Received: 10 July 2020 | Revised: 4 November 2020 | Accepted: 18 November 2020

DOI: 10.1002/ar.24573

REVIEW

The Anatomical Record | WILEY

Effect of human immunodeficiency virus on the brain: A review

Karen Cilliers[1] | **Christo J. F. Muller**[2,3]

[1]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Western Cape, South Africa

[2]Biomedical Research and Innovation Platform (BRIP), South African Medical Research Council, Tygerberg, Western Cape, South Africa

[3]Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Western Cape, South Africa

Correspondence
Dr. Karen Cilliers, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Western Cape, South Africa.
Email: karencilliers1@gmail.com

Funding information
South African Agency for Science and Technology Advancement, Grant/Award Numbers: SFH160606168484, SFH180605340831

Abstract

Thirty million people are infected with human immunodeficiency virus (HIV) worldwide, and HIV-associated neurocognitive disorder (HAND) is one of the most common comorbidities of HIV. However, the effect of HIV on the brain has not been fully investigated. This article aimed to review the changes to the brain due to HIV in terms of atrophy, diffusion changes, and hyperintensities. Studies have observed significant atrophy in subcortical gray matter, as well as in cortical white and gray matter. Moreover, the ventricles enlarge, and the sulci widen. Although HIV causes changes to the white and gray matter of the brain, few diffusion tensor imaging studies have investigated the changes to gray matter integrity. White and gray matter hyperintensities have frequently been observed in HIV-positive individuals, with the subcortical gray matter (caudate nucleus and putamen) and periventricular white matter frequently affected. In conclusion, subcortical gray matter is the first brain region to be affected and is affected most severely. Additionally, this review highlights the gaps in the literature, since the effect of HIV on the brain is not fully known. Future studies should continue to investigate the effect of HIV on the brain in different stages of the disease, and alternate therapies should be developed since highly active antiretroviral therapy is currently ineffective at treating HAND.

KEYWORDS

atrophy, brain matter hyperintensities, diffusion changes, HIV-associated neurocognitive disorder, subcortical gray matter

1 | INTRODUCTION

Thirty million people are infected with human immunodeficiency virus (HIV) worldwide. With the introduction of highly active antiretroviral therapy (HAART), HIV has become a manageable, chronic disease and more HIV-positive individuals are living with HIV for longer (Hellmuth, Milanini, & Valcour, 2014). With this increase in life expectancy, secondary problems of HIV and HAART have become a topic of interest. HIV-associated neurocognitive disorder (HAND) is one of the most common diseases observed in HIV-positive individuals (McArthur & Brew, 2010). However, the effect of HIV and HAND on the brain has not been fully investigated.

According to the 2007 "Frascati" guidelines, HAND can be classified into three subgroups; asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). Evaluation of cognitive abilities (such as memory, attention, learning, decision making) and functional impairment (normal activities and work) is done through neuropsychological tests (Nightingale et al., 2014). When

two or more cognitive abilities are impaired with no functional impairment, it is defined as ANI. If there is moderate functional impairment as well as cognitive impairment, it is defined as MND. In HAD, also referred to as HIV encephalopathy, or acquired immunodeficiency syndrome (AIDS) dementia complex, there is severe cognitive and functional impairment (Antinori et al., 2007; Jernigan et al., 1993; McArthur, Brew, & Nath, 2005; Tucker et al., 2004). It can take several months for neuronal decline to reach HAD status (McArthur et al., 2005; McArthur & Brew, 2010).

With HIV, regardless of AIDS progression or dementia status, there is neurodegeneration. This review included changes observed in asymptomatic, symptomatic, demented and non-demented HIV-positive individuals; the focus is on the effect of HIV, regardless of HIV progression. Most studies focusing on structural changes to the brain (due to HIV), focus on atrophy, diffusion changes, and brain matter hyperintensities. Thus, this article aimed to review the changes to the brain due to HIV in terms of atrophy, diffusion changes and hyperintensities.

1.1 | Atrophy

Progression of HIV is associated with brain atrophy, even before neurological symptoms appear. Atrophy is one of the most pronounced structural changes to the brains of HIV-positive individuals. This can be indicated by increased ventricular and sulcal size, as well as by a decreased gray matter volume.

Ventricular and sulcal enlargement indicates central and cortical atrophy, respectively (Jernigan et al., 1993). Several studies have investigated the volume of cerebrospinal fluid (CSF), ventricular and sulcal size, and these results indicate significant increases in CSF, ventricular and sulcal size (Archibald et al., 2004; Aylward et al., 1995; Di Sclafani et al., 1997; Jernigan et al., 1993; Kallianpur et al., 2014; Levin et al., 1990; Pfefferbaum et al., 2006; Stout et al., 1998; Wade et al., 2015). Aylward et al. (1995) observed 54.9% ($p < .001$) increase in CSF when comparing HIV-positive and HIV-negative men. Di Sclafani et al. (1997) also compared HIV-positive and HIV-negative men and observed that sulcal and ventricular CSF increased in HIV-positive individuals by 19.5 and 27.0%, respectively. This increase corresponded to the clinical stage of HIV stage of disease. With a similar study design, Archibald et al. (2004) observed a 107.8% increase in sulcal CSF and an 86.5% increase in ventricle CSF.

Several studies have assessed brain volume changes in HIV-positive individuals, using mostly magnetic resonance imaging. Studies agree that HIV causes general and region-specific brain atrophy, and individuals with HAND have a greater extent of atrophy (Aylward et al., 1993; Di Sclafani et al., 1997). With progression of the disease, HIV firstly infects the subcortical gray matter, secondly the white matter, and lastly the cortical gray matter (Aylward et al., 1995; Becker et al., 2012; Di Sclafani et al., 1997). Subcortical gray matter structures that have been commonly investigated include the caudate nucleus, putamen and globus pallidus.

The caudate nucleus is the area most consistently associated with neurocognitive impairment in HIV-positive patients (Paul, Cohen, Navia, & Tashima, 2002; Stout et al., 1998). Several authors have observed atrophy in the caudate nucleus of HIV-positive individuals, either significantly (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Archibald et al., 2004; Becker et al., 2011; Behrman-Lay et al., 2016; Di Sclafani et al., 1997; Stout et al., 1998; Wade et al., 2015) or as a trend (Castelo, Courtney, Melrose, & Stern, 2007; Heaps et al., 2012, 2015; Kallianpur et al., 2014; Ortega et al., 2013; Paul et al., 2008), in a range of 1.3–12.3%. According to Ances et al. (2012), for every 10 years with HIV-infection, the caudate nucleus emaciates with 6.0%. These changes in the caudate nucleus have been related to cognitive impairment in AIDS patients (Heaps et al., 2015).

Behrman-Lay et al. (2016), Wade et al. (2015), and Becker et al. (2011) observed significant atrophy in the putamen of HIV-positive individuals, while others (Paul et al., 2008; Ances et al., 2012; Ortega et al., 2013; Kallianpur et al., 2014; Heaps et al., 2015) only observed a trend. Although the caudate nucleus is believed to be the most affected, Becker et al. (2011) observed a 15.2% ($p < .001$) reduction in the putamen volume when comparing HIV-positive and HIV-negative individuals, and only a 9.7% ($p < .001$) loss in caudate nucleus volume. In contrast, Castelo et al. (2007) observed significant hypertrophy of the putamen (left hemisphere: $p = .05$, right hemisphere: $p = .01$) in HIV-positive non-demented patients. Fennema-Notestine et al. (2013) observed hypertrophy in the subcortical gray matter, although this increase was not significant. This may be due to increased water content (Fennema-Notestine et al., 2013), inflammation or inflammatory cell infiltration (Fennema-Notestine et al., 2013) or dysfunction of the dopaminergic systems (Castelo et al., 2007). In contrast to the caudate nucleus and putamen, few studies have investigated the globus pallidus independently. Castelo et al. (2007) and Kallianpur et al. (2014) observed a non-significant reduction in volume by 0.9% (right hemisphere: $p = .11$, left hemisphere: $p = .93$) and 3.3% ($p = .534$), respectively.

