Mental, Neurological, and Substance Use Disorders in People Living With HIV/AIDS in Low- and Middle-Income Countries

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Abstract: Depression, alcohol use disorders (AUD), and neurocognitive disorders are the 3 most prevalent mental, neurological, and substance use disorders in people living with HIV infection in low- and middle-income countries (LMICs). Importantly, they have an impact on everyday functions and on HIV outcomes. Many LMICs have validated tools to screen for and diagnose depression and AUD in the general population that can be used among people living with HIV infection. Current screening and diagnostic methods for HIV-associated neurocognitive disorders in the era of antiretroviral therapy are suboptimal and require further research. In our view, 2 research priorities are most critical. One is the development of an integrated screening approach for depression, AUD, and neurocognitive disorders that can be used by nonspecialists in LMICs. Second, research is needed on interventions for depression and AUD that also target behavior change, as these could impact on adherence to antiretroviral therapy and improve mental symptoms. Mentorship and fellowship schemes at an individual and institutional level need to be further supported to build capacity and provide platforms for research on HIV and mental, neurological, and substance use disorders in LMICs.

Key Words: depression, alcohol use disorders, neurocognitive disorders, low- and middle-income countries

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INTRODUCTION

Many mental, neurological, and substance use (MNS) disorders are more prevalent among people living with HIV infection (PLWH) than among non–HIV-infected persons, adding to disability and poor quality of life.[1] Several MNS disorders also directly or indirectly increase the risk of HIV treatment failure, and some also increase the risk of HIV acquisition[2,3] (Fig. 1). A focus on MNS is thus fundamental to addressing both the risk of contracting HIV and health outcomes for PLWH. This article will focus on 3 conditions considered to be high-priority MNS disorders by the World Health Organization (WHO)[4]: depression, alcohol use disorder (AUD), and neurocognitive disorders.

There is evidence that in low- and middle-income countries (LMICs), all 3 are more prevalent among PLWH than among the general population[1,5] and that in these countries, the disorders predict worse HIV clinical outcomes for PLWH[2,6] (Fig. 1). In this article, we review the evidence for the relationship of each of these interlinked conditions to HIV infection, antiretroviral therapy (ART) adherence, and HIV progression in LMICs, and we outline research priorities, making recommendations for interventions using an integrated approach that prevents and treats these conditions in resource-poor settings. Where data are lacking from LMICs, we will draw evidence from high-income countries (HICs).

Because of space constraints, this article will not review HIV MNS comorbidities such as epilepsy, stroke (discussed in this issue's article on cardiovascular and pulmonary diseases by Bloomfield et al[7]), peripheral neuropathy, psychotic disorders, anxiety disorders, and illicit drugs.

METHODS

We used a combination of systematic reviews of MNS disorders in PLWH conducted globally since 2005 and epidemiologic studies in LMICs since 1995. We constructed search terms to ensure that we captured studies measuring our 3 conditions of particular interest: depression, alcohol use, and neurocognitive disorder/dementia/neurocognitive impairment. We used LMIC regional names, exploding them when the database allowed and adding developing countries and low-income countries. We searched MEDLINE, EMBASE, PsycINFO, and Global Health databases. We also included literature cited in publications, when relevant.

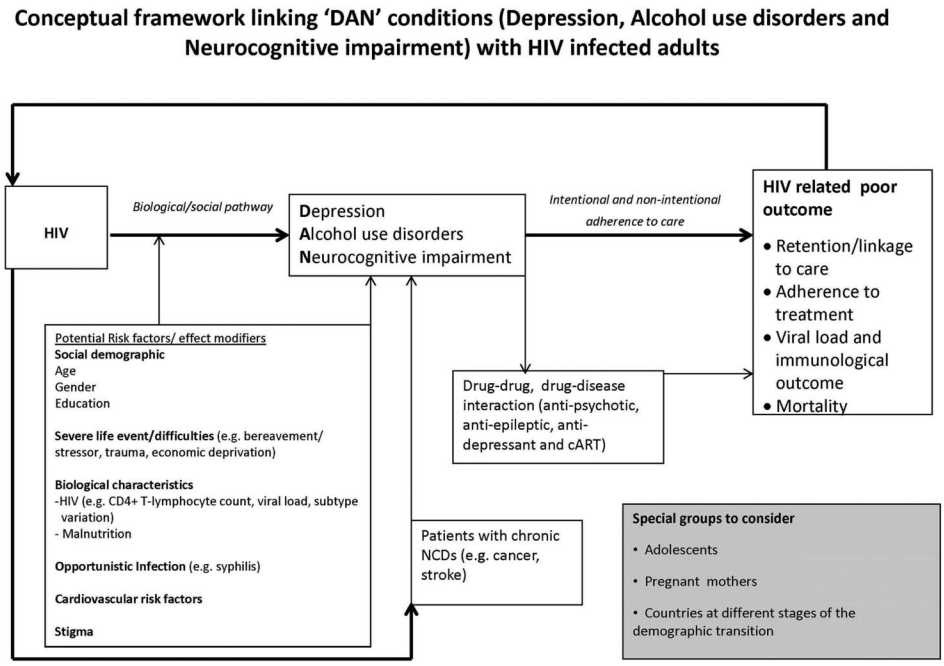

FIGURE 1. Conceptual framework linking HIV infection with depression, AUD, and neurocognitive impairment in adults. NCDs; noncommunicable diseases.

