et al., 2005; Kramer-Hammerle et al., 2005; Jones and Power, 2006; Saylor et al., 2016).

The neuropathology of HIV-1 infection is often described as HIV encephalitis (HIVE); displaying activated resident microglia, microglial nodules, multinucleated giant cells, infiltration predominantly by monocytoïd cells, including blood-derived macrophages, and decreased synaptic and dendritic density, combined with selective neuronal loss, widespread reactive astrocytosis, and myelin pallor (Petito et al., 1986; Masliah et al., 1997). A subset of those pathological features, namely the increased numbers of microglia (Glass et al., 1995), decreased synaptic and dendritic density, selective neuronal loss (Achim et al., 1994; Wiley et al., 1994; Masliah et al., 1997), elevated tumor necrosis factor (TNF)- $\alpha$  mRNA in microglia and astrocytes (Wesselingh et al., 1997), and evidence of excitatory neurotoxins in cerebrospinal fluid (CSF) and serum (Heyes et al., 1991) present the best correlates of *ante mortem* signs of cognitive impairment. Additionally, two reports have also suggested an important role for myeloid cells in the outcome of HIV-1 infection in the CNS, showing that the risk of developing HAD correlated better with the amount of proviral HIV DNA in circulating monocytes and macrophages than with viral load (Shiramizu et al., 2005; Shiramizu et al., 2006).

Distinct brain regions suffer neuronal damage and loss in association with HIV infection; including the frontal cortex (Ketzler et al., 1990; Everall et al., 1991), substantia nigra (Reyes et al., 1991), cerebellum (Graus et al., 1990), and putamen (Everall et al., 1993). Signs of neuronal apoptosis have also been observed in brains of HAD patients (Petito and Roberts, 1995; Adle-Biassette et al., 1999; Rostasy et al., 2000). Especially within subcortical deep gray structures, apoptotic neurons were localized and correlated with signs of structural damage and evidence of microglial activation (Adle-Biassette et al., 1999).

Introduction of cART changed HIV neuropathology. Although opportunistic infections were largely controlled or absent, two *post-mortem* studies found more macrophage/microglia infiltration and activation in the hippocampus and basal ganglia (Langford et al., 2003b; Anthony et al., 2005). However, whereas Anthony et al found an overall decrease in HIVE in the Edinburgh cohort post-cART, Langford et al observed an increase in HIVE in the University of California-San Diego (UCSD) cohort in the cART era. HIV patients in the UCSD cohort who had failed cART showed even more signs of encephalitis and severe leukoencephalopathy (Langford et al., 2003b). Another autopsy cohort from a population in Oslo, Norway has found that HIV-induced brain lesions increases with lengthened survival times (Maehlen et al., 1995). Interestingly, this study noted that antiretroviral treatment, particularly ZDV/AZT, reduced the incidence of brain lesions but only if continued until death; those who discontinued use presented an increase in HIVE. Another *post-mortem* study of 436 HIV-seropositive patients who died between 1985 and 1999 found an increase in HIVE over time ( $p=0.014$ ) despite increasing efficiency of cART regimens (Neuenburg et al., 2002). Likewise, a study performed in Brazil has found that HIVE is more frequent in autopsy cases performed on patients who received cART for 3 months or more than those who had no antiretroviral treatment (Silva et al., 2012). A study in Milan, Italy, which was divided into four time periods on the basis of wide treatment availability (1984–1987 no

therapy, 1988–1994 monotherapy, 1995–1996 dual combination therapy, 1997–2000 triple therapy) noted a marked decrease in HIV over time (Vago et al., 2002). Interestingly, differences in treated and untreated patients in the last period, for whom actual drug treatments received are known, were not statistically significant. It is important to note, as Bell points out in a review, that deaths and resulting *post-mortem* studies among cART recipients represent a population of HIV patients who experienced treatment failure; thus, neuropathology findings may not be representative of treated patients who survive (Bell, 2004). (Anthony et al., 2006). One report of the changing neuropathology in the era of cART described various forms of severe HIV and white matter injury with extensive perivascular lymphocytic infiltration, suggesting ‘burnt-out’ forms of HIV (Everall et al., 2005). Additional recent reports have shown *post-mortem* findings of aging-related accumulation of beta-amyloid implying an Alzheimer’s Disease-like neuropathology (Green et al., 2005) and cART-treated individuals presenting a greater number of hyperphosphorylated tau-positive neurofibrillary tangles and pre-tangles when compared with age-matched controls (Anthony et al., 2006). As the guidelines for antiretroviral therapies are still evolving, the neuropathological nature of HIV patients on modern drug regimens has yet to be fully elucidated.

### HIV-1 Neurotoxicity

Besides microglia and macrophages in the brain, neurons and astrocytes also express chemokine receptors, including CCR5 and CXCR4 (Asensio and Campbell, 1999; Kaul and Lipton, 1999; Miller and Meucci, 1999; Kaul et al., 2007), but the latter cell types do not obviously permit productive HIV-1 infection under *in vivo* conditions. However, numerous *in vitro* studies suggest that HIV-associated neuronal damage prominently involves CXCR4 while CCR5 appears to play a dual role by mediating either toxic or protective effects depending on the available ligands (Hesselgesser et al., 1998; Meucci et al., 1998; Kaul and Lipton, 1999; Zheng et al., 1999; Meucci et al., 2000; Kaul et al., 2007; Maung et al., 2014). Besides intact HIV-1, picomolar concentrations of isolated viral envelope gp120 suffice to trigger CXCR4 and CCR5 receptors to cause injury and death of neurons of humans and rodents (Brenneman et al., 1988; Hesselgesser et al., 1998; Meucci et al., 1998; Kaul and Lipton, 1999; Ohagen et al., 1999; Chen et al., 2002; Garden et al., 2004; Iskander et al., 2004; Walsh et al., 2004; O’Donnell et al., 2006; Kaul et al., 2007). In addition to the Env glycoprotein gp120, ample experimental evidence demonstrates that various other viral proteins such as Tat, Nef, Vpr, and gp41, the membrane anchor of gp120, have the potential to cause neuronal injury and death (Brenneman et al., 1988; Adamson et al., 1996; New et al., 1997; Piller et al., 1998; Koedel et al., 1999; Kaul et al., 2001; Kaul et al., 2005; Mattson et al., 2005; Ellis et al., 2007; Saylor et al., 2016; Langford et al., 2018).