The hippocampus, although not part of the subcortical gray matter, is frequently associated with cognitive decline. Comparing HIV-positive and HIV-negative individuals, HIV-positive individuals had significantly lower

hippocampal volume compared to healthy adults (Archibald et al., 2004; Behrman-Lay et al., 2016; Ortega et al., 2013; Wade et al., 2015). Archibald et al. (2004) and Behrman-Lay et al. (2016) observed a significant decrease in hippocampal volume with 10.8 and 5.5%, respectively. Some studies observed a difference, although this change in volume was not significant (Ances et al., 2012; Castelo et al., 2007; Kallianpur et al., 2014). This may be due to these studies including more asymptomatic HIV-infected individuals compared to other studies.

Not all authors discriminate between cortical and subcortical gray matter, complicating comparison between studies. However, significant reduction in total gray matter volume has been observed (Becker et al., 2012; Behrman-Lay et al., 2016; Heaps et al., 2012, 2015; Kallianpur et al., 2014). Additionally, atrophy in the temporal lobes and caudate nucleus can complicate the interpretation of gray matter volume loss (Di Sclafani et al., 1997).

1.2 | Diffusion changes

Several researchers have investigated the changes to the brain using diffusion tensor imaging (DTI). This method evaluates the magnitude and direction of the motion of water molecules, which indicates changes to the intrinsic tissue structure (Paul et al., 2002; Thurnher et al., 2005). With DTI studies, brain matter abnormalities can be observed that would not yet be evident in magnetic resonance imaging, and thus these changes can be observed earlier (Paul et al., 2002).

Fractional anisotropy, mean diffusivity and apparent diffusion coefficient can be evaluated. This gives information on the intrinsic structure of the tissue, and a change can indicate inflammation and structural abnormalities (Chang et al., 2008; Hoare et al., 2011; Tate et al., 2010). Fractional anisotropy measures the direction dependent and orientation specificity of water diffusion and reflects loss and injury of aligned cellular structures, typically axonal injury or demyelination (Hoare et al., 2011; Ragin et al., 2005; Tang et al., 2015; Tate et al., 2010). Mean diffusivity is an indication of the average of all the diffusion directions and these changes indicate tissue destruction as well as intracellular and extracellular volume changes (Ragin, Storey, Cohen, Epstein, & Edelman, 2004; Thurnher et al., 2005).

Numerous authors have examined the integrity changes in white matter and white matter structures. In HIV-positive individuals, most authors observed significant alterations in frontal (Chang et al., 2008; Chen et al., 2009; Corrêa et al., 2015; Pomara, Crandall, Choi, Johnson, & Lim, 2001; Zhu et al., 2013), parietal (Chang et al., 2008 ;Chen et al., 2009; Zhu et al., 2013), temporal (Chen et al., 2009; Zhu et al., 2013) and occipital (Chen et al., 2009) white matter, as well as associated white matter fiber tracts (Hoare et al., 2011, 2012). In addition, significant alterations have been noted for the corpus callosum (Chang et al., 2008; Chen et al., 2009; Corrêa et al., 2015; Filippi, Ulug, Ryan, Ferrando, & van Gorp, 2001; Hoare et al., 2011, 2012; Kamat et al., 2014; Leite et al., 2013; Nir et al., 2014; Ragin et al., 2015; Stubbe-Dräger et al., 2012; Tang et al., 2015; Thurnher et al., 2005; Wright et al., 2015; Wu et al., 2006), internal capsule (Hoare et al., 2011; Nir et al., 2014; Pomara et al., 2001; Tang et al., 2015) and corona radiata (Hoare et al., 2012; Kamat et al., 2014; Leite et al., 2013). Chen et al. (2009) noted that the corpus callosum was already significantly altered in non-demented HIV-infected individuals, when compared to healthy controls. Very few studies have investigated changes to the hippocampus, and published reports found no change in DTI metrics (Ragin et al., 2015; Thurnher et al., 2005).

In contrast to white matter, limited studies examined gray matter integrity changes. Most authors (Chang et al., 2008; Cloak, Chang, & Ernst, 2004; Ragin et al., 2005) observed no significant change in the caudate nucleus, putamen, globus pallidus or thalamus. This is in contrast to Ragin et al. (2015), who observed a significant increase in mean diffusivity in the caudate nucleus within the first 100 days of infection. However, the putamen did not indicate a significant difference between HIV-positive and HIV-negative individuals.

Even though HIV results in changes to the white and gray matter of the brain, few DTI studies have investigated the changes to gray matter integrity (Nir et al., 2014). Gray matter has a lower fractional anisotropy and changes are thus more difficult to observe due to the poorer signal-to-noise ratio (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). Thus, fractional anisotropy is more sensitive to white matter integrity changes. Gray matter diffusion is generally isotropic (exhibiting similar directions), which is not direction dependent and has the same value irrelative to the direction it is measured in. Since fractional anisotropy measures the direction dependent and orientation specificity of water diffusion, and mean diffusivity is the average of all the diffusion directions, mean diffusivity may indicate gray matter integrity changes more accurately (Ragin, Storey, Cohen, Edelman, & Epstein, 2004).

1.3 | Brain matter hyperintensities

Brain changes due to HIV-infection have been observed as areas with increased signal on T2-weighted scans (Fennema-Notestine et al., 2013), and these hyperintensities

indicate brain matter infarction, inflammation and damage (Seider et al., 2016). Studies have confirmed the presence of white and gray matter hyperintensities, as well as white matter lesions in association with advanced HIV infection and neurocognitive decline (Haddow et al., 2014; Hanning et al., 2011; Kugathasan et al., 2017; McMurtray, Nakamoto, Shikuma, & Valcour, 2008; Steinbrink et al., 2013; Su et al., 2016). Furthermore, the severity of hyperintensities have been associated with accelerated cognitive decline (Hanning et al., 2011; Steinbrink et al., 2013), atrophy (McMurtray et al., 2008), duration of infection (Steinbrink et al., 2013) and viral load (Steinbrink et al., 2013; van Arnhem et al., 2013).

Limited authors have investigated subcortical gray matter hyperintensities. Wehn, Heinz, Burger, and Boyko (1989) observed hyperintensities in the caudate nucleus, putamen and globus pallidus with some involvement of the surrounding white matter and thalamus. Similarly, Meltzer et al. (1998) observed bilateral caudate nucleus and putamen hyperintensity in nine AIDS patients, and two cases presented with globus pallidus hyperintensities. Furthermore, two post-mortem examinations were completed and multiple microinfarcts were observed corresponding to the hyperintensity regions. Kodama, Numaguchi, Gellad, and Sadato (1991) observed bilateral putamen hyperintensities in two HIV-positive individuals; however, the remaining basal ganglia and white matter were unaffected.

