An Exploration of Sociodemographic and Psychosocial Determinants of Cognitive Performance in a Peri-Urban Clinic Population of People with HIV in Cape Town, South Africa

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BSc (Human Bioscience), BSocSc Hons (Psychology), MA (Neuropsychology)

Thesis presented for the Degree

DOCTOR OF PHILOSOPHY- PhD (Neuropsychiatry)

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September 2022

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Declaration

I, Anna Jane Dreyer, present this thesis in fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town (UCT). I hereby declare that this thesis is my own work, and neither the whole work nor any part of it has been, is being, or will be submitted for another degree in this or any other university. This thesis has been submitted to the Turnitin module and I confirm that my supervisor has seen the report and there were no plagiarism concerns.

The study protocol was approved by UCT's Faculty of Health Sciences Human Research Ethics Committee (HREC 010/2018) and all participants provided written informed consent.

I confirm that I have been granted permission by the UCT's Doctoral Degrees Board to include the five publications listed below in my PhD thesis. Where co-authorships are involved, my co-authors have agreed that I may include the publications in my PhD thesis.

Dreyer, A. J., Munsami, A., Williams, T., Andersen, L. S., Nightingale, S., Gouse, H., Joska, J., & Thomas, K. G. F. (2022). Cognitive Differences between Men and Women with HIV: A Systematic Review and Meta-Analysis. *Archives of Clinical Neuropsychology*, 37(2), 479-496. https://doi.org/10.1093/arclin/acab068.

Dreyer, A. J., Nightingale, S., Andersen, L. S., Lee, J. S., Gouse, H., Safren, S. A., O'Cleirigh, C., Thomas, K. G. F., & Joska, J. Sex Differences in Cognitive Performance in a South African Cohort of People with HIV and Comorbid Major Depressive Disorder (Submitted to *Journal of the International Association of Providers of AIDS Care*)

Dreyer, A. J., Nightingale, S., Heaps-Woodruff, J. M., Henry, M., Gouse, H., Paul, R. H., Thomas, K. G., & Joska, J. A. (2021). Rates of cognitive impairment in a South African cohort of people with HIV: variation by definitional criteria and lack of association with neuroimaging biomarkers. *Journal of Neurovirology, 27(4),* 579-594. https://doi.org/10.1007/s13365-021-00993-x.

Dreyer, A. J., Nightingale, S., Andersen, L. S., Lee, J. S., Gouse, H., Safren, S. A., O'Cleirigh, C., Thomas, K. G. F., & Joska, J. (2022). Cognitive performance in a South African cohort of people with HIV and comorbid major depressive disorder. *Journal of Neurovirology.* https://doi.org/10.1007/s13365-022-01093-0

Dreyer, A. J., Nightingale, S., Andersen, L. S., Lee, J. S., Gouse, H., Safren, S. A., O'Cleirigh, C., Thomas, K. G. F., & Joska, J. (in press). Cognitive Performance, as well as Depression, Alcohol Use, and Gender, predict Anti-Retroviral Therapy Adherence in a South African Cohort of People with HIV and Comorbid Major Depressive Disorder. *AIDS and Behavior*.

Acknowledgements

One of my favourite things to do is a multi-day group hike. During the years of my doctoral research, I was lucky to be able to do a few such hikes, including the Fish River Canyon in Namibia, Otter Trail on the east coast of South Africa, and an annual pilgrimage through the mountains between the small South African towns of Greyton and McGregor.

Multi-day hiking has become a metaphor for doing a doctoral thesis:
You need snacks and breaks.
You need perseverance, belief in your capabilities, resilience, and patience.
Most importantly, you need good people in your group and the group dynamics determine the success of the hike.

In this regard, I have been extremely fortunate. I could not have asked for a better group to have embark on this journey with me. Each individual has been essential for the completion of this thesis.

Prof John Joska, you made it all possible, you ensured I was fully equipped with everything I needed. A brilliant, strong leader, leading with integrity and kindness. In any moment, whatever the need, you were there for me. I know you I could always go to your office for a chat, and we would figure out the way forward.

Prof Kevin Thomas, my supervisor for over 10 years, extremely dedicated and reliable, a calming and containing presence in my life. I admire you immensely. Thank you for the many hours you spent reviewing drafts, your thoroughness and care in which you engage in my work. I revere and fully trust your opinion. Without your support and guidance over the years, I would not be where I am.

Dr Sam Nightingale, your insight, and friendship has been integral to my PhD journey. I am constantly inspired by your vision, intelligence, and boldness.

Dr Lena Andersen, a power-woman, a role-model to me on how to navigate science as a woman. Your mentorship during the running of the project was so important to me.

Armien Abrahams, you have facilitated the process of understanding and developing my own mind. I believe this was a vital parallel process alongside the PhD journey because the PhD journey itself, is process of managing and optimising your mind.

Isabelle Nunes Da Costa Giddy, my dear friend, we have walked our PhD journeys together from start to finish. I'm in awe of your brilliance and deeply grateful we could navigate this together.

Mom and Dad, Joe and Harry, our deep love for each other and strong family bond is the foundation of my life. I'm so lucky to have you as a family. You believe I can do anything and do everything to ensure I am thriving and happy. Thank you for your selfless generosity, enabling me to choose my path in life. I am filled by your love.

Liz and Alan, my aunt and uncle, always supportive and generous, who allowed me to stay in their beautiful quiet Sea Point flat, where I could work on my PhD.

My friends, Amy, Amy, Ash, Chelsea, Erica, Justine, Isabel, Matty, Nasiphi, Coenie, Kirsty, Alice, Sarah, Michael, Lucy, MJ, Tim, Paulo, Sam, Jessica, Megs, Jen, Damo, El, Josh, Ffi, William, Celeste, you inspire me and make me brave, and fill my life with goodness. We have been on so many adventures together. Thank you for walking with me.

My Focusmate, Andrew, you were a gift to me the last 2 months.

Teboho Linda, the study neuropsychological technician, thank you for your dedication to the project, your hard work and commitment to collect high-quality data.

Thank you to the broader project team for making this work possible and all the members of the HIV Mental Health Research Unit for a lovely, supportive work environment.

Lastly, thank you to all the study participants for their time and willingness to participate in the research.

Funding

This research was supported by National Institute of Mental Health or the National Institutes of Health under award number R01MH103770. Some additional support came from supplement grant to investigate sex differences in cognitive performance in people with HIV under award number 5R01MH103770-S1.

Anna Jane Dreyer was supported by the Harry Crossley Research Fellowship, as well as an additional University of Cape Town's Foundation Contingency award.

Abstract

Introduction. Numerous studies, conducted in many different countries, report that cognitive impairment is highly prevalent in people with HIV (PWH). Such impairment can affect adherence to antiretroviral therapy (ART), and adherence is, in turn, essential for PWH to achieve viral suppression. The gold standard to confirm cognitive impairment is a neuropsychological assessment. However, accurate interpretation of neuropsychological test performance requires consideration of, for instance, how impairment is determined and how accurately the contribution of non-HIV factors to poor cognitive test performance is described. These non-HIV factors include sociodemographic variables (e.g., age, sex, educational attainment), psychosocial variables (e.g., socioeconomic status, food security, quality of life), psychiatric variables (e.g., depression, problematic alcohol use), and other medical co-morbidities. Because many existing studies of PWH do not account for (a) the fact that current quantitative methods for defining cognitive impairment may not accurately reflect HIV-associated brain injury, and (b) possible contributions of non-HIV factors to cognitive test performance, it is possible that the reported prevalence rates of cognitive impairment in PWH are inaccurate (or, at least, do not solely reflect the contributions of HIV disease to the impairment). Another uncertainty in the HIV neuropsychology literature concerns sex differences in the cognitive performance of PWH. Some recent studies suggest that women with HIV (WWH) may present with greater cognitive impairment than men with HIV (MWH). Such a sex difference is of potentially significant concern for South African clinicians because two-thirds of the population of PWH in this country are women. However, there is no definitive empirical evidence regarding whether this sex difference exists to a clinically significant degree (in South Africa, specifically, as well as globally) and what its underlying mechanisms might be. To address the knowledge gaps outlined above, this thesis set out to explore the following aims: (1) investigate sex differences in the cognitive performance of PWH by reviewing the current published literature; (2) determine if sex differences exist in a clinic sample of South African PWH; (3) determine how much variation in reported prevalence rates of HIV-associated cognitive impairment are due to the method used to define impairment, and which method correlates best with MRI biomarkers of HIV-related brain injury in a South African sample of PWH; (4) investigate the contribution of sociodemographic and psychosocial variables, as well as HIV-disease factors and other medical and psychiatric comorbidities, to cognitive performance in a South African sample of PWH; and (5) investigate associations between cognitive performance and ART adherence in

a South African sample of PWH. Each of these aims was explored in a separate study. Hence, this thesis reports on findings from five separate journal manuscripts.

Method. *Study 1* was a systematic review and meta-analysis summarizing the findings of published studies investigating differences in cognitive performance between WWH and MWH. An extensive systematic search of the literature across several databases found 4062 unique articles of potential interest. After thorough screening of that pool of articles, 11 studies (total $N = 3333$) were included in the narrative systematic review and 6 studies (total $N = 2852$) were included in the meta-analysis. Effect sizes were calculated to estimate between-sex differences in cognitive performance, both globally and within discrete cognitive domains. *Study 2* investigated sex differences in cognitive performance in a sample of PWH with comorbid MDD ($N = 105$). All participants were attending community clinics in Khayelitsha, a peri-urban community in Cape Town, South Africa, and were part of a larger research program for a randomised controlled trial of a cognitive-behavioral treatment for ART adherence and depression (CBT-AD). As part of this program, they completed baseline neuropsychological, psychiatric, and sociodemographic assessments. *T*-tests and multivariable regressions controlling for covariates compared baseline cognitive performance of WWH and MWH, both globally and within discrete cognitive domains. *Study 3* applied 20 different quantitative methods of determining cognitive impairment to existing data from a different sample of PWH ($N = 148$). These individuals had also been recruited from community clinics in Khayelitsha, and had completed a comprehensive neuropsychological assessment and a 3T structural MRI and diffusion tensor imaging (DTI) session. Logistic regression models investigated the association between each method and HIV-related neuroimaging abnormalities. *Study 4* again used data from the sample of PWH with comorbid MDD who participated in the larger CBT-AD research program. This study investigated which sociodemographic, psychosocial, psychiatric, and medical variables (as measured at baseline) were associated with baseline cognitive performance. Post-baseline, 33 participants were assigned to CBT-AD and 72 to standard-of-care treatment; 81 participants ($n_{\text{CBT-AD}} = 29$) had a follow-up assessment 8 months post-baseline. This study also investigated whether, from baseline to follow-up, depression and cognitive performance improved significantly more in the participants who had received CBT-AD, and examined associations between post-intervention improvements in depression and cognitive performance. *Study 5* assessed ART adherence in the same sample of PWH with comorbid MDD. Mixed-effects regression models estimated the relationship between ART adherence (as measured by both self-report and objective measures, and by degree of HIV viral suppression) with cognitive performance

and with other sociodemographic, psychosocial, and psychiatric variables at both baseline and follow-up.

Results. *Study 1*: Analyses suggested that, in terms of overall cognitive functioning, there were no significant differences in cognitive performance between WWH and MWH. However, WWH did perform significantly more poorly than MWH in the domains of psychomotor coordination and visuospatial learning and memory. Additionally, the review suggested that cognitive differences between WWH and MWH might be accounted for by sex-based variation in educational and psychiatric characteristics among study samples. *Study 2*: Analyses suggested that, in our sample of PWH with comorbid MDD, there were no significant differences in cognitive performance between WWH and MWH. *Study 3*: Findings suggested that there was marked variation in rates of cognitive impairment (20–97%) depending on which method was used to define impairment, and that none of these methods accurately reflected HIV-associated brain injury. *Study 4*: Analyses suggested that less education and greater food insecurity were the strongest predictors of global cognitive performance. Improvement in depression severity was not significantly associated with improved cognitive performance, except in the domain of Attention/Working Memory. Overall, factors associated with cognitive performance were unrelated to HIV disease and other medical factors. *Study 5*: Analyses identified poor global cognitive performance as a potential barrier to achieving HIV suppression.

Conclusion. Taken together, the findings from the five studies contained within this thesis suggest that one oft-mooted sociodemographic influence on cognitive performance in PWH, sex, was not a consistent influence on such performance. However, non-biological (mainly psychosocial and socioeconomic) factors were stronger predictors of cognitive performance in PWH than medical factors (including HIV-disease variables). Current quantitative criteria for defining cognitive impairment in PWH also do not accurately reflect the biological effects of HIV in the brain. The implication of these findings is that research studies may be misclassifying PWH as cognitively impaired and consequently overestimating the prevalence of cognitive impairment in this population. When conducting clinical assessments of PWH, future research studies should measure and consider the strong influence of psychosocial and socioeconomic factors on cognitive test performance. Ideally, a diagnosis of impairment should only be made after a comprehensive clinical assessment that includes a detailed history taking. Overall, we need new criteria for defining cognitive impairment in diverse global populations of PWH. Ideally these criteria should be applicable to both research and clinical settings. Assessing for cognitive impairment among PWH and then providing

appropriate support could help achieve viral suppression in patients with non-optimal adherence to ART. At public policy levels, addressing larger psychosocial issues (e.g., food insecurity and low educational attainment) may also help improve cognitive performance in PWH.

Chapter 1

Introduction

Global epidemiological statistics indicate that South Africa has the largest population of people with HIV (PWH) at 7.8 million. There is a distinctly gendered aspect to these statistics: Two-thirds of this population of PWH are women, and most new infections occur in women.

South Africa has adopted the current UNAIDS HIV testing and treatment targets. These assert that by 2025, globally and within all subpopulations and age groups, 95% of all PWH should know their status, 95% of PWH should be receiving antiretroviral therapy (ART), and 95% of all people receiving ART should be virally suppressed. If these 95-95-95 targets are reached, HIV-related mortality will be eliminated, and transmission will be prevented (UNAIDS, 2021a, 2021b). Because South Africa has adopted these and earlier UNAIDS HIV testing and treatment targets, it has the largest ART program in the world.

HIV infection can cause brain injury and dysfunction that may result in cognitive impairment (Winston & Spudich, 2020; Woods et al., 2009). Numerous studies, conducted in many different countries, report high rates of cognitive impairment in PWH. Prevalence rates of HIV-associated cognitive impairment (i.e., impairment assumed to be attributed to the effects of HIV rather than to other, perhaps non-organic, causes) typically range between 15% and 55% (Saylor et al., 2016). A recent meta-analysis of global studies showed the overall prevalence of HIV-associated cognitive impairment to be 43%, with higher rates reported in sub-Saharan African countries (Wang et al., 2020).

Cognitive impairment can have a negative impact on the daily functioning of PWH. One of the most significant functional outcomes affected by such impairment is treatment adherence (Andrade et al., 2013; Ettenhofer et al., 2010; Hinkin et al., 2002; Hinkin et al., 2004; Lovejoy & Suhr, 2009; Sayegh et al., 2016; Thaler et al., 2015). Impaired cognitive functioning can, for instance, make remembering to take medication more difficult and can make planning and organisation of medication management more challenging (Ettenhofer et al., 2010; Lovejoy & Suhr, 2009). This functional consequence of HIV-associated cognitive impairment is of particular relevance to the 95-95-95 targets because ART adherence is essential for PWH to achieve viral suppression (and, therefore, to reduce the risk of HIV-related morbidity and to improve quality of life).

Given this clinical context, a key task for HIV neuropsychologists is to use standardised tests to characterise the cognitive performance of PWH to determine cognitive impairment and to deduce whether poor performance reflects HIV-related brain injury and dysfunction, the effects of non-HIV factors, or some combination of these two categories of influence.

Among the non-HIV factors that are particularly relevant here are the medical and psychiatric comorbidities that are highly prevalent in PWH (Saloner et al., 2019). Common medical conditions that can contribute to cognitive impairment in PWH include cerebrovascular disease (Cruse et al., 2012; Vinikoor et al., 2013), central nervous system opportunistic infections (Bowen et al., 2016), and neurological insults such as head injuries (Lin et al., 2011). Psychiatric conditions that are highly prevalent in populations of PWH and that can strongly influence cognitive performance include substance use disorders and major depressive disorder (MDD; Chilunda et al., 2019; Fellows et al., 2013; Norman et al., 2009; Rubin & Maki, 2019). MDD is, in fact, the most diagnosed psychiatric condition in PWH and a diagnosis of MDD is more prevalent in PWH than in the general population (Lofgren et al., 2020; Too et al., 2021). It is not merely the presence of MDD that places PWH at risk of cognitive impairment: In dose-response fashion, increased severity of depressive symptomatology is associated with worse cognitive performance (Paolillo et al., 2020).

Sociodemographic factors such as age, ethnicity, language, level of education, and sex also have a large influence on cognitive test performance among PWH and in the general population (Strauss et al., 2006). Higher levels of education, for example, strongly predict better standardised test performance (Lenehan et al., 2015; Maki et al., 2015). Of particular interest for South African clinicians given that more than 60% of PWH in this country are women (Takuva et al., 2017; UNAIDS, 2021b) is recent literature reporting that women with HIV (WWH) may be more vulnerable to HIV-associated cognitive impairment than men with HIV (MWH; Gascón et al., 2018; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016; Rubin et al., 2019; Sundermann et al., 2018).

Given that South Africa's apartheid legacy has ensured ongoing psychosocial and socioeconomic inequalities, the effects of these factors on cognitive performance in South African PWH need to be considered. This is especially true given the fact that psychosocial factors, including socioeconomic variables can affect cognitive performance in both the general population and in PWH globally (Farah, 2017; Hobkirk et al., 2017; Watson et al., 2019; Yaple & Yu, 2020).

Of note here, however, is that poor cognitive test performance associated with factors such as education, sex, and socioeconomic status is not pathological and therefore does not indicate a diagnosis of cognitive impairment.

Of course, none of the medical, psychiatric, sociodemographic, psychosocial, socioeconomic factors operate independently on cognitive performance. For example, a typical patient requiring a cognitive assessment in Cape Town may be a first language

isiXhosa-speaking female with poorly controlled HIV, current MDD, a previous traumatic brain injury, and a socioeconomically disadvantaged background. The neuropsychologist conducting the assessment will need to take into account all relevant factors to diagnose cognitive impairment fairly and accurately.

To achieve such fair and accurate diagnosis in clinical practice, many South African neuropsychologists rely less on standardised test scores and normative data (because appropriate forms of those are not always available in the local context) and instead use a more flexible approach to assessment where we adapt test administration and interpret performance on cognitive tests subjectively, according to the context and background of the individual. A detailed history and clinical judgement is used to determine whether the individual's performance is indicative of cognitive impairment. Most neuropsychologists only give a diagnosis of cognitive impairment if there is a biological or pathological cause.

In research studies, this approach to neuropsychological assessment is not practical because of its lack of standardization, heavy reliance on the clinical competency of the individual doing the assessment, and need for a lengthy history taking session. Hence, HIV researchers tend to use more purely psychometric means to classify cognitive impairment, applying standardised cut-off scores to cognitive test scores (e.g., z = -1.5) to mark the threshold for cognitive impairment (see e.g., Cysique et al., 2014; De Francesco et al., 2016; Tierney et al., 2017).

One potential limitation of this approach is that, often, quantitatively defined cognitive deficits are attributed directly (and sometimes solely) to HIV-related brain injury or dysfunction. That is to say, the possible contribution of sociodemographic and psychosocial factors, as well as comorbid medical and psychiatric conditions, to poor cognitive performance is not considered carefully enough.

Failure to consider the contribution of these factors to cognitive outcomes might also have the knock-on effect of inflating the reported population prevalence rates of HIV-associated cognitive impairment. That is to say, neglecting to consider that observed low cognitive performance may not be attributable entirely to the organic damage inflicted by the infection itself means that one inevitably overestimates the prevalence of impairment that is truly HIV-associated. Given that most criteria for diagnosing cognitive impairment in PWH, employ a rigid psychometric means of classifying cognitive impairment (i.e., they advise the application of standardised cut-off scores), it is likely that research studies are overestimating prevalence rates of cognitive impairment in PWH.

The most commonly used criteria, the Frascati/HIV-associated neurocognitive disorder (HAND) criteria (Antinori et al., 2007), require that cognitive impairment should be reasonably attributable to HIV (and not other causes) before a syndromic HAND diagnosis (i.e., ANI, MND, HAD) is made. However, the role of non-HIV factors on cognitive performance are often overlooked in research studies and low cognitive performance in a person with HIV is often attributed directly to the effects of the HIV. Another concern with the Frascati criteria is that it still relies on a rigid psychometric approach to diagnosing impairment, in that a diagnose of ANI is based purely on poor performance on neuropsychological tests (i.e., if cognitive performance is ≥ 1 SD below the normative mean). Inaccurate diagnostic criteria and the consequential overestimation of prevalence rates, is a significant concern for the literature (Ciccarelli, 2020; Gisslén et al., 2011; Meyer et al., 2013; Nightingale et al., 2014; Underwood et al., 2018).

Overestimation of prevalence rates implies that PWH are at much higher risk of developing cognitive difficulties than they actually are, which can be stigmatizing and anxiety-provoking for those individuals (Nightingale et al., 2014). Moreover, a label of HIV-associated cognitive impairment can impact self-esteem, confidence, and fears for future health in PWH (Alford et al., 2022). Another consequence of a lack of diagnostic accuracy is that it can hinder the progress of HIV research. Inaccurate definitions of HIV-associated cognitive impairment will obscure the effects of trials investigating interventions and treatments for such impairment and frustrate attempts to identify biomarkers of HIV-associated cognitive impairment (Meyer, 2022).

In the vast majority of published HIV neuropsychology studies, researchers attempt to control for the contribution of non-HIV factors to poor cognitive performance by excluding from participation PWH with comorbid medical and psychiatric conditions, such as a history of neurological disorder or other medical disorder affecting the nervous system (eg, stroke, epilepsy, or head injury with consequent hospitalization and/or loss of consciousness for >30 minutes), the presence of a major psychiatric disorder (often not including major depressive disorder), history of a learning disability and current substance abuse (e.g., Gouse et al., 2022; Heaton et al., 2011; Nyamayaro et al., 2020). .

Study samples therefore seldom represent real-life clinic samples, and therefore results from research studies are often not useful in clinical practice. Additionally, many research studies give cursory (if any) consideration to the influence of sociodemographic or psychosocial factors on cognitive performance, thus at least tacitly leading to the assumption that poor performance in PWH is due solely to the direct effects of the infection.

The use of well-matched normative data in characterising the cognitive performance of PWH (e.g., comparing the performance of patient samples to normative samples matched on sociodemographic and psychosocial variables) can decrease the chances of inaccurately defining HIV-associated cognitive impairment in research studies. However, in multicultural and multilingual countries like South Africa that also have significant population-wide psychosocial and socioeconomic disparities, it is near-impossible to have well-matched normative data for every individual completing cognitive tests (Watts & Shuttleworth-Edwards, 2016). Moreover, in South Africa and many other countries there is a disproportionate burden of HIV disease in people who are poor and vulnerable (Shisana et al., 2010; Wabiri & Taffa, 2013). Therefore a group of PWH cannot be assumed to have comparable psychosocial and socioeconomic opportunities to people without HIV and as such, normative data drawn from people without HIV cannot be assumed to be comparable even if matched on basic demographics such as age, sex and education (Bunyasi & Coetzee, 2017; Ward-Peterson et al., 2018).

Research Rationale and Aims

Against the background of the literature reviewed above, the aims of this thesis were to investigate (a) sex differences in PWH cognitive performance, (b) efficacy of currently published neuropsychology criteria for defining cognitive impairment in PWH, (c) HIV and non-HIV factors associated with cognitive performance in a South African sample of PWH, and (d) influence of cognitive performance on ART adherence in the same sample of PWH.

As the review above intimates, there are many important reasons to conduct such investigations using South African samples of PWH.

First, recent literature regarding sex differences in the cognitive performance of PWH is somewhat equivocal, and so it is vital to conduct well-designed research investigating the question of whether those differences do exist and, if they do, what the direction and magnitude of effects are for different cognitive domains and what the mechanisms driving those effects might be. Equally important are the social justice implications of such research. If WWH in South Africa present with greater cognitive impairment than MWH, then existing and well-established gender inequalities in the country will be further exacerbated by the effects of that differential cognitive impairment on functional outcomes, quality of life, and opportunities for occupational success.

Second, it is currently unknown which set of quantitative neuropsychological criteria, and which method of application of those criteria, should be held as the gold standard for defining cognitive impairment in PWH. It is also unknown how well each set, and each

method of application within each set, corresponds to HIV-related brain injury as indicated by neuroimaging. Hence, research targeting those unknowns is important and, again, it is vital to conduct such research in clinically relevant contexts. In South Africa, a country with the largest number of PWH within its general population, there are significant implications of inaccurately defining HIV-associated cognitive impairment.

Third, understanding the contribution of non-HIV factors (e.g., sociodemographic and psychosocial variables, medical and psychiatric comorbidities) to cognitive impairment in PWH will assist in accurately defining HIV-associated neurocognitive disorders. This understanding is especially important when PWH are living in socioeconomically disadvantaged settings, such as those from which we recruited the current sample.

Fourth, ART adherence is one of the most important functional outcomes to consider in PWH. Hence, it is vital to investigate the barriers to ART adherence and to achieving HIV viral suppression. Prior research suggests that cognitive impairment might be one such barrier, but no extant published study has examined that association in a South African sample of PWH. Investigating whether cognitive performance is associated with ART adherence in South African samples of PWH is an essential step in ensuring that the country reaches the WHO 95-95-95 targets.

To summarise, then, this thesis sought to address four specific aims:

Investigate sex differences in cognitive performance in PWH by (a) conducting a systematic review and meta-analysis on the current published literature, and (b) determining if such differences exist in clinic sample of South African PWH and describing the factors associated with cognitive performance in WWH and MWH within that sample.

Investigate the fidelity of current quantitative neuropsychological criteria for defining cognitive impairment in PWH by determining how much variation in reported rates are due to the method used to define cognitive impairment, and by examining which method correlates best with MRI biomarkers of HIV-related brain injury in a South African sample of PWH.

Investigate the contribution of sociodemographic and psychosocial variables, as well as HIV-disease factors and other medical and psychiatric comorbidities, to cognitive performance in a South African sample of PWH.

Investigate associations between cognitive performance and ART adherence in a South African sample of PWH.

I took several steps to ensure that the current original empirical studies presented here were not afflicted by some of the limitations of previous studies in this literature. First, original data were collected from PWH attending community clinics in a low socioeconomic

status area of Cape Town, South Africa. This ensured that the sample was representative of real-world clinic patients. Second, cognitive performance was measured using a comprehensive battery of standardised neuropsychological tests based on the HIV Neurobehavioral Research Center (HNRC) set of tests (Grant, 2008) and that have been used frequently in South African HIV research studies (see, e.g., Gouse et al., 2022; Joska et al., 2011). This ensured the methods were consistent and comparable to global standards but also showed evidence of psychometric validity in these settings. These tests are considered to assess performance in the cognitive domains commonly affected by HIV. Third, normative standards for neuropsychological test scores were based on data from well-matched samples of healthy community-dwelling individuals who presented at the same community clinics from which the HIV-infected participants were recruited. This ensured that the effects of, for instance, sociodemographic and psychosocial variables (e.g., age, ethnicity, language, education) on cognitive performance were controlled by design, and that therefore the impact of those variables on cognitive outcomes were neither ignored nor overestimated. It is important to note that controlling for sociodemographic and psychosocial variables in this way minimizes the differences between people without HIV and PWH but likely does not eliminate them completely.