The mechanisms remain controversial of how exactly HIV-1 infection leads to neurocognitive and motor dysfunction and to neuronal injury and death (Kaul et al., 2001; Gonzalez-Scarano and Martin-Garcia, 2005; Kaul et al., 2005; Kramer-Hammerle et al., 2005; Mattson et al., 2005; Ellis et al., 2007; Smith et al., 2016). It is generally agreed upon that HIV-1 fails to infect post-mitotic, mature neurons but we and others observed more recently that HIV-1 proteins such as gp120 and Tat can compromise neurogenesis (Krathwohl and Kaiser, 2004; Okamoto et al., 2007; Schwartz et al., 2007; Kaul, 2008;

Langford et al., 2018). All the studies, especially those addressing neurotoxicity, have contributed to the development of at least two different scenarios describing how HIV-1 causes brain injury and neurocognitive dysfunction: the “direct injury” and the “indirect” or “bystander effect” hypothesis. The hypotheses are in no way mutually exclusive, and the available data suggest a role for both. The “direct injury” hypothesis poses that viral proteins directly damage neurons absent any contribution of non-neuronal cells (microglia/macrophages and/or astrocytes). Experiments supporting this scenario show that viral envelope protein gp120, Tat, and Vpr are toxic in serum free primary neuronal cultures (Meucci et al., 1998; Meucci et al., 2000) or in neuroblastoma cell lines (Hesselgesser et al., 1998; Piller et al., 1998; Mattson et al., 2005).

However, under conditions where glial and neuronal cells are present and which recapitulate the cellular composition of the brain, the indirect neurotoxicity mediated by macrophages and microglia may predominate (Giulian et al., 1990; Genis et al., 1992; Gartner, 2000; Kaul et al., 2001; Gonzalez-Scarano and Martin-Garcia, 2005; Kaul et al., 2005; Mattson et al., 2005; Medders et al., 2010; Maung et al., 2014). Intact HIV-1, gp120, and Tat seem to induce neuronal injury and apoptotic death predominantly in an indirect manner via the induction of soluble toxins from macrophages and microglia (Brenneman et al., 1988; Giulian et al., 1990; Kaul and Lipton, 1999; Chen et al., 2002; Garden et al., 2004; Iskander et al., 2004; Walsh et al., 2004; Sui et al., 2006; Medders et al., 2010; Gill et al., 2015).

HIV-1 infected or gp120-exposed microglia and macrophages produce factors that stimulate the *N*-methyl-*D*-aspartate-type receptor (NMDAR), an ionotropic glutamate and neurotransmitter receptor (Dreyer et al., 1990; Chen et al., 2002; O'Donnell et al., 2006). Under normal physiological conditions, activation of neuronal ionotropic glutamate receptors initiates a transient depolarization and excitation that serves a crucial role in neurocognitive function (Olney et al., 1991; Doble, 1999). However, excessive and/or extended stimulation of NMDARs leads to excitotoxicity through a sustained elevation of intracellular Ca<sup>2+</sup> concentration, which subsequently compromises mitochondrial function and cellular energy metabolism and eventually results in the excessive production of free radicals (Olney, 1969; Doble, 1999; Kaul et al., 2001; Gill et al., 2014). A mild but sustained insult, such as macrophage toxins exert in HIV infection, eventually triggers programmed cell death (apoptosis) of neurons for which evidence has been found in *post-mortem* brains of HIVE/HAD patients (Petito and Roberts, 1995; Adle-Biassette et al., 1999; Kaul and Lipton, 1999; Ohagen et al., 1999). Neuronal apoptosis resulting from toxicity of HIV-1 or gp120 or Tat or a direct excitotoxic insult involves neuronal, intracellular Ca<sup>2+</sup> overload, activation of p38 MAPK and p53, mitochondrial functional impairment with release of cytochrome c, activation of caspases, cell cycle protein and other molecules, such as apoptosis-inducing factor (AIF) from mitochondria, free radical formation, lipid release and peroxidation, and chromatin condensation (Tenneti et al., 1998; Asensio and Campbell, 1999; Kaul and Lipton, 1999; Garden et al., 2002; Haughey and Mattson, 2002; Jordan-Sciutto et al., 2002; Garden et al., 2004; Jana and Pahan, 2004; Kaul et al., 2007; Medders et al., 2010). Moreover, the activation of the unfolded protein response (UPR), amyloid precursor protein processing and changes of cellular lipid metabolism, including an increase in ceramide, sphingomyelin and hydroxynonenal have been linked to oxidative damage and

cellular distress occurring in the pathways of HIV neurotoxicity (Haughey et al., 2004; Mattson et al., 2005; Lindl et al., 2007; Saylor et al., 2016; Stern et al., 2018b).

### Antiretroviral drugs, neuropsychiatric adverse effects and HAND

There are currently over 30 US FDA-approved ARVs utilized for the treatment of HIV infection that have become available since 1987 (Fig. 1). ARV drugs are classified based on the mechanism of action and currently include i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), ii) non-nucleoside reverse transcriptase inhibitors (NNRTI), iii) protease inhibitors (PI), iv) integrase strand transfer inhibitors (INSTI), v) a fusion inhibitor (FI), and vi) two entry inhibitors (EI), one blocking chemokine receptor CCR5, the other inhibiting viral interaction with CD4. In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic enhancers (reviewed in (Badowski et al., 2016; Shah et al., 2016)). The first ARV was discovered in 1985 when a compound synthesized as a potential anti-cancer agent, 3'-azido-2',3'-dideoxythymidine, now known under the name azidothymidine (AZT), showed *in vitro* inhibition of HIV replication (Mitsuya et al., 1985). AZT was eventually approved by the Food and Drug Administration (FDA) in the United States in 1987. Several more drugs of the same pharmacological class were developed and used as monotherapy and later in dual combination, however these treatment strategies frequently led to mutations of HIV which rendered the virus resistant to the drugs. The discovery of new classes of antiretrovirals and the introduction of cART in the mid-1990s eventually changed the course of HIV-1 infection/AIDS into a chronic but manageable disease when treatment is available (Vella et al., 2012). The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a working group of the office of AIDS research) continues to update the combination regimens, utilizing more than 25 antiretroviral drugs in order to guide towards the best therapy for HIV<sup>+</sup> individuals (<http://aidsinfo.nih.gov/guidelines>). Currently both the National Institutes of Health (NIH) DHHS Guidelines and the World Health Organization (WHO) recommend a cART regimen consisting of two NRTIs (usually abacavir/lamivudine (ABC/3TC), tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)) in combination with either an INSTI such as bictegravir (BIC), dolutegravir (DTG), or raltegravir (RAL) or an NNRTI, such as efavirenz (EFV) (DHHS, 2018; 2018). Whereas the DHHS has created separate guidelines targeting i) adults and adolescents, ii) perinatal, and iii) pediatric populations; the WHO has a single set of abridged guidelines directed towards all of these groups. The DHHS guidelines for adults and adolescents contain multiple preferred regimens for adults and adolescents with multiple alternative regimens in certain clinical situations, while the WHO guidelines have preferred first-line regimens, alternative first-line regimens, and first-line regimens for special situations. These recommendations are for patients first initiating ART or ARV-naïve patients as other factors must be considered in the management of treatment-experienced patients. The DHHS suggests alternative recommended regimens for adults and adolescents and the WHO proposes preferred first-line and alternative first-line regimens for multiple populations as illustrated in Figure 2A and 2B, respectively. ARV combinations and/or regimens are chosen considering primarily antiviral efficacy, potential adverse effects (toxicity), pill burden, drug-drug interaction, comorbid conditions, and cost. Efficient cART has transformed HIV-1 infection into a chronic condition, and infected individuals are



approaching a near normal life span leading to aging with HIV as a new clinical phenomenon (Brew et al., 2009; Ciccarelli et al., 2011; Canizares et al., 2014; DeVaughn et al., 2015).

