Neurocognitive Complications of HIV Infection in Low-Income Countries

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Abstract There is a paucity of information on neurocognitive dysfunction in individuals with HIV in resource-limited regions, despite the fact that these areas have the greatest burden of infection. HIV-associated neurocognitive disorder (HAND) remains a common complication of HIV despite the use of effective antiretroviral therapy (ART). HAND is a major cause of morbidity of HIV+ individuals and is estimated to be the most prevalent form of neurocognitive impairment worldwide in young adults. This finding has drastic implications for the productivity and social engagement of young adults in the development of industry, education, and healthcare, which is particularly relevant in low-income countries. Building an infrastructure to examine the neurological and neuropsychological characteristics of

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HIV+ individuals in resource-limited settings (RLS) can advance the understanding of the unique contributing factors of HIV-1 clades in these regions of high prevalence, improve neurological monitoring, explore the CNS HIV reservoir, and provide key information on prevention/interventions to help manage/improve these neurological and neuropsychological complications.

Keywords ART · HIV · HIV-associated neurocognitive disorder · Low income countries · Resource limited settings

1 Introduction: Global Epidemiology of HIV and HIV-Associated Neurological Disorders

Globally, 36.7 million people were living with HIV at the end of 2016. The epicenter of the epidemic is in sub-Saharan Africa, where almost 70% of the world's HIV+ population resides, and nearly 1 in every 25 adults (4.2%) is living with HIV. Southeast Asia has the second highest regional concentration of people living with HIV (WHO 2016). In addition to the burden of disease, these regions also have the highest concentration of low-income (GNI per capita $1,025 or less) and low-middle-income (GNI per capita between $1,026 and $4,035) countries (World Bank 2017). Furthermore, over half of the global burden of dementia occurs in low- and middle-income countries, with statistics indicating it will only increase with the growing population (Ferri et al. 2005).

HAND is the term used to describe the spectrum of neurocognitive dysfunction caused by HIV infection, which includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). The graded classification, according to Frascati criteria, is based on abnormal performance on neuropsychological testing and the presence or absence of a patient's impairment in daily functions related to cognitive impairment (Antinori et al. 2007). The changes in memory, attention, motor skills, behavior, and other complications of cognitive impairment are direct results of HIV infection and subsequent impact on the CNS.

In 2015, the WHO recommended that all people living with HIV should receive ART, regardless of their CD4 count based on the results of the START study demonstrating the benefits of early ART initiation (INSIGHT 2015). However, despite the use of effective ART, HAND remains a common complication of HIV and a major cause of morbidity where 15–55% of HIV+ individuals from the United States are affected with HAND (Heaton et al. 2010). With proper adherence to ARTs, there has been a significant decrease in the incidence of the most severe manifestation of HAND (HIV-associated dementia), but in most studies, this has been counterbalanced by an increase in the prevalence of more mild stages of HAND (Heaton et al. 2011). There is a similar range in the prevalence in RLS, with studies showing 15–69% of individuals with HIV on ART are diagnosed with HAND (Table 1). However, there is limited longitudinal, standardized data collected on

Table 1 Prevalence of HAND and HIV-1 subtype in resource-limited settings

Country	Prevalence of HAND, pre-ART	Prevalence of HAND, on ART	Citation	Compared with normalized data	Country income status (World Bank 2017)	ART coverage %	Dominant regional HIV-1 subtype (Liner et al. 2007)
Thailand	26% (acute HIV)	15%	Chan et al. (2018)	Yes	Lower middle	69	A, E
India	56%		Yepthomi et al. (2006)	Yes	Lower middle	49	C
Indonesia	51% (HAD, 19%)		Estiasari and Lastri (2015)	Yes	Lower middle	13	CRF01_AE, CRF's and other recombinants
Malaysia		22.8% (HAD, 0%)	Mukherjee et al. (2018)	Yes	Upper middle	37	CRF01_AE, CRF's and other recombinants
Cameroon	25.69%	17%	Njamnshi et al. (2009)	Yes	Lower middle	37	A, G, L, CRF's and other recombinants
Nigeria		21.5% (HAD, 2.9%)	Yusuf et al. (2017)	No	Lower middle	30	A, G, L, CRF's and other recombinants
Uganda	59% (HAD, 15%)	52% (HAD, 5%)		Yes	Low	67	A, D
Ethiopia		33.30%	Belete et al. (2017)	No	Low	59	C
Zambia		34.60%	Kabuba et al. (2016)	No	Lower middle	65	C
Tanzania		19.30%	Sanmartí et al. (2018)	Yes	Low	62	A, C
Kenya		69% (HAD, 0%)	Awori et al. (2018)	No	Lower middle	64	A
Malawi	HAD 15.56%	HAD 13.43% (for 6 months)		No	Low	66	C
Botswana		38.33%	Lawler et al. (2010)	No	Upper Middle	83	C
South Africa	76.5 (HAD, 25.3%)		Joska et al. (2011)	No	Upper Middle	56	C
Brazil		36.20%	Troncoso and Conterno (2015)	No	Upper Middle	60	B, C

Adapted from Habib et al. (2013), World Bank Income Level (2017), Liner et al. (2007), and specific studies listed with citation

the prevalence and severity of HAND in RLS, which are the regions most affected by HIV. Furthermore, RLS still have unequal access to ART, which leads to more advanced cases of HIV and thus increased risk of severe manifestations of HAND.