Research Context

The research described in this doctoral thesis was centred at the HIV Mental Health Research Unit, Department of Psychiatry and Mental Health, University of Cape Town (UCT). Research sites were community clinics in Khayelitsha, a peri-urban community in Cape Town that features the highest burden of HIV in the province and one of the highest in South Africa. Khayelitsha was established under the principle of racial segregation executed by the apartheid regime. As a consequence of this legacy, today almost all of its residents are Black African and it is one of the poorest areas of Cape Town, marked by low rates of educational attainment (fewer than one-third of adult residents have completed high school) and high rates of crime and unemployment (Kehoe et al., 2020; Nleya & Thompson, 2009; Smit et al., 2016; Stern et al., 2017; City of Cape Town, 2013).

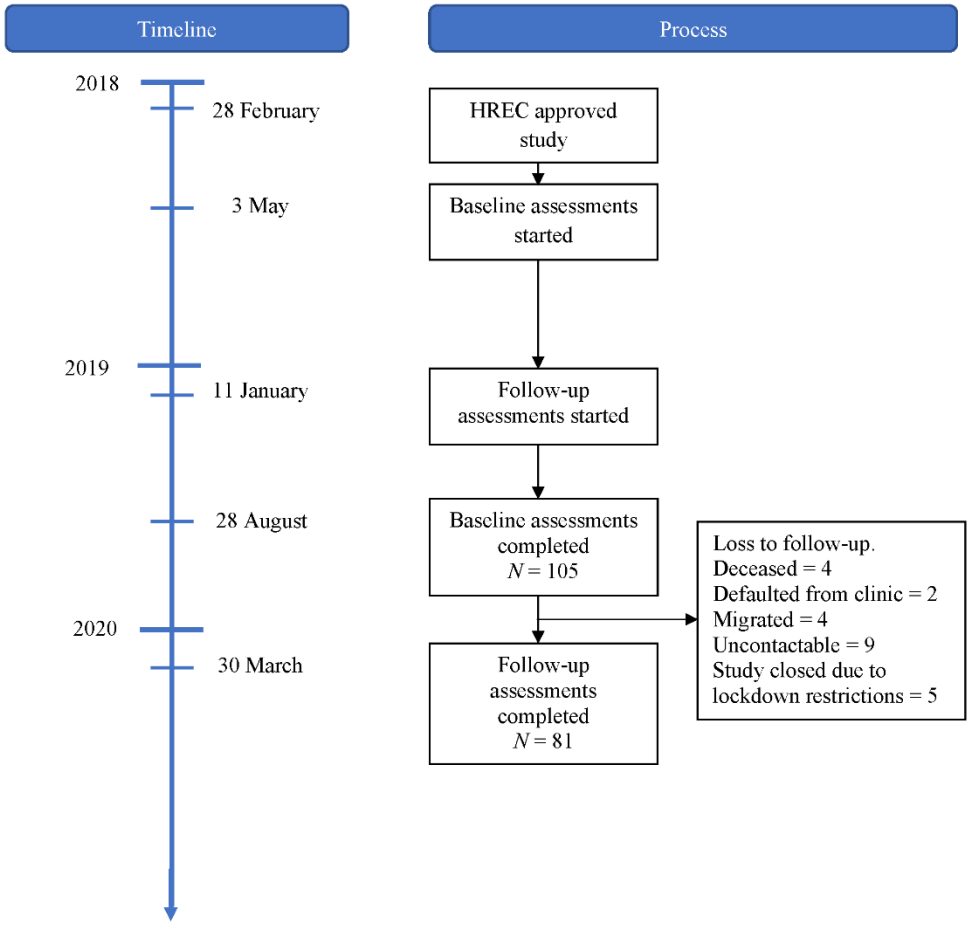
Three manuscripts contained within this thesis (presented here as Chapter 3, Chapter 5, and Chapter 6) investigated a sample of PWH with comorbid MDD and incomplete adherence to ART. This sample was drawn from participants who screened for a large randomised controlled trial of a cognitive-behavioural treatment for ART adherence and depression (CBT-AD; Joska et al., 2020; Safren et al., 2021) that had already begun running in the UCT HIV Mental Health Research Unit. I developed and implemented the protocol for

a supplement to this trial. The supplement was focused on conducting neuropsychological assessments in this sample so as to allow investigation of three of this thesis's specific aims (numbers 1, 3, and 4 listed above).

Figure 1 shows the timeline and process for this supplement project.

Figure 1

Supplement Project Process and Timeline



Overview of the Thesis

The thesis aims were explored in five different studies. Hence, this thesis reports on findings from five separate journal manuscripts. To date, three manuscripts have been published, one is in process of second round of review, and one has been submitted for publication.

Each manuscript contextualises the specific study in the current literature, outlines the aims, and describes how the study was conducted. The main findings are discussed, in

addition to limitations and potential areas for future research. The manuscripts are formatted identically (i.e., each is not necessarily in the format prescribed by the journal to which it was submitted) to ensure there is consistent formatting throughout the thesis.

This thesis, is therefore, comprised of seven chapters, with the five manuscripts as self-standing chapters (Chapters 2, 3, 4, 5, and 6), a general introduction that precedes those chapters (Chapter 1), and a discussion chapter that follows them and ties the various findings together (Chapter 7). Before each of Chapters 2–6, I also indicate my contribution and role in the study and the study abstract.

In this chapter, Chapter 1, I have briefly introduced the main themes of the thesis to provide a framework for the research rationale and aims.

In Chapters 2 and 3, I present investigations into sex differences in cognitive performance in PWH, thereby addressing the first research aim of the thesis. Chapter 2 presents a systematic review and meta-analysis of previously published studies that reported data on sex differences in PWH cognitive performance. This study summarised the literature on this topic and used a meta-analysis to compare cognitive performance in WWH and MWH. Chapter 3 presents an original empirical investigation into sex differences in the cognitive performance of a South African cohort of PWH. This study also investigated the contribution of sociodemographic, medical, and psychiatric comorbidities to cognitive performance within WWH and MWH groups.

Chapter 4 presents an original empirical investigation into the current quantitative neuropsychological criteria for classifying cognitive impairment, thereby addressing the second research aim of the thesis. Using data from a sample of South African PWH, I described how the application of different published criteria (e.g., Frascati/HAND criteria, Global Deficit Score) would affect the estimated prevalence rate of cognitive impairment in that sample. Further, I investigated the association of impairment, as classified by each set of criteria, with MRI biomarkers of HIV-related brain pathology, thus determining which set of criteria best corresponds to HIV-related brain injury.

Chapter 5 presents an original empirical investigation into the cognitive performance of a sample of PWH with comorbid MDD, thereby addressing the third research aim of the thesis. The study investigated the contribution of sociodemographic and psychosocial variables, as well as HIV-disease factors and other medical and psychiatric comorbidities, to cognitive performance in a South African sample of PWH. It also specifically examined the associations of depression severity with cognitive performance, analysed whether depression and cognitive performance improved significantly more from baseline to follow-up in

participants who had received CBT-AD as compared to those who had received standard-of-care treatment, and measured associations between post-intervention improvements in depression and cognitive performance

Chapter 6 presents an original empirical investigation into associations between cognitive performance and ART adherence in a South African cohort of PWH with comorbid MDD, thereby addressing the fourth research aim of the thesis. In this study, we measured adherence by self-report, objective measures (Wisepill usage and plasma tenofovir-diphosphate levels), and HIV viral suppression. The study investigated associations between global and domain cognitive performance and each ART adherence variable. It also investigated associations between ART adherence and a set of sociodemographic, psychosocial, and psychiatric variables. Among the psychiatric variables, depression was of primary interest.

Chapter 7 presents an integrated discussion that reviews the main findings of the thesis, explores implications for future work, and describes overall strengths and limitations of the research program.

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Chapter 2

Cognitive Differences between Men and Women with HIV: A Systematic Review and Meta-Analysis

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AJD was the first author of this manuscript. This entailed leading the drafting, analyses and conceptualising. AM contributed to the manuscript by screening a random sample of 10% of the titles and abstracts and full-text articles, to cross-check for fidelity and assisted with the quality assessment, TW provided guidance on conducting the meta-analysis, and JAJ and KGFT reviewed drafts. All co-authors reviewed drafts and approved the final manuscript.

Current status Published in Archives of Clinical Neuropsychology.

Dreyer, A. J., Munsami, A., Williams, T., Andersen, L. S., Nightingale, S., Gouse, H., Joska, J., & Thomas, K. G. F. (2022). Cognitive Differences between Men and Women with HIV: A Systematic Review and Meta-Analysis. *Archives of Clinical Neuropsychology, 37(2),* 479-496. https://doi.org/10.1093/arclin/acab068.

Abstract

Objective: Although many studies report that women with HIV (WWH) are more vulnerable to cognitive impairment than men with HIV (MWH), this trend is not described consistently in the literature. In this systematic review and meta-analysis, we investigated whether the weight of evidence supports the existence of a significant sex difference in cognitive functioning among people with HIV and, if so, whether specific domains are affected.
Method: A systematic literature search retrieved 4062 unique articles published between January 2000 and June 2019. Eligibility criteria were that studies directly compared adult WWH and MWH using a neuropsychological test battery. After extensive screening, we included 11 studies in the systematic review (N = 3333) and 6 in the meta-analysis (N = 2852).
Results: Six studies included in the systematic review found WWH performed significantly more poorly on measures of cognitive performance than MWH; the other five found no sex differences. Meta-analytic results indicated that WWH performed significantly more poorly than MWH in three cognitive domains (psychomotor coordination, visuospatial learning and memory), but magnitudes of effect sizes were small (d = -0.16, -0.43, and -0.30, respectively). Analyses detected no sex differences in global cognitive functioning and in the other cognitive domains.
Conclusions: Sex differences in cognitive performance are small, and sociodemographic and psychiatric characteristics of WWH and MWH differ between studies. Cognitive differences between WWH and MWH may be explained by sex-based variation in these characteristics, the impact of which seems to outweigh that of HIV-related clinical variables (e.g., CD4 count, viral load).

Keywords: HIV; memory; motor skills; neurocognitive disorders; sex differences

Introduction

HIV-associated cognitive impairment typically occurs following uncontrolled viral replication and subsequent invasion of the central nervous system (Grant, 2008). Neuropsychological studies report that, in the current era of widespread combination antiretroviral therapy (cART), the cognitive domains of motor speed and dexterity, information processing speed, attention and working memory, learning and memory, and executive function are most affected in people with HIV (PWH; Grant, 2008; Heaton et al., 2011; Walker & Brown, 2018; Woods et al., 2009). Prevalence rates of HIV-associated cognitive impairment typically range between 15% and 55% (Saylor et al., 2016).

Recent literature suggests that at least some of the cross-study variability in prevalence rates of HIV-associated cognitive impairment might be attributable to sex differences. Numerous studies report higher rates of cognitive impairment in women with HIV (WWH; 46–80%) than in men with HIV (MWH; 38–73%; McNamara et al., 2016; Robertson et al., 2007; Sundermann et al., 2018; Yakasai et al., 2015). These differential impairment rates are reported in studies emerging from low- and middle-income countries (LMICs; Gascón et al., 2018; Hestad et al., 2012; Holguin et al., 2011; Kabuba et al., 2016; Royal et al., 2016) and from high-income countries (Coban et al., 2017; Fogel et al., 2017; Melnick et al., 1994; Stern et al., 2001).

These differential impairment rates might be attributable to sex differences in biological factors. For instance, women's cognitive performance (but not men's) can be affected by an interaction between endocrine variables (menopause, menstrual cycle phase, and contraceptive use) and HIV infection (Greendale et al., 2009; Hausmann, et al., 2000; Maki et al., 2002; 2008; Rubin et al., 2014; Weber et al., 2014; Sundermann et al., 2007; Warren et al., 2014). Higher rates of cognitive impairment in WWH than in MWH may also be attributed to sex differences in (a) HIV-associated brain structure alterations (Smith et al., 2008) and (b) systemic immune activation/inflammation in response to HIV infection (Fitch et al., 2013; Raghavan et al., 2017; Ziegler & Altfeld, 2017).

Trends toward poorer neurological outcomes and higher rates of cognitive impairment among WWH are not described consistently in the literature, however. A few studies report the opposite pattern, with MWH displaying poorer cognitive performance, a higher prevalence of cognitive impairment, and more neurological impairment (Liu et al., 1997; Tozzi et al., 2005; Wisniewski et al., 2005). A larger group of studies reports no sex differences in HIV-associated cognitive impairment and/or no relationship between sex and

disease progression (Behrman-Lay et al., 2016; Bouwman et al., 1998; Everall et al., 2009; Faílde Garrido et al., 2008, 2013; Joska et al., 2010; Kinai et al., 2017; Robertson et al., 2004; Sibanda-Kunda et al., 2015).

Rubin et al. (2019) summarized this literature in a recent systematic review of 11 studies. Among reviewed studies that reported a summary score of global cognition, three of seven reported greater cognitive impairment in WWH than MWH, even after results were adjusted for relevant disease and demographic characteristics. Among those that measured motor speed and dexterity, information processing speed, learning and memory, or executive functioning, fewer than 50% in each case found greater impairment in WWH and none found greater impairment in MWH. No reviewed study found sex differences in the domains of verbal fluency and attention/working memory. Nonetheless, the authors' overall conclusion was that cognitive impairment appears to be more severe in WWH than in MWH.

In justifying this conclusion, Rubin et al. noted that Sundermann et al. (2018) and Maki et al. (2018) are the only two published studies adequately powered to examine sex differences in cognitive functioning in HIV, and that both found significant such differences. It is worth noting, however, that Maki et al. observed sex differences in cognitive performance (viz., greater impairment among WWH on tests of motor speed and dexterity, information processing speed, and executive function) even after controlling for HIV-related clinical characteristics (e.g., current and nadir CD4 count, history of an AIDS diagnosis, viral load, and medication use). This result suggests that the observed sex differences are likely explained by factors not directly related to the infection. Similarly, Sundermann et al. reported that higher prevalence of cognitive impairment in WWH was not associated with HIV-related clinical characteristics but was associated with lower reading level.

These observations indicate that many factors could contribute to sex differences in cognitive performance in HIV-infected samples. These differences may be explained by differences in the sex distribution of medical, psychosocial, and psychiatric factors that can affect cognitive performance. For instance, patients with low CD4 counts and high viral loads are at greater risk of cognitive impairment, whereas those who are stable on cART and with well-controlled HIV are at lower risk (Saylor et al., 2016). Hence, it should not be surprising that many studies reporting no sex differences in rates of cognitive impairment feature samples where the majority of both male and female samples are stable on cART. It is possible that the WWH in those samples have successfully overcome gender-based barriers to cART access and adherence (Behrman-Lay et al., 2016; Everall et al., 2009; Faílde Garrido et al., 2008, 2013; Kinai et al., 2017; Robertson et al., 2004; Sibanda-Kunda et al., 2015).

Similarly, variation in psychosocial factors such as years of completed education might contribute to sex differences in cognitive impairment in PWH. This is because (a) higher levels of education are often associated with better cognitive performance, and (b) women still tend to have less access to education (World Economic Forum, 2020; Lenehan et al., 2015; Strauss et al., 2006). Interestingly, Maki et al. (2015) found that, in their sample of 1521 women (n = 1019 WWH), reading level and years of education were more strongly associated with cognitive performance than HIV status.

Regarding psychiatric factors that may contribute to sex differences in cognitive impairment PWH, depression is a key consideration. A recent meta-analysis of 41 US-based studies (N = 813189; 52% women) showed that women are more likely than men to be diagnosed with, and to report more severe symptoms of, depression (Platt, 2020). This sex difference is also found in LMICs and is consistent across sociocultural settings (Hopcroft & Bradley, 2007; Kuehner, 2017; Seedat et al., 2009). Another recent meta-analysis showed that the presence of depression impairs cognitive performance in PWH (Rubin & Maki, 2019).

Finally, variation in basic sample characteristics (e.g., proportion of men and women) could also account for why some studies find sex differences in cognitive impairment in PWH while others do not. Those reporting no sex differences tend to feature samples with a greater number of MWH than WWH (see, e.g., Behrman-Lay et al., 2016; Everall et al., 2009; Faílde Garrido et al., 2008, 2013; Kinai et al., 2017). These samples may therefore underrepresent women's conditions and thus underestimate the potential disparity in cognitive sequelae between the sexes.

However, differences in the sex distribution of medical, psychosocial, or psychiatric factors, or of basic sample characteristics, does not provide a complete explanation for the discrepancies in the literature. For example, Joska et al. (2010) found no sex differences in cognitive performance in an adequately powered South African study (N = 536; 73.3% WWH, 47.8% on cART). Similarly, Robertson et al. (2004) studied an age- and education-matched sample of WWH and MWH and found no between-group differences, even after controlling for cART use, HIV RNA level, and disease stage.

Several other variables could also contribute to differences in cognitive performance between women and men (and therefore between WWH and MWH). Most notably, these variables include substance use, food insecurity, socioeconomic status, childhood trauma, sexual trauma, and domestic abuse – all influence cognitive performance and all often differ between men and women (Farinpour et al., 2003; Gao et al., 2009; Koyanagi et al., 2019; Martin et al., 2016; Spies et al., 2016; Sundermann et al., 2018; Watson et al., 2019).

It is important to determine whether there are differences in cognitive functioning between WWH and MWH to help us better understand cognitive impairment in PWH. Greater cognitive impairment is associated with poorer cART adherence and worse health outcomes (Lovejoy & Suhr, 2009; Sayegh et al., 2016; Thaler et al., 2015). In many contexts, WWH are already socially and economically disadvantaged and greater HIV-associated cognitive impairment will increase women's vulnerability to poorer health outcomes. Therefore, identifying whether these sex differences exist would have important implications regardless of cause. Elucidating the cause and their underlying mechanisms is critical for tailoring cognitive and health interventions to prevent and/or ameliorate these differences.

The Current Study

This systematic review and meta-analysis aimed to summarize literature investigating differences in cognitive functioning between WWH and MWH. We sought to clarify and extend the findings of the Rubin et al. (2019) systematic review, which concluded that WWH tend to show more cognitive impairment than MWH, particularly in the domains of motor speed and dexterity, information processing speed, and learning and memory. The key difference between our study and theirs is that where they addressed the issue of statistical power by including only studies with samples of PWH ≥ 100, we instead conducted a meta-analysis because the combined sample size of included studies would provide adequate power to address the relevant question. In addition, where they allowed inclusion of studies that measured cognitive performance using as few as two neuropsychological tests (an insufficient number to adequately measure global cognitive impairment), we instead included only studies that measured cognitive performance using a full battery of neuropsychological tests that at minimum covered the three domains most affected by HIV in the cART era (viz., information processing speed, memory, and executive function; Alford & Vera, 2018; Guha et al., 2016; Heaton et al., 2011).

Method

Protocol and Registration

The conduct and reporting for this systematic review and meta-analysis adhered to the PRISMA guidelines (Moher, 2009) and to the steps outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). We also consulted methodology described in Boland et al. (2017), Rosenthal and DiMatteo (2001), and Pollock and Berge (2018). The protocol was finalised a priori but was not published.

Search Strategy

We searched the PubMed (including MEDLINE), Scopus (excluding MEDLINE), Web of Science (excluding MEDLINE), and EBSCO Host (PsycINFO, Africa-Wide Information, PsycARTICLES, and CINAHL) electronic databases for relevant published literature. We also checked the Cochrane Library and the PROSPERO database to ensure that no similar systematic reviews had been conducted, other than Rubin et al. (2019).

We conducted several scoping reviews to refine the sensitivity and specificity of our search strategy. We developed our search terms by splitting the phrase *sex differences in HIV-associated cognitive impairment* into three parts (*HIV*, *cognition,* and *sex*). We investigated the MeSH terms and article keywords and free text to find any variation of these three terms in scientific use. Finally, we defined a final set of search terms (i.e., *HIV terms, cognition terms*, and *sex terms*).

Thereafter, we used this five-step search strategy. First, we located articles using individual search terms. Second, we grouped the individual search terms (separated by the Boolean operator 'OR') and conducted a search of the grouped HIV terms, then of the grouped cognition terms, and then of the grouped sex terms. Third, we combined all three grouped searches from step 2 using the Boolean operator 'AND.' Fourth, we added a filter to include only studies of human samples. Finally, we applied another filter to include only studies published after January 1 2000. The last search was conducted on June 13 2019. No language or resource restrictions were applied. Table 1 details the PubMed search strategy, which was modified as needed for other electronic databases.

Table 1

PubMed search strategy

HIV terms:		
#1	MeSH terms:	HIV
#2		HIV Infections
#3	Free text:	HIV
#4		human immunodeficiency virus
#5		HIV Infections
#6		HIV seropositivity
#7		Acquired Immunodeficiency Syndrome
#8		Acquired immunodeficiency virus
#9		AIDS viruses
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	
Cognition terms:		
#11	MeSH terms:	Neuropsychiatry
#12		Neuropsychology
#13		Neurocognitive Disorders
#14	Free text:	Neuropsychiatry
#15		Neuropsychology

#17		Neurocognitive profile
#18		Cognitive profile
#19		Neurocognitive functioning
#20		Cognitive functioning
#21		Neurocognitive Disorders
#22		Neurocognitive Disorder
#23		Cognition Disorders
#24		Cognitive Disorders
#25		Cognitive Disorder
#26		Neurocognitive Dysfunction
#27		Cognitive Dysfunction
#28		Neurocognitive Deficits
#29		Cognitive Deficits
#30		Neurocognitive Impairment
#31		Cognitive Impairment
#32		Neurocognitive problems
#33		Cognitive problems
#34		Dementia
#35		Dementia Complex
#36		NeuroAIDS
#37	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	
Sex terms:		
#38	MeSH terms:	Sex Factors
#39		Women
#40		Men
#41		Female
#42		Male
#43	Free text:	Sex Factors
#44		Women
#45		Woman
#46		Men
#47		Man
#48		Female
#49		Females
#50		Male
#51		Males
#52		Sex differences
#53		Sex difference
#54		Gender differences
#55		Gender difference
#56	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	
#57	#10 AND #37 AND #56	
#58	MeSH terms:	Animals
#59		Human
#60	#58 NOT #59	
#61	#57 NOT #60	
	Filter	Publication date from 2000/01/01 to 2019/06/31

Inclusion and Exclusion Criteria

Table 2 presents the eligibility criteria for studies that were part of the final review sample.

Table 2

Population, Intervention, Comparators, Outcomes, Study Design, and Setting (PICOSS) Table

	Inclusion Criteria	Exclusion Criteria
Population(s)	• Human samples only • Adult WWH and MWH	• An entire sample of individuals with disorders comorbid to HIV (e.g., substance abuse, depression) • Perinatally infected participants
Intervention(s)	• None	
Comparators	• Comparison of cognitive functioning in WWH and MWH	• No direct comparison of WWH and MWH
Outcomes	• Assessment of cognitive function using a battery of neuropsychological tests (including, at a minimum, the domains of information processing speed, memory, and executive function)	
Study design	• Any	
Setting	• Any	

There is evidence to show a shift in cognitive profile in PWH on cART toward a more cortical (vs. subcortical) presentation with deficits in executive functioning becoming more prominent (Alford & Vera, 2018; Guha et al., 2016; Heaton et al., 2011). To ensure the findings were generalizable to the current population of PWH, we included only studies conducted in the cART era. Although there is no consensus for the distinction between the pre-cART and cART eras, we chose the year 2000 as the cut-off following precedent set by previous reviews (see, e.g., Walker & Brown, 2018). We excluded sources of data presented in conference abstracts, unpublished material, or non-peer reviewed articles or chapters. When included studies had overlapping samples, we included the one with the largest sample size. We did not limit the review to people who were diagnosed with HIV-associated neurocognitive disorder (HAND).

Study Selection

We exported the references resulting from the search of each database into a single EndNote X9 library file (Clarivate Analytics, 2019). There, we deleted duplicate references and exported the remainder to Rayaan (Ouzzani et al., 2016) to facilitate the ease of subsequent screening procedures.

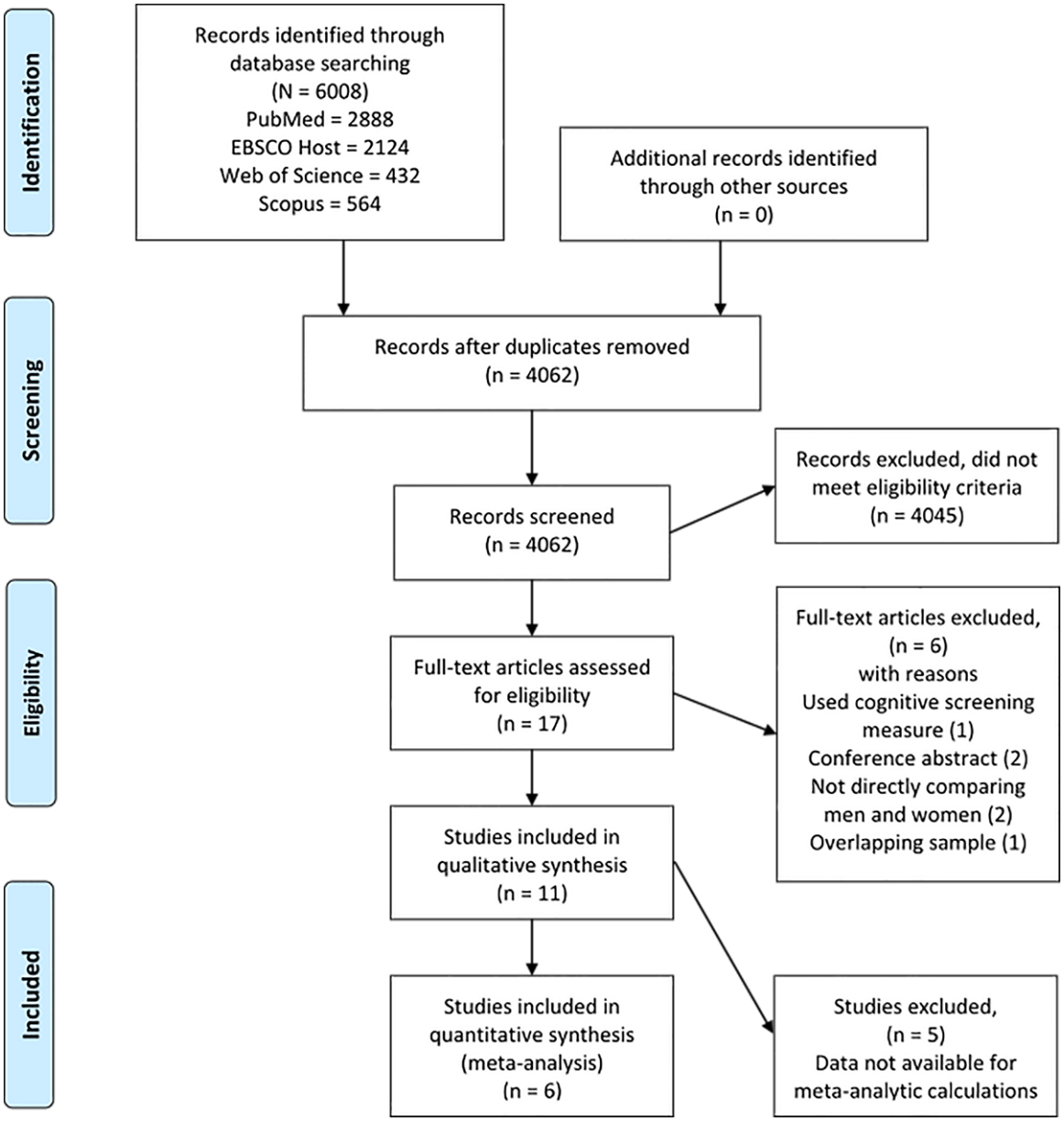
Those procedures were guided by a study-specific screening and selection table developed by AD. That table provides detailed outlines of the inclusion and exclusion criteria, thereby helping raters facilitate decisions regarding whether to include a study in the review. Two authors (AD and AM) piloted the screening and selection table by independently evaluating 30 titles and abstracts. A between-judge disagreement rate of 20% indicated that the table's resources were effective. Discussion to resolve the inconsistencies helped ensure the tool was reliable to use in screening the rest of the retrieved studies. AD then manually screened all 4062 titles and abstracts in the main search results, excluding studies that did not meet the eligibility criteria. AM screened a random sample of 10% to cross-check fidelity.