Not all authors analyzed separate regions of the basal ganglia (Gillams et al., 1997; Hanning et al., 2011; Miller et al., 1997; Newsome, Johnson, Pardo, McArthur, & Nath, 2011; Steinbrink et al., 2013). In HIV-positive individuals, Hanning et al. (2011) observed mild and moderate-to-severe basal ganglia hyperintensities in 23.8 and 5.0%, respectively. Similarly, Steinbrink et al. (2013) observed mild and moderate-to-severe basal ganglia hyperintensities in 27.7 and 4.3%, respectively. These hyperintensities have frequently been observed bilaterally (Gillams et al., 1997; Newsome et al., 2011).

Studies have commonly observed white matter hyperintensities in HIV-positive individuals, in a range of 38.0-63.4% (Ackermann et al., 2014; Haddow et al., 2014; McMurtray et al., 2008; van Arnhem et al., 2013). These white matter hyperintensities can be divided into periventricular (<10 mm from ventricles) and deep (>10 mm from ventricles) white matter regions. Most authors observed that white matter hyperintensities are commonly located in the periventricular region, and seldom in the deep white matter (Ackermann et al., 2014; Su et al., 2016). Ackermann et al. (2014) observed hyperintensities in frontal (91.0%), parietal (77.0%), temporal (5.0%) and occipital (14.0%) white matter. These lesions may be more prevalent in HIV-positive individuals with cognitive decline (Hanning et al., 2011).

1.4 | Mechanisms of HAND

The pathogenesis of HAND is not yet known. Shortly after infection with HIV, the virus migrates to the brain, possibly as early as 8 days after infection (McArthur et al., 2005; Nightingale et al., 2014; Robertson et al., 2004; Valcour et al., 2012; Zayyad & Spudich, 2015). The brain acts as a reservoir for the virus, which contributes to the difficulty in eradicating the virus (McArthur et al., 2005; Nightingale et al., 2014; Robertson et al., 2004). The mechanisms associated with HAND has been extensively reviewed elsewhere (Valcour, Sithinamsuwan, Letendre, & Ances, 2011). Shortly, with central nervous system (CNS) infection, different cell types are infected, including macrophages and microglial cells. These cells are the primary infected cells; however, astrocytes are also infected even though these cells lack CD4 receptors. Mechanisms of infection of astrocytes are unknown, possibly due to the selective pressure caused by CNS compartmentalization (Zayyad & Spudich, 2015). The mode of transmission into the brain is still unclear; the virus can enter through infected CD4 T lymphocytes, or free virus entry since HIV disrupts the blood brain barrier by altering the endothelial tight junctions (Awan et al., 2014). The act of immune cells entering the brain additionally stimulates increased movement of lymphocytes to the brain (Zayyad & Spudich, 2015).

Several mechanisms damage the CNS, either directly or indirectly. Once HIV-infected macrophages enter the brain, viral proteins are released (Tat, Gp120, Vpr, Nef). Viral protein release also causes additional activated macrophages to migrate to the brain. These infected and activated macrophages release cytokines (TNF-α, IL-1β), chemokines, and excitatory amino acids (glutamate and quinolinate), which causes neuronal damage though excitotoxicity (increased free radical production, overstimulated N-methyl-D-aspartate [NMDA] receptors and calcium influx). Some HIV proteins may be directly neurotoxic through the action of chemokines such as stromal cell-derived factor 1 (SDF-1; Brabers & Nottet, 2006; Kaul, Garden, & Lipton, 2001; Zayyad & Spudich, 2015). Moreover, there is increased oxidative stress due to increased TNF-α and nitric oxide (Bjugstad, Flitter, Garland, Su, & Arendash, 1998; Elbirt, Mahlab-Guri, Bazalel-Rosenberg, Attali, & Asher, 2015; Gannon, Khan, & Kolson, 2011; McArthur et al., 2005; Robertson et al., 2004; Scutari, Alteri, Perno, Svicher, & Aquaro, 2017; Stebbins et al., 2007; Vincent et al., 1999). These mechanisms result in damage or death of neural cells and eventually leads to neurocognitive impairment. While HAND typically develops with HIV immunosuppression, it can develop at any stage of infection (Elbirt et al., 2015; McArthur & Brew, 2010; Scutari et al., 2017; Tucker et al., 2004). This damage can thus occur due to direct infection of the cells, or due to secondary factors.

TABLE 1 The prevalence of HIV-associated neurocognitive disorder reported in different geographical locations

Author and date	Region	Prevalence (%)	Sample size	Data capturing period
Wadia et al., 2001	India	29.9	1,527	–
Sacktor et al., 2002	United States of America	74.3	272	1994–1995
		76.0	251	1998–1999
Tozzi et al., 2005	Italy	55.1	432	1996–2002
Yepthomi et al., 2006	Southern India	56.0	30	–
Wojna et al., 2006	Puerto Rico	77.6	49	2002–2004
Jowi, Mativo, & Musoke, 2007	Kenya	21.2	708	2000–2005
Bolokadze, Gabunia, Ezugbaia, Gatserelia, & Khechiashvili, 2008	Georgia	19.6	388	2006–2007
Wright et al., 2008	Asia-Pacific countries	11.7	658	2005–2006
Njamnshi et al., 2008	Cameroon	21.1	204	2006
Lawler et al., 2010	Botswana	38.0	120	2008
Joska, Fincham, Stein, Paul, & Seedat, 2010	South Africa	23.5	536	–
Simioni et al., 2010	Switzerland	74.0	200	–
Garvey, Surendrakumar, & Winston, 2012	United Kingdom	19.0	101	–
Hanning et al., 2011	Germany	37.6	32	–
Zhang et al., 2012	China	37.1	134	–
Chan, Kandiah, & Chua, 2012	Singapore	22.7	132	2010
Oshinaike et al., 2012	Nigeria	54.3	208	2007–2008
Crum-Cianflone et al., 2013	United Kingdom	19.0	200	2009–2011
Cross, Önen, Gase, Overton, & Ances, 2013	United States of America	41.2	507	2008
Atashili et al., 2013	Cameroon	85.0	400	2010
McDonnell et al., 2014	United Kingdom	21.0	248	2011–2012
Fasel et al., 2014	Switzerland	83.0	30	2011
Yusuf et al., 2017	Nigeria	21.5	418	–
Saini & Barar, 2014	India	32.5	80	2011–2012
Achappa et al., 2014	Asia	90.1	101	–
Kelly et al., 2014	Malawi	70.0	106	2011–2012
Lakatos, Szabo, Bozzai, Banhegyi, & Gazdag, 2014	Hungary	32.2	59	–
Robertson et al., 2014	Western Europe and Canada	41.5	2,863	2010–2011
Ene et al., 2014	Romania	59.1	49	–
Fazeli et al., 2014	San Diego	46.0	139	2006–2011
Yakasai et al., 2015	Nigeria	35.0	80	–
Vassallo et al., 2015	France	29.0	200	2007–2013
Zhao et al., 2015	Guangxi, China	37.4	230	2011
McNamara, Coen, Redmond, Doherty, & Bergin, 2016	Ireland	51.5	604	2010–2013
Sacktor et al., 2016	United States of America	25.0	197	2007–2008
		25.0	197	2009–2010
		31.0	197	2011–2012

(Continues)

TABLE 1 (Continued)

Author and date	Region	Prevalence (%)	Sample size	Data capturing period
Joska et al., 2016	South Africa	56.2	89	–
	United States of America	83.6	67	
Bloch et al., 2016	Australia	30.7	254	2011–2012
Pinheiro et al., 2016	Brazil	54.1	392	2015
Focà et al., 2016	Italy	47.1	206	2009–2013
Evering et al., 2016	New York	4.0	26	2010–2012
Belete, Medfu, & Yemiyamrew, 2017	Ethiopia	33.3	234	2016
Tsegaw, Andargie, Alem, & Tareke, 2017	Ethiopia	36.4	595	2015
Barber et al., 2017	London	13.9	205	–