Another factor to consider is that the prevalence of HIV type 1 (HIV-1) clades varies by region, and their unique neurovirulence factors may have functional implication on onset and progression of HAND. HIV-1 is characterized by genetic diversity and can be divided into three classes, the most common of which is Group M (major), which has nine major clades (A–D, F–H, J, and K) (Liner et al. 2007). Studies in sub-Saharan Africa, where clades A, C, and D predominate, have suggested that clade differences lead to disparate frequencies of HAND. A study in Uganda, where the prevalence of HAD was as high as 31% among antiretroviral-naïve HIV+ individuals (Wong et al. 2007), showed that antiretroviral-naïve HIV+ individuals with subtype D were more likely to develop HAD and at a faster progression than those with subtype A (Sacktor et al. 2009). However, a subsequent study among HIV+ individuals with subtypes D and A with less immunosuppression failed to show a difference in the risk of HAD (Sacktor et al. 2014). Most recently, a longitudinal study of neurocognitive impairment in HIV+ individuals in rural Uganda with both moderate and severe immunosuppression found that those with subtype D infection had more severe neurocognitive impairment than those with subtype A infection regardless of level of immunosuppression (Sacktor et al. 2019). These studies are unique from those in North America, where subtype B is predominant.

2 Neurocognitive Complications of HIV-1 in the ART Era: Prevalence and Persistence in Resource-Limited Settings

The neurological complications of HIV have evolved with the introduction of ART and subsequent prolonged life expectancy. There has been a shift from neurological conditions related to low CD4 cell counts with opportunistic infections to virally suppressed patients with prolonged inflammation and neuronal damage. This change followed the introduction of ART, which halts viral replication, decreasing viral load in plasma and CSF and restoring the systemic immune function. The use of ART has beneficial effects on improving and even preventing the most severe forms of HAND, but the mild-to-moderate stages (such as MND and asymptomatic cases (ANI)) remain prevalent and clinically relevant. The impact on the daily lives of individuals with HIV can be economically and socially devastating in low-income countries, as discussed below.

There have been country-specific studies to estimate the burden of HAND on and off ART (Table 1). Several prospective studies from sub-Saharan Africa using the International HIV Dementia Scale were included in a systematic review and a meta-analysis to demonstrate the significant burden of neurocognitive impairment on and off ART in high HIV-prevalent areas (Habib et al. 2013). While there is a range in

the prevalence across the countries, the overall results of the studies indicate an improvement of neurocognitive performance following ART. The high burden of HAND also highlights the need for standardized neurological testing in these regions. Several factors could account for the variability among these studies, including the presence of preexisting clinical infrastructure to assess HAND and the quality of routine HIV care available to patients. Although there has been an increase in standardized HAND research in RLS, limited existing research infrastructure and research funding results in reduced quantity and reach of longitudinal HAND studies compared to high-income regions (Robertson et al. 2009; Kalula and Petros 2011). Studies in North America and Europe represent populations with distinct cultures, HIV-1 subtypes, age of highest risk, gender distribution, access to ART, and education status. These differences make it difficult to apply the significance of their results to the African, Asian, and South American settings.

While the increasing availability and initiation at earlier HIV disease stages of ART in sub-Saharan Africa may result in less prevalent and less severe HAND in the future, it is important to note that guidelines to initiate ART at less severe stages of immunocompromise in RLS are relatively recent. As such, most HIV+ individuals in RLS – including those with currently virally suppressed HIV infection and high CD4 counts – have a history of severe immunocompromise at some point in their infection. Existing evidence suggests both current and prior immunosuppression increase HAND risk. For example, a study of an HIV+ cohort in Uganda measured the impact of low CD4 count on HAD. It found that every 100 cells/μL decrement in CD4 cell count was associated with a 60% increase in the odds of having HAD (Wong et al. 2007). Furthermore, many prior studies have shown that a history of severe immunocompromised (e.g., low CD4 cell nadir) is also associated with an increased risk of HAND and more severe HAND stages (Saylor et al. 2016). Taken together, this evidence reiterates the importance of preventing severe immunocompromise, namely, by initiating individuals with HIV on ART at earlier stages in infection to decrease the risk of HAD.