We then attempted to obtain full-text copies of all potentially relevant articles. If a full-text copy was not available online, we requested one directly from the corresponding author or via our institution's inter-library loan system. Once we had all possible full-text copies in hand, AD used the same selection and screening tool referred to above to scan the text and identify a final sample of papers to be included in the review. AM again screened a random sample of 10% to cross-check for fidelity.

Figure 1 is a flowchart describing the entire search process, with reasons for exclusion at each stage.

Figure 1

Flowchart depicting the article selection process used for the current systematic review and meta-analysis.



Ultimately, we included 11 studies as part of the systematic review and 6 of those in the meta-analysis. Because the samples described in the papers by Faílde Garrido et al. (2008) and Faílde Garrido et al. (2013) overlapped, we included only the latter in our review because its N was larger.

We required that studies included in the meta-analysis presented their data in a format suitable for the requisite calculations (specifically, for each individual neuropsychological measure *M*s and *SD*s had to be reported for WWH and MWH groups separately). Four of the identified 11 articles reported the data in this way (Behrman-Lay et al., 2016; Dolan et al., 2003; Maki et al., 2018; Royal et al., 2016). The other seven either did not report separate data for WWH and MWH or reported only global cognitive scores. In those cases, we

contacted the corresponding author to request the original data. If there was no reply within 2 weeks, we sent a second email. If there was still no reply after another 2 weeks, we excluded that study from our final analyses. The authors of two studies (Kabuba et al., 2016; Sundermann et al., 2018) responded to our email and provided the requested data.

Data Extraction

Using MSExcel, we developed a spreadsheet tool that described and indicated which data needed to be extracted from each article and provided space for the relevant information to populate individual cells in a spreadsheet. AD used the tool to extract data from the 11 included studies.

We extracted these descriptive data from each study: year of publication; country in which data were collected; sample size; sample demographic characteristics (i.e., age, sex, years of education); and sample clinical characteristics (i.e., mean duration of HIV diagnosis in months, the proportion of the sample using cART, mean/median duration of cART use in months, mean/median current CD4 count, mean/median nadir CD4 count, proportion of sample with undetectable viral load, proportion of sample using drugs, depression prevalence or mean score on scale measuring depressive symptomatology, and whether or not neurological confounders were present).

We extracted these data regarding study design and quality information: type of design (cross-sectional, longitudinal, mixed, and/or observational); study eligibility criteria; form of reported neuropsychological data (raw scores, *z*-scores, *T*-scores, or other type of scaled score); whether a control group or normative data were used (and sample size thereof) and whether it was demographically matched to the HIV+ group (and if not, if differences were demographically adjusted using statistical methods); statistical methods used; and whether there were pre-existing demographic or clinical differences between the WWH and MWH groups (and, if present, whether these were adjusted for in the statistical analysis).

Finally, for each of the six studies included in the meta-analysis, we extracted *M*s and *SD*s for group (WWH and MWH, independently) raw scores, *T*-scores, or *z*-scores for each neuropsychological test administered in the study. For each study included in the meta-analysis, a single outcome / neuropsychological test score to represent performance in each cognitive domain. Basing the meta-analytic calculations on these data allowed us to avoid the problem of non-independent effect sizes that arises when studies use multiple outcome measures taken on the same sample (Cheung, 2019; Moeyaert et al., 2017). In deciding which outcome / test score to select as a representation of performance within a domain, we chose the one most common to the included studies. If a particular study did not use that outcome /

test score, we chose the one used next most commonly. Recent studies in the field have used a similar approach (see, e.g., Cermak et al., 2021; Connors et al., 2021).

Risk of bias in individual studies

AD used the extracted information about study design to evaluate, along the following three dimensions, the risk of bias in each included study:

(a) Were appropriate methods and control or normative data used to calculate *T*-scores/*z*-scores?

(b) Were the WWH and MWH groups comparable (i.e., were there significant between-group differences) in terms of demographic and clinical variables?

(c) Were statistical methods used to adjust adequately if there were such between-group differences?

AD and AM also used the Downs and Black (1998) checklist to assess the methodological quality of the 11 studies included in the systematic review. Because this 27-item checklist was designed for evaluating both randomised controlled trials (RCTs) and non-RCT studies, only a subset of 16 items was applicable to the observational studies included in this review.

Meta-analytic Procedures

Data were analysed using RevMan version 5.3 software. For each outcome, we calculated Cohen's *d* effect sizes (Cohen, 1988) based on standardized mean differences between the WWH and MWH groups and calculated pooled effect size estimates for each cognitive domain and for the global score using random-effects models weighted by inverse variance.

Because we were interested in sex-based differences in HIV-associated cognitive performance, above and beyond the sex differences that one expects within the general population (i.e., that are eliminated in sex-based normative procedures), ideally all studies included in the meta-analysis would have used sex-based normative procedures. However, this was not the case; for 2 of the 6 studies (Behrman-Lay et al., 2016; Maki et al., 2018), only raw data were available.

To calculate this global score for each study, we averaged *T*-scores or *z*-scores for each test included in the meta-analysis. Such a calculation was not possible for the studies where we used raw scores for our meta-analytic computations (Behrman-Lay et al., 2016; Maki et al., 2018) because each raw score is scaled differently; hence, calculating an average of the raw scores will incorrectly summarise overall cognitive performance.

Given study-level differences in participant demographic and clinical characteristics known to affect performance on neuropsychological tests, we expected significant between-study heterogeneity and hence random-effects models were an appropriate choice (Hedges & Vevea, 1998). We used forest plots to report individual and pooled effect sizes. Finally, we evaluated between-study heterogeneity using a chi-square test (Cochran's Q) and estimated the degree of variation among study effect sizes using I^2. Statistically significant Q tests and I^2 values above 50% are considered indicators of heterogeneity (Higgins & Thompson, 2002) and are suggestive of study-level variation in effect sizes above that which would be expected due to chance alone.

Results

Study Characteristics

Table 3 presents the sociodemographic and HIV disease characteristics for the samples of women (n = 1220) and men (n = 2113) within the 11 studies included in the review. Where possible, we calculated summary statistics across these studies. These calculations indicated that the average age for the WWH ($M \pm SD$ = 35.99 ± 6.92 years) and MWH (36.92 ± 6.41) were similar (p = .76), as were the average number of years of completed education (WWH = 11.54 ± 1.18; MWH = 12.11 ± 1.51; p = .39).

Although the prevalence of cART use was similar across groups (WWH $M \pm SD$ = 78.11 ± 32.01%; MWH = 78.11 ± 32.10%), measures of HIV disease characteristics were better in WWH than MWH. On average, women had higher current CD4 and nadir CD4 counts than men ($M \pm SD$ = 423.6 ± 100.57 and 249.38 ± 47.54 compared to 363.96 ± 97.12 and 247.93 ± 88.34), and there was a greater prevalence of undetected viral load among women than men ($M \pm SD$ = 60.71 ± 34.91% versus 53.86 ± 33.45%).

Of the seven studies that reported on depression prevalence or severity, all but two (Burlacu et al., 2018; Maki et al., 2018) reported either higher prevalence or greater symptom severity in WWH.

Regarding substance use, only two studies reported including participants who were currently using injection drugs. In Maki et al.'s (2018) study, rates of injection drug use (as well as rates of other substance use) were significantly higher for MWH than WWH. In contrast, rates of injection drug use were quite similar across the sexes in the Robertson et al. (2004) sample. Although no participant in the Sundermann et al. (2018) study reported using injection drugs, 52% of their WWH and 69% of their MWH had a lifetime substance (i.e. alcohol, cocaine, methamphetamine, or opiates) use disorder and 24% of WWH and 29% of

MWH abused cannabis. In Behrman-Lay et al.'s (2016) sample, 79% of their MWH and 70% of their WWH had a history of injection drug use with at least 3-month abstinence. The other five reviewed studies (Burlacu et al., 2018; Dolan et al., 2003; Hestad et al., 2012; Kabuba et al., 2016, Royal et al., 2016) included samples with no history of substance abuse.

All nine studies that reported on the neurological status and history of their participants (Behrman-Lay et al., 2016; Burlacu et al., 2018; Dolan et al., 2003; Faílde Garrido et al., 2013; Hestad et al., 2012; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016; Sundermann et al., 2018) indicated that their samples did not include any individuals with a history of such confounders.

Table 3

HIV+ Participant Sociodemographic and Clinical Characteristics within Each Study (k = 11)

Study	Group	*n*	Age[a]	Education[a]	HIV diagnosis[a]	Current CD4[a]	Nadir CD4[a]	Und. VL[h]	cART use[h]	cART use (mos)	Depression[d]	Injection Drug use
Behrman-Lay et al. (2016)*	Women	44	44.0 (2.5)	13.3 (0.3)	97.0 (12.0)	668 (402-888)[c]	283 (67-430)[c]	84	100	> 3	11.6 (1.2)	None
	Men	93	41.7 (1.8)	13.5 (0.3)	123.0 (11.0)	553 (364-719)[c]	229 (24-346)[c]	77	100	> 3	9.5 (0.8)	None
Burlacu et al. (2018)	Women	129	22.9 (2.7)	11.6 (3.0)	260.4 (43.2)	516 (348-743)[c]	98 (36-206)[c]	71	NR	120 (71-164)[c]	15[e]	None
	Men	121	23.0 (2.5)	11.5 (2.6)	265.2 (43.2)	458 (234-667)[c]	74 (19-180)[c]	53	NR	123 (74-166)[c]	16[e]	None
Dolan et al. (2003)*	Women	57	38.0 (5.0)	12.3 (2.3)	108.0 (45.0)	318.0 (237.0)	NR	NR	88	> 1.5	15.5 (5.6)	None
	Men	24	37.0 (5.0)	13.5 (2.9)	57.0 (39.0)	366.0 (287.0)	NR	NR	88	> 1.5	11.7 (5.6)	None
Failde Garrido et al. (2013)	Women	33	33.4 (5.1)	10.4 (3.2)	NR	367.4 (220.7)	NR	33	97	NR	NR	None
	Men	57	34.2 (5.3)	9.3 (2.4)	None	286.7 (261.6)	NR	25	97	NR	NR	NR
Hestad et al. (2012)	Women	21	27.5 (6.7)	10.4 (2.3)	NR	368.7 (203.6)	238.4 (173.4)	100	NR	NR	16.5 (11.1)	None
	Men	16	29.4 (8.3)	11.8 (2.6)	None	328.2 (178.6)	198.6 (119.0)	100	NR	NR	13.4 (7.3)	NR
Kabuba et al. (2016)*	Women	159	39.5 (8.1)	9.7 (2.1)	NR	539.0 (230.7)	215.9 (156.1)	85	100	56.0 (31.4)[a]	NR	None
	Men	107	42.4 (9.4)	10.5 (2.3)	None	396.8 (235.5)	180.9 (136.9)	75	100	53.0 (32.8)[a]	NR	NR
Maki et al. (2018)*	Women	429	43.1 (7.5)	53[b]	NR	561.9 (314.1)	319.3 (207.0)	NR	81	NR	21[g]	0[h]
	Men	429	40.9 (7.6)	53[b]	None	516.8 (296.8)	375.8 (341.7)	NR	68	NR	38[g]	12[h]
Robertson et al. (2004)	Women	52	37.8 (8.5)	11.7 (1.9)	NR	343.0 (243.0)	NR	NR	66	NR	NR	35[h]
	Men	52	39.5 (6.6)	13.4 (2)	NR	266.0 (244.0)	NR	NR	83	NR	NR	31[h]
Royal et al. (2016)*	Women	92	32.10 (6.43)	12.70 (2.84)	NR	363 (243–508)[c]	NR	0	0	NA	7.60 (6.95)	None
	Men	57	38.32 (7.77)	12.11 (3.87)	NR	265 (171–419)[c]	NR	2	0	NA	6.70 (7.22)	None
Sibanda-Kunda et al. (2015)	Women	NR	NR	NR	NR	NR	NR	NR	100	NR	NR	NR
	Men	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sundermann et al. (2018)*	Women	204	41.6 (10.0)	11.8 (2.5)	99.6 (69.6)	527.8 (331.4)	223.9 (219.6)	52	71	NR	44[f]	None
	Men	1157	42.8 (9.9)	13.4 (2.6)	119.4 (87.6)	486.2 (303.1)	236.4 (212.5)	45	67	NR	37[f]	None

Note. *Included in meta-analysis. [a]Reported as *M* (*SD*), unless indicated otherwise; [b]Percentage less than high school; [c]Reported as median (interquartile range); [d]Reported as *M* (*SD*) of Beck Depression Inventory-Second Edition (BDI-II) scores, unless indicated otherwise; [e]Percentage BDI-II scores ≥13; [f]Percentage BDI-II scores ≥16; [g]Percentage Center for Epidemiologic Studies Depression Scale (CES-D) scores ≥ 16; [h]Reported as a percentage of total HIV+ sample. Data for the variables *Age* and *Education* are reported in years. Data for the variable *HIV Diagnosis* are reported in months. NR = data not reported; Und. VL = undetectable viral load; cART = combination antiretroviral therapy.

Risk of bias within studies

Our assessment, which is summarized in Table 4, showed that:

(a) Nine of the 11 studies calculated *T*-scores or *z*-scores, with seven of the 11 studies using appropriate methods and adequate control groups or normative data. Sibanda-Kunda et al. (2015) and Royal et al. (2016) did not report how they analysed the scores and Behrman-Lay et al. (2016) retained the raw scores.

(b) Six of the 11 studies (Burlacu et al., 2018; Dolan et al., 2003; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016; Sundermann et al., 2018) reported significant clinical and/or demographic differences between their WWH and MWH groups. In most cases, these differences indicated that WWH had better HIV disease parameters than MWH: They had higher current CD4 counts (Burlacu et al., 2018; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016), had less detectable plasma virus (Burlacu et al., 2018; Kabuba et al., 2016), had spent fewer years with a detectable viral load (Burlacu et al., 2018), were more likely to be on highly active antiretroviral therapy (HAART; Maki et al., 2018), and were less likely to have AIDS and tuberculosis (TB; Kabuba et al., 2016). In contrast, Maki et al. (2018) reported that their WWH had lower nadir CD4 counts and Dolan et al. (2003) reported that their WWH had been diagnosed with HIV for longer.

In addition, in the Maki et al. (2018) sample a greater proportion of the MWH were depressed, and in the Maki et al. (2018) and Sundermann et al. (2018) samples a greater proportion of the MWH had a history of substance use.

Sundermann et al. (2018), Dolan et al. (2003), and Kabuba et al. (2016) reported that their samples of WWH had significantly fewer years of education, and Sundermann et al. (2018) reported a significantly lower reading level in WWH. MWH in the Kabuba et al. (2016) and Royal et al. (2016) samples were significantly older, whereas WWH in the Maki et al. (2018) sample were significantly older.

(c) Four of the six studies that found significant clinical and/or demographic differences between WWH and MWH adjusted adequately for relevant factors in their statistical analyses. Royal et al. (2016) did not adjust for the between-group differences in age and current CD4 count in their sample, and Sibanda-Kunda et al. (2015) did not report whether such differences were present or whether they were adjusted for. Although Robertson et al. (2004) did not find such between-group differences, they did report adjusting for relevant covariates in the cognitive comparison between men and women.

Table 4

Risk of Bias Within Studies: Assessment summary (k = 11)

Study	Country	Design	Form of NP Data	Comparison Data	Matched Control Group/ Normative Data	WWH vs MWH Differences	Statistical Analysis	Analysis Adjusted for Differences
Behrman-Lay et al. (2016)*	USA	NR	Raw scores	NA	NA	No	MANCOVA	NA
Burlacu et al. (2018)	Romania	Cross-sectional	Scaled scores	Control group (*n* = 72)	Yes (age, recruited from same SES)	Yes	Regression	Yes
Dolan et al. (2003)*	USA	Cross-sectional	*z*-scores	Normative	Stratified by gender education and age[b]	Yes	Regression	Yes
Failde Garrido et al. (2013)	Spain	NR	*T*-scores	Control group (*n* = 61)	Yes (age, education, gender, recruited from same SES)	No	*t*-tests	NA
Hestad et al. (2012)	Zambia	NR	*T*-scores	Normative (*n* = 324)	Demographically corrected (age, sex, education, rural vs urban)	No	ANOVA	NA
Kabuba et al. (2016)*	Zambia	Cross-sectional	*T*-scores	Normative (*n* = 324)	Demographically corrected (age, sex, education, rural vs urban)	Yes	ANCOVA	Yes
Maki et al. (2018)*	USA	Longitudinal	*T*-scores[a]	Control group	Yes	Yes	Regression	Yes
Robertson et al. (2004)	USA	Longitudinal	*z*-scores	Normative	NR	NR	Mixed ANOVA	Yes
Royal et al. (2016)*	Nigeria	Cross-sectional	*T*-scores	NR	Demographically corrected (age, education and gender)	Yes	ANOVA	No
Sibanda-Kunda et al. (2015)	Zambia	Mixed methods	NR	NR	NR	NR	ANOVA	No
Sundermann et al. (2018)*	USA	Observational cohort	*T*-scores	Normative	Demographically corrected (age, sex, education, race)	Yes	Regression	Yes

Note. *Included in meta-analysis. [a]Raw data used in meta-analysis; [b]Normative data used was different for each test and were stratified for different variables (gender, age and education); [c]Did not adjust for differences in HIV disease characteristics. NP = neuropsychological; NR = data not reported; NA = not applicable; SES = socioeconomic status.

Results from our Downs and Black checklist assessment indicated that most studies in the sample had fair methodological quality (see Table 5).

Table 5

Methodological Quality of Studies Included in the Sample: Results of Downs and Black checklist assessment (10 studies)

Item	Behrman-Lay et al. (2016)*	Burlacu et al. (2018)	Dolan et al. (2003)*	Failde Garrido et al. (2013)	Hestad et al. (2012)	Kabuba et al. (2016)*	Maki et al. (2018)*	Robertson et al. (2004)	Royal et al. (2016)*	Sibanda-Kunda et al. (2015)	Sundermann et al. (2018)*
1. Reporting	1	1	1	1	1	1	1	1	0	1	1
2. Main outcomes	1	1	1	0	1	1	1	1	1	1	1
3. Patient characteristics	1	1	1	1	1	1	1	1	1	0	1
5. Principal confounders	1	1	1	1	1	1	1	0	1	0	1
6. Main findings	1	1	1	1	1	1	1	1	1	1	1
7. Random variability	1	0	1	1	1	1	1	1	1	0	1
10. Actual probability values	1	1	1	1	1	1	1	0	1	1	1
11. Representative sample (recruitment)	1	1	0	1	1	1	1	0	0	1	0
12. Representative sample (participation)	0	0	0	0	0	0	0	0	0	0	0
13. Representative setting	1	0	0	1	1	1	1	0	1	1	0
16. Data dredging	1	1	1	1	1	1	1	1	1	1	1
18. Appropriate statistics	1	1	1	1	1	1	1	1	0	1	1
20. Accurate outcome measures	1	1	1	1	1	1	1	1	1	1	1
21. Internal validity	1	1	0	1	1	1	0	1	1	1	1
22. Different groups	0	1	0	1	1	1	0	1	1	0	1
25. Confounding adjustment	1	1	1	1	1	1	1	1	0	0	1
TOTAL	14	13	11	14	15	15	13	11	11	10	13

Note. Because this checklist was designed for use in evaluating both randomised controlled trials (RCTs) and non-RCT studies, not all items were applicable to the studies included in this review. We excluded items 4, 8, 9, 14, 15, 19, 23, 24, 26, and 27 from our assessment. 1= yes, the study has met the criterion; 0 = no, the study has not met the criterion or unable to determine whether the study has met the criterion. *Study included in the meta-analysis.

Systematic Review

Five of the 11 studies in our sample reported no significant differences between WWH and MWH on measures of cognitive performance (Behrman-Lay et al., 2016; Faílde Garrido et al., 2013; Robertson et al., 2004; Sibanda-Kunda et al., 2015; Sundermann et al., 2018). The other six reported that WWH performed significantly more poorly (Burlacu et al., 2018; Dolan et al., 2003; Hestad et al., 2012; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016).

Importantly, results for 9 of the 11 studies were based on adjusted statistical methods that controlled for relevant clinical and demographic between-group differences where they existed. This adjustment sometimes made a substantial difference to the ultimate appraisal of between-group differences. For example, after Sundermann et al. (2018) adjusted for a significant difference in reading level between WWH and MWH, their analyses no longer detected significant sex differences in cognitive impairment. One of the studies that found no sex differences did not provide descriptive statistics for their sample and did not report whether the abovementioned adjusted statistical methods were used (Sibanda-Kunda et al., 2015).

Meta-analysis

We conducted 11 separate between-group comparisons: one each for the cognitive domains of psychomotor coordination, processing speed, attention and working memory, visuospatial learning, visuospatial memory, audioverbal learning, audioverbal memory, executive function (verbal fluency, inhibition, switching), and one for global cognitive functioning (see Table 6). For each cognitive domain depending on the proportion of WWH to MWH, the sample sizes of each group had 80% power to detect between-group differences, even if effect sizes were small (according to power calculations shown in Rubin et al., 2019). Values entered into the meta-analytic calculations were either raw scores (Behrman-Lay et al., 2016; Maki et al., 2018) or demographically-adjusted *T*- or *z*-scores. Regarding these adjusted scores, Kabuba et al. (2016) demographically adjusted for age, education, gender, and urban/rural background; Sundermann et al. (2018) adjusted for age, education, gender, and race; Royal et al. (2016) adjusted for age, education, gender; and Dolan et al. (2003) standardized raw scores to *z*-scores and used different normative data stratified according to age, education, or gender, depending on which variables were significantly associated with test performance.

Table 6

Meta-Analysis: Main results (k = 6)

Cognitive Domain	Studies	Total Participants	Women	Men	ESE [95% CI]	*p*
Psychomotor Coordination	6	2852	985	1867	-0.16 [-0.31, -0.00]	.04*
Processing Speed	6	2852	985	1867	-0.06 [-0.23, 0.11]	.48
Attention and Working Memory	4	1913	499	1414	-0.05 [-0.31, 0.20]	.69
Visuospatial Learning	3	1776	455	1321	-0.43 [-0.71, -0.15]	.002**
Audioverbal Learning	5	1994	556	1438	-0.24 [-0.53, 0.05]	.10
Visuospatial Memory	3	1776	455	1321	-0.30 [-0.58, -0.02]	.04*
Audioverbal Memory	5	1994	556	1438	-0.20 [-0.44, 0.05]	.12
Executive Functioning- Verbal Fluency	5	1994	556	1438	-0.04 [-0.19, 0.11]	.60
Executive Functioning- Inhibition	4	2634	884	1750	0.04 [-0.17, 0.25]	.72
Executive Functioning- Switching	6	2852	985	1867	-0.03 [-0.17, 0.10]	.63
Global Cognitive Functioning	4	1857	512	1345	-0.14 [-0.30, 0.01]	.06

Note. ESE = effect size estimate; CI = confidence interval. Psychomotor Coordination measured using the Grooved Pegboard Test (dominant hand), except for Behrman-Lay et al. (2016) which used Grooved Pegboard Test (non-dominant hand). Processing Speed measured using Trail Making Part A (TMT A). Attention and Working Memory measured using Paced Auditory Serial Addition Test Total Correct (PASAT), except for Behrman-Lay et al. (2016) which used Letter-Number Sequencing. Audioverbal learning and audioverbal memory measured using Hopkins Verbal Learning Test-Revised (HVLT-R), except for Dolan et al. (2003) which used California Verbal Learning Test (CVLT). Visuospatial Learning and Memory measured using Brief Visuospatial Learning Test-Revised (BVMT-R). Executive Functioning- Verbal Fluency measured using Controlled Oral Word Association Test (COWAT-FAS). Executive Functioning- Inhibition measured using Stroop Color-Word Test (SCWT) Inhibition Trial. Executive Functioning- Switching measured using Trail Making Part A (TMT A) except for Royal et al. (2016) and Kabuba et al. (2016) which used Colour Trails 2.