1.5 | Treatment for HAND

Currently the only treatment for HAND is HAART, which is a combination of at least three antiretroviral drugs (Elbirt et al., 2015). HAART restores immune function and reduces replication of HIV. However, immune activation persists regardless of antiretroviral treatment (Hellmuth et al., 2014). If antiretroviral drugs do not adequately penetrate the brain, the viral count in the CSF can be unchanged or minimally affected (Robertson et al., 2004). Some antiretroviral drugs, such as Abacavir and Nevirapine (Robertson, Liner, & Meeker, 2012), have a higher CNS penetration effectiveness (CPE); the higher the CPE, the lower the CSF viral count (Elbirt et al., 2015; Gannon et al., 2011; Letendre et al., 2008; Robertson et al., 2007, 2012). The end goal is to find an antiretroviral therapy that reduces the CSF viral load (high CPE), and increases neural function without causing neurotoxicity (Elbirt et al., 2015; Gannon et al., 2011; Letendre et al., 2008; McArthur et al., 2005; Nightingale et al., 2014). Unfortunately, studies do not show an increase in neural functioning with a high CPE drug (Elbirt et al., 2015). To assess if antiretroviral therapy can lower the CSF viral load, treatment must be adhered to for a sufficient period (Letendre et al., 2008). Robertson et al. (2007) stated that the CNS impairment of only 44.0% of individuals improved after the use of HAART. Therefore, even with HAART, there is still decline in neural functioning (Elbirt et al., 2015; Hellmuth et al., 2014; Letendre, Ellis, Ances, & McCutchan, 2010; Nightingale et al., 2014; Robertson et al., 2004, 2007). This could suggest that even if the virus is eradicated with HAART, other factors are still affecting cognition.

Almost half of HIV-positive individuals suffer from HAND, and with the introduction of HAART, the prevalence of HAND has remained mostly stable (Elbirt et al., 2015; Gannon et al., 2011; McArthur et al., 2005; McArthur & Brew, 2010; Nightingale et al., 2014). However, the prevalence of HAD has decreased, and the occurrence of ANI and MND has increased (Elbirt et al., 2015; Gannon et al., 2011; Heaton et al., 2010; Robertson et al., 2004). From the literature, HAND is observed in 4.0–90.1% of HIV-positive individuals (Table 1). Furthermore, since more HIV-positive individuals are living longer, they are exposed to HIV and HAART for a longer time, which can lead to more severe neurological damage (Elbirt et al., 2015; Hellmuth et al., 2014; McArthur, 2004; McArthur & Brew, 2010; Robertson et al., 2007). Thus, the prevalence of HAND can still possibly increase even with HAART (Elbirt et al., 2015; Hellmuth et al., 2014).

2 | CONCLUSION

In summary, HIV causes atrophy of the brain, both globally and region specific; studies have observed significant atrophy in subcortical gray matter, as well as in cortical white and gray matter. Moreover, the ventricles enlarge, and the sulci widen, leading to an increase in CSF. Although HIV causes changes to the white and gray matter of the brain, few DTI studies have investigated the changes to gray matter integrity, since changes are more difficult to observe due to poorer signal-to-noise ratio. White and gray matter hyperintensities have frequently been observed in HIV-positive individuals, with the subcortical gray matter (caudate nucleus and putamen) and periventricular white matter frequently affected. Not all brain regions are affected by HIV equally; this is possibly due to the proximity to the ventricles (which can allow for easier access of infected cells), or due to different distributions of perivascular macrophages in different brain regions (Ances et al., 2012; McArthur et al., 2005).

In conclusion, subcortical gray matter is the first brain region to be affected and is affected most severely. Additionally, this review highlights the gaps in the

literature, since the effect of HIV on the brain is not fully known. Future studies should continue to investigate the effect of HIV on the brain in different stages of the disease, and alternate therapies should be developed since HAART is currently ineffective at treating HAND.

ACKNOWLEDGMENTS

The financial assistance of the National Research Foundation (NRF) toward this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to the NRF.

AUTHOR CONTRIBUTIONS

Karen Cilliers: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; writing-original draft; writing-review and editing. **Christo Muller:** Conceptualization; supervision; writing-review and editing.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ORCID

Karen Cilliers https://orcid.org/0000-0001-7309-3277

REFERENCES

Achappa, B., Priyadarshni, S., Madi, D., Bhaskaran, U., Ramapuram, J. T., Rao, S., ... Mahalingam, S. (2014). Neurocognitive dysfunction among HIV positive patients using international HIV dementia scale. *Asian Journal of Medical Science*, *5*, 61–64.

Ackermann, C., Andronikou, S., Laughton, B., Kidd, M., Dobbels, E., Innes, S., ... Cotton, M. (2014). White matter signal abnormalities in children with suspected HIV-related neurologic disease on early combination antiretroviral therapy. *The Pediatric Infectious Disease Journal*, *33*, 207–212.

Ances, B. M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. *Journal of Acquired Immune Deficiency Syndromes*, *59*, 469–477.

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., ... Wojna, V. E. (2007). Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. *Neurology*, *69*, 1789–1799.

Archibald, S. L., Masliah, E., Fennema-Notestine, C., Marcotte, T. D., Ellis, R. J., McCutchan, J. A., ... Jernigan, T. L. (2004). Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss. *Archives of Neurology*, *61*, 369–376.

van Arnhem, L. A., Bunders, M. J., Scherpbier, H. J., Majoie, C. B. L. M., Reneman, L., Frinking, O., ... Pajkrt, D. (2013). Neurologic abnormalities in HIV-1 infected children in the era of combination antiretroviral therapy. *PLoS One*, *8*, 1–6.

Atashili, J., Gaynes, B. N., Pence, B. W., Tayong, G., Kats, D., O'donnell, J. K., ... Njamnshi, A. K. (2013). Prevalence, characteristics and correlates of a positive-dementia screen in patients on antiretroviral therapy in Bamenda, Cameroon: A cross-sectional study. *BMC Neurology*, *13*, 1–7.

Awan, F. M., Anjum, S., Obaid, A., Ali, A., Paracha, R. Z., & Janjua, H. A. (2014). In-silico analysis of claudin-5 reveals novel putative sites for post-translational modifications: Insights into potential molecular determinants of blood-brain barrier breach during HIV-1 infiltration. *Infection, Genetics and Evolution*, *27*, 355–365.

Aylward, E. H., Brettschneider, P. D., McArthur, J. C., Harris, G. J., Schlaepfer, T. E., Henderer, J. D., ... Pearlson, G. D. (1995). Magnetic resonance imaging measurement of gray matter volume reductions in HIV dementia. *The American Journal of Psychiatry*, *152*, 987–994.

Aylward, E. H., Henderer, J. D., McArthur, J. C., Brettschneider, P. D., Harris, G. J., Barta, P. E., & Pearlson, G. D. (1993). Reduced basal ganglia volume in HIV-1-associated dementia: Results from quantitative neuroimaging. *Neurology*, *43*, 2099–2104.

Barber, T. J., Bansi, L., Pozniak, A., Asboe, D., Nelson, M., Moyle, G., ... Boffito, M. (2017). Low levels of neurocognitive impairment detected in screening HIV-infected men who have sex with men: The MSM Neurocog Study. *International Journal of STD & AIDS*, *28*, 715–722.

Becker, J. T., Maruca, V., Kingsley, L. A., Sanders, J. M., Alger, J. R., Barker, P. B., ... Selnes, O. (2012). Factors affecting brain structure in men with HIV disease in the post-HAART era. *Neuroradiology*, *54*, 113–121.