Widespread availability and earlier initiation of ART in RLS had led to a shifting demographic with an increasing number of older HIV+ adults due to the increased life expectancy of HIV+ individuals on ART. Counterintuitively, this may actually lead to increases in HAND prevalence as older age is itself a risk factor for HAND. For example, a Ugandan study found each additional 10 years of age conferred a greater than twofold risk of HAD, and a South African cohort also found an association between older age and increased risk of HAND (Joska et al. 2012). These findings are potentially confounded by the increased prevalence of cerebrovascular events with older age (Heaton et al. 2012). They require further investigation as to whether prolonged HIV inflammation plays a synergistic role in atherosclerosis and whether the increasing rates of neurocognitive impairment are due to HAND alone or in combination with vascular cognitive impairment.

The first multinational neurological clinical trial to study HAND exclusively in RLS, the International Neurological Study (AIDS Clinical Trial Group (ACTG) A5199), found substantial neuropsychological and neurological improvement following the initiation of first-line ART in previously ART-naïve individuals with

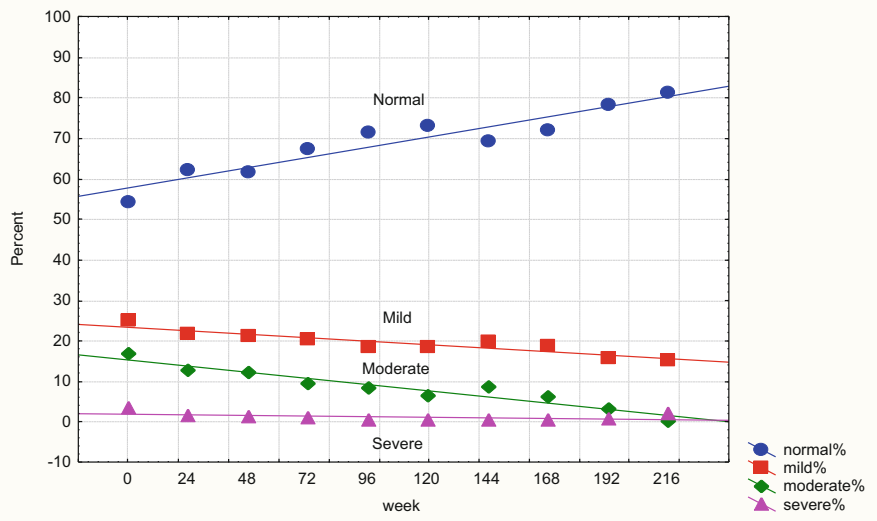

Fig. 1 Neurocognitive impairment over time following art initiation (the International Neurological Study (ACTG A5199))

HIV. Nearly a third of the ART naïve participants had abnormal neurological exams at the beginning of the study (Fig. 1), with significant country variation from 8% in Peru to 74% in Thailand. With the initiation of ART, the estimated odds of impairment were reduced by over 10% for every 24 weeks on ART (Robertson et al. 2018). Neuropsychological test battery improvement, except for semantic verbal fluency, was sustained over 3 years of follow-up while on ARTs, with no differences between treatment regimens detected (Robertson et al. 2012). This further indicates the importance of sustained effective ART in lowering the risk of HAND.

Although ART has decreased the incidence of HAD and moderated the symptoms of MND and HAD in most HIV+ individuals, neurocognitive impairment persists despite long-term administration of ART, as shown in Fig. 1 from the International Neurological Study. Current ART regimens have not been shown to fully reverse milder forms, even though they achieve virological suppression (Robertson et al. 2012; Heaton et al. 2011; Tozzi et al. 2007).

3 HAND in Low-Income Countries: Socioeconomic and Public Health Factors

While HIV/AIDS is a global epidemic with an objective pathology, the illness varies across regions with influences by the social context of HIV, socioeconomic status, capacity of health systems, and gender inequalities. These factors have a negative impact on the course of the infection, contributing to immune dysregulation and

subsequent increased risk of neuronal injury. The social inequality and political instability in low-income countries foster factors that influence HIV care and comorbidities that may potentiate neurological inflammation including coinfections, vitamin deficiency, low rate of educational attainment, and psychiatric illness.

3.1 Low Linkage to Care and Poor Health Status

According to the Global Health Workforce Alliance, 1.5 million additional healthcare workers are needed in sub-Saharan Africa to meet basic healthcare needs. Chronic management of HIV exaggerates the deficiency of skilled healthcare workers, clinics, and testing facilities. Access to the limited health centers may be impeded by relatively expensive transport, dangerous roads or access routes, and other obstacles associated with a lack of infrastructure. Even if the patients manage to arrive at the health center, there is the risk that they are not stocked with ART or the most up-to-date ART regimens based on delivery and/or funding. Thus, HIV+ individuals in RLS may present later in the disease course with more advanced neurocognitive impairment and/or interruptions in therapy due to inconsistent follow-up visits.