Depression

Background

Depression is the most common psychiatric disorder found among PLWH in LMICs.[1,8–10] It adversely impacts the lives and functionality of PLWH and their families[6,11,12] but remains mainly undiagnosed because few HIV care settings carry out routine screening.

Depression is defined by diagnostic (*Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* [DSM-V]; *International Classification of Diseases*, *Tenth Edition*) or screening criteria based on the number and severity of symptoms and behaviors, including sadness, loss of interest, lack of pleasure, poor sleep, concentration, and appetite, and impaired social and work roles. Screening tools for depression validated in LMICs in the general population are mostly those developed in HICs, such as the Hopkins Symptoms Checklist (HSCL-25) and the Patient Health Questionnaire (PHQ-9).[13–18] Challenges of diagnosing depressive disorder in PLWH in LMICs include the overlap in symptoms with HIV infection (eg, fatigue, memory loss, and weight loss)[19] and how to take into account locally meaningful symptoms of depression. For instance, in Zimbabwe, Tanzania, Rwanda, South Africa, and Zambia, "thinking too much" is an important symptom of depression[19–22] but does not appear in tools such as PHQ-9,[23–26] although it is now recognized in DSM-V.[27] Somatic symptoms, which are common and can be metaphors for distress, such as having a "heavy heart" (in Zimbabwe), are often attributed to social problems.[21,25,28] Cross-cultural methods have been used in a small number of settings, whereby local informants are consulted and indigenous idioms of distress are used to develop screening tools.[19,24] However, in the absence of culturally specific tools, international tools are acceptable if they are translated, back translated, and adapted to ensure the meaning stays close to the original and that the questions are understandable. If they are validated, the methods used should take into account local concepts of mental disorder.[18,19,25] In Uganda, a visual depression screening tool showed good psychometric properties among PLWH with low literacy.[29]

Relationship Between Depression and HIV Infection

Data from HICs show that depression is more common among PLWH than in the general population, with an estimated prevalence of 5%–20%.[30] However, the magnitude of the association of depression with HIV is difficult to estimate because of variability in diagnostic criteria and measures, lack of appropriate controls, and confounding factors.[31] Most studies of depression among PLWH in LMICs consisted of small clinical samples with varying methods of measurement and wide variation in reported prevalence.[32] For example, some studies report more than twice the prevalence of depression in PLWH compared with matched non–HIV-infected persons,[33–36] and some report a depression prevalence in PLWH of more than 30%.[6,20,35,37,38] Two large studies[39,40] using internationally accepted diagnostic criteria found a prevalence of major depression of 7%–8% in PLWH. These discrepancies may be due to methodological issues such as sampling and difference in HIV clinical stages. Also, depression symptoms, such as self-criticism, may be part of common reactions to an HIV diagnosis, co-existing severe life events,[35] or co-existing cognitive impairment and associated posttraumatic stress disorder symptoms rather than to a depressive disorder.[41–44] More than 80% of Zambians recently commenced on ART were found to have anxiety and depression symptoms severe enough to warrant additional intervention or support, and a higher burden of this psychiatric morbidity was associated with early mortality.[45]

Although the direct effects of HIV on depression are not well understood, studies from HICs have postulated

a biological mechanism for depression in HIV infection. For example, HIV virus penetration or HIV-induced exposure to proinflammatory cytokines of the brain's basal ganglia and hippocampal regions can cause depression symptoms such as insomnia, poor concentration, and psychomotor slowing.[46–48] These symptoms also overlap with HIV-associated neurocognitive disorders (HAND), prompting some to question whether depression and HAND could be part of the same disease spectrum.[49]

Depression and ART Adherence

A meta-analysis of 95 independent studies from HICs showed a consistent association between depression and ART nonadherence ($P < 0.0001$; 95% confidence interval: 0.14–0.25),[50] as did 2 systematic reviews in LMICs.[2,6] One of the systematic reviews showed that 5 of 6 prospective studies and 3 of 4 cross-sectional studies using multivariate analysis had adjusted odds ratios of 1.13–3.13 for association of depression and 1.75–3.36 for nonadherence to ART.[2] Poor adherence to ART at least partially explains the association between depression and increased risk of HIV disease progression.[50,51] Immunological effects of depression and stress may also hasten disease progression,[52] and risky behavior may confound the association between depression and HIV mortality.[53] Corollary effects of suicidal ideation and negative thinking, such as forgetfulness and poor concentration, or deficits in problem-solving that come about through a depressed mood, may contribute to poor adherence.[53]

Interventions to Address Depression in PLWH

A systematic review of interventions for the treatment of depression in PLWH revealed that psychological and psychotropic interventions were effective, whereas social interventions alone were ineffective.[54] In HICs, treatment of depression can also lead to improvements in HIV-related outcomes, especially when they are integrated with adherence interventions that make use of motivational and problem-solving approaches.[55,56] The poor availability of antidepressants in most LMICs makes the use of psychotropic interventions a challenge.[57,58] Clinical trials of psychological therapies among PLWH in Asia have demonstrated improved depression outcomes.[59–62] Psychological therapies require the availability of skilled health professionals, who are not readily accessible in LMICs. However, task shifting approaches in both HIV and non-HIV populations show that lower-level cadres can deliver adapted forms of psychological interventions, which can be escalated to more intense psychotherapy or antidepressants for those who do not recover.[63–67] Two studies from sub-Saharan Africa using simple structured approaches based on problem-solving therapy and other cognitive behavioral techniques provided preliminary evidence for the effectiveness of psychological interventions for depression in PLWH.[68,69] Expanded provision of antidepressants in Africa, especially low-cost serotonin-reuptake inhibitors such as Fluoxetine, which have fewer side effects than tricyclic antidepressants, needs to be studied to assess their effectiveness.[58]