The life-saving effect of cART is indisputable. However, the incidence of cognitive impairment milder than HAD persists in HIV patients on cART (Robertson et al., 2007; Tozzi et al., 2007; McArthur et al., 2010; Simioni et al., 2010; Heaton et al., 2011; Saylor et al., 2016). This situation and distinct patterns of viral drug resistance in plasma and cerebrospinal fluid (CSF) compartments might at least in part be explained by limited penetration of HIV protease inhibitors and several of the nucleoside analogues into the brain (Cunningham et al., 2000; Kaul et al., 2005; Kramer-Hammerle et al., 2005). The development of the CNS penetration effectiveness (CPE) rank score by Letendre et al was largely based on available pharmacokinetic rather than pharmacodynamic data of ARVs (Letendre et al., 2008). This score has been well correlated to suppression of CSF viral loads. However, there have been conflicting reports on the effect of ARV CNS penetration on patient cognition. Some studies report improved cognition with higher CPE scores (Tozzi et al., 2009; Smurzynski et al., 2011; Carvalhal et al., 2016) while others observe cognitive benefits from lower CPE regimens (Marra et al., 2009; Kahouadji et al., 2013; Caniglia et al., 2014). The disparate results of these studies are confounded further by other studies which have found no significant relationship between CPE score and cognitive functioning (Robertson et al., 2012b; Ellis et al., 2014).

Multiple reports have meanwhile provided evidence that many, if not the majority of approved ARVs and clinically prescribed cART regimens have neuropsychiatric adverse effects; ranging from headache to insomnia, to depression and anxiety to suicidal ideation among other symptoms. Neuropsychiatric adverse effects reported by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents and CPE scores (if available) are summarized in Table 1 (DHHS, 2018). Among patients with HIV or AIDS, prevalence of major depression is reported to be between 22% to 45% (Atkinson et al., 1988; Maj et al., 1994; Perkins et al., 1994; McDaniel et al., 1995; Kelly et al., 1998) yet it is prospectively underdiagnosed (Evans et al., 1996; Halman, 2001). Therefore it is possible that pre-existing conditions can confound, exacerbate, or mask neuropsychiatric symptoms caused by ARVs. Mania, psychosis, and major depression are associated with HIV infection (Treisman et al., 1998). Furthermore, the impact of depression on HIV patient health can be significant and has been correlated with a more pronounced decline in the number of CD4<sup>+</sup> cells, disease progression, and increased mortality (Safren et al., 2009). In an aging population of HIV patients, social isolation and depression are particularly common and may contribute to morbidity, mortality, poor medication adherence and retention in care (Kalichman et al., 2000; Grov et al., 2010). A summary of issues surrounding ART use specifically in the elderly population has been recently reviewed (Guaraldi et al., 2018).

### **Neurotoxicity of antiretroviral drugs**

Several studies observed that discontinuation of ARV use in HIV patients with controlled suppression of viral loads and neurocognitive impairment, resulted in significant improvement of cognitive function (Robertson et al., 2010; Evans et al., 2011; Evans et al.,

2012; Underwood et al., 2015). In addition, clinical and experimental evidence is accumulating that at least some ARV compounds or combinations thereof (cART) have themselves neurotoxic effects and therefore possibly contribute to the development of HAND (Lewin et al., 1995; Carr, 2003; Keswani et al., 2003; Robertson et al., 2012a; Akay et al., 2014; Ma et al., 2016; Shah et al., 2016). Table 2 summarizes reports of neurotoxicity observed for ARV compounds.

**NRTIs:** Early versions of these ARVs carry a high risk to trigger peripheral neuropathy, in particular didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) (Dragovic and Jevtovic, 2003). Mitochondrial polymerase  $\gamma$ , an enzyme required to maintain mitochondrial DNA (mtDNA) in axons and Schwann cells seems to be the major undesired ‘off target’ (Dalakas, 2001; Venhoff et al., 2010). NRTIs that appear less likely to induce peripheral neuropathy or cellular neurotoxicity are emtricitabine (FTC), lamivudine (3TC), tenofovir (TAF or TDF) and abacavir (ABC) (Robertson et al., 2012a). The earliest antiretroviral drug ZDV/AZT has also been reported to cause mitochondrial toxicity, impaired neurogenesis and to damage neuronal dendrites and presynaptic terminals (Lewis and Dalakas, 1995; Ewings et al., 2000; Haik et al., 2000; Sanchez et al., 2016). Overall, NRTIs seem to exert limited CNS neurotoxicity that is compound- and cell-specific (Robertson et al., 2012a; Shah et al., 2016).

**NNRTIs:** Rilpivirine (TMC278) and delavirdine (DLV) are considered to be non-toxic in the CNS (Shah et al., 2016). Etravirine (ETR) appeared so far to be clinically safe but signs of a potentially neurotoxic effect were observed *in vitro* (Robertson et al., 2012a; Floris-Moore et al., 2016). However, multiple lines of evidence indicate neurotoxicity of efavirenz (EFV) and nevirapine (NVP), which are approved by the FDA and still frequently used in NNRTI regimen because they are highly efficient antiretrovirals (<http://aidsinfo.nih.gov/guidelines>), (Robertson et al., 2012a; Brown et al., 2014; Funes et al., 2014). In the clinic, EFV has been found to be associated with deterioration of neurocognition (Ciccarelli et al., 2011; Decloedt and Maartens, 2013; Ma et al., 2016). In human neuron-like SHSY-5Y cells and primary rat striatal neurons EFV was found to cause a loss of ATP, depolarization and fragmentation of mitochondria and increased mitophagy and autophagy in general, indicating that interference with cellular energy homeostasis is a mechanism of toxicity (Blas-Garcia et al., 2014; Purnell and Fox, 2014). This ARV was also found to cause endoplasmic reticulum (ER) stress in human brain endothelial cells and in microvessels of the brain in HIV-transgenic mice (Bertrand and Toborek, 2015). This latter study reported that EFV compromised autophagy by binding to a complex consisting of beclin 1, ATG14 and phosphatidylinositol 3 kinase III (PI3KIII), which is necessary for assembly of an autophagosome. An enzyme of the cytochrome P450 (CYP) family, CYP2B6, influences the metabolism of EFV and therefore presumably, the concentration in the brain. Thus, CYP2B6 may influence neurocognition as the 8-hydroxy metabolite of EFV has been found to be neurotoxic (Gatanaga et al., 2007; Decloedt and Maartens, 2013).