The interplay of impoverished conditions and the management of HIV can be exemplified by the epidemic in Lesotho, which has nearly a quarter of the general population infected with HIV (Table 2). The mountainous country has limited road infrastructure, making travel difficult, centralizing advancements in education and medicine, and restricting access to healthcare facilities. Most of the population live in rural communities with high unemployment rates, low education attainment, and cultural practices (e.g., lack of medical circumcisions) that perpetuate the spread of HIV. The geographical restrictions, poverty, and stigma provide challenges to increasing HIV testing and expanding updated treatment coverage. The prevalence

Table 2 Lesotho HIV and country statistics (adapted from WHO and UNAIDS)

Indicator	Most recent data from 2012–2016
Adults (older than 15 years old) newly infected with HIV	19,000 [17,000–22,000]
ART coverage among people with HIV infection eligible for ART according to 2010 guidelines (%)	54 [52–57]
Deaths due to HIV/AIDS (per 100,000 population)	755
Gross national income per capita (PPP int. $)	2,990
Prevalence of HIV among adults 15–49 (%)	25.0 [22.7–26.5]
Incidence of tuberculosis (per 100,000 population per year)	852 [551–1,220]
Population living in urban areas (%)	23.74
Hospital beds (per 10,000 population)	13
Psychiatrists working in mental health sector (per 100,000)	0.1

and severity of HAND are relatively unknown in Lesotho due to the lack of research in this area.

The burden of disease is steep in many remote rural areas where in addition to deficient medical care, there can be a lack of running water, electricity, and other essentials for healthy sanitation. Furthermore, many of these RLS are in tropical regions where the climate can harbor several endemic microorganisms. Impoverished urban areas can mimic these sanitation problems with overcrowded living spaces, inadequate plumbing, and lack of clean water. Nutrition in both cases may be insufficient or lack vitamins and protein necessary for proper neurological development and function. A recent multinational study found that neurocognitive impairment among HIV-positive individuals was more prevalent in both overweight/obese and underweight than normal weight individuals in three RLS (Jumare et al. 2018).

Immunocompromised HIV+ patients are susceptible to the gamut of infectious diseases nurtured in these environments. The coinfections can exacerbate the immune dysregulation and ultimately influence the rate of neurological dysfunction. For example, most of the estimated number of TB incident cases in 2016 occurred in the WHO Southeast Asia region (45%). In the WHO African region, where the burden of HIV-associated TB is highest, 82% of TB patients had a documented HIV-positive test result (World Health Organization Global Tuberculosis Report 2017). TB, in HIV+ individuals, has been shown to be associated with more severe cognitive impairment (Robertson et al. 2018; Hestad et al. 2019). Although ART has been able to decrease the incidence of CNS coinfections, long-term HIV+ individuals with a history of immunosuppression may also have a history of brain injury from meningitis or other neurological infection and thus are more susceptible to further neuronal damage.

Early ART therapy has been shown to have promising effects on improving function and even preventing neurocognitive dysfunction. A Peru-based study enrolled HIV+ individuals identified within a month of acute HIV infection who did not yet meet the current national ART treatment initiation guidelines in Peru. Participants were randomized to immediate ART or initiation of ART after 6 months and then monitored for neuropsychologic outcomes. The immediately treated group showed improved neurocognitive performance at 48 weeks as compared to the deferred treatment group (Robertson et al. 2017). For underserved populations, a 6-month deferment of testing and subsequent treatment can be commonplace and may lead to poorer outcomes. The long-term benefits of early treatment were also illustrated in a study of acutely infected (within 30 days of diagnosis) HIV+ adults in Thailand who showed improved neurocognitive performance in the context of ART-induced viral suppression sustained over the 6-year course of treatment. The results exceeded the estimated practice effect and were compared with a group of healthy HIV-uninfected Thai individuals (Chan et al. 2018). Again, this highlights the need for early and reliable sustained treatment.

3.2 Cognitive Reserve and Education Inequality

Cognitive reserve can be operationalized as a higher IQ, greater level of educational attainment, highest level of occupation, or a combination of these factors that results in a higher residual cognitive capability. The concept of cognitive reserve is thought to represent a greater capacity to overcome neurodegeneration or at least the expression of such CNS insults (Stern 2002). Pathologically, the threshold of HIV neuronal injury at which an individual with a prominent level of cognitive reserve would develop HAND, particularly a syndromic case, appears to be higher relative to an individual with lower cognitive reserve (Morgan et al. 2012). A recent study in Zambia found that a higher education had a protective effect in young adults infected with HIV-1 clade C against neurocognitive impairments, specifically in the domains of executive functions, learning, and speed of information processing (Kabuba et al. 2018).