*$p < .05$. **$p < .01$. ***$p < .001$

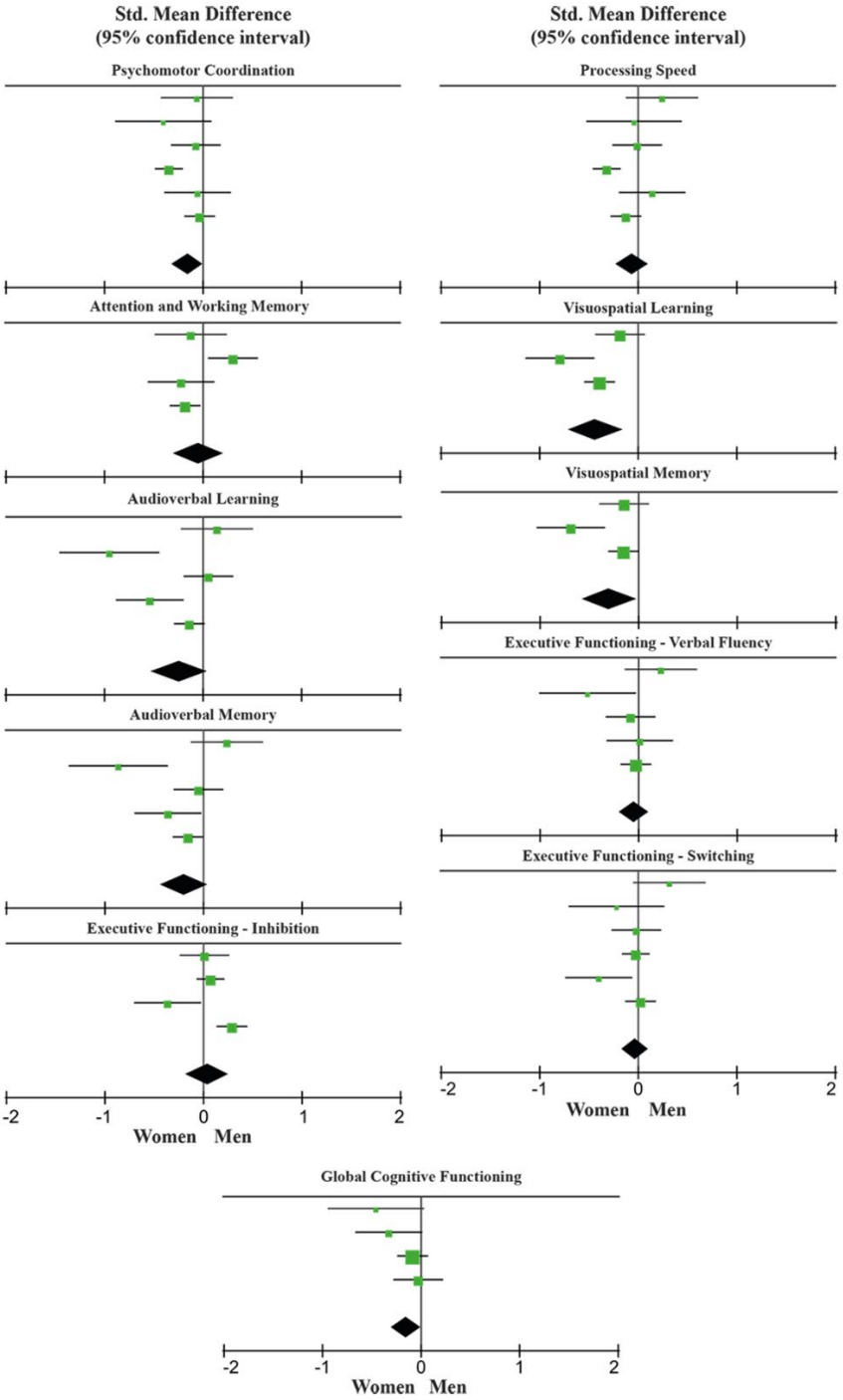
Our analyses detected statistically significant between-group differences for three of the ten discrete cognitive domains (psychomotor coordination, visuospatial learning and visuospatial memory). In each of those cases, the average performance of WWH was worse than that of MWH, even though the magnitude of effect sizes was small (see Figure 2 for forest plots).

For performance on the other seven domains (processing speed, attention and working memory, audioverbal learning, audioverbal memory, executive function [verbal fluency, inhibition, switching]), the analyses detected no statistically significant sex differences.

Our analyses detected no statistically significant between-group differences with regard to global cognitive functioning, although this outcome approached significance, $p = .06$.

Figure 2

Meta-analysis: Forest plots comparing HIV-infected male and female performance across 10 different cognitive domains (6 studies)



Heterogeneity assessment. The pertinent indicators (Q tests and I2 values) suggested there was significant between-study heterogeneity for all discrete cognitive domains except executive functioning. There was not significant heterogeneity between studies included in global score calculations (see Table 7).

Table 7

Meta-Analysis: Results of heterogeneity tests (k = 6)

Cognitive domain	All studies			Without Royal et al. (2016)			Without Dolan et al. (2003)			Without differing tests		
	χ^2 (*df*)	*p*	I^2(%)	χ^2 (*df*)	*p*	I^2(%)	χ^2 (*df*)	*p*	I^2(%)	χ^2 (*df*)	*p*	I^2(%)
Psychomotor Coordination	15.18 (5)	.01	67	12.02 (4)	.02	67	14.99 (4)	.005	73	NA	NA	NA
Processing Speed	12.06 (5)	.03	59	11.49 (4)	.02	65	11.19 (4)	.02	64	11.64 (4)	.02	66
Attention and Working Memory	11.88 (3)	.008	75	11.05 (2)	.004	82	NA	NA	NA	11.81 (2)	.003	83
Visuospatial Learning	8.05 (2)	.02	75	2.01 (1)	.16	50	NA	NA	NA	NA	NA	NA
Audioverbal Learning	20.26 (4)	<.001	80	14.63 (3)	.002	79	10.05 (3)	.02	70	10.05 (3)	.02	70
Visuospatial Memory	8.39 (2)	.02	76	0 (1)	.97	0	NA	NA	NA	NA	NA	NA
Audioverbal Memory	14.57 (4)	.006	73	12.94 (3)	.005	77	6.32 (3)	.10	53	6.32 (3)	.10	53
Executive Functioning- Fluency	6.08 (4)	.19	34	5.99 (3)	.11	50	2.05 (3)	.56	0	NA	NA	NA
Executive Functioning- Inhibition	14.29 (3)	.003	79	5.91 (2)	.05	66	NA	NA	NA	NA	NA	NA
Executive Functioning- Switching	9.35 (5)	.10	47	4 (4)	.41	0	8.65 (4)	.07	54	3.95 (3)	.27	24
Global Cognitive Functioning	4.11 (3)	.25	27	2.47 (2)	.29	19	2.16 (2)	.34	7	NA	NA	NA

Note. NA = not applicable because the study was not included in the domain or all studies used the same test to measure that domain.

For psychomotor domain, Behrman-Lay et al. (2016) used the Grooved Pegboard Test (non-dominant hand), whereas the other studies used the Grooved Pegboard Test (dominant hand). For Attention and Working Memory, Behrman-Lay et al. (2016) used Letter-Number Sequencing, whereas other studies used Paced Auditory Serial Addition Test Total Correct (PASAT). For audioverbal Learning and Memory, Dolan et al. (2003) used the CVLT whereas the other studies used the HVLT-R. For Executive Functioning- Switching, Royal et al. (2016) and Kabuba et al. (2016) used Colour Trails 2, whereas the other studies used Trail Making Part A (TMT A).

*$p < .05$. **$p < .01$. ***$p < .001$

One possible reason for the large amount of heterogeneity within the domains is that where possible we used the same test to represent that domain (i.e., the test most commonly used by the included studies) but since it was not available for all the studies, it is possible that when the test differed to one used by the rest of the studies, it would increase the heterogeneity of that domain. Therefore, to investigate whether this reason was contributing to the heterogeneity, we removed the studies with differing tests from the meta-analytic calculations for each domain. There was only one domain (audioverbal memory) where removal of the study that used a different test (Dolan et al. [2003] used the CVLT whereas the other studies used the HVLT-R) attenuated heterogeneity.

Another possible reason for the large amount of within-domain heterogeneity is differences across study samples. For instance, Royal et al.'s (2016) sample was all ART-naïve and the inclusion criteria of another study included low weight and weight loss because its aim was to investigate cognition in under-weight PWH (Dolan et al., 2003). We felt it was important to consider whether these studies were increasing the observed heterogeneity and therefore we removed each separately from the meta-analytic calculations for each domain. Their removal did not alter the level of heterogeneity significantly for any of the cognitive domains, with two exceptions: Without Royal et al. (2016) heterogeneity within the domains of visuospatial learning and visuospatial memory was markedly attenuated, and without Dolan et al. (2003) heterogeneity within the domain of audioverbal memory was attenuated.

Of note is that removal of each of these studies changed the meta-analytic results slightly in the domain of psychomotor coordination. Sex differences in this domain became not statistically significant ($p = .05$ without Royal et al. [2016], $p = .10$ without Dolan et al. [2003], and $p = .05$ without Behrman-Lay et al. [2016]). One explanation for these changes is that removal of studies reduces the power of the analyses to detect significant differences.

However, removal of Royal et al. (2016) did not change the meta-analytic results in the domains of visuospatial learning and visuospatial memory: Sex differences in these domains were still significant, $p = .002$ and .02 respectively. Note that we did not have to investigate the effects of removing any other studies because all studies included in the meta-analysis for the domains of visuospatial learning and visuospatial memory used the BVMT-R and Dolan et al. (2003) did not include any measures for this domain in their study.

Between-group differences for all other domains and for global cognitive functioning remained non-significant when these studies were removed, all ps > .10.

Discussion

The purpose of this systematic review and meta-analysis was to examine the literature regarding differences in cognitive functioning between WWH and MWH.

Systematic Review

Of the 11 studies included in the systematic review, six found that WWH performed more poorly on standardized cognitive tests than MWH (Burlacu et al., 2018; Dolan et al., 2003; Hestad et al., 2012; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016). The other five (Behrman-Lay et al., 2016; Faílde Garrido et al., 2013; Robertson et al., 2004; Sibanda-Kunda et al., 2015; Sundermann et al., 2018) found no sex differences in cognitive performance (i.e., none of the studies found more cognitive impairment in MWH than WWH).

Before moving on to discussing our results, two pertinent points regarding the Sibanda-Kunda et al. (2015) study must be noted. First, the authors do not report any descriptive data for their sample, and it is therefore unknown whether there were pre-existing differences between women and men in that study. Second, both they and Royal et al. (2016) did not adjust analyses for relevant clinical and demographic between-group differences where they existed, and hence their results should be interpreted with caution.

When interpreting the results of the systematic review, it is important to consider the proportion of WWH and MWH and the respective samples sizes of each group within the individual studies. Studies that report no sex differences in cognitive performance among HIV-infected samples tend to include a greater proportion of MWH than WWH (Everall et al., 2009; Kinai et al., 2017). Often these samples have less power to show the potential disparity in cognitive sequelae between the sexes. Rubin et al. (2019) ran a series of power analyses to determine the sample sizes required in each group to detect a small effect size at different proportions of WWH to MWH. For example, when the proportion of WWH and MWH is 40/60, samples of 480 MWH and 320 WWH are required to detect a small effect size in *T*-scores with 80% power. As the proportion of MWH and WWH in the sample diverge, larger sample sizes are needed to obtain similar levels of power.

Of the 11 studies included in this systematic review, only two (Maki et al., 2018; Sundermann et al., 2018) included large enough groups of WWH and MWH to generate at least 80% power to detect a small between-group effect size, if one follows the rubric provided by Rubin et al. (2019). Although adjusting for relevant covariates attenuated the sex differences originally found by Sundermann et al. (2018), Maki et al. (2018) continued to

find greater cognitive impairment in WWH than in MWH even after such adjustment. Moreover, some studies that were underpowered according to Rubin et al. (2019) did find sex differences (Burlacu et al., 2018; Dolan et al., 2003; Hestad et al., 2012; Kabuba et al., 2016; Royal et al., 2016). Therefore, inadequate power and the proportion of WWH and MWH do not offer a complete explanation for why some studies in this literature do not find sex differences while others do.

In comparing the characteristics of the six studies that found sex differences in cognitive performance to the five that did not, we identified at least three factors that might explain the sex differences.

First, among the studies that found sex differences in cognitive performance, the difference between average years of education between MWH and WWH was greater than that among the studies that found no such differences (0.72 versus 0.27, with men having completed more years of education in each case). Furthermore, among studies that found sex differences, the average years of education for WWH (11.42) was lower than that for WWH in studies that found no sex differences (11.80) and for MWH in both groups of studies (12.14 for those that found differences, 12.07 for those that did not). This observation is consistent with the fact that individuals with more exposure to formal educational experiences tend to perform better on standardized cognitive tests (Lenehan et al., 2015; Strauss et al., 2006). Of note here is that almost every study in our review sample used demographically adjusted norms to create *T*- or *z*-scores and also controlled for between-sex differences in level of education. However, controlling for years of education does not account for variation in quality of education and in other aspects of cognitive reserve for which years of education is often a proxy.

Second, among studies that found sex differences in cognitive performance and that reported Beck Depression Inventory-II scores (Behrman-Lay et al., 2016; Dolan et al., 2003; Hestad et al., 2012; Royal et al., 2016), the difference between MWH and WWH average BDI-II scores was greater than that among the studies that found no such sex differences (2.6 versus 2.1, with women reporting greater presence and severity of depressive symptoms in each case). Furthermore, the average BDI-II score for WWH (13.2) was higher in studies that found sex differences than it was for (a) WWH in studies that found no sex differences (11.6), and (b) MWH in both groups of studies (10.6 for those that found differences, and 9.5 for those that did not). Because the presence and severity of depression is associated with impaired cognitive performance (Rubin & Maki, 2019), these between-study differences in psychiatric profile might explain why one group of studies found sex differences while the

other did not. Of note here is that although some studies included in this systematic review did adjust for depression to control for the impact on cognitive performance (Maki et al., 2018; Sundermann et al., 2018), the other included studies did not.

Third, four of the six studies that found no sex differences in cognitive performance were conducted in high-income countries (the United States and Spain), whereas three of the six studies that found sex differences were conducted in low-income countries (Zambia and Nigeria). It is possible that sex differences in cognitive impairment are greater in the latter settings, where women have less access to healthcare and education and an overall lower socioeconomic status (World Economic Forum, 2020).

Meta-Analysis

Our meta-analysis of six studies (Behrman-Lay et al., 2016; Dolan et al., 2003; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016; Sundermann et al., 2018) detected no significant sex differences in performance on tests of processing speed, attention and working memory, audioverbal learning, audioverbal memory, executive function (verbal fluency, inhibition, switching), and on the global cognitive functioning score. The analysis did, however, suggest that significant sex differences, associated with small effect sizes, were present in three discrete cognitive domains: psychomotor coordination, visuospatial learning and visuospatial memory. In these cases, WWH performed more poorly than MWH. These results are consistent with the conclusions of Rubin et al.'s (2019) systematic review, which reported evidence for greater impairment in the domains of motor speed and dexterity and learning and memory (they did not differentiate between audioverbal and visuospatial learning and memory). Unlike them, however, we did not find a significant difference in the domain of information processing speed. Considering that their conclusions were based on only two out of seven studies that found greater impairment in information processing speed, it is likely that this difference was lost in our meta-analytic calculations.

Psychomotor Coordination

Five of the six studies included in the meta-analytic calculations for this domain (Dolan et al., 2003; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016; Sundermann et al., 2018) reported pre-existing sociodemographic and/or psychiatric differences between their WWH and MWH samples. The sociodemographic differences appeared to place WWH at a cognitive disadvantage relative to MWH: Dolan et al. (2003), Kabuba et al. (2016) and Sundermann et al. (2018) found that their samples of WWH had significantly fewer years of education. Data from the Women's Interagency HIV Study (WIHS) suggest that lower levels

of education interact with HIV status to produce stronger negative effects of the infection on psychomotor coordination (Maki et al., 2015).

The pre-existing psychiatric differences also appeared to place WWH at a cognitive disadvantage relative to MWH. The Dolan et al. (2003) sample of WWH had more severe depressive symptoms compared to their MWH, and a greater proportion of WWH in the Sundermann et al. (2018) sample were depressed (neither of these comparisons reached statistical significance, however, $p = .07$ and .09 respectively). Similarly, the sample of WWH described by Behrman-Lay et al. (2016) had significantly higher BDI-II scores than men and women without HIV. Only in the Maki et al. (2018) sample were a greater proportion of MWH and men without HIV depressed. Depression has been shown to impair psychomotor coordination in PWH (Rubin & Maki, 2019).

In contrast to pre-existing differences in demographic and psychiatric characteristics, the sex differences in HIV-associated clinical variables in this group of studies appeared, by and large, to place WWH at a cognitive advantage. For instance, Kabuba et al. (2016), Maki et al. (2018), and Royal et al. (2016) reported that their WWH had higher current CD4 counts than their MWH. The former also reported that their WWH had less detectable plasma virus and were less likely to have AIDS and TB, while the latter reported that they were more likely to be on HAART. On the face of it, reconciliation between WWH being medically healthier but cognitively more impaired than MWH appears difficult. There are at least two potential ways to explain this conundrum. One possibility is that, regardless of the individual's disease characteristics or relative medical health, HIV infection magnifies the cognitive effects that arise from pre-existing differences (as described above) in demographic and psychiatric characteristics (Burlacu et al., 2018). Another possibility is that the cognitive functioning of WWH is more likely than that of MWH to vary with clinical outcomes. This speculation is supported by data from within the current sample of studies suggesting that, in WWH but not in MWH, poorer HIV-associated clinical outcomes (e.g., lower current CD4 counts, longer duration with low current CD4 count) are associated with greater impairment in psychomotor coordination (Burlacu et al., 2018; Dolan et al., 2003).

Visuospatial Learning and Memory

All three studies included in the meta-analytic calculations for these domains (Kabuba et al., 2016; Royal et al., 2016; Sundermann et al., 2018) reported pre-existing between-group differences. As noted above, Kabuba et al. (2016) and Sundermann et al. (2018) featured samples within which WWH had significantly fewer years of education than MWH, and Kabuba et al. (2016) and Royal et al. (2016) reported that their sample of WWH had better

HIV-disease outcomes (i.e., current CD4 count) than their sample of MWH. A question worth consideration, then, is what (if any) impact these demographic and clinical differences might have on the observed sex differences in performance on tests of visuospatial learning and memory.

Education significantly affects BVMT-R performance of healthy adults (De Wit et al., 2017) and lower levels of education are associated with poorer learning and memory performance in PWH even after scores are normed based on education (see, e.g., Kabuba et al., 2018; Wright et al., 2015; Yakasai et al., 2015). It is therefore possible that the observed sex differences in this domain are at least partially accounted for by between-group educational differences. A possible explanation for this is that lower levels of education are often, even in healthy individuals, associated with lower levels of cognitive reserve (Roldán-Tapia et al., 2017). Individuals with less cognitive reserve will likely show less resilience to the damaging effects of HIV (Kaur et al., 2020; Lenehan et al., 2015; Strauss et al., 2006).

Limitations

Two major limitations should be borne in mind when reflecting on the results of this study. First, our sample sizes (11 studies in the systematic review [N = 3333, WWH = 1220] and 6 in the meta-analysis [N = 2852, WWH = 985]) were quite small. Although many studies in the HIV neuropsychology literature include both men and women in their samples, few report sex-based data separately or directly compare male versus female test scores. The small sample sizes limit the generalizability of our results.

Second, there was significant between-study heterogeneity in terms of both method and samples. Regarding method, scores used in meta-analysis were either demographically adjusted using different methods or kept as raw scores. We were unable to adjust for these in the analyses. Regarding sample heterogeneity, there were preexisting demographic and clinical differences between WWH and MWH in five of the six studies included in the meta-analysis. Unfortunately, because of the small sample size we were unable to conduct subgroup analyses to investigate potential moderators. Likewise, meta-regression elucidating which variables might contribute to added WWH vulnerability was not possible because the standard recommendation is that such an analysis should only be considered when at least 10 studies comprise the sample of a meta-analysis (Higgins et al., 2019).

Conclusions

Our review suggests that, currently, there is not an unequivocal answer to whether there are significant sex differences in cognitive functioning in PWH. The sex difference in global cognitive functioning approached significance. It is possible that this difference may

have been significant if the sample size was larger. For most (but not all) cognitive domains, there are no such differences. Where there are significant differences (e.g., in the domains of psychomotor coordination, visuospatial learning, and visuospatial memory), the effects are relatively small and may be explained (at least partially) by sex-based variation in sociodemographic and psychiatric characteristics. Moreover, the effects on cognitive performance of these characteristics appears to outweigh that of HIV-related clinical variables (e.g., CD4 count, viral load, detectable plasma virus). Future studies, with large sample sizes, that include between group comparisons of WWH and MWH, that are well-matched for duration of viral suppression, as well as duration of HIV disease, are important to support these findings.

Overall, these findings suggest that there are no biologically based differences in cognitive performance between WWH and MWH. Sex differences reported in the literature are likely driven by demographic, socioeconomic, lifestyle, and educational factors. These factors are particularly relevant to PWH populations because, generally, in high-income countries (such as the United States, where most of the reviewed studies were conducted) there are sociodemographic differences between the MWH and WWH populations. For instance, a higher proportion of MWH are White and from higher socioeconomic status backgrounds, whereas a higher proportion of WWH are African-American or Black immigrants from high HIV-prevalence regions such as sub-Saharan Africa and from lower socioeconomic status backgrounds (European Centre for Disease Prevention and Control, 2018; UNAIDS, 2020). Such between-group sociodemographic differences might contribute to sex differences in cognitive performance, and hence it is worth considering that most studies in this literature may be reporting sex differences that arise from non-biological causes. Likewise, in most LMICs HIV prevalence is highest in women and in communities with higher levels of poverty, poorer education, and less access to socioeconomic opportunities and hence it is worth considering the contribution of these factors to the observed deficits in cognitive test performance of WWH in these populations (Farinpour et al., 2003; Maki et al., 2015; UNAIDS, 2020; Watson et al., 2019).

In closing, we acknowledge that these results are derived from analyses of a small sample of studies, most of which were conducted in high-income northern hemisphere countries. Furthermore, most studies in this field do not measure several other variables (e.g., poverty, food insecurity, socioeconomic opportunities, childhood trauma) that could contribute to differential vulnerability of WWH to cognitive impairment (Farinpour et al., 2003; Gao et al., 2009; Koyanagi et al., 2019; Spies et al., 2016; Watson et al., 2019). Hence,

we could not review or provide summary quantification of the impact of those variables. We recommend that future research measure those variables, report male and female data separately, and analyse the independent and interacting contributions of medical, psychosocial, and psychiatric factors to sex differences in the cognitive performance of PWH. In addition, classification of cognitive performance into separate domains will provide more detail regarding cognitive functioning in PWH and may be more sensitive to sex differences than global scores (Phillips et al., 2018). Careful application based on such analyses will assist in planning cognitive testing strategies, benefit the clinical interpretation of cognitive performance, and aid in setting treatment priorities.

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Chapter 3

Sex Differences in the Cognitive Performance of a South African Cohort of People with HIV and Comorbid Major Depressive Disorder

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Description of the contribution of candidate and co-authors

AJD was the first author of this manuscript. This entailed leading the drafting, analyses and conceptualising. These data were collected as part of a larger research program for a randomised controlled trial of a cognitive-behavioral treatment for ART adherence and depression (CBT-AD), which involved JAJ, SAS, CO and JL. AJD developed and implemented the study protocol for the neuropsychological supplement project, with guidance from JAJ, LSA and KGFT. This involved writing the protocol, obtaining ethical approval, and ensuring ethical standards and procedures were followed, including protocol modifications, deviations and annual progress reports. AJD managed the daily running of the supplement project, including the finances, the care of the participants, overseeing the data collection and quality checking the data.

In this manuscript, AJD formulated the research questions, cleaned, analysed and interpreted the data, and wrote the manuscript. JAJ, SN and KGFT contributed to the manuscript by providing guidance, discussing ideas and reviewing drafts and JL provided input into data management and analyses. All co-authors provided input, reviewed drafts and approved the final manuscript.

Current status Submitted to Journal of the International Association of Providers of AIDS Care for publication

Abstract

Although some previous research suggests that women with HIV (WWH) may be more vulnerable to cognitive impairment than men with HIV (MWH), this finding is not replicated consistently across studies. If this sex difference is present, it may be explained by the direct effects of HIV or by sociodemographic and psychiatric characteristics, such as level of education and depression severity. We sampled from a population of people with HIV (PWH) with specific clinical and sociodemographic characteristics (viz., incomplete ART adherence, comorbid major depressive disorder, socioeconomically disadvantaged background) that allowed us to explore both biological and psychosocial effects on cognitive performance. Neuropsychological testing and measures gathering sociodemographic, medical, and psychiatric information were completed by 105 PWH (76 women). We compared WWH and MWH cognitive performance using unadjusted and adjusted regressions. Then, within each of the WWH and MWH groups separately, we explored the associations of cognitive performance with HIV disease factors, other medical and psychiatric variables, and sociodemographic characteristics. Results showed no significant between-sex differences in cognitive performance, both globally and within domains. Fewer years of education (β = 0.94), illiteracy (β = 4.55), and greater food insecurity (β = -0.28) were independently associated with lower cognitive performance in WWH but not MWH. Education and food insecurity remained predictors in multivariable modelling for WWH. We conclude that sex differences in PWH are likely due to sample characteristics that may represent broader inequalities, rather than true biological differences. Findings suggest that food security, education, and literacy may be protective against cognitive impairment for WWH managing depression, and that food insecurity interventions in the context of supporting HIV treatment may be beneficial.

Keywords: cognition, depression, food insecurity, HIV, sex differences

Introduction

Although some studies suggest that women with HIV (WWH) may be more vulnerable to cognitive impairment than men with HIV (MWH; Burlacu et al., 2018; Dolan et al., 2003; Fogel et al., 2017; Gascón et al., 2018; Hestad et al., 2012; Holguin et al., 2011; Kabuba et al., 2016; Maki et al., 2018; Qiao et al., 2019; Royal et al., 2016), this finding is not replicated consistently across studies (Behrman-Lay et al., 2016; Faílde Garrido et al., 2013; Faílde Garrido et al., 2008; Joska et al., 2010; Robertson et al., 2004; Sibanda-Kunda et al., 2015). A recent systematic review of 11 studies summarising this literature suggested that WWH perform more poorly in the cognitive domains of motor skills, information processing speed, audioverbal learning and memory, and executive functioning (Rubin et al., 2019a). Within each of these domains, fewer than 50% of the studies that measured performance in that particular domain found WWH performed more poorly. The rest found no sex differences in performance. Six studies included in the review measured global cognitive performance; none of those six, found WWH performed more poorly than MWH after analyses were adjusted for disease and demographic characteristics.

A more recent meta-analysis of six studies in this literature (Dreyer et al., 2022a) found small performance differences between WWH and MWH in three specific cognitive domains. WWH tended to perform significantly more poorly than MWH on tests measuring motor skills, visuospatial learning, and visuospatial memory, although effect sizes were small (d = -0.16, -0.43, and -0.30, respectively). The meta-analysis detected no sex differences in global cognitive performance and in performance in other cognitive domains (e.g., information processing speed, attention and working memory, audioverbal learning, audioverbal memory, and executive functioning [verbal fluency, inhibition, and switching]).

HIV-disease factors may contribute to the manifestation of sex differences in cognitive performance. People with HIV (PWH) who have sub-optimal antiretroviral therapy (ART) adherence and who therefore may not have well-controlled HIV-disease factors (e.g., viral load, CD4 count) are at greater risk for developing HIV-associated cognitive impairment (Ettenhofer et al., 2010; Winston & Spudich, 2020). Some studies have found that WWH have less optimal ART adherence than MWH (Andrade et al., 2013; Puskas et al., 2011). Of particular interest here is that a few studies also report that WWH may have higher levels of systemic immune activation and inflammation in response to HIV infection, which may contribute to higher rates of cognitive impairment (Fitch et al., 2013; Raghavan et al., 2017; Royal et al., 2016; Ziegler & Altfeld, 2017).