Research Priorities

One research priority is the development and validation of screening tools for depression that are integrated with screening tools for cognitive impairment and alcohol abuse, particularly for use in primary health care in LMICs. Another key priority is randomized controlled trials (RCTs) of the effectiveness and cost-effectiveness of interventions for depression (Table 2) in HIV care programs in LMICs,[70] especially those that can be delivered by lower-level cadres through stepped care or task shifting models.[71] Evidence from HICs suggests that problem-solving approaches to ART adherence should be integrated with depression interventions.[56]

Alcohol Use

Background

We focused on alcohol use because it is the most abused substance in sub-Saharan Africa, where 70% of PLWH reside globally, making this the substance use problem of greatest public health importance in the HIV population. However, we acknowledge that substance abuse varies by country and that a limitation of this review is that it does not address the occurrence of other important kinds of substance use among HIV-infected individuals.

AUD is defined by diagnostic (DSM-V; *International Classification of Diseases*, *Tenth Edition*) or screening criteria that include the pattern of drinking (quantity, frequency, binge drinking) and the consequences of use (eg, harmful drinking or dependence). A commonly used screening test in both HICs and LMICs is the Alcohol Use Disorders Identification Test (AUDIT),[72] a 10-item test that categorizes high-scoring patients as hazardous, harmful, or alcohol-dependent drinkers. Alcohol use is the leading risk factor for mortality and disability-adjusted life years in several LMIC regions, including southern Africa, Eastern Europe, and Andean Latin America.[73] The prevalence of AUD varies geographically, and many of the LMICs with the heaviest alcohol use burdens also have high HIV prevalence or rapidly emerging HIV epidemics, such as in Eastern Europe, where prevalence of AUD is estimated at 16%. In southern Africa, the region with the highest HIV prevalence globally, more than one third of adults are estimated to be engaged in heavy episodic drinking (defined as drinking at least 60 g of pure alcohol on at least 1 occasion in the past week).[73]

Relationship Between Alcohol Use and HIV Infection

There is strong and consistent evidence that alcohol use is associated with HIV incidence and prevalence in LMICs. A recent meta-analysis of studies in sub-Saharan Africa identified 35 studies with a summary odds ratio of 1.61 (95% confidence interval: 1.44 to 1.80).[74] The association held among both high-risk groups and the general population and was stronger among heavier drinkers. There are several possible mechanisms for this association: the biological plausibility that heavy alcohol use increases susceptibility to and severity of HIV infection through effects on innate and adaptive immune system aspects, the central nervous system (CNS), the liver, and other organ systems; the direct effect of alcohol consumption on cognitive capacity and its disinhibiting effect on behavior, which can affect consistent condom use or the ability to negotiate safe sex; the co-occurrence of

TABLE 1. Key Defining studies* From LMICs of HIV and Depression, AUD, and HAND

Disease	Reference	Country	Sample	HIV+ (n)	Study Type	Brief Study Description	Key Findings
Depression	Collins et al, 2006[32]				Systematic review	Systematic review of the relevance of mental health to HIV/AIDS care and treatment programs in developing countries	There is a need for methodologically sound studies of mental health throughout the course of HIV, including factors that support good mental health
Depression	Sherr et al, 2011[54]				Systematic review	Systematic review of interventions in HIV and depression	Of the 90 selected studies, the rate of depression ranged from 0% to 80%. Measurement of depression needs to be harmonized
Depression	Brandt, 2009[1]				Systematic review	Systematic review on the mental health of people living with HIV/AIDS in Africa	Depression is the most common condition. Research is needed into predictors of mental health outcomes and factors associated with adherence to ART
Depression	Akena et al, 2012[17]				Systematic review	Systematic review on accuracy of brief vs long depression screening instruments validated in LMICs	A total of 19 studies met the inclusion criteria; of these, 5 were carried out in an HIV population. Statistically significant heterogeneity meant that a meta-analysis could not be carried out
Depression	Antelman et al, 2007[51]	Tanzania	996 HIV+ women	100%	Sub-study of an RCT	Women participating in a trial on micronutrients were screened for depression and social support. Followed up at 2, 6, and 12 months	57% of the women had symptoms of depression. Depression increases the rate of HIV disease progression
Depression	Gaynes et al, 2012[39]	Cameron	400	100%	C	A structured interview for depression was administered to 400 patients consecutively attending the Bamenda Regional Hospital	1 in 5 met lifetime criteria for depression. The management of depression needs to be incorporated in HIV care guidelines
Depression	Kinyanda et al, 2011[40]	Uganda	618	100%	C	A cross-sectional study of 618 respondents attending 2 HIV clinics in Uganda	Psychological and social factors were the main risk factors for depression
Depression	Nakasujja et al, 2010[33]	Uganda	127	80%	C	A case control study of 102 HIV+ vs 25 HIV−	The HIV+ group had higher likelihood for cognitive impairment. Depression symptomatology is distinct and common among cognitively impaired HIV patients
Depression and AUD	Mayston et al, 2012[2]				Systematic review	Systematic review of mental disorders and the outcome of HIV/AIDS in LMICs	Psychosocial factors, namely depression and alcohol, may have adverse effects on HIV-related outcomes
Depression and AUD	Nakimuli-Mpungu et al, 2012[6]				Systematic review	Systematic review on depression, alcohol use, and adherence to ART in sub-Saharan Africa	Interventions to improve mental health of HIV-positive individuals and to support adherence are urgently needed in sub-Saharan Africa