**PIs:** This category of ARVs is very effective as antiretrovirals and part of numerous treatment regimens (Fig. 2 and Table 1). Saquinavir (SQV) and nelfinavir (NFV) are apparently well tolerated in HIV patients whereas ritonavir (RTV) can be associated with

adverse and toxic effects (Bonfanti et al., 2000). PI, NTRI, INSTI and the CCR5 inhibitor maraviroc are all metabolized by enzymes of the CYP450 family, which plays crucial roles in the metabolism/activation/inactivation of most pharmaceutical drugs (Ingelman-Sundberg, 2004). Many human CYP450 enzymes are membrane-associated and located in the inner membrane of the mitochondria or in the endoplasmic reticulum of cells. The subclasses CYP2 and CYP3 are particularly important in the metabolism of drugs and steroids, which explains why polypharmacy in the form of cART generates a significant risk of drug-drug interactions. However, on occasion the interactions can be harnessed for therapeutic applications. RTV, previously used as an active PI antiretroviral, has been employed at low doses to boost mono- or triple therapy due to the drug's ability to inhibit cytochrome P450 isoenzymes (Hsu et al., 1998; Gonzalez-Baeza et al., 2014). Other PIs have also been linked to neurotoxicity, including amprenavir (APV), indinavir (IDV) and atazanavir (ATV) (James et al., 2002; Pettersen et al., 2006; Vivithanaporn et al., 2016). A recent study found that in non-human primates, rodents, and *in vitro* neuroglial cell cultures, the PIs SQY and ATV in combination with the NRTI tenofovir (TDF) and an INSTI and RTV and SQV separately all triggered stress in the endoplasmic reticulum (ER), activated the  $\beta$ -site amyloid precursor protein cleaving enzyme-1 (BACE-1), and induced neuronal damage (Gannon et al., 2017).

**INSTIs:** A number of reports have implicated raltegravir (RAL) and elvitegravir (EVG) in CNS toxicity because of neuropsychiatric adverse effects (Harris et al., 2008; Cohen et al., 2011; Teppler et al., 2011). Both bicitgravir (BIC) and dolutegravir (DTG) containing regimens are supposed to provide the advantages of a low pill burden, high barrier to resistance, and better tolerability than alternative ARVs, but at least DTG is well recognized to cause neuropsychiatric adverse effects, and the WHO international pharmacovigilance database has reported neuropsychiatric events with all approved INSTIs (Table 1) (Kheloufi et al., 2017).

**FI:** Enfuvirtide (T-20) is the only FDA approved fusion inhibitor and has not displayed any conclusive evidence for neurotoxicity. Although, some earlier reports suggested an increased prevalence of sensory neuropathy (Lalezari, 2003; Fung and Guo, 2004), others found no indications of toxicity (Lazzarin et al., 2003; Fung and Guo, 2004; Cherry et al., 2008).

**EI:** The CCR5 blocker maraviroc (MVC) is the only FDA-approved synthetic molecule in its class. There is currently no evidence of neurotoxicity, and to the contrary, several studies found evidence for a neuroprotective effect of MVC (Boesecke and Pett, 2012; Garvey et al., 2012; Robertson et al., 2012a; Kelly et al., 2013; Maung et al., 2014). Ibalizumab is the first humanized monoclonal antibody recently approved by the FDA for treatment of HIV-1 infection, in particular for highly drug-resistant virus (Markham, 2018). Ibalizumab binds CD4 and blocks HIV entry into target cells while apparently largely preserving the proteins physiological function. The antibody is applied intravenously in the periphery and it is not clear how much of it reaches the CNS. The only current suggestion of a potential neuropsychiatric effect is dizziness in treated individuals (Markham, 2018).

The risks of neuropsychiatric polypharmacy created by cART as treatment for HIV-1 infection are frequently further complicated by the recreational use of psychostimulant drugs, such as methamphetamine (METH) (Urbina and Jones, 2004; Kapadia et al., 2005;

Mitchell et al., 2006; Soontornniyomkij et al., 2016). Notably, drug abuse itself, including that of METH, increases the risk of contracting HIV-1 (Urbina and Jones, 2004; Kapadia et al., 2005; Mitchell et al., 2006), and METH using cART-treated HIV positive individuals often show elevated viral loads (Ellis et al., 2003; Hinkin et al., 2007). Under these conditions, the brain of a significant proportion of HIV patients is exposed to HIV-1, combinations of ARVs and psychostimulants at the same time, and METH-use results in more neurocognitive deficits, neuropathology and neuronal injury than either virus and psychostimulant alone (Langford et al., 2003a; Langford et al., 2003b; Chana et al., 2006; Cadet and Krasnova, 2007; Pang et al., 2012; Soontornniyomkij et al., 2016; Sanchez and Kaul, 2017). While we and others have been able to recapitulate in animal models some of the combined effects (Roberts et al., 2010; Pendyala et al., 2012; Bortell et al., 2015; Hofer et al., 2015; Soontornniyomkij et al., 2016) the interplay of virus and psychostimulant and cART regimen is incompletely understood (Langford et al., 2003a; Cadet and Krasnova, 2007; Sanchez et al., 2016; Soontornniyomkij et al., 2016).

For that reason, our group investigated recently *in vitro* the potential contributions of the various factors to neuronal damage and loss (Sanchez et al., 2016). We exposed mixed neuronal-glia cerebral cortical cell cultures to ARVs of four different pharmacological categories (NRTI: AZT, NNRTI: NVP, PI: SQV and INSTI 118-D-24) in the presence or absence of METH, and HIV-1 envelope gp120, an established inducer of viral neurotoxicity. In order to assess acute, short-term and long-term effects, respectively, the cerebral cortical cells were incubated with the treatments for 24 h and 7 days. We observed that ARVs caused changes to neurites and presynaptic terminals predominantly during the 7-day exposure and alterations depended on specific compounds and their combinations with and without METH. In contrast to ARVs applied as single compounds, specific drug combinations with and without METH or viral envelope gp120 as well as METH and gp120 each alone, all significantly diminished neuronal ATP levels. Loss of ATP was associated with activation of adenosine monophosphate-activated protein kinase (AMPK) and autophagy, which, however, failed to restore neuronal ATP to normal levels. In contrast, boosting autophagy with rapamycin abrogated the lasting reduction of ATP during exposure to cART in the presence or absence of METH or gp120.

The findings of our investigation speak to the complexities of the overall effects of exposure to HIV and cART in the presence and absence of the psychostimulant METH (Sanchez et al., 2016). The ARVs/cART, HIVgp120 and METH triggered each alone and in combination a comparable loss of neuronal ATP but showed no additive effect. Also, ARVs/cART, METH or HIV/gp120 could each induce neuronal damage in terms of compromising neuronal dendrites and presynaptic terminals or depleting neuronal ATP or, in the case of gp120, causing the frank loss of neurons themselves when applied separately, but not necessarily when combined with ARVs. Distinct ARV combinations lacked a detectable effect on neuronal dendrites or presynaptic terminals in the presence or absence of METH, yet significantly reduced neuronal ATP levels. Thus, neurons managed to maintain their dendrites and presynaptic terminals despite compromised neuronal energy homeostasis, a scenario that may explain, at least in part, a slow, yet progressive neurological disease, such as HAND. Notably, METH, which itself is toxic to neurons (Cadet and Krasnova, 2007), lacked any detectable damaging effect on neurites and synapses in combination with several

ARVs and even counteracted a significant loss of neuronal ATP in combination with cART. In contrast, long-term exposure to the admixture of four ARVs and psychostimulant compromised neuronal dendrites and synapses, an injury that others observed too, as a result of ARV treatment (Robertson et al., 2012a). Similarly, a loss of neuronal ATP occurred when four ARVs and METH were combined with HIV-1 gp120.