Becker, J. T., Sanders, J., Madsen, S. K., Ragin, A., Kingsley, L., Maruca, V., et al. (2011). Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*, *5*, 77–85.

Behrman-Lay, A. M., Paul, R. H., Heaps-Woodruff, J., Baker, L. M., Usher, C., & Ances, B. M. (2016). Human immunodeficiency virus has similar effects on brain volumetrics and cognition in males and females. *Journal of Neurovirology*, *22*, 93–103.

Belete, T., Medfu, G., & Yemiyamrew, E. (2017). Prevalence of HIV associated neurocognitive deficit among HIV positive people in Ethiopia: A cross sectional study at Ayder Referral Hospital. *Ethiopian Journal of Health Sciences*, *27*, 67–76.

Bjugstad, K. B., Flitter, W. D., Garland, W. A., Su, G. C., & Arendash, G. W. (1998). Preventive actions of a synthetic antioxidant in a novel animal model of AIDS dementia. *Brain Research*, *795*, 349–357.

Bloch, M., Kamminga, J., Jayewardene, A., Bailey, M., Carberry, A., Vincent, T., ... Cysique, L. A. (2016). A screening strategy for HIV-associated neurocognitive disorders that accurately identifies patients requiring neurological review. *Clinical Infectious Diseases*, *63*, 687–693.

Bolokadze, N., Gabunia, P., Ezugbaia, M., Gatserelia, L., & Khechiashvili, G. (2008). Neurological complications in patients with HIV/AIDS. *Georgian Medical News*, *165*, 34–38.

Brabers, N. A. C. H., & Nottet, H. S. L. M. (2006). Role of the pro-inflammatory cytokines TNF-α and IL-1β in HIV-associated dementia. *European Journal of Clinical Investigation*, *36*, 447–458.

Castelo, J. B. M., Courtney, M. G., Melrose, R. J., & Stern, C. E. (2007). Putamen hypertrophy in nondemented patients with human immunodeficiency virus infection and cognitive compromise. *Archives of Neurology*, *64*, 1275–1280.

Chan, L. G., Kandiah, N., & Chua, A. (2012). HIV-associated neurocognitive disorders (HAND) in a South Asian population—contextual application of the 2007 criteria. *BMJ Open*, *2*, 1–6.

Chang, L., Wong, V., Nakama, H., Watters, M., Ramones, D., Miller, E. N., … Ernst, T. (2008). Greater than age-related changes in brain diffusion of HIV patients after 1 year. *Journal of Neuroimmune Pharmacology*, *3*, 265–274.

Chen, Y., An, H., Zhu, H., Stone, T., Smith, J. K., Hall, C., … Lin, W. (2009). White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients, *47*, 1154–1162.

Cloak, C. C., Chang, L., & Ernst, T. (2004). Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV. *Journal of Neuroimmunology*, *157*, 147–152.

Corrêa, D. G., Zimmermann, N., Doring, T. M., Wilner, N. V., Leite, S. C. B., Cabral, R. F., … Gasparetto, E. L. (2015). Diffusion tensor MR imaging of white matter integrity in HIV-positive patients with planning deficit. *Neuroradiology*, *57*, 475–482.

Cross, S., Önen, N., Gase, A., Overton, E. T., & Ances, B. M. (2013). Identifying risk factors for HIV-associated neurocognitive disorders using the international HIV dementia scale. *Journal of Neuroimmune Pharmacology*, *8*, 1114–1122.

Crum-Cianflone, N. F., Moore, D. J., Letendre, S., Roediger, M. P., Eberly, L., Weintrob, A., … Hale, B. R. (2013). Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. *Neurology*, *80*, 371–379.

Elbirt, D., Mahlab-Guri, K., Bazalel-Rosenberg, S., Attali, M., & Asher, I. (2015). HIV-associated neurocognitive disorders. *The Israel Medical Association Journal*, *17*, 54–59.

Ene, L., Franklin, D. R., Burlacu, R., Luca, A. E., Blaglosov, A. G., Ellis, R. J., … Marcotte, T. D. (2014). Neurocognitive functioning in a Romanian cohort of young adults with parenterally-acquired HIV-infection during childhood. *Journal of Neurovirology*, *20*, 496–504.

Evering, T. H., Applebaum, A., La Mar, M., Garmon, D., Dorfman, D., & Markowitz, M. (2016). Rates of non-confounded HIV-associated neurocognitive disorders in men initiating cART during primary infection. *AIDS*, *30*, 203–210.

Fasel, D., Kunze, U., Elzi, L., Werder, V., Niepmann, S., Schumacher, R., … Battegay, M. (2014). A short tool to screen HIV-infected patients for mild neurocognitive disorders – A pilot study. *BMC Psychology*, *2*, 1–9.

Fazeli, P. L., Woods, S. P., Heaton, R. K., Umlauf, A., Gouaux, B., Rosario, D., … Moore, D. J. (2014). An active lifestyle is associated with better neurocognitive functioning in adults living with HIV infection. *Journal of Neurovirology*, *20*, 233–242.

Fennema-Notestine, C., Ellis, R. J., Archibald, S. L., Jernigan, T. L., Letendre, S. L., Notestine, R. J., et al. (2013). Increases in brain white matter abnormalities and subcortical gray matter are linked to CD4 recovery in HIV infection. *Journal of Neurovirology*, *19*, 393–401.

Filippi, C. G., Ulug, A. M., Ryan, E., Ferrando, S. J., & van Gorp, W. (2001). Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. *American Journal of Neuroradiology*, *22*, 277–283.

Focà, E., Magro, P., Motta, D., Compostella, S., Casari, S., Bonito, A., … Castelli, F. (2016). Screening for neurocognitive impairment in HIV-infected individuals at first contact after HIV diagnosis: The experience of a large clinical center in Northern Italy. *International Journal of Molecular Sciences*, *17*, 1–9.

Gannon, P., Khan, M. Z., & Kolson, D. L. (2011). Current understanding of HIV-associated neurocognitive disorders pathogenesis. *Current Opinion in Neurology*, *24*, 275–283.

Garvey, L., Surendrakumar, V., & Winston, A. (2012). Low rates of neurocognitive impairment are observed in neuro-asymptomatic HIV-infected subjects on effective antiretroviral therapy. *HIV Clinical Trials*, *12*, 333–338.

Gillams, A. R., Allen, E., Hrieb, K., Venna, N., Craven, D., & Carter, A. P. (1997). Cerebral infarction in patients with AIDS. *American Journal of Neuroradiology*, *18*, 1581–1585.

Haddow, L. J., Dudau, C., Chandrashekar, H., Cartledge, J. D., Hyare, H., Miller, R. F., & Jäger, H. R. (2014). Cross-sectional study of unexplained white matter lesions in HIV positive individuals undergoing brain magnetic resonance imaging. *AIDS Patient Care and STDs*, *28*, 341–349.

Hanning, U., Husstedt, I. W., Niederstadt, T. U., Evers, S., Heindel, W., & Kloska, S. P. (2011). Cerebral signal intensity abnormalities on T2-weighted MR images in HIV patients with highly active antiretroviral therapy. Relationship with clinical parameters and interval changes. *Academic Radiology*, *18*, 1144–1150.

Heaps, J. M., Joska, J., Hoare, J., Ortega, M., Agrawal, A., Seedat, S., … Paul, R. (2012). Neuroimaging markers of human immunodeficiency virus infection in South Africa. *Journal of Neurovirology*, *18*, 151–156.