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TABLE 1. (*Continued*) Key Defining studies* From LMICs of HIV and Depression, AUD, and HAND

Disease	Reference	Country	Sample	HIV+ (n)	Study Type	Brief Study Description	Key Findings
Depression and AUD	Etienne et al, 2010[124]	Kenya, Nigeria, Uganda, Zambia	921 patients on ART	100%	C	A cross-sectional study of 921 adults on ART for 1 year	Depression negatively affects a patient's adherence to ART
AUD	Woolf-King et al 2013[74]				Systematic review	Systematic review of the association of HIV infection and alcohol use in sub-Saharan Africa	Alcohol use associated with prevalent or incident HIV infection (pooled adjusted OR = 1.61, 95% CI: 1.44 to 1.80). Strongest association among problem drinkers and drinking in sexual contexts
AUD	Kalichman et al, 2007[75]				Systematic review	Systematic review of the association of alcohol use and HIV risk behaviors in sub-Saharan Africa	Alcohol use associated with increased risk taking behavior
AUD	Abaynew et al, 2011[125]	Ethiopia	320		R	Case–control study of factors associated with late presentation to HIV care	Frequent alcohol users were more likely to present late for HIV/AIDS care (OR = 3.55, 95% CI: 1.63 to 7.71)
AUD	Beyene et al, 2009[126]	Ethiopia	422		C	Cross-sectional study of factors associated with adherence among PLWH	Alcohol use was significantly associated with nonadherence to ART after adjusting for other factors
AUD	Bonolo et al, 2005[127]	Brazil	306	100%	P	Cohort study of factors associated with ART nonadherence	On multivariate analysis, alcohol use was associated with a 3-fold increase in nonadherence
AUD	Dahab et al, 2010[128]	South Africa	344	100%	P	Cohort study of factors associated with poor treatment outcomes (viral load >400 copies/mL) or discontinued treatment)	Drinking more than 20 units of alcohol per week was associated with worse HIV treatment outcomes
AUD	Fritz et al, 2011[129]	Zimbabwe	413	—	Cluster RCT	RCT of a male-focused peer-based intervention to reduce high-risk sexual encounters associated with alcohol drinking	No evidence of an impact on unprotected sex with nonspousal partners
AUD	Jaquet et al, 2010[130]	Benin, Cote d'Ivoire, Mali	2920	100%	C	Cross-sectional study in 8 adult HIV treatment centers in Benin, Cote D'Ivoire and Mali	Nonadherence to ART was associated with current drinking (OR = 1.4, 95% CI: 1.1 to 2.0)
AUD	Kalichman et al, 2008[131]	South Africa	353	4%	RCT	RCT of a brief community-based alcohol-related HIV risk reduction intervention in Cape Town, South Africa	The intervention resulted in significantly less unprotected intercourse, alcohol use before sex, number of partners, and greater condom use. However, the benefits dissipated by 6 months
AUD	Kalichman et al, 2011[132]	South Africa	617	8%	RCT	RCT of a brief risk reduction counseling intervention, including alcohol use, for STI clinic patients in Cape Town, South Africa	Significantly reduced alcohol use, and incident STI infections associated with the intervention up to 12 months of follow-up

TABLE 1. (*Continued*) Key Defining studies* From LMICs of HIV and Depression, AUD, and HAND