Level of education plays a prominent role in cognitive functioning (De Ronchi et al. 2002). Even as primary school enrollments have increased in most low-income countries, levels of educational attainment remain low and highly unequal relative to the developed world. There are areas in the African continent that have less than 50% literacy among children, compared to the nearly 100% youth literacy in South America and Europe (UNESCO 2016). Southern Asia is home to almost half (49%) of the world's adult illiterate population (UNESCO 2016) (Fig. 2). This vast disparity in education in the African and Asian countries, that bare a disproportionally high HIV burden, may contribute to the susceptibility for acquiring HIV, accessing regular healthcare and perhaps accelerated neurocognitive decline.

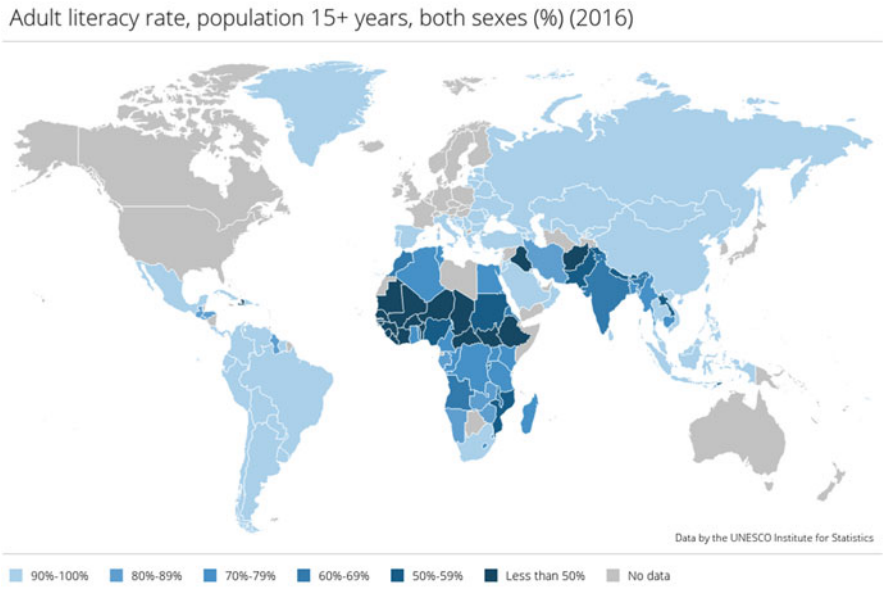

Fig. 2 Global adult literacy rate by country (UNESCO Institute for Statistics 2016)

A recent study from a large East African cohort found a 38% prevalence of cognitive impairment among virally suppressed HIV+ participants. They underwent a 30-min cognitive testing battery and six domain neuropsychological testing with results compared to demographically similar seronegative individuals at the same sites. The inability to read and higher initial WHO stage were strongly associated with increased risk of cognitive impairment (Milanini et al. 2018). A recent study in Uganda comparing cognitive performance in 400 HIV+ and 400 demographically matched HIV-uninfected individuals found cognitive impairment – and especially severe cognitive impairment – was more common among HIV+ than HIV-uninfected participants. However, baseline cognitive impairment was highly prevalent in both groups, occurring in 59% of HIV+ participants and 44% of HIV-uninfected participants (Sacktor et al. 2019). While HAND is a direct result of HIV infection of the CNS, understanding other causes of cognitive impairment and multivariate pathogenic factors can potentially highlight HIV+ individuals at particular risk of more rapid and/or more severe impairment. Furthermore, this highlights another important difference between research conducted in Western countries and RLS, since the participants have vastly different access to education and thus will have distinct levels of cognitive reserve.

3.3 Mental Health and HIV-Related Stigma in Vulnerable Populations

People living with HIV have a higher prevalence of depression and anxiety than non-HIV-infected individuals (Brandt 2009; Mayston et al. 2012). This increased burden of common mental health conditions in areas of high HIV prevalence, namely, low-income countries, often goes untreated (Marwick and Kaaya 2010; Chibanda et al. 2014). The WHO estimated that the ratio of mental health professionals to the population in sub-Saharan Africa stood at 1 per 2.5 million for psychologists and 1 per 2 million for psychiatrists (WHO 2011). Furthermore, a very small percentage of the healthcare budget in low- and middle-income countries is spent on mental health, even though these environments often have persistent stress and trauma due to political and economic instability (Cournos et al. 2014). The consequences of unaddressed mental health diseases in HIV+ individuals can start with delayed diagnosis and continue with suboptimal treatment (Mayston et al. 2016; Parcesepe et al. 2018a, b; Bigna et al. 2018). This delay in ART initiation and then potential poor ART adherence can lead to a lack of viral suppression and overall increased risk for HAND.