Significant sex differences in cognitive performance may also be explained (at least partially) by sex-based variation in sociodemographic and psychiatric characteristics, such as level of educational attainment and presence/severity of depressive symptomatology (Donne et al., 2022). For instance, Sundermann et al (2018) found that statistically significant sex differences in global cognitive performance no longer existed after analyses were adjusted for lower reading levels in WWH. Women are also known to have higher rates of depression than men (Freeman et al., 2008; Platt, 2020; Rubin et al., 2019b; Seedat et al., 2009), which could contribute to impaired cognitive performance (Fellows et al., 2013; Rock et al., 2014).

Hence, the inconsistent appearance of sex differences in HIV neuropsychology studies might be explained by variability in the magnitude of between-sex sociodemographic and psychiatric differences across studies. In other words, if a study finds differences in cognitive performance between WWH and MWH, those differences might arise from study-specific sampling issues or might represent broader structural and psychosocial inequalities between sexes in the populations from which they are drawn. In contrast, a study finding no such performance differences might have sampled from a population where there are less marked sex-based structural and psychosocial inequalities. For instance, in samples drawn from populations where women have less overall access to education, restricted access to high-quality education, or a higher likelihood of greater depression severity, WWH will likely perform more poorly on cognitive testing (Bragança & Palha, 2011; Lenehan et al., 2015; Paolillo et al., 2020; Rubin & Maki, 2019; Strauss et al., 2006). It is important to note, that of all 17 studies on sex differences in cognitive performance reviewed in this manuscript, only two (i.e., Gascón et al., 2018; Behrman-Lay et al., 2016) excluded for depression as a comorbidity.

In low-and middle-income countries (LMICs), women often experience a disproportionate burden of poverty, greater levels of stress and trauma, and greater food insecurity (World Economic Forum, 2022; United Nations Children's Fund, 2021; Maki & Martin-Thormeyer, 2009; Maki et al., 2015; Misselhorn & Hendriks, 2017; UNICEF, 2022). All of these are associated with lower performance on cognitive tests generally (Duval et al., 2017; Koyanagi et al., 2019; Spies et al., 2016; Watson et al., 2019), and with lower performance in PWH specifically (Hobkirk et al., 2017; Tamargo et al., 2021). Furthermore, in most LMICs HIV prevalence is highest in women and in communities with higher levels of poverty, poorer education, and less access to socioeconomic opportunities. Hence, it is worth considering the contribution of these factors to lower cognitive test performance of WWH in these populations (UNAIDS, 2021).

Despite this growing circumstantial evidence that sex differences in the cognitive performance of PWH might be driven by sociodemographic (including psychosocial) and psychiatric factors, these variables are not routinely measured in HIV neuropsychology research studies.

South Africa has the highest number of PWH in the world, two-thirds of whom are women (Takuva et al., 2017; UNAIDS, 2021). Therefore, the question of whether WWH are more vulnerable to cognitive impairment than MWH, and which factors might contribute to this differential vulnerability, is of particular importance in this setting. Consequently, the aim of the current study was to compare global and domain cognitive performance in a well-defined and clinically important population of South African WWH and MWH, with a particular focus on the performance contributions of HIV-disease variables related to incomplete ART adherence (e.g., greater viral load, lower current and nadir CD4 count), depression severity, and psychosocial factors (e.g., quality of life and food security). To that end, we sampled from a population of PWH with incomplete ART adherence, current major depressive disorder (MDD), and a socioeconomically disadvantaged background – due to the factors outlined in the review above, sex differences are more likely to manifest in a group with these characteristics than in the general population of PWH. In other words, if sex differences in cognitive performance exist in South African PWH, then we would be more likely to find them in this sample and we could explore both biological and psychosocial effects driving the differences. Research on such clinically important samples is vital: It helps inform public health interventions that focus on the increased risk for HIV-related morbidity and potential for onward transmission of the virus in this group.

Based on extant findings in the HIV neuropsychology literature, we tested these specific hypotheses: (1) WWH will perform more poorly than MWH in the domains of motor skills and visuospatial learning and memory; (2) sociodemographic (e.g., level of education and literacy), psychosocial (e.g., quality of life and food security), and psychiatric (e.g., depression severity) factors will be associated with cognitive performance in both WWH and MWH.

Method

Setting and Participants

Data were collected, as part of a larger research program, from two primary care clinics in Khayelitsha, a peri-urban community in Cape Town, South Africa (Dreyer et al.,

2022b; Joska et al., 2020; Safren et al., 2021). Khayelitsha was established under the principle of racial segregation executed by the apartheid regime. As a consequence of this legacy, today almost all of its residents are Black African and it is one of the poorest areas of Cape Town. Most adult residents of Khayelitsha speak isiXhosa as a first language. Fewer than one-third of those residents have completed high school, and there are high levels of HIV infection, crime, and unemployment (Crush et al., 2012; Nleya & Thompson, 2009; Smit et al., 2016; Stern et al., 2017; City of Cape Town, 2013).

Participants were 105 PWH. Inclusion criteria were (a) age ≥ 18 years; (b) HIV-seropositive status (confirmed via medical record); (c) current diagnosis of MDD as measured on the Mini International Neuropsychiatric Interview, Version 7.0 (MINI) (Sheehan, 2014); and (d) having failed first-line ART (i.e., being identified by the community clinic as not having collected their medication regimen for > 3 months).

Because we wanted the sample to be representative of the clinical population of interest (i.e., PWH with MDD and incomplete ART adherence), we did not exclude participants with medical and psychiatric comorbidities (other than those noted below) and/or other factors that could influence cognitive performance. The only exclusion criteria were (a) active and untreated serious mental illness (e.g., psychosis or mania) that would interfere with study participation, (b) inability or unwillingness to provide informed consent, and (c) lack of sufficient fluency in English or isiXhosa. Participants using antidepressants were eligible if they met criteria for a current depressive episode; however, they had to have been on a stable antidepressant regimen and dose for at least 2 months.

All participants provided written informed consent. The study protocol was approved by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee and the University of Miami Institutional Review Board.

Materials

Cognitive assessment

The neuropsychological battery comprised 12 standardized tests, each of which assessed performance in one of seven cognitive domains commonly affected by HIV (Grant, 2008). This battery of tests has been used extensively in studies of South African PWH (Gouse et al., 2022; Joska et al., 2011).

The domains, tests, and outcome variables were: (1) *executive functioning*, as measured by the Color Trails Test 2 (CTT2) – completion time; Wisconsin Card Sorting Test (WCST) – perseverative errors; (2) *verbal learning and memory*, Hopkins Verbal Learning Test-Revised (HVLT-R) – total across the three immediate recall trials, total on the delayed

recall trial; (3) *visuospatial learning and memory,* Brief Visuospatial Memory Test-Revised (BVMT-R) – total across the immediate recall trials, total on the delayed recall trial; (4) *verbal fluency*, category fluency test – total number of animals / total number of fruits and vegetables named in 1 minute; (5) *attention/working memory*, Wechsler Memory Scale-Third Edition (WMS-III) Spatial Span subtest – total raw score; Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span subtest – total raw score; (6) *processing speed*, CTT1 – completion time; WAIS-III Digit Symbol Coding subtest – total raw score; WAIS-III Symbol Search – total raw score; (7) *motor skills*, Grooved Pegboard Test (GPT) dominant (DH) and nondominant hand (NDH) – completion time; Finger Tapping Test DH and NDH – completion time.

Tests were administered in either English or isiXhosa, depending on the participant's preference, by a bilingual neuropsychology technician. AJD, a registered clinical neuropsychologist, supervised test administration and scoring protocols.

Measures

Sociodemographic variables. Participants self-reported basic sociodemographic information (i.e., gender, age, highest level of education, monthly household income, primary language, and employment status) as well as details of their school performance (e.g., whether they had ever been held back or repeated a year in school, whether they were fully literate).

Psychosocial and socioeconomic variables. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993) assessed overall satisfaction with the quality of daily life. A modified version of the Adult AIDS Clinical Trials Group [ACTG] SF-21 (Wu et al., 1997) assessed health-related quality of life (asking, for example, if health interferes with or limits physical, social, or cognitive functioning and emotional well-being). The Household Food Insecurity Access Scale (HFIAS; Coates et al., 2007) measured household food insecurity. Each of these was completed by interviewer-administered self-report.

HIV disease variables. HIV viral load and current CD4 cell number were extracted from medical records. Participants self-reported whether their nadir CD4 count had ever been below 100 cells/μL. If participants did not have recent (1-month) testing, we collected blood samples (see Joska et al., 2020, for additional detail). Details regarding ART regimens (i.e., reinitiated on first line, second line, or third line) were also extracted from the participant's medical record.

Medical history. Participants were classified as having a significant history of neurological problems if they reported ever having experienced one or more of the following: closed or open head injury with loss of consciousness > 30 minutes; stroke; coma; epilepsy; seizure without a diagnosis of epilepsy; bacterial meningitis (including TB meningitis).

Participants were classified as having a significant history of vascular risk factors if they reported two or more of the following: any heart problem (e.g., coronary artery disease, heart arrhythmia, or other heart diseases); heart attack; diagnosis of hypertension (irrespective of whether they were on medication or not); diagnosis of diabetes; history of having smoked cigarettes.

Psychiatric variables. Psychiatric disorders were diagnosed using the MINI structured diagnostic interview (Sheehan, 2014). This interview was conducted by a psychiatric nurse and supervised by a clinical psychologist. The Alcohol Use Disorders Identification Test (AUDIT; cut off >20; Saunders et al., 1993) was used to identify high-risk alcohol use. The Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960; Williams et al., 2008) was used to assess depression severity.

Statistical Analyses

We used R version 4.1.2 (2021-11-01) and RStudio version 2021.09.0 to complete all analyses, with the threshold for statistical significance set at $\alpha = .05$.

First, we calculated sample descriptive statistics for the WWH and MWH groups and used *t*-tests (or Welch two-sample *t*-tests when groups had unequal variance) and chi-square analyses (or Fisher's exact tests if cell sample sizes were too small) to investigate between-group differences on sociodemographic, psychosocial, medical, and psychiatric variables.

Second, we processed and standardized the neuropsychological data. Normative standards for the tests were based on raw control data collected in previous studies conducted by the UCT HIV Mental Health Research Unit (Joska et al., 2011; Paul et al., 2014; Robbins et al., 2018). Data were provided on personal request from co-authors JJ (personal communication, November 2017) and HG (personal communication, June 2018). To assure similarity across key sociodemographic (age, ethnicity, language, education), psychosocial, and socioeconomic characteristics, these data were collected between 2008 and 2016 from healthy community-dwelling individuals ($N = 233$) who presented at the same community clinics in Khayelitsha from which the current sample was recruited. In the studies that collected the control data, participant inclusion criteria were (1) HIV seronegative, (2) ≥ 18 years of age, and (3) at least 5 years of formal education. Exclusion criteria were the presence of (1) a major psychiatric condition, (2) neurological disease that could affect brain integrity,

(3) lifetime history of head injury resulting in loss of consciousness >30 min, or (4) current substance use disorder.

We used the control data to calculate demographically corrected *z*-scores ($M = 0$, $SD = 1$), using standard regression-based norming processes. The *z*-scores were then converted to demographically corrected *T*-scores ($M = 50$, $SD = 10$). If participants had *z*-scores more than 5 *SD* below the mean, the conversion to a *T*-score resulted in negative value. In these cases, we assigned a score of zero, the lowest possible *T*-score to maintain the clinical significance of the low performance. Neuropsychological data were summarised into domain and global *T*-scores by taking the average of *T*-scores within each domain and then the average across domain *T*-scores.

Third, bivariable linear regression models compared domain and global *T*-scores between the WWH and MWH groups.

Fourth, multivariable linear regression models compared domain and global *T*-scores while adjusting for potential confounders (i.e., sociodemographic, psychosocial, medical, and/or psychiatric variables that earlier analyses had identified as being significantly different between the WWH and MWH groups).

Finally, a secondary sub-analysis focused on the WWH and MWH groups separately investigated univariable associations with the global *T*-score, using linear regression models. Variables significantly associated with global *T*-scores were entered into multivariable linear regression models to determine those that best explained cognitive performance in each of the WWH and MWH groups. A backwards stepwise approach was used for model building (i.e., the variable with the smallest *t*-value was removed from the model first). Cook's *D* was used to investigate influential outliers. A similar analysis conducted on the whole sample is presented in another manuscript (Dreyer et al., 2022b).

Results

Participant Characteristics

The sample included 76 WWH and 29 MWH. As Table 1 shows, analyses detected no significant between-group differences with regard to most sociodemographic and clinical variables. However, MWH had significantly fewer years of education and a significantly worse HIV-disease profile (i.e., higher HIV RNA viral loads and lower current CD4 counts) than WWH. Moreover, a significantly greater proportion of MWH than WWH met the AUDIT criterion for high-risk alcohol use. Finally, WWH scored significantly lower than

MWH on the ACTG SF-21, indicating that they reported experiencing worse health-related quality of life.

Table 1

Sample Sociodemographic and Clinical Variables: Descriptive Statistics (N = 105)

	Study Group					
	WWH (n = 76)	MWH (n = 29)				
Variable	*M (SD)*	*M (SD)*	*t*	*df*	*p*	ESE [a]
Age (yrs)	39.09 (9.38)	41.62 (8.34)	-1.27	103	.206	0.28
Education (yrs completed)	9.67 (2.11)	8.35 (3.00)	2.18	39.05	.035* [b]	-0.56
Monthly household income (ZAR)	2152.11 (2012.13)	1906.55 (3226.80)	0.38	36.62	.704 [b]	-0.1
HAM-D	26.22 (7.04)	24.07 (7.15)	1.39	103	.165	-0.31
Log_{10} HIV viral load	3.39 (1.48)	4.02 (1.25)	-2.02	102	.046*	0.45
Current absolute CD4	282.29 (225.20)	161.07 (127.52)	3.45	87.89	.001* [b]	-0.60
HFIAS [c]	12.56 (7.27)	13.21 (5.94)	-0.43	102	.670	0.09
ACTG SF-21	44.40 (16.71)	52.47 (13.29)	-2.33	102	.022*	0.51
Q-LES-Q [d]	40.67 (12.83)	44.83 (12.63)	-1.49	102	.140	0.33
	f (%)	*f* (%)	χ^2	*df*	*p*	ESE [e]
Self-reported nadir CD4 count < 100 cells/ml	48 (63.2%)	20 (69.0%)	0.11	1	.743	0.05
Held back in school	51 (67.1%)	21 (72.4%)	0.08	1	.773	0.05
Literacy	66 (86.8%)	25 (86.2%)	-	-	1 [f]	0.01
High risk alcohol use [g]	17 (22.7%)	13 (44.8%)	3.98	1	.046*	0.22
History of neurological events	25 (32.9%)	12 (41.4%)	0.34	1	.558	0.08
Vascular risk	10 (13.2%)	6 (20.7%)	0.43	1	.512	0.09
ART regimen			-	-	.321 [g]	0.19
Reinitiated on first line	39 (52.0%)	17 (58.6%)				
Second line	36 (48.0%)	11 (37.9%)				
Third line	0 (0%)	1 (3.5%)	-			

Note. [a]The effect size here is estimated by Cohen's *d*; [b]Welch *t*-test used due to unequal between-group variance; [c]Higher score indicates greater food insecurity; [d]Score recorded as a percentage; [e]The effect size here is estimated by the Cramer's *V* statistic; [f]Fisher's Exact Test used instead of conventional chi-square analysis due to small group size; [g]High-risk alcohol use indicated if Alcohol Use Disorders Identification Test (AUDIT) score >20. WWH = women with HIV; MWH = men with HIV; ESE = effect size estimate; ZAR = South African Rands; HAM-D = Hamilton Rating Scale for Depression; HFIAS = Household Food Insecurity Access Scale; ACTG SF-21 = Adult AIDS Clinical Trials Group SF-21; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; ART = antiretroviral therapy. *$p < .05$.

Differences in Cognitive Performance between WWH and MWH

Unadjusted linear regression models detected no significant sex differences with regard to either global or domain *T*-scores (see Table 2). A post hoc power analysis (Faul et al., 2007) indicated that the current sample size of WWH (n = 76) and MWH (n = 29) would only have 39% power for detecting a small-sized difference between cognitive performance

in WWH and MMW (d = 0.5). For the most part, mean global and domain T-scores for both the WWH and MWH groups fell within the average range of cognitive performance (i.e., T = 45 – 54). The only exceptions were the T-scores for audioverbal learning and memory and executive functioning, both of which fell within the low average range for both WWH and MWH (Woods et al., 2004).

Table 2

Cognitive Test Performance: Descriptive Statistics and Sex Differences (N = 105)

	WWH (n = 76)	MWH (n = 29)			
Outcome Variable	*M* (*SD*)	*M* (*SD*)	*β*	95% *CI*	*p*
Domain *T*-score					
Motor skills	46.80 (11.84)	45.82 (9.99)	-0.98	-5.90 – 3.94	.693
Information processing speed	46.30 (10.10)	46.53 (9.27)	0.23	-4.04 – 4.51	.914
Verbal fluency	50.03 (8.03)	51.35 (7.45)	1.32	-2.09 – 4.73	.443
Attention and working memory	48.57 (7.72)	47.13 (7.01)	-1.43	-4.69 – 1.83	.385
Audioverbal learning and memory	44.28 (10.02)	41.44 (9.33)	-2.84	-7.10 – 1.42	.189
Visuospatial learning and memory	49.60 (10.54)	51.05 (12.58)	1.45	-3.37 – 6.27	.553
Executive function	43.00 (11.13)	43.61 (5.98)	0.62	-3.71 – 4.95	.778
Global *T*-score	46.94 (6.75)	46.71 (5.22)	-0.23	-2.99 – 2.52	.867

Note. Data presented are means, with standard deviations in parentheses. WWH = women with HIV; MWH = men with HIV; CI = confidence interval.

Linear regression models that adjusted for covariates (i.e., potentially confounding sociodemographic, psychosocial, medical and/or psychiatric variables) also detected no significant sex differences with regard to either global or domain T-scores (see Table 3).

Table 3

Cognitive Test Performance: Sex Differences When Controlling for Covariates (N = 105)

	Motor Skills			Information Processing Speed			Verbal Fluency			Attention and Working Memory		
Predictor	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*
Sex (MWH vs. WWH)	1.18	-4.28 – 6.65	.668	-0.94	-5.60 – 3.72	.689	-0.53	-4.34 – 3.27	.781	-0.57	-4.26 – 3.12	.760
Education (yrs completed)	1.12	0.17 – 2.07	.021*	0.63	-0.18 – 1.44	.128	-0.80	-1.46 – -0.14	.018*	0.56	-0.08 – 1.21	.085
Log_{10} HIV viral load	0.19	-1.56 – 1.94	.830	0.06	-1.44 – 1.55	.938	0.41	-0.81 – 1.63	.510	-0.05	-1.19 – 1.18	.988
Current absolute CD4	0.01	-0.01 – 0.02	.462	-0.00	-0.01 – 0.01	.627	0.00	-0.01 – 0.01	.675	0.00	-0.00 – 0.01	.314
ACTG SF-21	-0.06	-0.21 – 0.08	.370	0.03	-0.09 – 0.15	.632	-0.01	-0.10 – 0.09	.924	0.02	-0.08 – 0.12	.678
High-risk alcohol use	1.20	-3.78 – 6.19	.634	6.58	2.33 – 10.83	.003**	1.87	-1.60 – 5.34	.288	0.76	-2.61 – 4.12	.655
	Audioverbal Learning and Memory			Visuospatial Learning and Memory			Executive Function			Global *T*-Score		
Predictor	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*	*β*	95% *CI*	*p*
Sex (MWH vs. WWH)	-2.27	-7.06 – 2.52	.349	1.80	-3.55 – 7.15	.506	1.05	-3.49 – 5.59	.658	-0.04	-3.06 – 2.98	.979
Education (yrs completed)	0.87	0.04 – 1.70	.041*	0.94	0.01 – 1.87	.048*	1.34	0.55 – 2.13	.001**	0.67	0.14 – 1.19	.014*
Log_{10} HIV viral load	-0.39	-1.92 – 1.15	.617	-1.36	-3.08 – 0.35	.118	-0.24	-1.69 – 1.22	.756	-0.19	-1.16 – 0.78	.696
Current absolute CD4	-0.01	-0.02 – 0.01	.396	-0.01	-0.02 – 0.01	.281	0.00	-0.01 – 0.01	.631	-0.00	-0.01 – 0.01	.700
ACTG SF-21	0.02	-0.10 – 0.15	.718	0.03	-0.11 – 0.17	.675	-0.02	-0.14 – 0.10	.704	0.00	-0.08 – 0.08	.972
High-risk alcohol use [a]	0.69	-3.67 – 5.06	.753	2.79	-2.09 – 7.66	.260	5.38	1.24 – 9.52	.011*	2.75	-0.00 – 5.51	.050

Note. [a]High-risk alcohol use indicated if Alcohol Use Disorders Identification Test (AUDIT) score > 20. WWH = women with HIV; MWH = men with HIV; ACTG SF-21 = Adult AIDS Clinical Trials Group SF-21; CI = confidence interval.

*$p < .05$. **$p < .01$.

Associations with Cognitive Performance in WWH and MWH

For WWH, level of education, HFIAS score, and literacy (i.e., whether the participant was illiterate or not) were significant predictors of global *T*-score (see Table 4). For every year of education completed, the global *T*-score increased by 0.94 points; for every one unit increase in HFIAS score (i.e., every one unit increase in food insecurity), the global *T*-score decreased by 0.28 points; and for WWH who reported being literate, global *T*-score was, on average, 4.55 points higher than WWH who were illiterate.

Table 4

Cognitive Test Performance: Within-Group Univariable Associations with Global T-score (N =105)

	Study Group							
	WWH (n = 76)				MWH (n = 29)			
Predictors	*β*	95% *CI*	*p*	ESE	*β*	95% *CI*	*p*	ESE
Age (yrs) [a b]	-0.16	-0.32 – 0.00	.054	-0.22	-0.23	-0.46 – 0.00	.051	-0.37
Education (yrs completed) [a b]	0.94	0.18 – 1.70	.016*	0.28	0.04	-0.65 – 0.72	.908	0.02
Monthly household income [a c]	0.00	-0.00 – 0.00	.951	0.01	-0.00	-0.00 – 0.00	.263	-0.22
Held back in school [d]	0.66	-2.64 – 3.96	.692	0.05	-1.50	-5.99 – 3.00	.501	0.13
Literacy [d b]	4.55	0.02 – 9.08	.049*	0.23	3.77	-9.45 – 1.92	.185	0.25
HFIAS [a b]	-0.28	-0.48 – -0.07	009*	-0.30	-0.08	-0.42 – 0.27	.657	-0.09
ACTG SF-21 [a]	-0.05	-0.14 – 0.05	.319	-0.12	0.09	-0.06 – 0.24	.247	0.22
Q-LES-Q [a]	-0.08	-0.20 – 0.04	.187	-0.15	0.01	-0.15 – 0.17	.913	0.02
Log_{10} HIV viral load [a]	0.09	-0.98 – 1.16	.870	0.02	-1.07	-2.67 – 0.52	.178	-0.26
Current absolute CD4 [a]	0.00	-0.01 – 0.01	.830	0.03	-0.01	-0.03 – 0.00	.110	-0.30
History of neurological events [d]	-2.67	-5.92 – 0.57	.105	0.19	-1.32	-5.40 – 2.76	.513	0.13
Vascular risk [d]	-0.79	-5.38 – 3.80	.732	0.04	-1.36	-6.33 – 3.61	.579	0.11
ART regimens [d]				0.04				0.10
Reinitiated vs. Second	-0.57	-3.72 – 2.58	.719		0.67	-3.44 – 4.77	.742	
Reinitiated vs. Third	NA	NA	NA		-8.10	-19.01 – 2.82	.139	
Nadir CD4 count [d e]	-0.33	-3.55 – 2.89	.839	0.02	-1.97	-6.28 – 2.34	.357	0.18
HAM-D [a]	0.06	-0.16 – 0.28	.607	0.06	-0.16	-0.44 – 0.12	.257	-0.22
High risk alcohol use [d f]	2.94	-0.76 – 6.63	.118	0.18	2.85	-0.03 – 0.30	.147	0.28

Note. [a]The effect size here is estimated by Pearson correlation; [b]Removed a participant's data from the analyses because was an influential outlier; Cook's *D* for this participant's models with age, education, HFIAS and literacy are 0.14, 0.18, 0.24 and 0.18 respectively; [c]Removed an outlier who had a monthly household income of ZAR15000 (> 4 *SD* above the mean for MWH) and whose data were therefore disproportionately influencing the model; [d]The effect size here is estimated by point-biserial correlation; [e]Self-reported nadir CD4 < 100; [f]High-risk alcohol use indicated if Alcohol Use Disorders Identification Test (AUDIT) score > 20. WWH = women with HIV; MWH = men with HIV; CI = confidence interval; ESE = effect size estimate; HFIAS = Household Food Insecurity Access Scale; ACTG SF-21 = Adult

AIDS Clinical Trials Group SF-21; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; ART = antiretroviral therapy; HAM-D = Hamilton Rating Scale for Depression; NA = not applicable.
*$p < .05$.

When building the multivariable linear regression models to determine the best model of global cognitive performance in WWH, we entered the three variables whose individual associations with global-*T* score were statistically significant: education (years completed), HFIAS score, and literacy.

The first iteration of the multivariable model indicated that literacy had the smallest *t*-value. Hence, we removed that variable and reran the model. Comparing this model to the previous one showed that the removal made no significant difference to overall predictive power ($p = .276$).

Therefore, the final model (adjusted $R^2 = .12$; $p = .004$) included years of education and HFIAS score. For every year of education completed, global *T*-score increased by 0.82 points (CI: 0.06, 1.59; $p = .036$) and for every one unit increase in HFIAS score, global *T*-score decreased by 0.24 points (CI: -0.44, -0.03; $p = .023$), on average. Data from one participant were removed from the analyses because they contained influential outliers (Cooks' $D = 0.23$).

For MWH, analyses detected no significant univariable predictors of global *T*-scores (see Table 4). Hence, we could not build a multivariable linear regression model of global cognitive performance. A post hoc power analysis (Faul et al., 2007) indicated that there was only 47% power to detect a small significant correlation within the MWH group.

Discussion

This study set out to investigate (a) if there were differences in cognitive performance between WWH and MWH in a distinct and clinically important sample of PWH with incomplete ART adherence, comorbid major depressive disorder, and a background of socioeconomic disadvantage, (b) the sociodemographic, medical, and psychiatric variables associated with cognitive performance within the WWH and MWH groups.