Disease	Reference	Country	Sample	HIV+ (n)	Study Type	Brief Study Description	Key Findings
AUD	Papas et al, 2011[133]	Kenya	102	100%	RCT	Stage 1 trial of a CBT intervention to reduce alcohol use among PLWH on ART	Significant impact of reported alcohol use (abstinence, percentage of drinking days, mean drinks per drinking days) at 90-day follow-up
AUD	Peltzer et al, 2011[134]	South Africa	735	100%	P	Prospective study of attrition from ART among newly eligible PLWH	No effect of baseline AUDIT score (≥2) on attrition
AUD	Sharma et al, 2013[135]	India	183	100%	P	Cohort of PLWH who reported alcohol use in the past week and were on ART	Among participants without viral suppression, alcohol use was associated with nonadherence, and was related to missing medications when drinking
AUD	Venkatesh et al, 2010[136]	India	198	100%	C	Cross-sectional study of PLWH on ART	Nonadherence was significantly associated with reported alcohol use (adjusted OR = 2.22, 95% CI 1.04 to 4.75)
HAND	Kamminga et al, 2013[113]				Systematic review	A systematic review to assess the strengths and weaknesses in detecting HAND when compared with gold-standard neuropsychological testing in HICs and LMICs	Thirty-five studies were identified. Studies were characterized by a wide variation in validity primarily because of nonstandard definition of neurocognitive impairment, and to the demographic and clinical heterogeneity of samples
HAND	Haddow et al, 2013[114]				Systematic review	A systematic review to estimate the accuracy of HIV Dementia scale and International HIV Dementia scale for the diagnosis of HIV-associated dementia and mild neurocognitive disorder in HICs and LMICs	Fifteen studies were identified. Both scales were low in accuracy. Variation in estimates of accuracy is likely to be due to differences in reference standard
HAND	Joska et al, 2011[102]				Systematic review	A systematic review of the association of HAART and neurocognitive function in HICs and LMICs	Fifteen studies were identified. HAART improved cognition but did not fully eradicate impairments
HAND	Nakasujja et al, 2013[120]	Uganda	73		RCT	To evaluate the efficacy and safety of minocycline in the management of HIV-associated cognitive impairment in HICs and LMICs	Minocycline was safe and well-tolerated in HIV-positive individuals. However, it did not improve HIV-associated cognitive impairment
HAND	Nakku et al, 2013[106]	Uganda	680	100%	C	To determine the prevalence of neurological and neurocognitive function	The prevalence of probable HIV-associated dementia was 64.4% in an adult HIV clinic population, the majority of whom (75.2%) were on HAART

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TABLE 1. (*Continued*) Key Defining studies* From LMICs of HIV and Depression, AUD, and HAND

Disease	Reference	Country	Sample	HIV+ (n)	Study Type	Brief Study Description	Key Findings
HAND	Joska et al, 2012[118]	South Africa	82	100%	P	To assess the impact of HAART on cognition	Severe baseline neuropsychological impairment improved significantly more than those less impaired among individuals with late stage HIV infection commencing HAART in South Africa
HAND	Ruel et al, 2012[105]	Uganda	199	47%	C	To determine whether children with CD4 cell measures above the WHO thresholds for ART initiation suffer significant impairment	Significant motor and cognitive deficits were found in HIV-infected ART-naive children with CD4 cell counts of ~350 cells/μL and percentages of >15%
HAND	Robertson et al, 2011[100]	Multinational	860	100%	C	To determine the prevalence of neurological and neurocognitive function in antiretroviral-naive individuals	Two-hundred forty nine (29%) had one or more abnormalities on neurological examinations, but there was a 6% prevalence of HIV-associated dementia and minor neurocognitive disorder
HAND	Holguin et al, 2011[101]	Zambia	141	61%	C	To determine the prevalence of HAND in a randomly selected cohort	Twenty-two percent HIV+ ART-naive individuals met the criteria for NP impairment. Gender significantly influenced the performance on NP tests with females performing more poorly compared with males
HAND	Joska et al, 2011[102]	South Africa	283	—	C	To evaluate neurocognitive disorder status and possible risk factors among HIV+ individuals awaiting HAART in South Africa	The prevalence of mild neurocognitive disorder and HIV-associated dementia were 42.4% and 25.4%, respectively. There were significant associations between lower levels of education and older age with HIV-associated dementia, and a trend to association with HIV-associated dementia and lower CD4 count
HAND	Lawler et al, 2011[103]	Botswana	140	43%	C	To determine the prevalence of HAND	Thirty-seven percent of HIV+ HAART-treated subjects met criteria for cognitive impairment, compared with matched, uninfected control subjects
HAND	Kanmogne et al 2010[94]	Cameroon	88	50%	C	To evaluate cognitive function in HIV+ and HIV− demographically matched individuals	Significantly lower performance in the HIV+ sample on tests of executive function, speed of information processing, working memory, and psychomotor speed

TABLE 1. (*Continued*) Key Defining studies* From LMICs of HIV and Depression, AUD, and HAND

Disease	Reference	Country	Sample	HIV+ (n)	Study Type	Brief Study Description	Key Findings
HAND	Wright et al, 2010[95]	Australia, North America, Brazil, and Thailand	292	100%	C	To determine factors associated with baseline neurocognitive performance in HIV+ participants	HIV+ population with high CD4 cell counts, with more than 90% on ART, had neurocognitive impairment and was associated with prior cardiovascular disease
HAND	Nakasujja et al, 2010[33]	Uganda	127	80%	P	(1) To assess depression among HIV+ patients about to initiate HAART and HIV− individuals; (2) to determine the association of depression and cognitive function among HIV+ and HIV− individuals; and (3) to evaluate changes in depression among HIV+ individuals receiving HAART	The HIV+ group had higher likelihood of cognitive impairment (OR 8.88, 95% CI 2.64 to 29.89, $P < 0.001$). Both depression and cognitive impairment improved after initiation of ART
HAND	Patel et al, 2010[104]	Malawi	179	100%	C	To determine the prevalence of HIV-associated dementia.	The overall prevalence of suspected HIV-associated dementia was 14.0% (95% CI: 8.9% to 19.1%); there was no significant difference in prevalence between those on ART (13.4%) for at least 6 months and 45 patients not on ART (15.6%). Male gender and low education level were independent risk factors of suspected HIV-associated dementia
HAND	Gupta et al, 2007[99]	India	245	48%	C	To determine the prevalence of HIV-associated dementia in HAART-treated individual	Among HIV+ subjects, 60.5% had mild-to-moderate cognitive deficits characterized by deficits in the domains of fluency, working memory, and learning and memory. None of the subjects had severe cognitive deficits

C, cross-sectional; CBT, cognitive behavioral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV+, human immunodeficiency virus seropositive; HIV+, human immunodeficiency virus seronegative; NP, neuropsychological test; P, prospective; R, retrospective; STI, sexually transmitted infection.