Our findings were in accordance with earlier reports that ARVs disturb mitochondrial function by altering mitochondrial membrane components, such as transporters, and mitochondrial bioenergetics, in particular membrane potential, by affecting mitochondrial kinases, such as Thymidine kinase 2 (TK2) and deoxyguanosine kinase (dGK) (Sun et al., 2014), and by inhibiting mitochondrial polymerase  $\gamma$  and consequently mtDNA homeostasis (Arnaudo et al., 1991; Cherry et al., 2002; Cote et al., 2002) or by stimulating major deletions in neuronal mtDNA (Apostolova et al., 2011; Zhang et al., 2014). Moreover, our results indicated that neuronal energy homeostasis could significantly change without precipitating obvious structural neuronal damage or loss. The mechanism regulating such neuronal adaptation may serve cellular robustness and resilience and remain to be elucidated.

### **Approaches to balancing viral suppression with neuropsychiatric adverse effects and neurotoxicity**

In advancing the 90-90-90 world treatment targets launched by the UNAIDS in 2014, speed has been emphasized in terms of scaling-up and providing early initiation of HIV treatment. Accordingly, strides have been made in providing safe, tolerable, effective ARVs with higher barriers to resistance and lower pill burden in therapy regimes (DHHS, 2018). There has been an increasing interest in simplifying drug regimens of HIV patients from three drugs to two drug regimens. However, a recent study into this strategy discovered that the majority of these patients had a decline in neurocognition. Only patients switched to an INSTI/PI combination remained neurocognitively stable (Arendt et al., 2019).

With the popularization of commercialized direct-to-consumer genetic testing kits capable of detecting single nucleotide polymorphisms (SNPs), the information available to clinicians and the general public is higher than ever. The Precision Medicine Initiative, launched in 2015, is a data-driven field of medicine that attempts to take into account individual differences in people's genes, microbiomes, environments, and lifestyles. Pharmacogenomic testing for HIV patients can be performed on several genes to guide selection of antiretroviral therapy (ART). Genotypic co-receptor tropism assays should be used if prescription of a CCR5 antagonist is being considered. Due to the ability of HIV to develop resistance to ARVs, genotypic and tropism testing is recommended at entry into care. The genotypic assay to assess mutations in the gp41 gene is associated with resistance to the fusion inhibitor enfuvirtide while phenotypic tropism assays can determine whether the virus is susceptible to CCR5 inhibition by maraviroc (DHHS, 2018). In prescribing the NRTI abacavir, the major histocompatibility complex class I allele HLA-B\*5701 confers a 60% chance of a hypersensitivity reaction to the drug and genotyping for the gene has become standard clinical practice (Hetherington et al., 2002; Mallal et al., 2002; Saag et al., 2008; Novelli, 2010). In the case of efavirenz, CYP2B6 polymorphisms can result in poor

metabolism thus increasing the plasma concentration of the drug and causing more severe CNS symptoms (Marzolini et al., 2001). The pharmacogenetics of ARVs has been reviewed previously (Tozzi, 2010; Pavlos and Phillips, 2012).

Polypharmacy and comorbidity is unavoidable in an aging population of HIV patients and raises the risk of drug-drug interactions. In fact, HIV infected individuals have an increased risk for cardiovascular disease, hepatic and renal disease, osteoporosis, in addition to mental, neurological and substance-use disorders (Esser et al., 2013; Brothers et al., 2014; Guaraldi et al., 2014; Achhra et al., 2015; Nedelcovych et al., 2017; Cook et al., 2018). The risk of adverse effects and outcomes increases with the increasing number of medications and nearly 50% of older adults take one or more medications that are not medically necessary (Maher et al., 2014). Drug to drug interactions can delay, decrease, or enhance absorption of drugs, thus decreasing or increasing their efficacy and causing adverse effects. For example, the ARVs atazanavir and rilpivirine require an acidic gastric pH for effective dissolution and absorption and antacids, H2 blockers, and proton pump inhibitors are likely to lower treatment efficacy (Luber, 2005; Beique et al., 2007; Crauwels et al., 2013). In contrast, ritonavir or cobicistat potently inhibit CYP3A and cause drugs metabolized through the CYP3A pathway, such as statins and antipsychotics, to accumulate (Fichtenbaum et al., 2002; Chauvin et al., 2013; DHHS, 2018). Opioid use among HIV-infected individuals is common with prescription rates as high as 53%, due to the prevalence of chronic pain caused by HIV infection, aging, and adverse effects of medications. This high proportion of opioid use in the HIV-infected population puts them at risk for addiction (Cunningham, 2018). The pharmacokinetics of both methadone and naloxone are effected by boosted protease inhibitors and certain NNRTIs (Clarke et al., 2001a, b; McCance-Katz et al., 2003; Scholler-Gyure et al., 2008; Sekar et al., 2011; Gruber et al., 2012; Bruce et al., 2013a; Bruce et al., 2013b; Bruce et al., 2013c; Crauwels et al., 2014). These extensive pharmacological interactions can be further compounded by coinfection with hepatitis C, a common comorbidity which the CDC estimates that approximately 25% of HIV patients in the US have. Co-infected individuals require complicated multi-drug antiretroviral therapy (Cope et al., 2015; Wyles, 2015; King and Menon, 2017). Furthermore, certain ARVs have been implicated in higher rates of comorbidities as a result of drug toxicity (Chow et al., 2003; Palacios et al., 2006; Guaraldi et al., 2014; Schouten et al., 2014). Highlighting this issue further, a recent study by Molas et al surveying 1259 HIV patients has found that 70% of patients receiving ART took co-medication with 44.7% having at least one clinically relevant potential drug-drug interaction (Molas et al., 2018). Individual differences in viral resistance and tropism as well as the patient's pharmacogenetic and pharmacoecologic background highlight the importance of developing personalized drug regimes in an era of precision medicine.

In achieving active viral suppression and providing treatments with speed and early initiation, it is important to consider not only increasing lifespan but also preservation of quality of life. In addition to direct neurotoxicity, the neuropsychiatric adverse effects related to certain ARVs can lead to poor adherence, treatment interruptions, or change of drug regimens. These factors are confounded further by polypharmacy, viral resistance, and a patient's pharmacogenetic and pharmacoecologic situation. Discerning the safety of strategies to increase cART penetration into the CNS may be a balancing act of suppressing

viral replication while minimizing neurotoxicity, impairment of neurocognition and neuropsychiatric adverse effects.