Despite the small sample of MWH ($n = 29$) in this study, the findings we report are novel and important because the sample was drawn from a particularly vulnerable population of PWH: those with incomplete ART adherence, a background of socioeconomic

disadvantage, and a comorbid mood disorder. We did not exclude from participation any individual with medical and psychiatric comorbidities (other than active and untreated serious mental illness) and/or other factors that could influence cognitive performance because we wanted to ensure our sample represented the population of PWH attending primary care clinics in South Africa. These PWH are important to study because they are especially vulnerable to HIV-related morbidities and there is an increased risk for the onwards transmission of the virus. Moreover, the specific adherence, psychosocial, sociodemographic, and psychiatric characteristics of our sample means that sex differences in cognitive performance are more likely to manifest in this group than in the general population of PWH. These sex differences, in this population, have not been described before.

Regarding sample sociodemographic and clinical characteristics, analyses detected several significant differences between the MWH and WWH groups. First, on average MWH had significantly fewer years of education than WWH. Broadly speaking, this statistic reflects the current state of the educational landscape in South Africa. Government school enrolment statistics report relative equality in access to education for men and women and note that, if anything, a slightly greater proportion of females are enrolled in secondary and tertiary level education (Statistics South Africa, 2020; Kirkwood, 2018; Orzolek, 2019). Many non-South African studies have found the opposite pattern (e.g., Dolan et al., 2003; Kabuba et al., 2016; Sundermann et al., 2018); these data may reflect the persistent global gap in educational attainment and opportunity between women and men (World Economic Forum, 2022).

Second, a significantly greater proportion of MWH than WWH met the criteria for high-risk alcohol use. This sex disparity is well-known in the general population of PWH (Agabio et al., 2017), including in South Africa (Andersson et al., 2018; Olley et al., 2004). MWH also had significantly higher HIV RNA viral loads and significantly lower current CD4 counts than WWH. Similar sex differences have been reported in many studies (see, e.g., Burlacu et al., 2018; Kabuba et al., 2016; Maki et al., 2018; Royal et al., 2016).

Third, MWH had a significantly worse HIV-disease profile (i.e., higher HIV RNA viral loads and lower current CD4 counts) than WWH. In South Africa, MWH are less likely than WWH to seek access to HIV care; if they do seek such access, they tend to present later than WWH. Hence, they are more likely to present with more advanced disease and to have increased mortality risk (Braitstein et al., 2008; Cornell et al., 2012). Several mechanisms have been offered to explain this gender disparity. These include gender differences in health-seeking behaviour, a generally higher mortality risk for men than women in South Africa, and

the fact that South African public health systems prioritize maternal and child services (Osler et al., 2020).

Despite this sample of MWH having a worse HIV disease profile, WWH experienced worse health-related quality of life. WWH reported to a significantly greater degree than MWH that their poorer health interfered with their physical, occupational, social, and cognitive functioning, and reduced their emotional wellbeing. Similar results have been reported in studies emerging from other LMICs such as Ethiopia and Vietnam (Tesfay et al., 2015; Tran et al., 2012). Gender-related socioeconomic and structural inequalities may explain these findings. For instance, socioeconomic status (which, in LMICs particularly, is much likelier to be lower in women than in men) has been more strongly associated with health-related quality of life than disease factors (Vidrine et al., 2005). Relatedly, women living in LMICs consistently report worse quality of life than men in the same countries (Gupta, 2000; Lee et al., 2020; Logie et al., 2018), and there are strong and consistent sex differences in the expression of somatic complaints and psychological illness (Tesfay et al., 2015).

Our first a priori hypothesis, that WWH will perform more poorly than MWH in the cognitive domains of motor skills and visuospatial learning and memory, was not supported. Analyses (both those unadjusted and adjusted for covariates) detected no significant between-sex differences, both globally and in any specific domain of cognitive functioning. The result with regard to global cognitive performance is consistent with that reported in previous systematic reviews and meta-analyses (Dreyer et al., 2022a; Rubin et al., 2019a).

However, the non-significant findings in the domains of motor skills and visuospatial learning and memory contrast with the results reported by the most recent meta-analysis summarizing this literature (Dreyer et al., 2022a). However, the effect sizes detected by the meta-analysis were relatively small and might be explained by between-group differences in depression severity and educational level.

Other individual studies have reported sex differences in specific cognitive domains such as information processing speed, audioverbal learning and memory, and executive functioning (see, e.g., Maki et al., 2018; Royal et al., 2016). Notably, however, the samples used in those studies differ in several ways from the sample described here. For instance, whereas Maki et al (2018) analysed data from the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) based in the United States, we collected data from socioeconomically disadvantaged South African PWH with comorbid MDD. Hence, we conclude that sex differences in PWH cognitive performance do not appear

universally, and that when they do they are likely explained by sociodemographic and/or psychosocial characteristics that vary significantly across the samples of WWH and MWH within the individual study.

Our second a priori hypothesis was that sociodemographic, psychosocial, and psychiatric (e.g., depression severity) factors will be associated with cognitive performance in both WWH and MWH. This prediction was partially supported. Our analyses detected no significant influence of depression severity on global cognitive performance in either WWH or MWH. This result is inconsistent with a report from a recent systematic review, which observed a significant relationship between depression and cognitive outcomes (Rubin & Maki, 2019). It is possible that our analyses did not detect such a relationship because depression affects domain-specific, but not global, cognitive performance and we did not examine whether depression affected the individual domain scores. This speculation is supported by studies observing significant effects of depression on performance in the specific domains of motor skills, processing speed, attention/working memory, learning and memory, and executive functioning (Bragança & Palha, 2011; Fellows et al., 2013; Goggin et al., 1997; Rock et al., 2014; Rubin & Maki, 2019).

Consistent with our a priori prediction, fewer years of education, the presence of illiteracy, and greater food insecurity were independently associated with lower cognitive performance in WWH. Multivariable analyses further established that, in the sample of WWH, the variables that best explained global cognitive performance were level of education and food insecurity.

Lower education and illiteracy are both well-established predictors of cognitive performance in the general population (Lenehan et al., 2015; Strauss et al., 2006). In the HIV literature, the WIHS (one of the largest studies of WWH neuropsychology) found that years of education and reading level were strong predictors of cognitive performance; in fact, reading level was the strongest such predictor, exceeding even the influence of HIV disease variables (Maki et al., 2015). A South African study found similar results: Educational attainment and cognitive reserve were the only factors consistently associated with cognitive performance in PWH from socioeconomically disadvantaged settings (Narsi et al., 2021).

Food insecurity is, similarly, well-established as a significant correlate of poor cognitive performance, especially among older adults. This association has been described in both high-income countries, such as the United States (see, e.g., Gao et al., 2009) and LMICs, such as South Africa (see, e.g., Koyanagi et al., 2019).

Several different mechanisms might explain the association between food insecurity and cognitive performance. One possible mechanism is that insufficient intake of vitamins and nutrients directly impairs cognitive functioning (Bourre, 2006; Scarmeas et al., 2006). Interestingly, however, when Gao et al (2009) controlled for plasma homocysteine (a biomarker of the intake of B vitamins) and for the intake of fruit and vegetables, they found no attenuation of the relationship between self-reported food insecurity and objectively measured cognitive performance. One interpretation of this result is that food insecurity may be a proxy for socioeconomic disadvantage, and that therefore the relationship being scrutinized in such studies is actually the well-established association between lower levels of socioeconomic status and lower performance on cognitive tests (Farah, 2017; Yaple & Yu, 2020). This interpretation would certainly make sense in the context of the current study: In South Africa, poverty is the main driver of food insecurity (Misselhorn & Hendriks, 2017). However, monthly household income is also a measure of socioeconomic status and this variable was not significantly associated with cognitive performance in this study. This implies that food insecurity itself is driving the association observed between cognitive performance and food security and not lower socioeconomic status.

Few published studies have investigated the relationship between food insecurity and cognitive performance in PWH. Two studies with majority MWH samples from the United States both found that food insecurity was associated with worse global cognitive performance (Hobkirk et al., 2017; Tamargo et al., 2021).

It may be regarded as surprising that our analyses detected no strong influence of HIV disease factors in predicting cognitive performance. Given that many previous studies have reported such associations (Ellis et al., 2011; Heaton et al., 2011; Jumare et al., 2018; Robertson et al., 2007; Sacktor et al., 2002; Starace et al., 2002), we might have expected to find the same, especially in a sample with poorly controlled viral replication. However, our results are consistent with those from the WIHS, which that found that reading level, age, years of education, and income were all more strongly associated with cognitive performance than HIV status (Maki et al., 2015).

The results of this study should be interpreted with the following limitations in mind. First, many psychosocial variables that were not measured in this study (e.g., socioeconomic opportunities, stress levels, trauma history) could have influenced cognitive performance. Determining the impact of such variables on cognitive performance would have strengthened the study. Second, the sample included a relatively small number of MWH. Although the proportion of MWH to WWH is representative of the South African PWH population

(George et al., 2019), the small sample of MWH meant we may not have had sufficient statistical power to detect significant associations between cognitive performance and individual sociodemographic, psychosocial, HIV disease, and psychiatric predictors. For similar reasons, the non-significant between-group analyses should be interpreted with caution. Third, because our design dictated that all participants had to be incompletely ART adherent and diagnosed with MDD, there may not have been enough variation in HIV disease characteristics or depression severity to find associations between these variables and cognitive performance. Fourth, Nadir CD4 count, considered one of the strongest predictors of cognitive impairment (Ellis et al., 2011) was self-reported by participants in this study. Self-reported medical record data is not as accurate as objective measures such as medical record data or biological measures, especially in patients with depression, from socioeconomically disadvantaged areas. Patient characteristics such as age, education level, literacy, substance use, and comorbidities have all been associated with worse self-reporting validity (Phillips et al., 2019; Merckelbach et al., 2019; Voss et al., 2015).

Although MWH might, in global terms, be underrepresented in this study, the fact that we studied a majority-female sample makes our results novel and useful because in this research field WWH tend to be underrepresented and understudied (Fox-Tierney et al., 1999; Rubin et al., 2019a). A peculiarity of this field is that most HIV studies are conducted in high-income countries (such as the United States and United Kingdom) and include majority-male samples, notwithstanding the fact that WWH (most of whom live in sub-Saharan Africa) comprise the majority of PWH globally (UNAIDS, 2021).

Summary and Conclusion

We found, in a sample of South African PWH from socioeconomically disadvantaged settings, with incomplete antiretroviral adherence and comorbid MDD, that there were no significant differences in cognitive performance between WWH and MWH. This result held even after analyses were adjusted for potentially confounding variables (i.e., education level, viral load, CD4 count, health-related quality of life, and high-risk alcohol use), and it remained stable whether considering global cognitive functioning or performance within discrete cognitive domains. We therefore conclude that sex differences in cognitive performance do not exist in all study populations of PWH, and that where they are observed they may be accounted for by variation in sociodemographic and psychosocial characteristics (representing broader issues of population-based gender inequality) within individual samples of WWH and MWH. These characteristics and their variation are not routinely measured in HIV research studies.

Our analyses also suggested that psychosocial factors (viz., level of education and food insecurity) best explained global cognitive performance in this group of WWH, exceeding the influence of mooted predictors such as depression severity and HIV-disease variables. We detected no significant influence of sociodemographic, psychosocial, medical, or psychiatric variables on cognitive performance in this group of MWH, although this result must be interpreted with caution given the small number of men in our sample.

In conclusion, we recommend that future studies not simply focus on investigating sex differences in cognitive performance in PWH. Instead, they should ensure WWH are adequately represented in their research samples and that issues of gender inequality are addressed not only in their interpretation but in their design. Regarding recommendations for care and treatment of WWH, the results suggest that educational attainment and literacy may protect against cognitive impairment for WWH managing depression and interventions aimed at food insecurity in the context of support for HIV treatment may be beneficial.

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Chapter 4

Rates of Cognitive Impairment in a South African Cohort of People with HIV: Variation by Definitional Criteria and Lack of Association with Neuroimaging Biomarkers

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Description of the contribution of candidate and co-authors

AJD was the first author of this manuscript. This entailed leading the drafting, analyses and conceptualising. These data were originally collected in a study exploring viral clade effects on brain signatures of HIV, which involved JAJ, RP and JW. In this manuscript, AJD formulated the research questions, conducted the literature search for methodology, applied the methods to the neuropsychological data, analysed and interpreted the data, and wrote the manuscript. JAJ and SN contributed to the manuscript by provided general guidance and discussing ideas, MH provided guidance on processing and analysing the neuropsychological normative data, JHW on neuroimaging data, RP and HG on neuropsychological data and SN reviewed drafts. All co-authors reviewed drafts and approved the final manuscript.

Current status Published in Journal of Neurovirology

Dreyer, A. J., Nightingale, S., Heaps-Woodruff, J. M., Henry, M., Gouse, H., Paul, R. H., Thomas, K. G., & Joska, J. A. (2021). Rates of cognitive impairment in a South African cohort of people with HIV: variation by definitional criteria and lack of association with neuroimaging biomarkers. *Journal of Neurovirology, 27(4),* 579-594. https://doi.org/10.1007/s13365-021-00993-x.

Abstract

There is wide variation in the reported prevalence of cognitive impairment in people with HIV (PWH). Part of this variation may be attributable to different studies using different methods of combining neuropsychological test scores to classify participants as either cognitively impaired or unimpaired. Our aim was to determine, in a South African cohort of PWH ($N = 148$), (a) how much variation in reported rates was due to method used to define cognitive impairment, and (b) which method correlated best with MRI biomarkers of HIV-related brain pathology. Participants completed detailed neuropsychological assessment and underwent 3T structural MRI and diffusion tensor imaging (DTI). We used the neuropsychological data to investigate 20 different methods of determining HIV-associated cognitive impairment. We used the neuroimaging data to obtain volumes for cortical and subcortical grey matter and total white matter and DTI metrics for several white matter tracts. Applying each of the 20 methods to the cognitive dataset resulted in a wide variation (20–97%) in estimated rates of impairment. Logistic regression models showed no method was associated with HIV-related neuroimaging abnormalities as measured by structural volumes or DTI metrics. We conclude that, for the population from which this sample was drawn, much of the variation in reported rates of cognitive impairment in PWH is due to the method of classification used, and that none of these methods accurately reflects biological effects of HIV in the brain. We suggest that defining HIV-associated cognitive impairment using neuropsychological test performance only is insufficient; pre-morbid functioning, co-morbidities, cognitive symptoms, and functional impairment should always be considered.

Keywords: cognitive impairment; DTI; HIV; neurocognitive disorder; neuroimaging.

Introduction

Despite the use of combination antiretroviral therapy (cART), HIV-related brain pathology may persist, with consequent cognitive impairment (Heaton et al., 2011; Joska et al., 2010). There is, however, wide variation in reported rates of cognitive impairment in people with HIV (PWH), with published estimates ranging from 22% to 80% (Joska et al., 2011; Wang et al., 2020; Yakasai et al., 2015; Yusuf et al., 2017). Some of this variation may be explained by between-sample differences in HIV disease characteristics, neurological and psychiatric comorbidities, and socioeconomic attributes. Additional variation may emerge from inconsistent norming practices and erratic availability of well-matched normative data in different populations and regions (Gates & Cysique, 2016; Winston & Spudich, 2020). Of interest here, however, is the variation due to differences between the actual criteria used to define cognitive impairment in PWH.

Within the HIV literature, several different sets of criteria have been used to determine whether cognitive performance indicates impairment. Differences between these sets of criteria result from different approaches to combining neuropsychological test scores to classify participants as either cognitively impaired or unimpaired. There is no consensus on which set of criteria is the gold standard, and there are often no specific guidelines on how criteria are to be applied. Hence, it is unsurprising that there are between-study differences in approaches and, consequently, variable rates of reported cognitive impairment in PWH. Indeed, several studies have demonstrated empirically that the application of different criteria to define cognitive impairment results in different estimated rates of such impairment within the same group of participants (De Francesco et al. 2016; Tierney et al. 2017; Wang et al. 2019).

The most commonly used set of criteria used to define cognitive impairment in PWH are the updated American Academy of Neurology criteria (also known as the HIV-associated neurocognitive disorder [HAND] or Frascati criteria; Antinori et al., 2007) and the global deficit score (GDS) criteria (Carey et al., 2004). Under the Frascati criteria, one cut-off for cognitive impairment is established as being when neuropsychological test performance in at least two cognitive domains is 1 *SD* below the normative mean (indicating a diagnosis of asymptomatic neurocognitive impairment [ANI] or mild neurocognitive disorder [MND]). Another, more stringent, cut-off is defined when neuropsychological test performance in at least two cognitive domains is 2 *SD* below the normative mean (indicating a diagnosis of HIV-associated dementia [HAD]). Some studies suggest that the Frascati criteria risk

overestimating the rate of cognitive impairment in both PWH and healthy controls (Meyer et al., 2013; Nightingale et al., 2014; Underwood et al., 2018). For instance, Gisslén et al. (2011) demonstrated that, because cognitive test performance ought to be normally distributed, 16% of the general population should score more than 1 *SD* below the normative mean on any given neuropsychological test. Moreover, they noted that this probability can change depending on how many cognitive domains are assessed by a test battery, how many tests are contained within each domain, and the magnitude of correlations between individual test scores and overall domain scores. Depending on the values of those variables, 20% or more of healthy controls can meet Frascati criteria for cognitive impairment. Similarly, Underwood et al. (2018) used simulated 'normative' data informed by the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) dataset (a multi-centre, prospective cohort from the United Kingdom and Republic of Ireland; De Francesco et al., 2016) to show that using the Frascati and GDS approaches resulted in 26% and 21% of their HIV-uninfected population meeting criteria for cognitive impairment.

Recently developed classification methods such as the Multivariate Normative Comparison (MNC; Huizenga et al., 2016; Huizenga et al., 2007) and the Novel Multivariate Method (NMM; Underwood et al., 2019) attempt to reduce the number of false positives in estimates of cognitive impairment in PWH. The developers of these methods suggest that their approaches reduce the problem of Type I errors by accounting for inherent correlation between test scores and cognitive domain scores. They also argue that their methods are appropriate for dichotomizing cognitive outcomes (impaired/unimpaired). Those two sets of criteria, as well as the GDS criteria, rely solely on the interpretation of neuropsychological test performance to define cognitive impairment. They are not informed by, for instance, subjective reports regarding cognitive symptoms, measures of functional impairment in daily living, or pre-morbid functioning. The classification of cognitive impairment using other methods, such as the Frascati criteria, incorporate data on daily functioning into the categories of classification (i.e., a classification of MND or HAD requires functional impairment in daily living alongside measured cognitive impairment).

Another source of variation in estimated rates of cognitive impairment in PWH is that many of the classification criteria can be applied to cognitive test scores in different ways; there are no specific guidelines and no consensus agreement stating how they should be applied. For example, the application of some criteria first requires the researcher to define "within-domain impairment" (e.g., as noted above, the Frascati criteria defines impaired performance as 1 *SD* below the normative mean within at least two different cognitive

domains), but there is no standard, agreed-upon definition of that term. Hence, where some might define it as being poor performance on one test within a domain, others might define it as being poor performance on multiple tests within that domain, or poor performance on all tests within that domain, or a poor average of all test scores within a domain. Although some of these definitions are used more frequently than others, all are viable options and all have been used in the literature. Meyer et al. (2013) used the Frascati criteria to show that, depending on the definition of within-domain impairment (and correlations between test scores and domain scores), false-positive rates of cognitive impairment ranged from 2% to 74% in their sample (normative data simulated from a Kenyan HIV-negative sample without neurologic comorbidities, depression, substance abuse, or learning disorders).

Given that the use of different criteria, and different application of components of those criteria, gives rise to different rates of cognitive impairment in PWH (and to different rates of false positives), some criteria and their applications may be better at identifying actual HIV-related brain pathology than others. However, no published study has investigated how different classification criteria and variations in their application relate to HIV-associated brain pathology. Such pathology is often measured by the proxies of regional brain volumes and diffusion metrics on MRI. Compared to HIV-negative controls, PWH have significantly lower volumes of total white matter, subcortical grey matter, and cortical grey matter (Heaps et al., 2012; Ortega et al., 2013; Paul et al., 2017), as well as diffusion tensor imaging (DTI) abnormalities across multiple tracts (Leite et al., 2013; Paul et al., 2017; Underwood et al., 2017). Moreover, regional brain volumes have also been shown to correlate with cognitive impairment as defined independently by the Frascati, GDS, or MNC criteria (Campbell et al., 2020; Underwood et al., 2019).

The Current Study

There is no consensus in the literature on which set of criteria used to define cognitive impairment in PWH is the gold standard, and there are no guidelines about whether any of the classification methods should vary by setting. For instance, it is unclear whether some methods are better suited for use in high-income versus low-income countries. In South Africa, a low- and middle-income country (LMIC) that has the highest number of HIV infections in the world (7.7 million PWH), the issue of prevalence of cognitive impairment is highly relevant to the allocation of resources and the setting of research agendas. Hence, the first aim of this study was to investigate how much variation in the rates of cognitive impairment in PWH is due to variation in classification methods used to indicate impairment. To achieve this aim, we scoured the HIV literature to identify all sets of classification criteria

(and all of their viable methods of application) used to combine scores from a battery of neuropsychological tests in order to classify cognitive impairment. We then classified PWH from a South African cohort as either cognitively impaired or unimpaired using the different existing classification methods and calculated all of the resulting rates of cognitive impairment. Because we wanted to determine the effectiveness of an approach to diagnosing impairment that utilizes cognitive test scores alone, we did not include data on functional impairment.

The second aim of this study was to determine which method of classifying cognitive impairment correlated best with regional brain volumes and DTI metrics (i.e., proxies for HIV-associated brain pathology). Studies in high-income countries have shown that some classification methods are associated with neuroimaging abnormities. Currently, there is no research guiding choice of criteria in LMICs such as South Africa and so findings related to this second aim will guide local researchers and clinicians on which classification method to use.

Method

Participants

Participants (N = 148) were recruited from primary care clinics in Khayelitsha (a peri-urban township in Cape Town, South Africa) as part of a study exploring viral clade effects on brain signatures of HIV (Paul et al., 2014). Khayelitsha was established by the apartheid regime in 1985 to relocate poor Black people. As a consequence of this legacy, today, almost all of its residents are Black, the predominant language spoken is Xhosa, and fewer than one-third of adults have completed high school. There are high levels of HIV infection, poverty, and unemployment (Smit et al., 2016; City of Cape Town, 2013).

Our study's inclusion criteria required that participants (1) be HIV seropositive, (2) have Xhosa as their home language, (3) be aged 18–50 years at the time of recruitment (we specified this age range so as to avoid central nervous system [CNS] complications associated with neurodevelopment and advanced age), (4) have at least 5 years of formal education, and (5) have initiated cART within 3 months of enrollment into the original study. Exclusion criteria were (1) any self-reported major DSM Axis I psychiatric condition that could significantly affect cognitive functioning (e.g., schizophrenia or bipolar disorder), (2) neurological disease that could affect brain integrity, (3) Centers for Disease Control and Prevention (CDC) stage A, (4) opportunistic CNS infection, (5) lifetime history of head injury resulting in loss of consciousness for > 30 mins, and (6) current substance use disorder

as determined by the Mini International Neuropsychiatric Interview Plus (MINI Plus; Sheehan et al., 1998)). All participants gave written informed consent, and study procedures were approved by the University of Cape Town (UCT) Faculty of Health Sciences and the University of Missouri-St. Louis Human Research Ethics Committees.

Measures and Procedure

Cognitive Testing. Participants were administered a comprehensive neuropsychological test battery. The battery comprised 17 standardized tests, each of which assessed performance in one of six cognitive domains commonly affected by HIV (Grant, 2008). The domains, tests, and outcome variables were: (1) Executive Functioning: Color Trails Test 2 (CTT2) - completion time; Stroop Color Word Test - number of items completed accurately in 45 seconds; Wisconsin Card Sorting Test (WCST) - perseverative errors; (2) Learning and Memory: Hopkins Verbal Learning Test-Revised (HVLT-R) - total learning total and delayed recall total; Brief Visuospatial Memory Test-Revised (BVMT-R) - total learning total and delayed recall total; (3) Language: category fluency - total number of animals / total number of fruits and vegetables named in 1 minute; (4) Attention/Working Memory: Wechsler Memory Scale-Third Edition (WMS-III) Spatial Span - total score; WMS-III Mental Alternation Test - total score; WMS-III Mental Control Test - total score; (5) Processing Speed: Trail Making Test Part A (TMT-A) - completion time; CTT1 - completion time; Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol Coding - total score; (6) Motor Function: Grooved Pegboard Test (GPT) nondominant hand (NDH) - completion time; Finger Tapping Test NDH - completion time. Tests were administered in either English or Xhosa depending on the participant's preference.

Normative standards for these neuropsychological tests were based on control data from the UCT HIV Mental Health Research Unit (Westgarth-Taylor & Joska, personal communication, November 2017). These data were collected between 2008 and 2011 from 119 healthy community-dwelling individuals who presented at the same Khayelitsha clinics from which the current sample was recruited. Hence, the control sample and the current sample of HIV seropositive participants were similar across key sociodemographic (age, ethnicity, language, education), psychosocial, and socioeconomic characteristics. Inclusion/exclusion criteria were also similar; the sole exception was that all controls were required to have laboratory-confirmed seronegative status.

Control data allowed calculation of demographically corrected *T*-scores, the type of standard score used most frequently by HIV neuropsychologists. To complete this calculation, we used standard regression-based norming processes. First, linear regressions

were applied to the raw scores for each test outcome variable with age, years of education, and sex as predictors. Predictors were removed from the regression model if they were not significantly associated with the test score. Then, coefficients were used to calculate a predicted score based on the age, education, and/or sex of the participant for each test outcome variable. Each participants' predicted score was subtracted from their raw score to calculate the residual. The residual was divided by the standard error of the residuals to calculate the *z*-score ($M = 0$, $SD = 1$). *Z*-scores were reversed if a higher score on the test indicated poorer performance (e.g., as was the case with all test for which completion time was the outcome variable). The *z*-scores were then converted to demographically corrected *T*-scores ($M = 50$, $SD = 10$). This process removes the effects of age, years of education, and sex, and so demographically corrected *T*-scores allow for fair interpretation of HIV-related disease effects across sociodemographic boundaries (Gates and Cysique 2016).

Methods of Defining Cognitive Impairment. A search of the HIV literature identified eight different sets of criteria used to define cognitive impairment in PWH. We limited the search to criteria in use since 2007, when the Frascati criteria were proposed, and we excluded methods requiring subjective application of clinical judgment, such as those described by Woods et al. (2004) and by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013).

The eight sets of criteria can be applied to demographically adjusted *T*-scores in different ways, resulting in 20 separate methods that can be used to define cognitive impairment in PWH (see Table 1). Although it is not clear whether all 20 methods have been used empirically in the published literature (studies do not always provide sufficient details of their methods and statistical procedures), all are viable ways in which to apply the criteria.

We classified each participant in our sample as either cognitively impaired or unimpaired using the cut-offs proposed by each method.