*Observational or intervention studies conducted in LMICs that examined the relationship between HIV status or therapy and depression, AUD and HAND based on published data between 1996 and present.

alcohol use and risky sexual behavior among individuals with risk-taking personality characteristics[75]; and the dual character of places that sell alcohol, which are also sometimes meeting spots for potential sex partners (Fig. 1).

Relationship to ART Adherence

In the ART era, the primary predictor of HIV-related mortality, morbidity, and treatment failure is nonadherence to ART.[76] Systematic reviews have shown that alcohol use is strongly associated with poor adherence to ART,[77,78] with alcohol users being around 50%–60% less likely to adhere to ART than nonusers. For example, a recent study from South Africa found that good adherence was reported by 65% of nondrinkers but only 39.7% of drinkers ($P < 0.001$).[79] Adherence was lower still among hazardous or harmful drinkers (30.3%). The evidence for a causal effect of AUD on ART adherence is strengthened by dose–response and temporal relationships.[79–82]

The mechanisms by which alcohol consumption reduces ART adherence are similar to those that increase the risk of HIV acquisition, that is, cognitive factors (due to acute intoxication), personality factors (eg, risk taking), structural

TABLE 2. Research Priorities and Approaches to Address These Priorities in Depression, AUD and HAND

Disease	Study Area/Study Type	Research Priority	Approaches to Address Priority
ALL	Screening and diagnosis	Development/standardization of an integrated screening tool for depression, AUD and HAND	Multisite, multinational validation study
Depression	Clinical trials and implementation research	Develop interventions that can be delivered through task-shifting by community health workers as part of routine chronic disease care	Evidence-based models such as cognitive behavior therapy, behavior activation, problem solving therapy, interpersonal therapy
		Cost-effectiveness of interventions for depression in PLWH in improving disability and reducing HIV treatment failure	RCTs
AUD	Clinical trials and implementation research	To understand the role of alcohol on HIV acquisition through event-level data	Longitudinal studies and qualitative studies
		Adaptation and evaluation of evidenced-based alcohol-reduction interventions among HIV-infected populations in LMICs	RCTs to evaluate the impact of such interventions on ART adherence and disease
		Research into strategies to address the structural drivers of alcohol use and implement these synergistically with HIV prevention and treatment strategies	Strategic plans for HIV prevention and treatment that include evidence-based policy initiatives to reduce harmful effects of alcohol
HAND	Epidemiology	Standardized neuropsychological screening tool that is resource and culturally appropriate	Develop/standardize/pilot/validate a resource and culturally appropriate neuropsychological test
		Resource appropriate screening for treatable etiologies in those diagnosed with HAND Neuropathological confirmation of HAND in the ART era Long-term outcome of HAND after ART initiation	Well-powered, longitudinal study that includes (1) well-characterized individuals (with brain imaging, exclusion of secondary etiologies and autopsy confirmation (when available) (2) standardized neuropsycological tests that are resource appropriate (3) a follow-up component of more than 3 years. The latter could use existing HIV cohorts
	Pathophysiology	Mechanisms of the interplay of HIV/inflammation, HIV-1 subtype, ART, and risk factors (eg, cardiovascular) in development and progression of HAND	Conduct mechanistic studies (using brain imaging, blood, and CSF samples) that elucidate the pathogenesis of HAND in the ART era
		Developing robust biomarkers that predict HAND or are used for monitoring disease progression	
	Clinical trials	To determine the benefit of neuroprotective/anti-inflammatory agents in reducing the burden of HAND	RCTs

factors (eg, chaotic environment), and misconceptions about toxic interactions of alcohol use and ART.[83] These factors can contribute to poor adherence when alcohol users taking medications off-schedule or missing doses, not renewing prescriptions, or having decreased access to ART.[78,84]

Interventions to Address Alcohol Use Among PLWH

The primary evidence-based interventions to reduce AUD are structural interventions (eg, comprehensive policy measures to regulate the availability of alcohol and reduce demand through taxation and pricing mechanisms) and individual psychotherapeutic interventions (eg, screening and brief interventions by trained primary health care professionals). There have been few RCTs assessing the effects of psychotherapeutic interventions on alcohol use and ART adherence in HIV-infected alcohol users. One trial found a significant intervention effect on ART adherence and HIV virological and immunological outcomes at the 3-month follow-up, but not at 6 months,[82] and a second trial found no significant intervention effects on adherence or virological endpoints.[83,85] The difference may have been attributable to key variations between these trials, including the behavior change model used, the intensity and duration of the intervention, the type of counselor, the control condition, and the duration of follow-up. Another RCT found that a motivational enhancement intervention had a significant effect on HIV viral load at 6 months[86] among PLWH aged 16–25 years, including a borderline significant reduction in alcohol use. Three other studies have evaluated the effect of motivational interview-based counseling on alcohol use among PLWH with AUD,[87–90] but they did not measure ART adherence at HIV-related endpoints. Each of these studies found a large and significant intervention effect on alcohol use (Table 1). Further research is needed to refine and evaluate interventions to improve adherence among alcohol users in LMICs.