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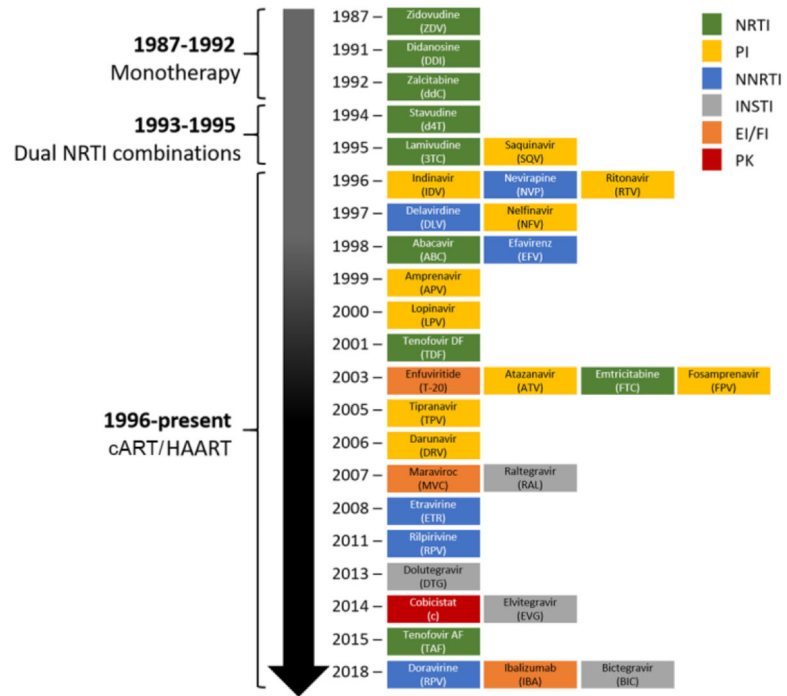
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**Fig. 1. Timeline of FDA approval of ARVs.**  
See main text for additional information on the various compounds.

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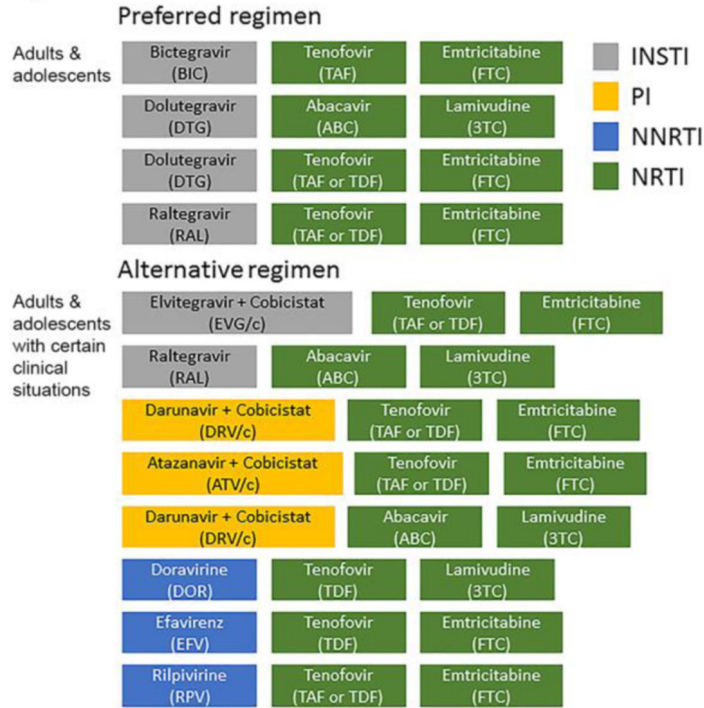
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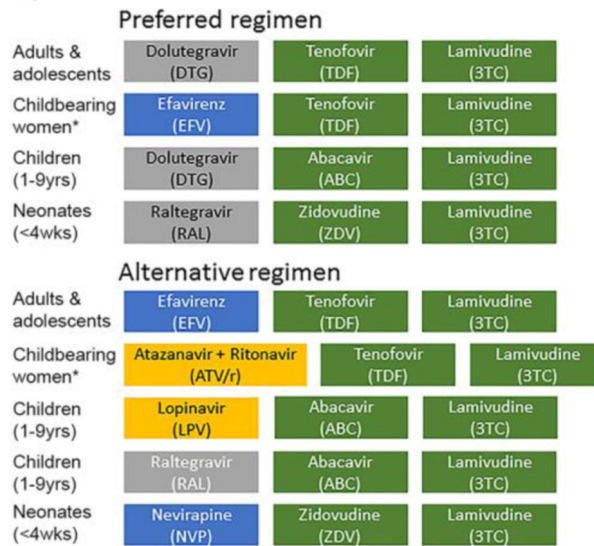
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**A) DHHS/US**



**B) WHO**



**Fig. 2. Antiretroviral treatment regimen.**

A) DHHS guidelines, the representation is based on the Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed [4/23/2019] [F-5, Table 6a]; B) WHO recommendations, the representation is based on updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines.

Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.51). Licence: CC BY-NC-SA 3.0 IGO. \*For recommendations for childbearing women see neuropsychiatric and developmental effects of ARV in tables 1 and 2. Modified from (Reust, 2011)

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**Table 1.**  
**Neuropsychiatric adverse effects of ARV.**

Summary of adverse effects reported by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS, 2018) and CPE scores (if available) based on available clinical observations (Letendre et al., 2008). Other references mentioned in table: (Maxwell et al., 1988; Finlayson and Laing, 1998; de la Garza et al., 2001; Peyriere et al., 2001; Colebunders and Florence, 2002; Colebunders et al., 2002; Morlese et al., 2002; Puzantian, 2002; Wise et al., 2002; Foster et al., 2003; Lalezari, 2003; Moreno et al., 2003; Shah and Balderson, 2003; Foster et al., 2004; Hasse et al., 2005; Letendre et al., 2008; Toby, 2013; DHHS, 2018; Schomaker et al., 2018; Zash et al., 2018).