Heaps, J. M., Sithinamsuwan, P., Paul, R., Lerdlum, S., Pothisri, M., Clifford, D., … Raudabaugh, B. (2015). Association between brain volumes and HAND in cART naïve HIV+ individuals from Thailand. *Journal of Neurovirology*, *21*, 105–112.

Heaton, R., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., et al. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology*, *75*, 2087–2096.

Hellmuth, J., Milanini, B., & Valcour, V. (2014). Interactions between aging and NeuroAIDS. *Current Opinion in HIV and AIDS*, *9*, 527–532.

Hoare, J., Fouche, J.-P., Spottiswoode, B., Sorsdahl, K., Combrinck, M., Stein, D. J., … Joska, J. A. (2011). White-matter damage in clade C HIV-positive subjects: A diffusion tensor imaging study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*, 308–315.

Hoare, J., Westgarth-Taylor, J., Fouche, J.-P., Spottiswoode, B., Paul, R., Thomas, K., … Joska, J. (2012). A diffusion tensor imaging and neuropsychological study of prospective memory impairment in South African HIV positive individuals. *Metabolic Brain Disease*, *27*, 289–297.

Jernigan, T. L., Archibald, S., Hesselink, J. R., Atkinson, J. H., Velin, R. A., McCutchan, J. A., … Grant, I. (1993). Magnetic resonance imaging morphometric analysis of cerebral volume loss in human immunodeficiency virus infection. *Archives of Neurology*, *50*, 250–255.

Joska, J. A., Fincham, D. S., Stein, D. J., Paul, R. H., & Seedat, S. (2010). Clinical correlates of HIV-associated neurocognitive disorders in South Africa. *AIDS and Behavior*, *14*, 371–378.

Joska, J. A., Witten, J., Thomas, K. G., Robertson, C., Casson-Crook, M., Roosa, H., … Sacktor, N. C. (2016). A comparison of

five brief screening tools for HIV-associated neurocognitive disorders in the USA and South Africa. *AIDS and Behavior*, *20*, 1621–1631.

Jowi, J. O., Mativo, P. M., & Musoke, S. S. (2007). Clinical and laboratory characteristics of hospitalised patients with neurological manifestations of HIV/AIDS at the Nairobi hospital. *East African Medical Journal*, *84*, 67–76.

Kamat, R., Brown, G. G., Bolden, K., Fennema-Notestein, C., Archibald, S., Marcotte, T. D., … Heaton, R. K. (2014). Apathy is associated with white matter abnormalities in anterior, medial brain regions in persons with HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *36*, 854–866.

Kallianpur, K. J., Valcour, V. G., Lerdlum, S., Busovaca, E., Agsalda, M., Sithinamsuwan, P., … Shiramizu, B. T. (2014). HIV DNA in CD14+ reservoirs is associated with regional brain atrophy in cART-naïve patients. *AIDS*, *28*, 1619–1624.

Kaul, M., Garden, G. A., & Lipton, S. A. (2001). Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature*, *410*, 988–994.

Kelly, C. M., Van Oosterhout, J. J., Ngwalo, C., Stewart, R. C., Benjamin, L., Robertson, K. R., … Solomon, T. (2014). HIV associated neurocognitive disorders (HAND) in Malawian adults and effect on adherence to combination anti-retroviral therapy: A cross sectional study. *PLoS One*, *9*, 1–11.

Kodama, T., Numaguchi, Y., Gellad, F. E., & Sadato, N. (1991). High signal intensity of both putamina in patients with HIV infection. *Neuroradiology*, *33*, 362–363.

Kugathasan, R., Collier, D. A., Haddow, L. J., El Bouzidi, K., Edwards, S. G., Cartledge, J. D., … Gupta, R. K. (2017). Diffuse white matter signal abnormalities on magnetic resonance imaging are associated with human immunodeficiency virus type 1 viral escape in the central nervous system among patients with neurological symptoms. *Clinical Infectious Diseases*, *64*, 1059–1065.

Lakatos, B., Szabo, Z., Bozzai, B., Banhegyi, D., & Gazdag, G. (2014). Neurocognitive impairments of HIV infected individuals - preliminary results of a national prevalence study in Hungary. *Ideggyógyászati Szemle*, *67*, 409–414.

Lawler, K., Mosepele, M., Ratcliffe, S., Seloilwe, E., Steele, K., & Nthobatsang, R. (2010). Neurocognitive impairment among HIV-positive individuals in Botswana: A pilot study. *Journal of the International AIDS Society*, *13*, 1–9.

Leite, S. C. B., Corrêa, D. G., Doring, T. M., Kubo, T. T. A., Netto, T. M., Ferracini, R., … Gasparetto, E. L. (2013). Diffusion tensor MRI evaluation of the corona radiata, cingulate gyri, and corpus callosum in HIV patients. *Journal of Magnetic Resonance Imaging*, *38*, 1488–1493.

Letendre, S., Marquie-Beck, J., Capparelli, E., Best, B., Clifford, D., Collier, A. C., … Morgello, S. (2008). Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Archives of Neurology*, *65*, 65–70.

Letendre, S. L., Ellis, R. J., Ances, B. M., & McCutchan, J. A. (2010). Neurologic complications of HIV disease and their treatment. *Topics in HIV Medicine*, *18*, 45–55.

Levin, H. S., Williams, D. H., Borucki, M. J., Hillman, G. R., Williams, J. B., Guinto, J. F., … Pollard, R. B. (1990). Magnetic resonance imaging and neuropsychological findings in human immunodeficiency virus infection. *Journal of Acquired Immune Deficiency Syndromes*, *3*, 757–762.

McArthur, J. C. (2004). HIV dementia: An evolving disease. *Journal of Neuroimmunology*, *157*, 3–10.

McArthur, J. C., & Brew, B. J. (2010). HIV-associated neurocognitive disorders: Is there a hidden epidemic? *AIDS*, *24*, 1367–1370.

McArthur, J. C., Brew, B. J., & Nath, A. (2005). Neurological complications of HIV infection. *Lancet Neurology*, *4*, 543–555.

McDonnell, J., Haddow, L., Daskalopoulou, M., Lampe, F., Speakman, A., Gilson, R., … Cognitive Impairment in People with HIV in the European Region (CIPHER) Study Group. (2014). Minimal cognitive impairment in UKHIV-positive men who have sex with men: Effect of case definitions and comparison with the general population and HIV-negative men. *Journal of Acquired Immune Deficiency Syndromes*, *67*, 120–127.

McMurtray, A., Nakamoto, B., Shikuma, C., & Valcour, V. (2008). Cortical atrophy and white matter hyperintensities in HIV: The Hawaii aging with HIV cohort study. *Journal of Stroke and Cerebrovascular Diseases*, *17*, 212–217.

McNamara, P. H., Coen, R., Redmond, J., Doherty, C. P., & Bergin, C. (2016). A high prevalence rate of a positive screen for cognitive impairment in patients with human immunodeficiency virus attending an Irish clinic. *Open Forum Infectious Diseases*, *4*, 1–9.

Meltzer, C. C., Wells, S. W., Becher, M. W., Flanigan, K. M., Oyler, G. A., & Lee, R. R. (1998). AIDS-related MR hyperintensity of the basal ganglia. *American Journal of Neuroradiology*, *19*, 83–89.

Miller, R. F., Lucas, S. B., Hall-Craggs, M. A., Brink, N. S., Scaravilli, F., Chinn, R. J. S., … Harrison, M. J. G. (1997). Comparison of magnetic resonance imaging with neuropathological findings in the diagnosis of HIV and CMV associated CNS disease in AIDS. *Journal of Neurology, Neurosurgery, and Psychiatry*, *62*, 346–351.