Depression is a common comorbidity of HIV and can be difficult to differentiate whether it makes an additional contribution to HAND since it is a confounder of neuropsychological testing performance (Antinori et al. 2007; Tedaldi et al. 2015). Thus, many HAND studies will have depression as an exclusion factor (Robertson et al. 2012; Tedaldi et al. 2015). Nonetheless, depressive symptoms have been

studied for the potential association with cognitive impairment among HIV+ individuals (Heaton et al. 2011; Grant et al. 2014). There has been research indicating a particular association between the chronic and unstable forms of major depressive disorder with HAND (Cysique et al. 2016). Depression on its own, without HAND, can impact quality of life, productivity, and medical compliance. For example, depression was found to be associated with a near doubling of HIV viral load in an East African cohort with a point prevalence of depression up to 25% (Meffert et al. 2018). This suggests that HIV itself, depression, and, possibly, HAND would benefit from mental health screening and treatment to improve comprehensive care. As a comorbidity with HAND, depression could be considered in diagnostic strategies aimed at identifying HIV+ individuals with cognitive impairment.

Women are generally at a higher risk of depression and anxiety, and they account for the majority of HIV cases in Africa (UNAIDS 2013). They are twice as likely to contract HIV than their male counterparts and typically seroconvert at a younger age, meaning they can have chronic HIV infection for the majority of their lives. Sexual and gender-based violence contribute to the transmission of HIV, with gender disparities – both cultural and social – still evident in many areas (Teitelman et al. 2016). A study of a Ugandan HIV+ female cohort estimated a prevalence of depressive symptoms to be 47% and associated with a low CD4 count (less than 50) (Kaharuza et al. 2006). With higher rates of HIV infection and mental health diseases, women are at risk for severe manifestations of HAND, compounded by the lack of social support, particularly in patriarchal settings.

In addition to psychological stress, HIV-related stigma and low social support can delay HIV testing and treatment (Parcesepe et al. 2018a, b). Fear of exclusion from community and workplace due to the cultural construct of HIV stigma may be heightened in low-income settings where jobs are limited, and families are central to social support. Key populations including men who have sex with men (MSM), vulnerable youth, transgender people, and sex workers are at particular risk for these gaps in HIV care and mental health services, social isolation, and even political persecution under certain governments. For example, sex workers contributed to between 7 and 11% of new infections in Uganda, Swaziland, and Zambia and up to a third of new infections in West Africa (Gouws et al. 2012). Delayed counseling and testing among these vulnerable groups and a lack of social support could result in more advanced cases of HIV, lack of ART adherence, and again an associated increase in the risk of advanced cases of HAND and other complications related to untreated HIV infection.

4 Consequences of HAND: Productivity, Quality of Life, and Morbidity

As the leading cause of neurocognitive dysfunction in young adults in sub-Saharan Africa, HIV has negative implications on patients' daily activity, including their ability to work, socialize, and overall quality of life. HAND also impacts an HIV+

individuals' daily functioning which can be seen even with early neurocognitive impairment (Tozzi et al. 2007; Doyle et al. 2013).

The majority of HIV-infected individuals in RLS are in their prime working and reproductive age (15–45 years old), when it would be necessary to financially support themselves and potentially a family. Cognitively impaired HIV+ patients with a low socioeconomic status were found to be more likely to be unemployed and fail social planning tasks (Benedict et al. 2000). Being unable to support themselves and their household can lead to further health vulnerability, including depression, decreased access to medical care, and inadequate nutrition.

In RLS, this loss of productivity extends beyond the individual level and debilitates the economic development in countries where poverty is already rampant. In Ethiopia, HIV+ farmers spend between 11.6 and 16.4 h per week farming compared with 33.6 h weekly for healthy farmers (Food and Agriculture Organization 2001). Furthermore, it is expensive to manage millions of HIV+ individuals while preventing the spread of HIV, particularly when there is a lack of infrastructure to meet the increased disease burden and to provide lifesaving but lifelong medication. The national debt and dependence on foreign aid has increased exponentially for the countries most affected by the AIDS epidemic, perpetuating the entanglement of HIV and poverty in areas of limited resources and competing needs. Although there has been tremendous progress in managing HIV, there is still a need for sustainable, affordable interventions to prevent the spread of HIV, retain individuals in care, and improve health outcomes.

Impairment in memory, executive function, and psychomotor functioning can promote significant difficulties with adherence to medication regimens, independence in daily activities, and general health management (e.g., safe sex practices) (Heaton et al. 2004). This impairment can impede independence of HIV+ individuals and require assistance from a caretaker, subtracting another salary from the low-income household. The caretaker's role can have essential medical importance from aiding in the diagnosis of HAND (Kisakye et al. 2018) to ART adherence, which can be essential in RLS where there is limited access to clinics. Thus, the clinical manifestations of HAND do not only plague the patient's quality of life but can also contribute to the long-term stress of a caretaker responsible for a cognitively impaired HIV+ individual (Small et al. 2017).