Table 1

Criteria Used to Define Cognitive Impairment in PWH and Methods of Application

Set of Criteria Used to Define Cognitive Impairment	Method(s) of Applying Each Set of Criteria		Studies Using the Method
Global Deficit Score (GDS; Carey et al., 2004) *T*-scores are converted to deficit scores following these guidelines: $T > 39 = 0$ (normal); $39 \geq T \geq 35 = 1$ (mild impairment); $34 \geq T \geq 30 = 2$ (mild-to-moderate impairment); $29 \geq T \geq 25 = 3$ (moderate impairment); $24 \geq T \geq 20 = 4$ (moderate-to-severe impairment); $T < 20 = 5$ (severe impairment). The overall GDS is calculated by averaging deficit scores. Cognitive impairment is indicated when this overall GDS ≥ 0.5.	GDS 1	The *T*-score for each test in the battery is converted to a deficit score. The sum of these deficit scores is then divided by the number of individual tests to compute the overall GDS.	Bloch et al. (2016) Campbell et al. (2020) Cysique et al. (2014) Heaton et al. (2008) Kamminga et al. (2017) Kelly et al. (2014) McDonnell et al. (2014)
	GDS 2	An average domain *T*-score is calculated by taking the mean of all *T*-scores within a domain. Each average domain *T*-score is then converted to a deficit score. The sum of these deficit scores is then divided by the number of domains to compute the overall GDS.	Cysique and Brew (2011) De Francesco et al. (2016) McDonnell et al. (2014) Underwood et al. (2017) Underwood et al. (2018)
Frascati (Antinori et al., 2007) Cognitive impairment is indicated if there is impaired test performance in two or more discrete cognitive domains.	Frascati 1	Within-domain impairment is indicated if performance on one test within a domain is ≥ 1 *SD* below the normative mean.	Joska et al. (2011)
	Frascati 2	Within-domain impairment is indicated if performance on two tests within a domain is ≥ 1 *SD* below the normative mean.	NA
	Frascati 3	An average domain *T*-score is calculated by taking the mean of all *T*-scores within a domain. Within-domain impairment is then defined as an average domain *T*-score ≥ 1 *SD* below the normative mean.	Arenas-Pinto et al. (2016) Chockanathan et al. (2019) De Francesco et al. (2016) McDonnell et al. (2014) Sacktor et al. (2016) Tierney et al. (2017) Underwood et al. (2017) Underwood et al. (2018) Wang et al. (2019)
Gates and Cysique (2016) Cognitive impairment is indicated if there is impaired test performance in two or more discrete cognitive domains.	The definition of within-domain impairment varies according to the number of tests within a domain. If there is one test in a domain, then impaired performance is indicated by a test score ≥ 1 *SD* below the normative mean. If there are two tests in a domain, then impaired performance is indicated by scores on both tests being ≥ 1 *SD* below the normative mean or by a score on at least one test being ≥ 1.5 *SD* below that mean. If there are three or more tests in a domain, then impaired performance is indicated by scores on at least two tests being ≥ 1 *SD* below the normative mean or by a score on at least one test being ≥ 1.5 *SD* below that mean.		Kamminga et al. (2017)
Gisslen et al. (2011) Cognitive impairment is indicated if there is impaired test performance in two or more discrete cognitive domains.	Gisslen 1	Within-domain impairment is indicated if performance on any single test within a domain is ≥ 1.5 SD below the normative mean.	
	Gisslen 2	An average domain *T*-score is calculated by taking the mean of all *T*-scores within a domain. Within-domain impairment is then defined as an average domain *T*-score ≥ 1.5 SD below the normative mean.	Tierney et al. (2017) Wang et al. (2019)
Milanini et al. (2018)	Cognitive impairment is indicated if performance on any: (a) two tests is ≥ 1 *SD* below the normative mean, or (b) single test is ≥ 2 *SD* below the normative mean.		Milanini et al. (2018)
Wright et al. (2015)	Cognitive impairment is indicated if:		Wright et al. (2015)

	(a) performance on any single test is ≥ 1 *SD* below the normative mean, or (b) any average domain *T*-score (this is calculated by taking the mean of all test scores within a domain) is ≥ 1.5 SD below normative mean.		
Multivariate Normative Comparison (MNC; Huizenga et al., 2016; Huizenga et al., 2007) This statistical method simultaneously compares multiple cognitive scores for participants to the average test scores of the same tests in a healthy-control group, considering the variances and covariance between all scores. For each participant, a continuous measure of the deviation of the participant's cognitive profile from the average cognitive profile in the control group is then obtained (this is called Hotelling's T2). If this deviation exceeds a critical value associated with a 5% statistical significance, the individual is classified as cognitively impaired.	MNC 1	The method is applied across the test battery on individual tests.	NA
	MNC 2	An average domain *T*-score is calculated by taking the mean of all *T*-scores within a domain. The method is applied across the domain *T*-scores.	De Francesco et al. (2016) Schouten et al. (2016) Underwood et al. (2017) Wang et al. (2019)
Novel Multivariate Method (NMM; Underwood et al., 2019) This method is similar to the MNC method, but it does not require a study-specific control group. Instead, a multivariate mean is calculated from a hypothetical normative population informed by the measured cognitive data for the PWH group. It incorporates a user-defined threshold (alpha) which allows one to set the specificity.	NMM 1	Across the test battery on individual tests when the alpha is set at 10%, 15%, 20%, or 25%.	NA
	NMM 2	Across the domain *T*-scores when the alpha is set at 10%, 15%, 20%, or 25%.	Underwood et al. (2019)

Note. NA = Our literature search did not locate any studies that used this method. We also found a method that is similar to Gisslen 2 (Meyer et al., 2013). However, the Meyer method requires that only three to five discrete cognitive domains are included in analysis. Because our test battery assesses performance across six cognitive domains, we did not evaluate the performance of this method.

Neuroimaging Acquisition. Images were acquired on a Siemens Allegra 3T scanner (Siemens AG, Erlangen Germany), with a 4-channel phased array head coil. We acquired a T1-weighted 3-D MPRAGE sequence (TR = 2400 ms, TE = 2.38 ms, TI = 1000 ms, flip angle = 8°, slices = 162, voxel size = 1 × 1 × 1 mm3) for volumetric analyses. For a detailed description of these methods, see Paul et al. (2017).

Volumetric Analysis. Freesurfer software suite (v5.1) (Martinos Center, Harvard University, Boston, MA, USA; http://surfer.nmr.mgh.harvard.edu) was used for volumetric quantification. Briefly, MPRAGE scans were transformed into a template space with the skull stripped and the brain segmented into white matter, grey matter, and ventricles. Brain regions were parcellated into subcortical and cortical regions of interest using a surface deformation

program (Desikan et al., 2006; Fischl & Dale, 2000; Fischl et al., 2002). Images from all subjects were aligned to the Desikan-Killiany atlas (Desikan et al., 2006). Variables included in the present study included total white matter volume, total cortical grey matter volume and subcortical grey matter volume (composite variable of the volumes of the caudate, putamen, thalamus, globus pallidus, and hippocampus). Volumes were measured bilaterally and aggregated across hemispheres.

Normative data for the neuroimaging measures were collected from 34 HIV-negative community-dwelling individuals. They were recruited from local voluntary counseling and testing clinics in Khayelitsha. This control group was well-matched to the current patient group on key sociodemographic variables (e.g., language, socioeconomic status). Despite the relatively small size of the control group, their data were normally distributed; this indicates that it was representative of a normal population and that we could therefore capture a normative brain signature.

The control data were used to standardize the raw imaging scores to *z*-scores. We standardized the imaging data in this way so as to capture the effects of the HIV disease process on the brain and to be consistent with how the neuropsychological data were processed.

Diffusion Metrics. Diffusion-weighted images (DWIs) were preprocessed using FSL 5.0 (Jenkinson et al., 2012) as follows. They were corrected for motion and eddy-current induced artifacts through affine registration to the first baseline volume using FSL FLIRT (Jenkinson & Smith, 2001) with the mutual information criteria. The orientations of the gradient encoding directions were corrected by the rotation induced by these registrations (Leemans & Jones, 2009), and the brain tissue was extracted using FSL brain extraction tool (BET; Smith, 2002) with a fraction threshold of 0.45. DTIs were estimated for each subject using FSL DTIFIT. Then, a study-specific white matter atlas was created using DTI-TK (Zhang et al., 2007). The template DTI was computed by iteratively deforming and averaging the population imaging data using the tensor-based deformable registration algorithm in DTI-TK (Zhang et al., 2006) with finite strain tensor reorientation and the deviatoric tensor similarity metric. This template was used to define inclusion and exclusion region of interest (ROI) masks for the anterior thalamic radiation (ATR), cingulum bundle (CING), uncinate fasciculus (UNC), and corpus callosum (CC) (Mori & Van Zijl, 2002). Whole brain tractography was performed in the template image, and subsets of curves were interactively selected to represent each tract-of-interest (TOI). For each bundle, two

inclusion ROI masks and one exclusion ROI mask were drawn in template space using ITK-SNAP (Yushkevich et al., 2006). These masks were placed at opposite ends of each tractography bundle template and drawn in reference to standard white matter atlases (Catani & de Schotten, 2012; Oishi et al., 2010).

Subject-specific fiber bundle metrics were computed as follows. First, the TOI inclusion and exclusion masks were deformed to subject native space using the DTI-TK registration. Whole brain tractography was then performed in subject native space and a subset of curves in the TOI was selected using the two inclusion and exclusion masks. Tractography was performed using deterministic streamline integration (Zhang et al., 2003) with a step size of 1 mm, tricubic interpolation, and four jittered seeds per voxel. Termination criteria included an angle threshold of 45 degrees and minimum fractional anisotropy (FA) of 0.15 mm2/msec. Fiber curves with a length less than 10 mm were excluded from the analysis. The following bundle average metrics (averaged across hemispheres) were computed from the resulting curves and retained for statistical analyses: radial diffusivity (RD), axial diffusivity (AD), mean diffusivity (MD), and FA (Correia et al., 2008).

Data Analysis

Statistical analyses were conducted using Microsoft Excel, RStudio version 1.2.5019, and R version 3.6.1.

Application of the different methods (expect for MNC and NMM) to define cognitive impairment was accomplished in Microsoft Excel. Application of the MNC method was accomplished by running the R-script provided by the authors (Agelink van Rentergem, personal communication, August 2017). Application of the NMM method was accomplished using the web-based interface developed by the authors (*https://jonathan-underwood.shinyapps.io/cognitive_calculator/*).

Regarding volumetric data, 20 separate logistic regression models were conducted for each cognitive impairment classification method. Total white matter, total cortical grey matter, and subcortical grey matter volumes were used as predictors, with cognitive impairment (impaired/not impaired, as classified by each method) as the outcome variable.

Regarding diffusion metrics, we calculated the mean of each TOI (ATR, CING, UNC, CC) for each of the DTI metrics to obtain an overall average for MD, FA, RD, and AD. Pairwise Pearson's correlations between RD, AD, MD, and FA indicated that MD was highly correlated (r

> 0.90) with AD and RD. Because of this redundancy and because MD is used more widely in HIV studies (Stebbins et al. 2007; Su et al. 2015), AD and RD were dropped from the analysis. Methods used to analyse the DTI data were consistent with the methods used to analyse the volumetric data. We conducted 20 separate logistic regressions for each classification method, with overall average for MD and FA as predictor variables and cognitive impairment as the outcome variable.

Overall model significance for the logistic regressions was calculated by investigating the difference in chi-square statistics and degrees of freedom between the null model (i.e., the model with only the constant term) and the model with the predictor variables. This approach allowed us to determine whether the deviance for the model with the predictors is significantly different from the model with only the constant term. False discovery rate (FDR) was controlled at ≤ .05 to correct for the multiple comparisons.

Results

Sample Characteristics

Most participants were female, had not completed high school, and were unemployed (see Table 2). The sample's mean monthly household income amounted to approximately USD30, a value that at the time of the study fell well below the lower bound of the South African poverty line (Statistics South Africa, 2019). Although more than two-thirds of participants lived in a shack or a wendy house (a small informal house constructed from corrugated iron or wood), most had running water and electricity.

Regarding psychiatric status, although Center for Epidemiologic Studies Depression Scale (CES-D) scores varied quite widely the average score was in the range that conventionally describes mild depressive symptoms (Vilagut et al., 2016).

Regarding HIV-related clinical variables, mean time since HIV diagnosis was approximately 1 year. Almost all participants had clade C HIV (confirmed by HIV genome sequencing; Paul et al., 2014) and a detectable viral load.

Table 2

Sample Demographic and Clinical Characteristics (N = 148)

Variable	*n*	Range	*M (SD)*

Age	148	22-46	31.69 (5.14)
Years of Education	148	6-15	10.21 (1.57)
Time since diagnosis (months)	126	0-116	11.53 (22.64)
Household income (ZAR)	117	0-3500	563.68 (906.02)
	n	**Interquartile range**	**Median**
Log_{10} HIV viral load	141	3.41-4.86	4.19
Current absolute CD4	146	120.25-313.50	195.50
CES-D scores	117	4-7	5
	n	**Frequency**	**%**
Sex			
Female	148	120	81
Household Resources			
Running water	50	49	98
Electricity	118	106	90
Television	118	95	81
Housing			
Own house/family home	50	15	30
Shack	50	33	66
Wendy house	50	2	4
Employment Status			
Casual	115	21	18
Fulltime	115	14	12
Seeking	115	2	2
Unemployed	115	78	68
HIV-1 subtype C	133	129	97
Detectable viral load	145	141	97

Note. CES-D = Center for Epidemiologic Studies Depression Scale; ZAR = South African rands.

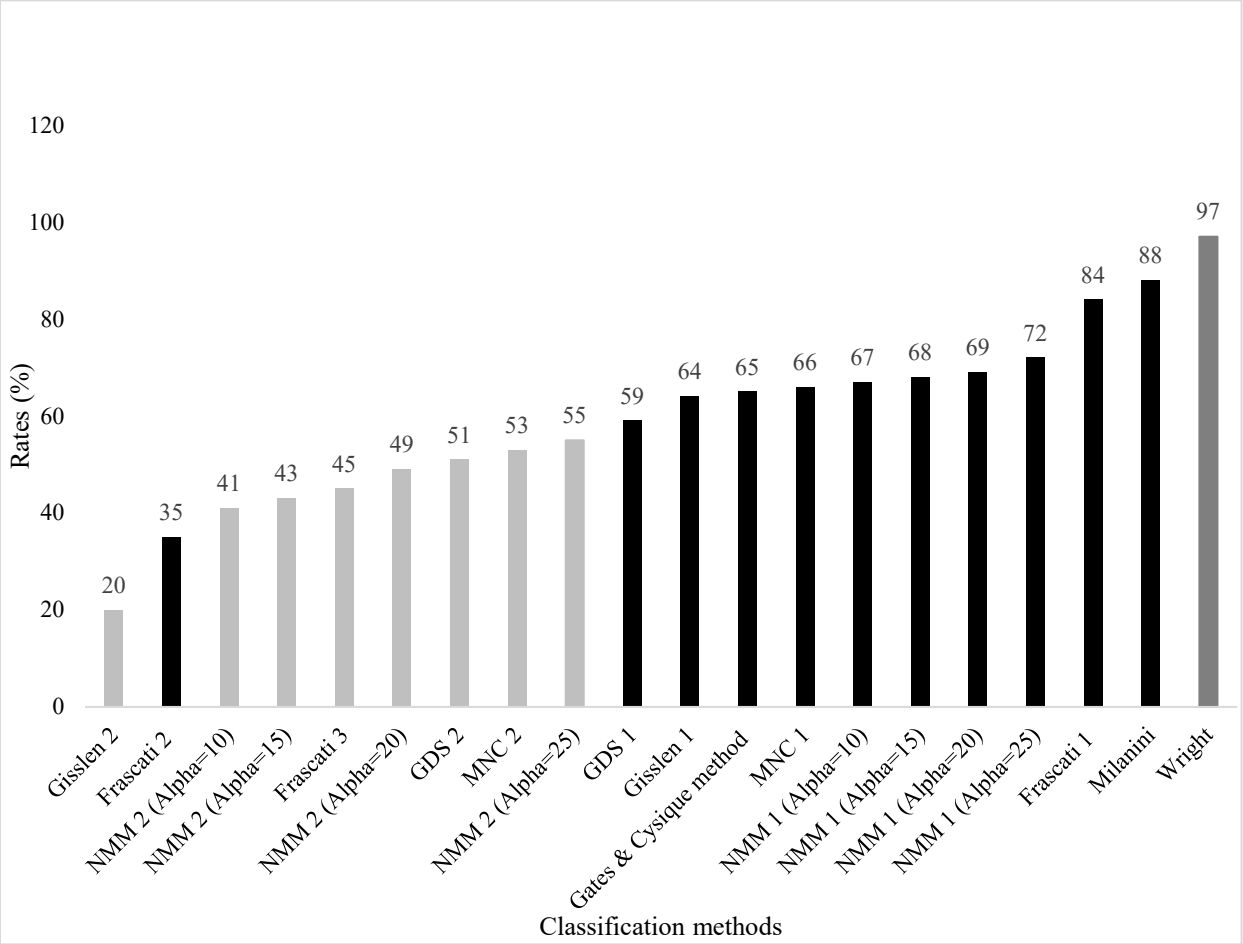
Rates of Cognitive Impairment by Method of Definition

Figure 1 shows that, depending on which of the 20 methods was used to define cognitive impairment, rates of cognitive impairment in the current sample of PWH ranged from 20% to 97%. The Gisslen 2 and Frascati 2 methods classified the fewest participants as cognitively impaired (20% and 35% respectively), whereas Wright method classified the most (97%).

Methods that involved first calculating an average domain *T*-score and then applying the criteria across the domain *T*-scores (i.e., those depicted by light grey bars in the Figure) tended to produce lower rates (the average rate is 45% for these methods) than those where criteria were applied across individual test scores (i.e., those depicted by black bars; average rate = 67%). There was less variability among the former set of methods than among the latter (range = 35 versus 53, *SD* = 11.08 versus 13.65).

Figure 1

Cognitive impairment rates according to 20 Methods



Note. Light grey bars are methods where criteria for cognitive impairment are applied across average domain *T*-scores. Black bars are methods where criteria for cognitive impairment are applied across the test battery on individual tests. The dark grey bar is a method that is applied across the domain *T*-scores and across the test battery on individual tests.

Associations between Cognitive and Neuroimaging Outcomes

Logistic regression models detected no significant associations between the volumes of interest (total white matter, total cortical grey matter, subcortical grey matter) and cognitive impairment as defined by each of the 20 methods (see Table 3).

Table 4 shows logistic regression results models for the DTI data. Despite one of the models initially meeting the $p \leq .05$ significance threshold, it was no longer significant after controlling for FDR.

Table 3

Volumetric Data: Results from the logistic regression models for the 20 methods of defining cognitive impairment (N = 148)

				95% CI		
		p	*OR*	*Lower*	*Upper*	*Overall model p*
GDS 1	Total white matter	.61	0.86	0.48	1.55	.31
	Total cortical grey	.15	0.74	0.48	1.11	
	Subcortical grey	.42	1.34	0.66	2.73	
Frascati 1	Total white matter	.74	1.15	0.52	2.64	.54
	Total cortical grey	.16	0.66	0.36	1.16	
	Subcortical grey	.51	1.37	0.53	3.57	
Frascati 2	Total white matter	.69	1.13	0.62	2.05	.71
	Total cortical grey	.91	0.98	0.64	1.49	
	Subcortical grey	.33	0.70	0.34	1.43	
Gates & Cysique	Total white matter	.63	0.86	0.47	1.58	.22
	Total cortical grey	.10	0.70	0.45	1.06	
	Subcortical grey	.32	1.45	0.70	3.04	
Gisslen 1	Total white matter	.44	0.79	0.43	1.44	.16
	Total cortical grey	.10	0.70	0.45	1.07	
	Subcortical grey	.26	1.52	0.74	3.18	
Milanini	Total white matter	.90	0.95	0.40	2.34	.47
	Total cortical grey	.17	0.64	0.33	1.19	
	Subcortical grey	.42	1.55	0.54	4.52	
MNC 1	Total white matter	.25	0.70	0.38	1.27	.63
	Total cortical grey	.33	1.24	0.81	1.91	
	Subcortical grey	.76	1.12	0.55	2.29	
NMM 1 (Alpha = 10)	Total white matter	.10	0.60	0.32	1.09	.42
	Total cortical grey	.41	1.20	0.78	1.85	
	Subcortical grey	.60	1.21	0.59	2.52	
NMM 1 (Alpha = 15)	Total white matter	.17	0.65	0.35	1.19	.56
	Total cortical grey	.50	1.16	0.76	1.80	
	Subcortical grey	.73	1.14	0.55	2.37	
NMM 1 (Alpha = 20)	Total white matter	.14	0.63	0.34	1.15	.52
	Total cortical grey	.57	1.13	0.74	1.76	
	Subcortical grey	.56	1.25	0.60	2.62	
NMM 1 (Alpha = 25)	Total white matter	.22	0.67	0.36	1.26	.53
	Total cortical grey	.91	0.98	0.62	1.53	
	Subcortical grey	.63	1.21	0.56	2.61	
Wright	Total white matter	.06	0.25	0.06	1.08	.06
	Total cortical grey	.52	0.72	0.22	1.90	
	Subcortical grey	.65	1.60	0.22	13.10	
GDS 2	Total white matter	.45	0.80	0.45	1.42	.30
	Total cortical grey	.24	0.79	0.52	1.18	
	Subcortical grey	.56	1.23	0.61	2.47	
Frascati 3	Total white matter	.15	0.65	0.35	1.16	.10
	Total cortical grey	.20	0.76	0.50	1.15	
	Subcortical grey	.19	1.61	0.80	3.30	
Gisslen 2	Total white matter	.69	0.86	0.40	1.79	.11
	Total cortical grey	.52	0.84	0.50	1.42	
	Subcortical grey	.37	0.67	0.27	1.60	
MNC 2	Total white matter	.21	0.69	0.38	1.23	.60
	Total cortical grey	.99	1.00	0.67	1.51	

	Subcortical grey	.50	1.26	0.64	2.52	
NMM 2 (Alpha = 10)	Total white matter	.71	0.90	0.50	1.59	.83
	Total cortical grey	.91	0.98	0.65	1.48	
	Subcortical grey	.80	0.92	0.46	1.83	
NMM 2 (Alpha = 15)	Total white matter	.69	0.89	0.50	1.58	.86
	Total cortical grey	.83	0.96	0.64	1.44	
	Subcortical grey	.94	0.97	0.49	1.93	
NMM 2 (Alpha = 20)	Total white matter	.15	0.65	0.36	1.15	.45
	Total cortical grey	.98	1.01	0.67	1.52	
	Subcortical grey	.52	1.25	0.63	2.50	
NMM 2 (Alpha = 25)	Total white matter	.15	0.65	0.36	1.15	.38
	Total cortical grey	.76	0.94	0.62	1.41	
	Subcortical grey	.34	1.40	0.70	2.83	

Note. OR = Odds ratio; CI = confidence interval; GDS = global deficit score; MNC = multivariate normative comparison; NMM = novel multivariate method.

*Significant at $p \leq .05$; **Significant after controlling False Discovery Rate (FDR) ≤ 0.05

Table 4

Diffusion Tensor Imaging Data: Results from the logistic regression models for the 20 methods of defining cognitive impairment (N = 148)

				95% CI		
		p	*OR*	*Lower*	*Upper*	*Overall model p*
GDS 1	FA	.77	0.97	0.78	1.20	.22
	MD	.16	1.09	0.97	1.25	
Frascati 1	FA	.78	1.04	0.78	1.39	.36
	MD	.18	1.13	0.95	1.37	
Frascati 2	FA	.56	0.94	0.75	1.17	.68
	MD	.73	1.02	0.90	1.16	
Gates & Cysique	FA	.23	0.87	0.69	1.09	.37
	MD	.89	1.01	0.89	1.15	
Gisslen 1	FA	.39	0.91	0.72	1.13	.54
	MD	.79	1.02	0.90	1.16	
Milanini	FA	.93	0.99	0.70	1.36	.07
	MD	.06	1.25	1.01	1.59	
MNC 1	FA	.80	0.97	0.78	1.21	.47
	MD	.34	1.07	0.94	1.22	
NMM 1 (Alpha = 10)	FA	.59	0.94	0.75	1.18	.45
	MD	.43	1.05	0.93	1.20	
NMM 1 (Alpha = 15)	FA	.56	0.94	0.74	1.17	.42
	MD	.42	1.06	0.93	1.21	
NMM 1 (Alpha = 20)	FA	.58	0.94	0.74	1.18	.22
	MD	.22	1.09	0.95	1.25	
NMM 1 (Alpha = 25)	FA	.50	0.92	0.72	1.17	.03*
	MD	.05	1.16	1.00	1.36	
Wright	FA	.81	0.92	0.48	1.70	.97
	MD	.88	0.97	0.70	1.43	
GDS 2	FA	.60	0.94	0.76	1.17	.64
	MD	.63	1.03	0.91	1.16	
Frascati 3	FA	.19	0.87	0.69	1.07	.35
	MD	.28	0.94	0.83	1.05	

Gisslen 2	FA	.38	0.89	0.68	1.16	.64
	MD	.51	0.95	0.81	1.10	
MNC 2	FA	.42	0.92	0.74	1.13	.61
	MD	.86	1.01	0.90	1.14	
NMM 2 (Alpha = 10)	FA	.40	0.91	0.73	1.13	.69
	MD	.86	0.99	0.88	1.12	
NMM 2 (Alpha = 15)	FA	.53	0.93	0.75	1.16	.79
	MD	.98	1.00	0.89	1.13	
NMM 2 (Alpha = 20)	FA	.12	0.84	0.67	1.04	.28
	MD	.61	0.97	0.86	1.09	
NMM 2 (Alpha = 25)	FA	.18	0.86	0.69	1.07	.32
	MD	.99	1.00	0.89	1.13	

Note. MD = mean diffusivity (x100000); FA = fractional anisotropy (x100000); GDS = global deficit score; MNC = multivariate normative comparison; NMM = novel multivariate method. *Significant at $p \leq .05$; **Significant after controlling False Discovery Rate (FDR) ≤ 0.05

Discussion

We identified, after a thorough literature search, eight different sets of criteria used by research studies to define cognitive impairment in PWH. These eight sets of criteria can be applied to neuropsychological test scores in different ways, resulting in 20 separate methods that can be used to classify PWH as impaired or unimpaired. Although it is not clear whether all of these methods have been used in the literature (many studies do not provide sufficient details of their analytic procedures), all are viable ways to classify cognitive impairment. After applying each method separately to our data (demographically adjusted *T*-scores from 148 South African PWH), we found that rates of cognitive impairment ranged from 20% to 97%.

We then sought to determine which of the 20 methods correlated best with neuroimaging biomarkers that served as proxies for HIV-brain pathology. The answer to this question would, we thought, provide guidance as to which method we might implement in our setting (a peri-urban South African township with high HIV prevalence, high levels of poverty and low levels of education; Smit et al., 2016; City of Cape Town, 2013). However, no cognitive outcome was significantly associated with any neuroimaging outcome. The great variation in results depending on method used, and lack of any association between cognitive impairment and imaging biomarkers, raises interesting questions about the validity of these methods and interpretation of cognitive data in this population of PWH.