Research Priorities

Further qualitative studies should be conducted to understand the role of alcohol in HIV acquisition through event-level data (eg, an in-depth examination of alcohol use and sexual activity occurring on particular occasions). Pilot studies are needed that would adapt alcohol-reduction interventions to suit HIV-infected populations in LMICs, followed by RCTs to evaluate the impact of such interventions on ART adherence and disease progression.

HIV-Associated Neurocognitive Disorder (HAND)

Background

HAND is a general term that includes a number of disorders that are complications of HIV infection. The definition is based on the consensus opinion of experts in the field, and patients are diagnosed using a battery of neuropsychological tests.[91] The term HAND includes asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia.[91]

HIV-associated dementia is the severe form of HAND. Prevalence in HICs has declined after the introduction of ART.[92] HIV-associated dementia is characterized by subcortical dementia, which involves motor and cognitive slowing, with a neuropathology consistent with HIV encephalitis.[49] Prognosis is poor and survival is usually less than a year.[93]

Asymptomatic neurocognitive impairment and mild neurocognitive disorders are the most common manifestations of HAND in the era of ART in HICs.[92] This phenotype is characterized by cortical symptoms such as memory loss and seems to be distinct from HIV-associated dementia; however, our understanding of this phenotype is still evolving.[49,94] Unlike HIV-associated dementia, milder cognitive disorders are not associated with higher HIV viral load and lower $CD4^+$ T-lymphocyte count, but they are associated with previous cardiovascular disease.[92,95] A longitudinal study with a follow-up period of 3 years showed that symptoms were nonprogressive, but the very long-term prognosis is unclear.[96] Postulated mechanisms for mild cognitive disorders include direct ART toxicity, chronic immune activation, or immune reconstitution syndrome.[97,98] In addition to ART toxicity, the direct and indirect effects of HIV also play a role in cognitive disorders.[49]

The prevalence of HAND in LMICs varies, ranging from 6% to 64% in children and adults[99–106] (Table 1). Not all of the individuals in these studies were on ART, which could partially account for the variation. Other factors that may also explain the differing prevalence rates are people's HIV subtypes, which may contribute to more severe forms of HAND, as seen in some subtypes found in Uganda[107,108]; the increasing burden of comorbidities related to cognition such as stroke[109]; demographic, educational, and cultural differences; or differing approaches to measurement of impairment. Because treatment of HIV infection is often delayed in LMICs, the added burden of opportunistic infections mimicking HAND (eg, cryptococcal infection, tuberculosis, meningitis, or neurosyphilis) is also a possibility. Notably, in HICs, the norm is screening non-HIV populations with cognitive impairment for infections like syphilis.[110] However, in LMICs, screening is neither routine for non-HIV populations nor for individuals with HAND, which could mean that the burden of HAND is overestimated and that treatable conditions are being neglected.[111]

Neuropsychological tests are pivotal to the definition of HAND but have several restrictions. First, the diagnosis by neuropsychological tests does not account for disease mechanism. Importantly, it does not differentiate between progressive disease directly associated with HIV infection and nonprogressive disease owing to HIV-associated insult to the brain.[49] Including the latter cases could overestimate the milder forms of HAND. Second, neuropsychological tests should have at least the following neurocognitive domains: verbal/language, attention/working memory, abstraction/executive function, learning/recall, speed of information processing, and motor skills. However, the choice of domains used varies between the different tests.[112–115] Third, normative data for healthy age- and sex-matched community controls, crucial for the interpretation of neuropsychological tests, are limited in LMICs. Furthermore, these neuropsychological tests should be validated for the target population's culture and language and administered and interpreted by appropriately trained professionals; this is not always the case in LMICs.[49,116] Each neuropsychological test varies in length, and weighing the need for lengthy and more sensitive tests versus shorter and more conveniently administered tests is challenging. Currently, there is no consensus on the best approach.[112] Although the development of standardized tools is important, linking these tools to biomarkers of HAND would make them dynamic and more specific. Biomarkers for HAND are currently in the process of being identified, and those related to monocyte activation (eg, CD14) have shown promising results.[49] Depression and AUD overlap with cognitive impairment (Fig. 1); integrating a screening tool that encompasses both disorders may be an efficient way forward.[110] This approach could reduce the time spent screening for these noncommunicable diseases separately in busy and overstretched ART clinics.

Despite the availability of numerous, albeit limited, neuropsychological tools, routine screening in ART clinics in LMICs is still not the norm. This could have important implications for people who have HIV–dementia but are not eligible to start ART based on their $CD4^+$ T-lymphocyte cell count. HIV–dementia is an AIDS-defining illness and justifies starting ART.