Drug class	Drug	Acronym	CNS symptoms (DHHS, 2018)	CPE ranking (Letendre et al., 2008)
NRTI	Abacavir	ABC	Case reports include headache (Colebunders et al., 2002; Foster et al., 2004), depression, anxiety, auditory hallucinations (Colebunders et al., 2002), mutism, catatonia, homicidal behavior, persecutory delusions (Foster et al., 2003), night terrors (Foster et al., 2004)	3
NRTI	Emtricitabine	FTC		3
NRTI	Lamivudine	3TC		2
NRTI	Stavudine	d4T	Peripheral neuropathy	2
NRTI	Tenofovir alafenamide	TAF	Headache	N/A
NRTI	Tenofovir disoproxil fumarate	TDF	Headache	1
NRTI	Zidovudine	ZDV	Headache, insomnia, confusion, agitation, mania, depression, myalgia. Case reports include delusions, auditory hallucinations (Maxwell et al., 1988), agitation, bizarre behavior, psychosis (1988), and mania (1988)	4
NNRTI	Doravirine	DOR	Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality/self-harm	N/A
NNRTI	Efavirenz	EFV	Dizziness, abnormal dreams, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalization, hallucinations, depression, suicidality, somnolence, insomnia, neural tube birth defects, convulsions Case reports include irritability, aggression, antisocial behavior (Peyriere et al., 2001), excitability, anxiety (Peyriere et al., 2001), mental confusion (Peyriere et al., 2001), mania (Blanch et al., 2001; Shah and Balderson, 2003), disinhibition, grandiosity (Shah and Balderson, 2003), PTSD, intrusive recollections (Moreno et al., 2003), severe psychosis (Hasse et al., 2005), disorientation, paranoid delusions, violent behavior (de la Garza et al., 2001), anhedonia (Puzantian, 2002)	3
NNRTI	Nevirapine	NVP	Case reports of cognitive impairment, impulsive suicide attempts, persecutory delusions (Wise et al., 2002), and depression (Colebunders and Florence, 2002), vivid dreams (Morlese et al., 2002)	4
NNRTI	Rilpivirine	RPV	Depression, headache, suicidality, sleep disturbances	N/A
INSTI	Bictegravir	BIC	Headache, insomnia, depression, anxiety, suicidal ideation	N/A
INSTI	Dolutegravir	DTG	Headache, insomnia, depression, anxiety, suicidal ideation, neural tube birth defects (Schomaker et al., 2018; Zash et al., 2018)	N/A
INSTI	Elvitegravir	EVG	Headache, insomnia, depression, anxiety, suicidal ideation	N/A

Drug class	Drug	Acronym	CNS symptoms (DHHS, 2018)	CPE ranking (Letendre et al., 2008)
INSTI	Raltegravir	RAL	Headache, insomnia, depression, anxiety, suicidal ideation	3
PI	Atazanavir	ATV	Case reports of headache, agitation, difficulty sleeping, disorientation, dizziness, tremulousness (Toby, 2013)	2
	Atazanavir + ritonavir	ATV/r		2
PI	Darunavir	DRV	Headache	N/A
	Darunavir + ritonavir	DRV/r		3
PI	Fosamprenavir	FPV	Headache	2
	Fosamprenavir + ritonavir	FPV/r		3
PI	Indinavir	IDV	Headache, dizziness	3
	Indinavir + ritonavir	IDV/r		4
PI	Lopinavir	LPV		N/A
	Lopinavir + ritonavir	LPV/r		3
PI	Saquinavir	SQV	Headache Case report of acute paranoid psychosis (Finlayson and Laing, 1998)	1
	Saquinavir + ritonavir	SQV/r		1
PI	Tipranavir	TPV	Intracranial hemorrhage	N/A
	Tipranavir + ritonavir	TPV/r		1
EI	Enfuvirtide	T-20	Case reports of higher prevalence of neuropathy (Lalezari, 2003)	1
EI	Ibalizumab	IBA	Dizziness	N/A
EI	Maraviroc	MVC	Dizziness	3
PK	Cobicistat	c		N/A
PI/PK	Ritonavir	RTV or r		1

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**Table 2.**  
**Neurotoxicity of ARV.**

Summary of studies investigating neurotoxicity of clinically used ARV compounds. References mentioned in table: (O'Mahony et al., 2005; Pettersen et al., 2006; Grigorian et al., 2008; Manda et al., 2010; Giunta et al., 2011; Lisi et al., 2012; Robertson et al., 2012a; Tovar et al., 2012; Akay et al., 2014; Blas-Garcia et al., 2014; Brown et al., 2014; Purnell and Fox, 2014; Apostolova et al., 2015; Bertrand and Toborek, 2015; Demir and Laywell, 2015; Funes et al., 2015; Jin et al., 2016; Tricarico et al., 2016; Vivithanaporn et al., 2016; Ciavatta et al., 2017; Stern et al., 2018a; Lu et al., 2019)

Drug class	Drug	Acronym	CNS symptoms	System	References
NRTI	Abacavir	ABC	↓ MAP-2 at CSF concentrations, ↓ MAP-2 at therapeutic concentrations	Primary cultures rat forebrain	(Robertson et al., 2012a)
			↑ Neuronal beta-amyloid production	SweAPP N2a cells	(Giunta et al., 2011)
NRTI	Emtricitabine	FTC			(Robertson et al., 2012a)
NRTI	Lamivudine	3TC	↓ MAP-2 at therapeutic concentrations, ↓ MAP-2 at CSF concentrations	Primary cultures rat forebrain	(Robertson et al., 2012a)
			↑ Neuronal beta-amyloid production	SweAPP N2a cells	(Giunta et al., 2011)
NRTI	Stavudine	d4T	↓ Neuronal viability at 100 x plasma concentrations	Primary rat cortical neuron culture	(Ciavatta et al., 2017)
NRTI	Tenofovir alafenamide	TAF			
NRTI	Tenofovir disoproxil fumarate	TDF	↓ MAP-2 at therapeutic concentrations	Primary cultures rat forebrain	(Robertson et al., 2012a)
			↓ Mitochondrial membrane potential, ↓ Cellular proliferation, ↑ Cellular apoptosis	PC-12 cell line	(Lu et al., 2019)
			↓ Dendritic length and branching at 3x plasma concentrations	Primary rat cortical neuron culture	(Ciavatta et al., 2017)
NRTI	Zidovudine Azidothymidine	ZDV AZT		Primary cultures rat forebrain	(Robertson et al., 2012a)
				primary rat cortical neuroglial cultures	(Akay et al., 2014)
				Primary rat mixed neuronal-glial cerebrocortical cultures	(Sanchez et al., 2016)
			↑ Neuronal beta-amyloid production	SweAPP N2a cells	(Giunta et al., 2011)
			↓ Proliferating NSCs	C57 BL/6 mice	(Demir and Laywell, 2015)
NNRTI	Doravirine	DOR			
NNRTI	Efavirenz	EFV	↓ MAP-2 at therapeutic concentrations, ↓ Mitochondrial membrane potential, ↓ Proliferating NSCs, ↓ Neuronal viability at 7x plasma concentrations, ↓ Neuronal respiration at 3x plasma concentrations, ↓ Neuronal excitability at 3x plasma concentrations, ↓ Mitochondrial respiration at 3x plasma concentrations, ↓ Dendritic length	Primary cultures rat forebrain	(Robertson et al., 2012a)