The most severe consequences conferred by HAND are disabling dementia and increased risk of mortality. HAD has been found to be an independent predictor of death (Lescure et al. 2011; Sevigny et al. 2007), typically seen in advanced stages of HIV, but ANI has also been implicated in earlier mortality (Heaton et al. 2011). Despite greater access to treatment, the HIV epidemic has significantly burdened the most heavily impacted societies, so the morbidity and mortality associated with HAND require urgent attention in RLS.

5 Advancing NeuroAIDS: Building an Infrastructure for Neurocognitive Testing in RLS

Poverty undermines advances in HIV research and treatment, particularly in specialized sectors such as neurology, psychiatry, and psychology that require trained investigators and clinicians, specific tools, and local interest. There is insufficient data on the neurocognitive effects of HIV in RLS since the neuropsychological studies carried out thus far are marked by inconsistent methods, test batteries, and rating systems for levels of cognitive impairment (Robertson et al. 2009).

The neuropsychological (NP) battery and neurological exams are sensitive tools for diagnosing HAND. Screening tools, such as the International HIV Dementia Scale (IHDS), play an essential role for directing limited resources for the more severe cases. The original HIV Dementia Scale (Power et al. 1995) was modified to simplify the administration to patients by eliminating the antisaccades subtest and replacing the timed written alphabet and cube copy time subtests with tests of motor speed (finger tapping) and psychomotor speed (an alternating hand sequence test) (Sacktor et al. 2005). The IHDS was evaluated in both American and Ugandan clinics to determine if it can easily be performed across cultures. However, there have been additional studies in RLS that have raised concerns regarding the psychometric properties across culture and low sensitivity for milder manifestations of HANDS (Joska et al. 2011). A recent study in Brazil found that a higher cutoff point for impairment improved the marginal sensitivity but still compiled data to suggest that the IHDS has limited utility as a screening measure when compared to other commonly used three-test screening batteries (de Almeida et al. 2017). Although IHDS has limitations, it is a publicly available tool that has shifted the focus to simplicity and standardization to allow for easier integration into practice and consistent data among diverse settings.

A major limitation in analyzing the clinical data from studies of HAND in RLS is the lack of local, culturally relevant normative cognitive data. Normative datasets consist of large cohorts stratified by age, gender, and education level to account for region-specific characteristics of language, culture, healthcare barriers, endemic infectious diseases, and genetic variability of both virus and host. The International Neurocognitive Normative Study (ACTG A5271) established normative data to provide a valid interpretation of the results from the study mentioned above on ART naive HIV+ individuals enrolled in the International Neurological Study (ACTG 5199). The substantial variations on the neurocognitive tests between countries indicated the need for country-based normative data for an appropriate comparison with HIV+ cohorts to create a sensitive screening and diagnosis of HAND in specific RLS. It also became apparent that age, education, and, to a lesser extent, gender are important variables in the variance associated with neurocognitive test differences and thus necessary to control for (Robertson et al. 2016). A Thai-based study evaluated this need for local norms by comparing normative data obtained locally in Thailand to Western norms. The Thai and US groups performed significantly differently on all neuropsychological measures except for verbal fluency (Heaps et al. 2012).

Heaton et al. (2008) have refined Western assessment methods to ensure they are suitable in international settings, such as a large study in rural China that developed demographically corrected neuropsychological test norms based upon HIV-negative individuals (Heaton et al. 2008). A similar battery by Heaton has also estimated the prevalence of HAND with demographically matched controls in diverse settings, including Cameroon (Kanmogne et al. 2010), Nigeria (Akolo et al. 2014), and Zambia (Kabuba et al. 2016). A recent study in Southern India (Kamat et al. 2017) confirmed that this neuropsychological battery, when translated into Tamil, was still understood by participants and identified a similar prevalence of HIV neurocognitive deficits as an earlier study in Central India where the battery was available in Marathi (Ghate et al. 2015). Modifying neuropsychological tests to the local language requires more than a translation, since the battery must retain cultural relevance with specific terms understood by the local population. These studies have expanded the versatility of a sensitive battery in regions with prevalent HIV-1 clade C infections and advanced knowledge through the collaboration with international researchers.

At the premise of the gaps in conducting neuropsychological research in RLS is the lack of trained personnel. The WHO Global Burden of Disease 2010 analysis estimates that, together, neurological and psychiatric disorders account for more than 13% of global disease burden, with much of this burden borne by the developing world (Mohammadi 2011). Yet, there are deficient educational resources for physicians and social awareness of these conditions. The International Neurological Study laid infrastructure for future studies by training the site staff to administer the neuropsychological tests and neurological assessments, as have the studies by Heaton et al. These instruments, including the user-friendly IHDS, were previously absent in many of these settings, and now there are translated exams with trained administrators to conduct the assessments for both research and clinical purposes. The ability to conduct neurological and neuropsychological research in RLS will facilitate an expansion of the NeuroAIDS field.