Newsome, S. D., Johnson, E., Pardo, C., McArthur, J. C., & Nath, A. (2011). Fulminant encephalopathy with basal ganglia hyperintensities in HIV-infected drug users. *Neurology*, *76*, 787–794.

Nightingale, S., Winston, A., Letendre, S., Michael, B. D., McArthur, J. C., Khoo, S., & Solomon, T. (2014). Controversies in HIV-associated neurocognitive disorders. *Lancet Neurology*, *13*, 1139–1151.

Nir, T. M., Jahanshad, N., Busovaca, E., Wendelken, L., Nicolas, K., Thompson, P. M., & Valcour, V. G. (2014). Mapping white matter integrity in elderly people with HIV. *Human Brain Mapping*, *35*, 975–992.

Njamnshi, A. K., Djientcheu, V. D. P., Fonsah, J. Y., Yepnjio, F. N., Njamnshi, D. M., & Muna, W. F. (2008). The international HIV dementia scale is a useful screening tool for HIV-associated dementia/cognitive impairment in HIV-infected adults in Yaoundé—Cameroon. *Journal of Acquired Immune Deficiency Syndromes*, *49*, 393–397.

Ortega, M., Heaps, J. M., Joska, J., Vaida, F., Seedat, S., Stein, D. J., … Ances, B. M. (2013). HIV clades B and C are associated with reduced brain volumetrics. *Journal of Neurovirology*, *19*, 479–487.

Oshinaike, O. O., Akinbami, A. A., Ojo, O. O., Ojini, I. F., Okubadejo, U. N., & Danesi, A. M. (2012). Comparison of the minimentalstate examination scale and the international HIV dementia scale in assessing cognitive function in Nigerian HIV patients on antiretroviral therapy. *AIDS Research and Treatment*, *2012*, 1–6.

Paul, R., Cohen, R., Navia, B., & Tashima, K. (2002). Relationships between cognition and structural neuroimaging findings in adults with human immunodeficiency virus type-1. *Neuroscience and Biobehavioral Reviews*, *26*, 353–359.

Paul, R. H., Ernst, T., Brickman, A. M., Yiannoutsos, C. T., Tate, D. F., Cohen, R. A., & Navia, B. A. (2008). Relative sensitivity of magnetic resonance spectroscopy and quantitative magnetic resonance imaging to cognitive function among nondemented individuals infected with HIV. *Journal of the International Neuropsychological Society*, *14*, 725–733.

Pfefferbaum, A., Rosenbloom, M. J., Rohlfing, T., Adalsteinsson, E., Kemper, C. A., Deresinski, S., & Sullivan, E. V. (2006). Contribution of alcoholism to brain dysmorphology in HIV infection: Effects on the ventricles and corpus callosum. *NeuroImage*, *33*, 239–251.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*, 637–648.

Pinheiro, C. A. T., Souza, L. D. M., Motta, J. V. S., Kelbert, E. F., Souza, M. S., Martins, C. S. R., ... Pinheiro, R. T. (2016). Depression and diagnosis of neurocognitive impairment in HIV-positive patients. *Brazilian Journal of Medical and Biological Research*, *49*, 1–7.

Pomara, N., Crandall, D. T., Choi, S. J., Johnson, G., & Lim, K. O. (2001). White matter abnormalities in HIV-1 infection: A diffusion tensor imaging study. *Psychiatry Research*, *106*, 15–24.

Ragin, A. B., Storey, P., Cohen, B. A., Edelman, R. R., & Epstein, L. G. (2004). Disease burden in HIV-associated cognitive impairment: A study of whole-brain imaging measures. *Neurology*, *63*, 2293–2297.

Ragin, A. B., Storey, P., Cohen, B. A., Epstein, L. G., & Edelman, R. R. (2004). Whole brain diffusion tensor imaging in HIV-associated cognitive impairment. *American Journal of Neuroradiology*, *25*, 195–200.

Ragin, A. B., Wu, Y., Gao, Y., Keating, S., Du, H., Sammet, C., ... Epstein, L. G. (2015). Brain alterations within the first 100 days of HIV infection. *Annals of Clinical Translational Neurology*, *2*, 12–21.

Ragin, A. B., Wu, Y., Storey, P., Cohen, B. A., Edelman, R. R., & Epstein, L. G. (2005). Diffusion tensor imaging of subcortical brain injury in patients infected with human immunodeficiency virus. *Journal of Neurovirology*, *11*, 292–298.

Robertson, K., Bayon, C., Molina, J. M., McNamara, P., Resch, C., Muñoz-Moreno, J. A., et al. (2014). Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in Western Europe and Canada. *AIDS Care*, *26*, 1555–1561.

Robertson, K., Liner, J., & Meeker, R. B. (2012). Antiretroviral neurotoxicity. *Journal of Neurovirology*, *18*, 388–399.

Robertson, K. R., Robertson, W. T., Ford, S., Watson, D., Fiscus, S., Harp, A. G., & Hall, C. D. (2004). Highly active antiretroviral therapy improves neurocognitive functioning. *Journal of Acquired Immune Deficiency Syndromes*, *36*, 562–566.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., ... Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, *21*, 1915–1921.

Sacktor, N., McDermott, M. P., Marder, K., Schifitto, G., Selnes, O. A., McArthur, J. C., et al. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *Journal of Neurovirology*, *8*, 136–142.

Sacktor, N., Skolasky, R. L., Seaberg, E., Munro, C., Becker, J. T., Martin, E., ... Miller, E. (2016). Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. *Neurology*, *86*, 334–340.

Saini, S., & Barar, K. (2014). Assessment of neurocognitive functions in HIV/AIDS patients on HAART using the international HIV dementia scale. *International Journal of Nutrition, Pharmacology, and Neurological Diseases*, *4*, 252–255.

Di Sclafani, V., Mackay, R. D. S., Meyerhoff, D. J., Norman, D., Weiner, M. W., & Fein, G. (1997). Brain atrophy in HIV infection is more strongly associated with CDC clinical stage than with cognitive impairment. *Journal of the International Neuropsychological Society*, *3*, 276–287.

Scutari, R., Alteri, C., Perno, C. F., Svicher, V., & Aquaro, S. (2017). The role of HIV infection in neurologic injury. *Brain Sciences*, *7*, 1–17.

Seider, T. R., Gongvatana, A., Woods, A. J., Chen, H., Porges, E. C., Cummings, T., ... Cohen, R. A. (2016). Age exacerbates HIV-associated white matter abnormalities. *Journal of Neurovirology*, *22*, 201–212.

Simioni, S., Cavassini, M., Annoni, J. M., Rimbault Abraham, A., Bourquin, I., Schiffer, V., ... Du Pasquier, R. A. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*, *24*, 1243–1250.

Stebbins, G. T., Smith, C. A., Bartt, R. E., Kessler, H. A., Adeyemi, O. M., Martin, E., ... Moseley, M. E. (2007). HIV-associated alterations in normal-appearing white matter: A voxel-wise diffusion tensor imaging study. *Journal of Acquired Immune Deficiency Syndromes*, *46*, 564–573.

Steinbrink, F., Evers, S., Buerke, B., Young, P., Arendt, G., Koutsilieri, E., ... Husstedt, I. W. (2013). Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. *European Journal of Neurology*, *20*, 420–428.

Stout, J. C., Ellis, R. J., Jernigan, T. L., Archibald, S. L., Abramson, I., Wolfson, T., ... Grant, I. (1998). Progressive cerebral volume loss in human immunodeficiency virus infection. *Archives of Neurology*, *55*, 161–168.