Relationship to ART

Overall, ART has been beneficial for HAND in both HICs and LMICs. Eleven of 15 studies in a systematic review in 11 HICs and 4 LMICs showed improvement in neurocognitive status after treatment.[111] The studies that showed no association were usually statistically underpowered and sometimes lacked appropriately matched normative data. Although ART may improve cognitive function in those with severe impairment, it does not seem to fully eradicate the milder forms of HAND.[33,99,111,117,118]

A multinational study evaluated the outcome of neurocognitive impairment and the degree of CNS penetration for 3 ART regimes (including WHO-recommended first-line treatments) in a large randomized trial.[119] The study found no differences in the degree of CNS penetration of WHO-recommended ART regimens.[119] Minocycline, a neuroprotective agent, was explored as an adjunct to ART in managing HAND in LMICs.[120] Although this trial was unsuccessful, this should not discourage future trials from exploring the role of adjunctive neuroprotective/anti-inflammatory agents in reducing the burden of HAND.[49]

Relationship to ART Adherence

A prospective cohort study in Zambia showed that 495 PLWH who had recently commenced ART had cognitive

impairment and poorer ART adherence.[45] In HICs, mild neurocognitive impairment was associated with poorer quality of life, unemployment, worse medication adherence, lower driving ability, and reduced survival.[121] Furthermore, HAND may also be associated with adverse HIV outcomes, including HIV resistance and poor ART adherence due to prospective memory impairment.[122] Alcohol misuse may coexist in patients with HAND, which could also impact on adherence. However, the extent to which these factors play a role in HIV acquisition and disease progression in LMICs has yet to be completely understood.

Research Priorities

Of high priority is the development and validation of a standardized neuropsychological test that is resource appropriate, culturally tailored, and includes biomarkers of HAND to improve specificity (Table 2). Well-powered studies with appropriate normative data that examine the effect of ART in a well-characterized cohort (with brain imaging, exclusion of opportunistic infections, and autopsy confirmation of underlying pathologies) are needed in LMICs. Ideally, longitudinal studies should have a follow-up beyond the longest observation period of 3 years to determine the long-term prognosis of HAND in the ART era. In the meantime, screening for HAND needs to be instituted in clinics in LMICs, especially for patients not otherwise qualifying for ART.

Research Platforms and Training Opportunities

Existing research and care platforms could be harnessed to conduct MNS studies. New scientific collaborations could be established, for instance, with Demographic Surveillance Systems, such as those in the INDEPTH Network (www.indepth-network.org), and HIV research centers in LMICs, such as those supported by the UK Medical Research Council, the Wellcome Trust, and the US National Institutes of Health. Opportunities exist for incorporating MNS research into existing HIV research platforms. For example, researchers could use the IeDEA network, AIDS clinical trials group sites, the WHO STEPS surveys, and the African Partnership for Chronic Diseases. Challenges in implementing such research may include the lack of awareness among many HIV researchers, funders, and policymakers of the importance of mental health in addressing HIV/AIDS.

Strengthening research capacity in many LMICs that have exceedingly low numbers of specialists in neurology and psychiatry, a situation exacerbated by the ongoing brain drain, will be important. New initiatives are supporting capacity building in mental health research, particularly the research hubs in Africa, Asia, and Latin America funded by the US National Institute of Mental Health (www.fic.nih.gov/programs/Pages/medical-education), consortia funded through the UK Department for International Development (www.prime.uct.ac.za), and Grand Challenges Canada (www.grandchallenges.ca), which funds projects and rising investigators in global mental health. The US President's Emergency Plan for AIDS Relief/National Institutes of Health–funded Medical Education Partnerships Initiative (MEPI)[123] is another potential platform on which to build research capacity in HIV mental health and neurology in Africa. Existing initiatives such as Fogarty International Center fellowships (http://www.fic.nih.gov/programs/pages/scholars-fellows.aspx) and Wellcome Trust international training fellowships (www.liverpoolwttc.org.uk) also fund research and training of investigators in global mental health and neurology. At an institutional level, mentorship schemes are needed to pair clinical academics in psychiatry and neurology with centers requesting support. Examples of specific training priorities include grant writing, qualitative methods, formative research, cross-cultural methods in psychiatry, clinical trials training, database management, and biostatistics.

CONCLUSION AND RECOMMENDATIONS

Addressing the burden of MNS conditions among PLWH in LMICs will contribute significantly to health, social, and economic outcomes as ART is scaled up. We focused this review on the 3 key MNS conditions most prevalent in HIV populations in LMICs, based on the current literature. Epilepsy, stroke, peripheral neuropathy, psychotic disorders, anxiety disorders (including post-traumatic stress disorder), and illicit drug use are other MNS conditions that we did not discuss in this review, but that are important areas for future research in LMICs.

Depression, AUD, and HAND contribute to poor HIV outcomes and are interlinked. Research is needed that improves our understanding of the underlying mechanism of these overlapping conditions. One research priority is to determine an integrated screening approach for depression, AUD, and neurocognitive disorders that can be used by nonspecialists in LMICs. Such a tool should ideally achieve a balance between time, skill needed to administer it, and the validity of the test. Another research priority is testing depression and AUD interventions that also target behavior change, as these could have an impact on ART adherence, accessing health care, and the improvement of mental symptoms. RCTs of such interventions, preceded by culturally informed formative work, are urgently needed.

Limited access to psychiatrists and neurologists in LMICs has been a long-standing issue; mentorship and fellowship schemes at an individual and institutional level do exist, but they need to be further supported. In the short-term, task shifting in the care of MNS disorders in HICs and LMICs has been successful and should be integrated into routine HIV care in LMICs.

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