6 Clinical Implications, Translational Aspects, and Future Directions

By mid-2017, 20.9 million people were receiving ART globally (WHO 2017). While this number illustrates a formidable global health success, many are still without treatment. As the population rapidly expands in African and Asian countries, there will be a new, larger generation of adolescent and young adults, who are at the highest risk for HIV. The combination of these factors could lead to an inevitable rebound in the epidemic unless prevention, treatment, and research efforts to combat the infection are enhanced. Furthermore, the burden of dementia is increasing in low-middle-income countries without a proportional increase in the availability of treatment for those with severe cognitive and psychiatric problems

(Ferri et al. 2005). This is in direct contrast to Western Europe and the United States, where a 22–40% decrease in prevalence has been observed and has been attributed to improved education, lifestyle, and living conditions (Wu et al. 2016; Langa et al. 2017).

For those without proper access to testing and treatment of HIV, the symptoms of HAND may be more advanced and could even be a presenting symptom of HIV in those previously undiagnosed. Clinical knowledge and awareness of HAND is thus essential in areas of high HIV prevalence, particularly in low-income countries that have barriers to testing and treatment. Signs of cognitive impairment in young adults should be noted by healthcare professionals as additional incentive for the patient to be tested for HIV infection. As discussed earlier, signs and symptoms of HAND can interfere with an individual's daily activities and financial stability. Thus, physicians need to be informed on the diagnostic process for HAND, along with the resources for their patients, to ensure that ART is started as early as possible to prevent progression of the neurocognitive impairment.

Besides managing HIV infection with ART, there are no other specific treatments for HAND. Innovative studies could aim to identify ART with beneficial effects on the CNS, as well as novel adjuvant therapy. A better understanding of the HIV-1 clades and their neurovirulence factors can contribute to both a more effective treatment as well as the quest for a cure. The immunopathology of these strains has not been fully examined because of the research constraints in these low-income regions, and this may be a missed opportunity for insight into the virus that continues to evade efforts for developing a cure.

Furthermore, the fact that residual mild neurocognitive impairment is unaddressed by effective ART is still a clinical and research concern (Marra et al. 2009). A recent study from the United States study showed continued neurocognitive impairment among a cohort with long-term suppressive ART (median of 8.5 years). The CSF samples collected from this cohort showed that nearly half of the cells had detectable HIV DNA. There was an association between the poor neurocognitive performance and the isolated CSF cells with detectable HIV DNA, suggesting a functional neurocognitive consequence to persistent HIV in the brain (Spudich et al. 2018). Additional research needs to be performed to understand HIV reservoirs in the brain and its clinical manifestation as persistent neurocognitive impairment.

7 Conclusion

Since the advent of ART, HIV+ individuals have a longer life expectancy and less risk of central nervous system opportunistic infections. However, in order for these individuals to not only live a longer but have a productive and improved quality daily life, more attention needs to be focused on preventing and treating milder HIV neurocognitive complications. This is particularly relevant in low-income countries that continue to have barriers to ART availability, psychosocial stressors, high rates

of coinfections, low educational attainment, nutritional deficiency, and possibly more neurovirulent HIV-1 clades.

By improving access to equal quality healthcare and education in RLS, the neurocognitive functioning of HIV+ individuals can be recognized and treated earlier. This would minimize the risks associated with a low CD4 count and higher viral loads. However, it will involve both social and medical advocacy to secure the infrastructure necessary to improve the healthcare and educational sectors.

Though there have been strides in improving research and clinical care for HAND in these regions, more steps must be taken to fully understand the dynamics of the virus and disease course in the areas of highest HIV prevalence. Neuropsychological examinations can allow clinicians and researchers to create a better understanding of the causes of neurocognitive impairment and whether it is directly attributable to HIV, comorbid factors, and/or immune factors associated with the HIV disease course. Establishing the causes and severity of the impairment further dictates the treatment and impacts the patient's daily life. Thus, there are meaningful outcomes to implementing standardized, normalized neuropsychological exams in RLS, as several studies from this region have shown, and this offers additional incentive to make them widely available with training opportunities for clinical staff.

Overall, there is a steep burden of disease in low-income countries with insufficient means to meet the medical demand in a manner that offers optimal patient care. The lack of infrastructure, healthcare workers, education, sanitation, and social policies has facilitated the spread of HIV in RLS and perpetuates the complications of the disease, including HAND. It is necessary to continue scale up of ART and build an infrastructure for sustainable healthcare and research to manage the common complication of neurocognitive impairment in HIV+ individuals. Otherwise, HAND will continue to lead to a loss in productivity and more HIV-associated deaths in areas that have already suffered the brunt of the HIV epidemic.

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