Drug class	Drug	Acronym	CNS symptoms	System	References
			and branching at 3x plasma concentrations, ↓ Dendritic spines using EFV metabolites at CSF concentrations, ↑ Intraneuronal Ca <sup>2+</sup> using EFV metabolites at CSF concentrations, ↓ Neuronal survival at CSF concentrations, ↓ Neuronal survival using EFV metabolites at CSF concentrations		
			↓ Proliferating NSCs, ↓ ATP stores, ↓ Mitochondrial membrane potential, ↑ Ph-p38 MAPK, ↑ Bax	Rat NSCs	(Jin et al., 2016)
			↓ BrdU+ area in SVZ, ↑ Caspase-3+ area in SVZ	C57BL/6J mice	
			↓ Neuronal viability at 7x plasma concentrations, ↓ Neuronal respiration at 3x plasma concentrations, ↓ Neuronal excitability at 3x plasma concentrations, ↓ Mitochondrial respiration at 3x plasma concentrations, ↓ Dendritic length and branching at 3x plasma concentrations	Primary rat cortical neuron culture	(Ciavatta et al., 2017),
			↓ Dendritic spines using EFV metabolites at CSF concentrations, ↑ Intraneuronal Ca <sup>2+</sup> using EFV metabolites at CSF concentrations, ↓ Neuronal survival at CSF concentrations, ↓ Neuronal survival using EFV metabolites at CSF concentrations	Primary rat hippocampal neuronal cultures	(Tovar-y- Romo et al., 2012)
			↑ TNF-α in blood, ↑ IL-1β in blood, Spatial memory deficits	Wistar rats	(O'Mahony et al., 2005)
			↓ ATP production, ↑ Autophagy, ↑ Mitochondrial fragmentation, ↑ Mitochondrial depolarization, Changes in mitochondrial morphology	SH-SY5Y cells	(Purnell and Fox, 2014)
			↓ ATP production, ↑ Autophagy, Changes in mitochondrial morphology	Primary rat striatal neurons	
			↑ LC3-II, ↑ CHOP, ↓ Mitochondrial membrane potential, ↑ Mitochondrial ROS	Primary rat cerebral cortex neurons	(Blas-Garcia et al., 2014)
			↑ Aβ <sub>1-42</sub> protein, ↑ BACE-1 protein, ↑ ROS, ↓ ATP levels	SweAPP N2a cells	(Brown et al., 2014)
			↓ Microglial Aβ <sub>1-42</sub> phagocytosis	Primary mouse microglia	
			↑ Aβ <sub>1-42</sub> protein in brain homogenate, ↑ BACE-1 protein	Tg2576 mice	
			↓ Mitochondrial respiration	SH-SY5Y cells U-251MG cells	(Funes et al., 2015)
			↑ NOS activation in glial cells, ↓ Mitochondrial respiration, ↑ Mitochondrial ROS, ↓ Mitochondrial membrane potential, ↓ Activity of components in mitochondrial electron transport chain	SH-SY5Y cells	(Apostolova et al., 2015)

Drug class	Drug	Acronym	CNS symptoms	System	References
				U-251MG cells	
			↓ IRE1α protein, ↓ LC3bII protein, ↑ Intracellular Ca <sup>2+</sup> , ↓ Cytosolic PI3P levels, ↓ Association of Atg2a with Atg9, ↑ Sqstm1/p62 levels, Dysregulation of ER stress and autophagy	hCMEC/D3 cell line	(Bertrand and Toborek, 2015)
			↓ Autophagy	Primary human brain endothelial cells	
			↓ Autophagy	SVGPI2 cells	
			↑ BiP protein, ↓ LC3b protein	HIV transgenic mice	
NNRTI	Nevirapine	NVP	↓ MAP-2 at CSF concentrations, ↓ MAP-2 at therapeutic concentrations	Primary cultures rat forebrain	(Robertson et al., 2012a)
				Primary rat mixed neuronal-glia cerebral cortex cultures	(Sanchez et al., 2016)
NNRTI	Rilpivirine	RPV			
INSTI	Bictegravir	BIC			
INSTI	Dolutegravir	DTG		Primary rat cortical neuroglial cultures	(Stern et al., 2018a)
INSTI	Elvitegravir	EVG	↓ MAP-2 at CSF concentrations	Primary rat cortical neuroglial cultures	(Stern et al., 2018a)
INSTI	Raltegravir	RAL	↑ IL-8	Primary rat cortical neuroglial cultures	(Stern et al., 2018a)
PI	Atazanavir	ATV	↓ MAP-2 at therapeutic concentrations, ↓ Mitochondrial membrane potential	Primary cultures rat forebrain	(Robertson et al., 2012a)
PI	Darunavir	DRV		Primary rat cortical neuroglial cultures	(Stern et al., 2018a)
PI	Fosamprenavir	FPV			
PI	Indinavir	IDV	↑ Neuronal beta-amyloid production	SweAPP N2a cells	(Giunta et al., 2011)
			↑ ROS, ↓ Notch4 protein	Human cerebral endothelial cells	(Grigorian et al., 2008)
			↓ Neurite length, ↓ Neuronal processes, and ↓ Neuronal soma diameter in combination with HIV infection	Primary rat dorsal root ganglion cells	(Pettersen et al., 2006)
PI	Lopinavir	LPV	↓ MAP-2 at CSF concentrations	Primary rat cortical neuroglial cultures	(Stern et al., 2018a)
			↓ EAAT2 expression in astrocytes, ↓ Intracellular glutamate levels, ↓ PNCA and Ki-67	Primary human fetal astrocytes	(Vivithanaporn et al., 2016)
			↓ Mitochondrial activity, ↑ ROS production, ↑ Apoptosis	SH-SY5Y cell line	(Tricarico et al., 2016)
PI	Saquinavir	SQV	↓ MAP-2 at therapeutic concentrations	Primary rat cortical neuroglial cultures	(Akay et al., 2014)
				Primary rat mixed neuronal-glia cerebral cortex cultures	(Sanchez et al., 2016)

Drug class	Drug	Acronym	CNS symptoms	System	References
			↑ ROS, ↓ Notch4 protein	Human cerebral endothelial cells	(Grigorian et al., 2008)
			↑ ROS, ↓ Notch4 protein, ↓ ZO-1	Primary rat brain microvascular endothelial cells	(Manda et al., 2010)
			↑ ROS, ↓ Notch4 protein	Fischer-344 rats	
PI	Tipranavir	TPV			
EI	Enfuvirtide	T-20			
EI	Ibalizumab	IBA			
EI	Maraviroc	MVC		Primary cultures rat forebrain	(Robertson et al., 2012a)
			↑ Microglial activation with co-administration of gp120 (CN54) and IFN $\gamma$	Primary enriched cultures of rat glial cells	(Lisi et al., 2012)
PK	Cobicistat	c			
PI/PK	Ritonavir	RTV or r	↓ MAP-2 at therapeutic concentrations, ↓ Mitochondrial membrane potential	Primary cultures rat forebrain	(Robertson et al., 2012a)
			↓ MAP-2 at therapeutic concentrations, ↓ Synaptophysin at therapeutic concentrations, ↑ Oxidative stress	Primary rat cortical neuroglial cultures	(Akay et al., 2014)
			↓ Mitochondrial activity, ↑ ROS production	SH-SY5Y cell line	(Tricarico et al., 2016)
			↑ ROS, ↓ Notch4 protein	Human cerebral endothelial cells	(Grigorian et al., 2008)
			↑ ROS	Primary rat brain microvascular endothelial cells	(Manda et al., 2010)

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