Stubbe-Dräger, B., Deppe, M., Mohammadi, S., Keller, S. S., Kugel, H., Gregor, N., ... Husstedt, I. W. (2012). Early microstructural white matter changes in patients with HIV: A diffusion tensor imaging study. *BMC Neurology*, *12*, 23–33.

Su, T., Wit, F. W., Caan, M. W., Schouten, J., Prins, M., Geurtsen, G. J., ... Portegies, P. (2016). White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on cART. *AIDS*, *30*, 2329–2339.

Tang, V. M., Lang, D. J., Giesbrecht, C. J., Panenka, W. J., Willi, T., Procyshyn, R. M., et al. (2015). White matter deficits assessed by diffusion tensor imaging and cognitive dysfunction in psychostimulant users with comorbid human immunodeficiency virus infection. *BMC Research Notes*, *8*, 1–15.

Tate, D. F., Conley, J., Paul, R. H., Coop, K., Zhang, S., Zhou, W., ... Cohen, R. (2010). Quantitative diffusion tensor imaging tractography metrics are associated with cognitive performance among HIV-infected patients. *Brain Imaging Behaviour*, *4*, 68–79.

Thurnher, M. M., Castillo, M., Stadler, A., Rieger, A., Schmid, B., & Sundgren, P. C. (2005). Diffusion-tensor MR imaging of the

brain in human immunodeficiency virus-positive patients. *American Journal of Neuroradiology*, *26*, 2275–2281.

Tozzi, V., Balestra, P., Lorenzini, P., Bellagamba, R., Galgani, S., Corpolongo, A., ... Narciso, P. (2005). Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: Results from an urban observational cohort. *Journal of Neurovirology*, *11*, 265–273.

Tsegaw, M., Andargie, G., Alem, G., & Tareke, M. (2017). Screening HIV-associated neurocognitive disorders (HAND) among HIV positive patients attending antiretroviral therapy in south Wollo, Ethiopia. *Journal of Psychiatric Research*, *85*, 37–41.

Tucker, K. A., Robertson, K. R., Lin, W., Smith, J. K., An, H., Chen, Y., ... Hall, C. D. (2004). Neuroimaging in human immunodeficiency virus infection. *Journal of Neuroimmunology*, *157*, 153–162.

Valcour, V., Chalermchai, T., Sailasuta, N., Marovich, M., Lerdlum, S., Suttichom, D., et al. (2012). Central nervous system viral invasion and inflammation during acute HIV infection. *The Journal of Infectious Diseases*, *206*, 275–282.

Valcour, V., Sithinamsuwan, P., Letendre, S., & Ances, B. (2011). Pathogenesis of HIV in the central nervous system. *Current HIV/AIDS Reports*, *8*, 54–61.

Vassallo, M., Durant, J., Lebrun-Frenay, C., Fabre, R., Ticchioni, M., Andersen, S., et al. (2015). Virologically suppressed patients with asymptomatic and symptomatic HIV-associated neurocognitive disorders do not display the same pattern of immune activation. *HIV Medicine*, *16*, 431–440.

Vincent, V. A. M., de Groot, C. J. A., Lucassen, P. J., Portegies, P., Troost, D., Tilders, F. J. H., & van Dam, A. M. (1999). Nitric oxide synthase expression and apoptotic cell death in brains of AIDS and AIDS dementia patients. *AIDS*, *13*, 317–326.

Wade, B. S. C., Valcour, V. G., Wendelken-Riegelhaupt, L., Esmaeili-Firidouni, P., Joshi, S. H., Gutman, B. A., & Thompson, P. M. (2015). Mapping abnormal subcortical brain morphometry in an elderly HIV + cohort. *NeuroImage Clinical*, *9*, 564–573.

Wadia, R. S., Pujari, S. N., Kothari, S., Udhar, M., Kulkarni, S., Bhagat, S., & Nanivadekar, A. (2001). Neurological manifestations of HIV disease. *The Journal of the Association of Physicians of India*, *49*, 343–348.

Wehn, S. M., Heinz, E. R., Burger, P. C., & Boyko, O. B. (1989). Dilated Virchow-Robin spaces in cryptococcal meningitis associated with AIDS. *Journal of Computer Assisted Tomography*, *13*, 756–762.

Wojna, V., Skolasky, R. L., Hechavarría, R., Mayo, R., Selnes, O., McArthur, J. C., ... Nath, A. (2006). Prevalence of human immunodeficiency virus-associated cognitive impairment in a group of Hispanic women at risk for neurological impairment. *Journal of Neurovirology*, *12*, 356–364.

Wright, E., Nunn, M., Joseph, J., Robertson, K., Lal, L., & Brew, B. (2008). NeuroAIDS in the Asia Pacific region. *Journal of Neurovirology*, *14*, 465–473.

Wright, P. W., Vaida, F. F., Rutlin, J., Richard, W. P., Lee, E., Peterson, J., et al. (2015). Cerebral white matter integrity during primary HIV infection. *AIDS*, *29*, 433–442.

Wu, Y., Storey, P., Cohen, B. A., Epstein, L. G., Edelman, R. R., & Ragin, A. B. (2006). Diffusion alterations in corpus callosum of patients with HIV. *American Journal of Neuroradiology*, *27*, 656–660.

Yakasai, A. M., Gudaji, M. I., Muhammad, H., Ibrahim, A., Owolabi, L. F., Ibrahim, D. A., ... Habib, A. G. (2015). Prevalence and correlates of HIV-associated neurocognitive disorders (HAND) in northwestern Nigeria. *Neurology Research International*, *2015*, 1–9.

Yepthomi, T., Paul, R., Vallabhaneni, S., Kumarasamy, N., Tate, D. F., Solomon, S., & Flanigan, T. (2006). Neurocognitive consequences of HIV in southern India: A preliminary study of clade C virus. *Journal of the International Neuropsychological Society*, *12*, 424–430.

Yusuf, A. J., Hassan, A., Mamman, A. I., Muktar, H. M., Suleiman, A. M., & Baiyewu, O. (2017). Prevalence of HIV-associated neurocognitive disorder (HAND) among patients attending a tertiary health facility in northern Nigeria. *Journal of the International Association of Providers of AIDS Care*, *16*, 48–55.

Zayyad, Z., & Spudich, S. (2015). Neuropathogenesis of HIV: From initial neuroinvasion to HIV-associated neurocognitive disorder (HAND). *Current HIV/AIDS Reports*, *12*, 16–24.

Zhang, Y., Qiao, L., Ding, W., Wei, F., Zhao, Q., Wang, X., ... Chen, D. (2012). An initial screening for HIV-associated neurocognitive disorders of HIV-1 infected patients in China. *Journal of Neurovirology*, *18*, 120–126.

Zhao, T., Wei, B., Long, J., Tang, X., Zhou, M., & Dang, C. (2015). Cognitive disorders in HIV-infected and AIDS patients in Guangxi, China. *Journal of Neurovirology*, *21*, 32–42.

Zhu, T., Zhong, J., Hu, R., Tivarus, M., Ekholm, S., Harezlak, J., ... Schifitto, G. (2013). Patterns of white matter injury in HIV infection after partial immune reconstitution: A DTI tract-based spatial statistics study. *Journal of Neurovirology*, *19*, 10–23.

How to cite this article: Cilliers K, Muller CJF. Effect of human immunodeficiency virus on the brain: A review. *Anat Rec*. 2021;304:1389–1399. https://doi.org/10.1002/ar.24573