Some variability in our observed rates arose from whether the chosen criteria for defining cognitive impairment were applied across individual test *T*-scores (i.e., each test score is

considered separately) or across average domain *T*-scores. The choice of whether or not to calculate average domain *T*-scores is a decision researchers make early in the process of applying criteria for cognitive impairment. Of note here is that, within the current data, methods using average domain *T*-scores produced lower estimates of cognitive impairment and less variation.

Some variability in our observed rates arose from how within-domain impairment was defined by different sets of criteria. For example, within the Frascati criteria, we applied three methods of indicating within-domain impairment: if performance on one test within a domain was ≥ 1 *SD* below normative mean, if performance on two tests within a domain was ≥ 1 *SD* below normative mean, and if an average domain *T*-score was ≥ 1 *SD* below the normative mean. These three approaches resulted in quite different estimated rates of cognitive impairment: 84%, 35%, and 45%, respectively. Hence, even when the choice of criteria is consistent, the subsequent choice of how within-domain impairment is defined appears to produce inconsistent estimates of impairment.

Criteria for defining cognitive impairment in PWH (and/or applications of methods within those criteria) that lead to calculations of high rates risk overestimating the extent of the problem, leading to potential for unnecessary anxiety and stigma (Nightingale et al., 2014). Conversely, overly stringent methods risk missing some people who could benefit from help (Grant et al., 2014; Tierney et al., 2017). Our data suggest that calculating domain *T*-scores before applying criteria is preferable to applying criteria across individual test scores because the methods that calculate domain *T*-scores are slightly more stringent and substantially less variable. Calculating domain *T*-scores (or domain *z*-scores) before applying the method to define cognitive impairment is also more common in the literature and has been recommended as being a better approach (Meyer et al., 2013). Even if researchers choose different criteria to define cognitive impairment, consensus among researchers to calculate average domain *T*-scores will reduce the amount of variability that arises from different definitions of within-domain impairment, will ensure greater consistency and less variation in across-study reporting of rates, and will reduce the risk of prevalence overestimation.

In this study, the mean rate of cognitive impairment defined by the methods applied across average domain *T*-scores was 45%, which is consistent with a recent meta-analysis of global HAND prevalence. The meta-analysis showed a mean HAND prevalence of 45% in Sub-Saharan Africa, and 43% overall (prevalence rates varied from 11-92%; Wang et al., 2020). The

mean rate of cognitive impairment defined by methods applied across individual test *T*-scores was higher (67%) than the mean reported in the meta-analysis. It is possible that this indicates a higher rate of impairment in our population compared to some other studies or a tendency of this application of the methods to overestimate impairment.

We found no relationship between cognitive impairment (no matter which method defined it) and regional brain volumes or DTI metrics. One possible explanation for this lack of association is that regional brain volumes and DTI metrics are inaccurate proxies for HIV-related brain pathology for the population from which this sample was drawn. However, several studies have demonstrated the utility of MRI in this context (Heaps et al., 2012; Ortega et al., 2013; Paul et al., 2017) and cognitive impairment (as defined by various methods) has been associated with diffusion abnormalities and brain volumes in other cohorts from high-income countries (Alakkas et al., 2019; Campbell et al., 2020; Underwood et al., 2017; Underwood et al., 2019). Unfortunately, studies with detailed neuroimaging data from PWH in low-income settings, such as ours, are scarce. One study conducted in Thailand also found no difference in brain volumes between those with or without cognitive impairment (as classified using Frascati criteria in a consensus case conference). In an attempt to explain this result, the authors indicated that the largest subgroup was comprised of participants classified with ANI, and that therefore their impaired cognitive performance may not be reflected in measures of brain pathology (Heaps et al., 2015). Those authors did find, however, that PWH had smaller regional brain volumes compared to HIV-negative individuals. Similarly, in another study conducted on same sample as the one studied here, PWH exhibited smaller total grey matter volumes and total white matter volumes compared to HIV-negative controls (Paul et al., 2017).

Because there are differences in brain volumes between PWH and controls, we assume that this metric can indicate HIV-related brain pathology, and that the classification methods themselves are limited in their ability to diagnose this. Therefore, another possible reason our analyses did not detect significant associations between cognitive impairment and neuroimaging outcomes is that test performance may be a poor indicator of HIV-related brain pathology in this population (i.e., test performance may be better explained by non-biological factors). Numerous previous studies have established that cognitive impairment in PWH can be multifactorial (Ciccarelli, 2019; Torti et al., 2011). For instance, in communities with high levels of social and economic deprivation, socioeconomic factors can strongly influence cognitive test performance

(see, e.g., Spies et al., 2016; Watson et al., 2019). Although we used normative data that was matched for demographic and educational characteristics to reduce the impact of such factors, we did not measure and control for all possible non-organic contributors to poor cognitive performance in vulnerable populations (e.g., low-quality education, food insecurity, poor access to resources, high levels of co-morbidities, childhood trauma, etc.). Control for these sources of variation is, however, rare in HIV studies.

The results reported here should be considered with several limitations in mind. First, the methods used to define cognitive impairment involved analysis of cognitive test performance alone, without data from additional clinical measures such as subjective reports of cognitive symptoms or functional scales. Although assessment of functional impairment is a part of the application of, for instance, the Frascati criteria, many research studies do not include such assessment, and the minimum criteria for HAND is met without functional impairment (i.e. ANI). In the clinical setting, however, there is an emphasis on symptom reports (both from the patient themself and from collateral sources) and cognitive test performance is interpreted in the context of the patient's presentation and estimates of premorbid functioning. This context can be lacking in research settings and may explain some of the lack of association between test performance and neuroimaging. Second, there are areas we did not consider which create the potential for further between-study variability in rates. These include how the normative data are derived and applied, how the cognitive domains are constructed, and the number of tests/subtests included. We attempted to reduce the influence of these factors by processing the cognitive data according to best-practice means, or in ways consistent with most studies in the field. Third, our study sample was small and drawn from a specific peri-urban Cape Town population. Hence, it is unclear how the current findings extrapolate to PWH more broadly, in southern Africa and beyond. Fourth, the participants had recently started ART and the vast majority remained viraemic. Hence, this sample is not representative of the general population of clinic patients, most of whom are suppressed on effective ART. Since participants in this study had uncontrolled HIV, HIV-associated brain injury is more likely and a stronger association between neuroimaging markers and cognitive impairment would have been expected.

Finally, relationships between cognitive and neuroimaging outcomes are complex, and we did not investigate whether non-linear approaches (such as quantile regression analysis) might have detected a statistically significant relationship between the two. Neuroimaging

metrics as a biological basis of cognitive impairment are also limited in that the approach does not account for cognitive reserve nor plasticity. Therefore, neuroimaging biomarkers may not accurately reflect cognitive impairment, and vice versa. It is possible that CSF biomarkers of HIV-related brain injury (e.g., neurofilament light protein [NFL]), would have more accurately reflected cognitive impairment than neuroimaging biomarkers (Gisslén et al., 2016).

A consideration for future studies is that classification of cognitive performance into separate cognitive domains may be more sensitive than dichotomized outcomes (Phillips et al., 2018). In addition to investigating cognitive domains separately, investigation of specific brain volumes of interest (vs. whole-brain volumes) might be better able to tease out the differing effects of HIV and socioeconomic status on the brain (Lotze et al., 2020; Ortega et al., 2013; Yaple & Yu, 2020). In addition, future studies should investigate the current question with regard to sex differences in cognitive functioning (i.e., whether some methods are more effective in defining cognitive impairment in women/men).

Overall, our results imply that perhaps no method of defining cognitive impairment in PWH that is based entirely on cognitive performance accurately reflects HIV-related brain pathology in this population, and that the high rates of cognitive impairment in this population may be attributed to non-biological causes. If none of the current methods used to define cognitive impairment are able to adequately identify HIV-related brain pathology in a setting such as ours, we may be misclassifying and over-estimating the prevalence rates of HIV-associated impairment in our population. This carries the risk of stigma and discrimination for an already marginalized group. Hence, as others (see, e.g. Ciccarelli, 2019; Saloner & Cysique, 2017) have highlighted, there is a need for updated research criteria, particularly for diverse low- and middle-income settings. Such criteria should (a) consider that performance on cognitive tests may bear a statistically non-significant relationship with HIV-related biological damage, and (b) use clinical measures such as symptom report questionnaires and functional scales that gauge estimates of premorbid functioning and clinical progression alongside cognitive test performance to define cognitive impairment.

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Chapter 5

Cognitive Performance in a South African Cohort of People with HIV and Comorbid Major Depressive Disorder

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Description of the contribution of candidate and co-authors

AJD was the first author of this manuscript. This entailed leading the drafting, analyses and conceptualising. These data were collected as part of a larger research program for a randomised controlled trial of a cognitive-behavioral treatment for ART adherence and depression (CBT-AD), which involved JAJ, SAS, CO and JL. AJD developed and implemented the study protocol for the neuropsychological supplement project, with guidance from JAJ, LSA and KGFT. This involved writing the protocol, obtaining ethical approval, and ensuring ethical standards and procedures were followed, including protocol modifications, deviations and annual progress reports. AJD managed the daily running of the supplement project, including the finances, the care of the participants, overseeing the data collection and quality checking the data.

In this manuscript, AJD formulated the research questions, cleaned, analysed and interpreted the data, and wrote the manuscript. JAJ, SN and KGFT contributed to the manuscript by providing guidance, discussing ideas and reviewing drafts and JL provided input into data management and analyses. All co-authors provided input, reviewed drafts and approved the final manuscript.

Current status Published in Journal of Neurovirology

Dreyer, A. J., Nightingale, S., Andersen, L. S., Lee, J. S., Gouse, H., Safren, S. A., O'Cleirigh, C., Thomas, K. G. F., & Joska, J. (2022). Cognitive performance in a South African cohort of people with HIV and comorbid major depressive disorder. *Journal of Neurovirology.* https://doi.org/10.1007/s13365-022-01093-0

Abstract

Cognitive performance in people with HIV (PWH) may be affected by brain injury attributable to the infection itself, by other medical and psychiatric comorbidities (including major depressive disorder; MDD), and by psychosocial factors (e.g., education, food insecurity). We investigated effects of these variables on cognitive performance in a South African cohort of PWH with comorbid MDD and incomplete adherence to antiretroviral therapy (ART). We also examined (a) associations of depression severity with cognitive performance, and (b) whether improvement in depression led to improved cognitive performance. Participants (N = 105) completed baseline neuropsychological, psychiatric, and sociodemographic assessments. Subsequently, 33 were assigned to a cognitive-behavioural therapy for ART adherence and depression (CBT-AD) and 72 to standard-of-care treatment. Eight months post-baseline, 81 (nCBT-AD = 29) repeated the assessments. We investigated (a) baseline associations between sociodemographic, medical, and psychiatric variables and cognitive performance, (b) whether, from baseline to follow-up, depression and cognitive performance improved significantly more in CBT-AD participants, and (c) associations between post-intervention improvements in depression and cognitive performance. At baseline, less education (β = 0.62) and greater food insecurity (β = -0.20) predicted poorer overall cognitive performance; more severe depression predicted impairment in the Attention/Working Memory domain only (β = -0.25). From baseline to follow-up, depression decreased significantly more in CBT-AD participants (p = .017). Improvement over time in depression and cognitive performance were not significantly associated except in the Attention/Working Memory domain (p = .026). Overall, factors associated with cognitive performance were unrelated to brain injury. We conclude that clinicians examining PWH presenting with cognitive difficulties must assess depression, and that researchers investigating cognitive impairment in PWH must collect information on psychosocial factors.

Keywords: cognition; depression; food insecurity; HIV; socioeconomic status

Introduction

Various factors contribute to the low cognitive performance often observed in people with HIV (PWH). This is because cognition in PWH can be affected by a range of insults to neurological function, including direct injury to the brain from the infection itself and/or from other medical and psychiatric comorbidities (Hong & Banks, 2015; Nightingale & Winston, 2017; Winston & Spudich, 2020).

Co-morbid and co-occurring medical conditions that are highly prevalent in populations of PWH and that contribute to cognitive impairment include cerebrovascular disease (Vinikoor et al., 2013), substance use disorders (Millar et al., 2017), central nervous system (CNS) opportunistic infections (Saloner et al., 2019), and neurological insults such as head injuries (Lin et al., 2011). Among psychiatric conditions that are notable for the same reasons, major depressive disorder (MDD) is the most significant. Depression is more prevalent in PWH than in the general population (Freeman et al., 2008; Lofgren et al., 2020; Rezaei et al., 2019). Broadly speaking, a comorbid diagnosis of MDD in PWH negatively affects performance across the cognitive domains of motor function, processing speed, attention/working memory, learning and memory, and executive function (Bragança & Palha, 2011; Fellows et al., 2013; Goggin et al., 1997; Rock et al., 2014; Rubin & Maki, 2019). More severe depression is associated with greater impairment in these domains (McDermott & Ebmeier, 2009; Paolillo et al., 2020; Shimizu et al., 2011).

Two distinct reasons may explain why PWH with comorbid MDD display these cognitive impairments. First, in cases where there is no identifiable pathological mechanism, the depression itself may give rise to cognitive deficits (Kang et al., 2014; Kiloh, 1961). Second, the depression and cognitive impairment may share a common underlying pathological mechanism (neuroinflammation, caused by HIV infection of the CNS; Del Guerra et al., 2013; Fellows et al., 2013; Leonard & Maes, 2012; Miller et al., 2009).

Incomplete adherence to antiretroviral therapy (ART) can also contribute to poor cognitive performance in PWH. Lack of adherence can lead to worse HIV disease outcomes (i.e., higher HIV RNA viral load, lower current and nadir CD4 count) and, consequently, a greater risk of cognitive impairment. In addition, ART can be associated with neurotoxicity. Efavirenz, particularly, has neuropsychiatric side effects (Cysique & Becker, 2017; Saylor et al., 2016; Winston & Spudich, 2020).

Aside from medical and psychiatric comorbidities, psychosocial factors (e.g., educational level, socioeconomic status, and food insecurity) can also strongly influence

cognitive performance in PWH (Cysique & Becker, 2015; Dreyer et al., 2021b; Kabuba et al., 2018; Nightingale et al., 2021; Watson et al., 2019; Winston & Spudich, 2020).

Despite the numerous and varied factors that might contribute to poor cognitive performance in PWH, interventions targeted at improving that performance are rare: Most extant intervention programs tend to focus on improving HIV disease outcomes via management of ART (Alford & Vera, 2018; Winston & Spudich, 2020). Of particular interest here is that no studies to date have investigated whether treating depression improves cognitive performance in PWH and whether depression-related cognitive deficits are reversible in PWH. This is a notable knowledge gap especially given that cognitive-behavioural therapy for adherence and depression (CBT-AD) has an accumulated evidence base, including for PWH in South Africa (Mendez et al., 2021; Safren et al., 2014; Safren et al., 2021; Safren et al., 2009; Sherr et al., 2011). If cognitive impairment is non-organic (i.e., caused by the depression itself, without an identifiable pathological mechanism), successful treatment of the depressive disorder with CBT-AD should improve cognitive outcomes (Connors et al., 2019).

Hence, the current study had two primary aims. First, we sought to investigate the contribution of HIV-related factors, medical and psychiatric comorbidities, and psychosocial variables to cognitive performance in a sample of PWH and comorbid major depressive disorder, who have incomplete ART adherence. Identifying potentially modifiable contributors to cognitive impairment in PWH could aid treatment strategies and help improve the functioning of PWH. Second, we sought to determine whether (a) depression severity in that sample is associated with impaired cognitive performance, and (b) improvement in depression over time, as a consequence of exposure to either CBT-AD or standard of care, leads to improved cognitive test performance.

Method

Participants and Setting

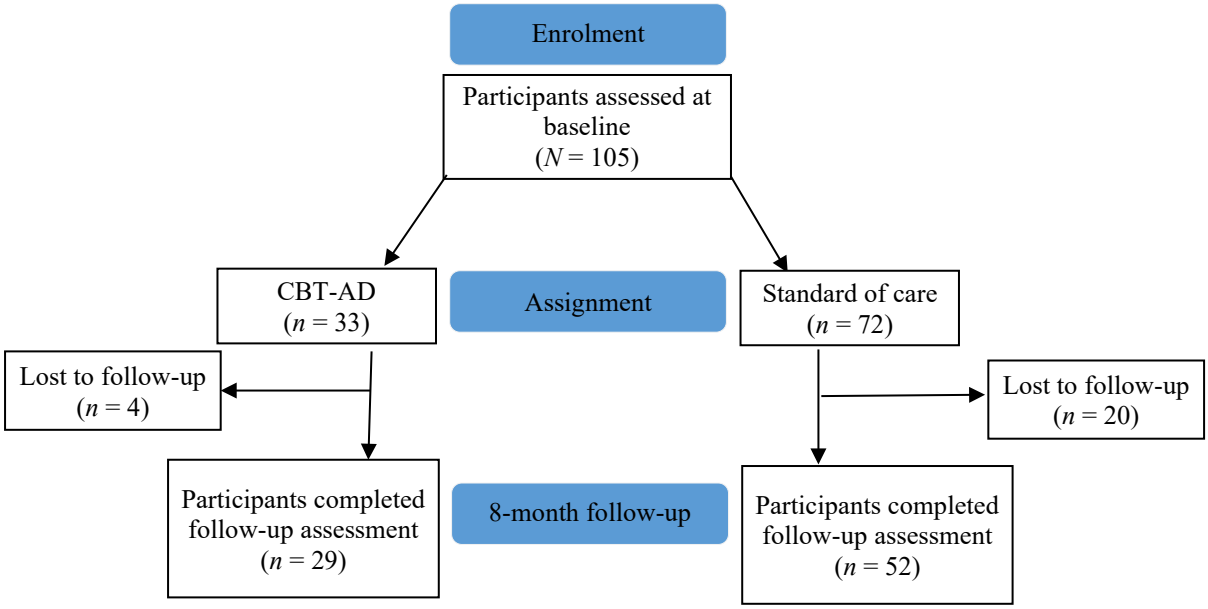
Participants were 105 PWH with MDD who had failed first-line ART. Those who were not virally suppressed (HIV RNA viral load > 400 copies/mL) at baseline (n = 72) were part of the sample of a large randomised controlled trial of a cognitive-behavioural treatment for ART adherence and depression (CBT-AD; Joska et al., 2020; Safren et al., 2021). Of those 72, 33 had been assigned to the treatment arm and 39 to a standard of care condition. As part of this study, an additional 33 participants who were not part of the trial were also assigned to

a standard of care condition. Hence, in this study, we had 33 participants in the CBT-AD group and 72 participants in the standard of care group.

Of the total sample of 105 participants, 81 (29 in the CBT-AD group, 52 in the standard of care group) were assessed again 8 months later (see Figure 1).

Figure 1

Flowchart depicting stages of the study protocols



Note. CBT-AD = cognitive-behavioural treatment for ART adherence and depression.

Data collection occurred at two primary care community clinics in Khayelitsha, a peri-urban community in Cape Town, South Africa. Khayelitsha was established under the principle of racial segregation executed by the apartheid regime. As a consequence of this legacy, today almost all of its residents are Black African and it is one of the poorest areas of Cape Town. Most adult residents of Khayelitsha speak isiXhosa as a first language, fewer than one-third of adult residents have completed high school, and there are high levels of HIV infection, crime, and unemployment (Crush et al., 2012; Nleya & Thompson, 2009; Smit et al., 2016; Stern et al., 2017; City of Cape Town, 2013).

Inclusion criteria for this study were (a) ≥ 18 years of age, (b) HIV-seropositive status (confirmed via medical record), (c) current diagnosis of MDD (according to the Mini International Neuropsychiatric Interview [MINI; Sheehan 2014]), and (d) failed first-line ART (identified by the community clinic as not having collected ART for > 3 months).

We did not exclude participants with medical and psychiatric co-morbidities and/or other factors that could influence cognitive performance because we wanted the sample

population to be representative of the clinical population of interest (i.e., PWH with MDD and incomplete ART adherence). The only exclusion criteria were (a) active and untreated major mental illness (i.e., psychosis or mania) that would interfere with participation, (b) inability or unwillingness to provide informed consent, and (c) lack of sufficient fluency in English or isiXhosa. Participants using antidepressants were eligible even if they met criteria for a current depressive episode; however, they had to have been on a stable antidepressant regimen and dose for at least 2 months.

All participants provided written informed consent. The study protocol was approved by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee and the University of Miami Institutional Review Board.

Materials

Participants completed a neuropsychological test battery and measures of sociodemographic, HIV disease, and psychiatric characteristics. We also collected information not routinely gathered in HIV studies: psychosocial data, including those related to socioeconomic status (e.g., income, food insecurity), and medical history (neurological and cerebrovascular risk factors).

Neuropsychological assessment. The neuropsychological battery comprised 17 standardized tests, each of which assessed performance in one of seven cognitive domains commonly affected by HIV (Grant, 2008). This battery of tests has demonstrated adequate psychometric properties in this setting (Joska et al., 2011; Nyamayaro et al., 2020).

The domains, tests, and outcome variables were: (1) *executive functioning*, as measured by the Color Trails Test 2 (CTT2), with the specific outcome variable being completion time; Wisconsin Card Sorting Test (WCST) - perseverative errors; (2) *verbal learning and memory*, Hopkins Verbal Learning Test-Revised (HVLT-R) - total across the three immediate recall trials, total on the delayed recall trial; (3) *visuospatial learning and memory,* Brief Visuospatial Memory Test-Revised (BVMT-R) – total across the immediate recall trials, total on the delayed recall trial; (4) *verbal fluency*, category fluency test - total number of animals / total number of fruits and vegetables named in 1 minute; (5) *attention/working memory*, Wechsler Memory Scale-Third Edition (WMS-III) Spatial Span subtest – total raw score; Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span subtest - total raw score; (6) *processing speed*, CTT1 - completion time; WAIS-III Digit Symbol Coding subtest - total raw score; WAIS-III Symbol Search - total raw score; (7) *motor skills*, Grooved Pegboard Test (GPT) dominant (DH) and nondominant hand (NDH) - completion time; Finger Tapping Test DH and NDH - completion time.

Tests were administered in either English or isiXhosa, depending on the participant's preference, by a bilingual neuropsychology technician.

Measures of sociodemographic variables. Participants self-reported basic sociodemographic information (i.e., gender, age, highest level of education, monthly household income, primary language, and employment status) as well as details of their school performance (e.g., whether they had ever been held back or repeated a year in school, whether they were fully literate).

Measures of HIV disease variables. HIV viral load and current CD4 cell number were extracted from the medical records. If participants did not have recent (1-month) testing, we collected blood samples (see Joska et al. 2020 for additional detail). ART regimens (i.e., reinitiated on first line, second line, or third line) were also extracted from the participant's medical record. Participants also self-reported whether their nadir CD4 count had ever been below 100 cells/μL.

Measures of psychiatric variables. Psychiatric disorders were diagnosed using the MINI structured diagnostic interview (Sheehan, 2014). This interview was conducted by a psychiatric nurse and supervised by a clinical psychologist. The Alcohol Use Disorders Identification Test (AUDIT; cut off >20; Saunders et al., 1993) was used to indicate high risk alcohol use and the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960; Williams et al., 2008) was used to assess depression severity. HAM-D scores between 0 and 7 indicate no depression; 8–16, mild depression; 17–23, moderate depression; ≥24, severe depression (Zimmerman et al., 2013).

Measures of psychosocial and socioeconomic variables. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993) assessed satisfaction in daily life. A modified version of the Adult AIDS Clinical Trials Group [ACTG] SF-21 (Wu et al., 1997) assessed health-related quality of life (i.e., related to physical, social and cognitive functioning and emotional well-being). The Household Food Insecurity Access Scale (HFIAS; Coates et al., 2007) measured household food insecurity. Each of these was completed by the participant with the help of the research team.

Measures of medical history. Participants were classified as having a significant history of neurological problems if they reported ever having experienced one or more of the following neurological events: a closed or open head injury with loss of consciousness > 30 minutes; a stroke; a coma; epilepsy; a seizure without a diagnosis of epilepsy; bacterial meningitis.

Participants were classified as having a significant history of vascular risk factors if they reported two or more of the following vascular risk factors: any heart problem (such as coronary artery disease, heart arrhythmia or other heart diseases); heart attack; diagnosis of hypertension (irrespective of whether they were on medication or not); diagnosis of diabetes; history of having smoked cigarettes.

Procedure

Individuals who remained eligible for study participation after the screening procedures were scheduled for the set of baseline visits. The baseline neuropsychological assessment, along with the measures of medical history, happened on a separate visit to the rest of the measures (these two visits were separated by approximately 2 weeks). After the baseline visits, participants randomised to the CBT-AD condition received the intervention described by Joska et al. (2020) and Safren et al. (2021). Briefly, the intervention was organized across five modules, with one each covering psychoeducation about depression, motivational interviewing, problem solving, behavioural activation, and medication adherence (Safren et al., 1999). It was delivered over eight sessions by trained nurses, using a task-sharing approach.

Participants in the comparison group received standard of care offered at the community clinic, along with a letter of referral to the medical officer listing the psychiatric and cognitive disorders for which they had met diagnostic criteria.

All participants were scheduled for a follow-up visit 8 months post-baseline. At that visit, they were readministered the neuropsychological test battery and the HAM-D.

Statistical Analysis

We used R version 4.1.2 (2021-11-01) and RStudio version 2021.09.0 to complete all analyses, with the threshold for statistical significance set at $\alpha = .05$.

First, we processed and standardized the neuropsychological data. Normative standards for the neuropsychological tests were based on control data collected by two previous studies in the UCT HIV Mental Health Research Unit (Gouse & Robbins, personal communication, June 2018; Westgarth-Taylor & Joska, personal communication, November 2017). To assure similarity across key demographic (age, ethnicity, language, education), psychosocial, and socioeconomic characteristics, these data were collected between 2008 and 2016 from healthy community-dwelling individuals ($N = 233$) who presented at the same community clinics in Khayelitsha from which the current sample was recruited. In the studies that collected the control data, participant inclusion criteria (1) HIV seronegative, (2) ≥ 18 years of age, and (3) at least 5 years of formal education. Exclusion criteria were (1) major

psychiatric conditions, (2) neurological disease that could affect brain integrity, (3) lifetime history of head injury resulting in loss of consciousness >30 min, and (4) current substance use disorder.

We used the control data to calculate demographically corrected *z*-scores, using standard regression-based norming processes. The *z*-scores were then converted to demographically corrected *T*-scores ($M = 50$, $SD = 10$). If participants had *z*-scores greater than 5 SD below the mean, the conversion to a *T*-score resulted in negative *T*-score. In these cases, we assigned a score of zero, the lowest possible *T*-score to maintain the clinical significance of the low performance. Neuropsychological data were summarised into domain and global *T*-scores by taking the average of *T*-scores within each domain and then across domain *T*-scores.

Second, we calculated sample descriptive statistics (values taken at the baseline assessment). Categories for food insecurity (food secure/mildly food insecure/moderately food insecure/severely food insecure) and the prevalence of different levels of household food insecurity were calculated using the equations provided in the HFIAS Guide, v.3 (Coates et al., 2007). These equations were coded in R to calculate the proportion of participants classified as experiencing severe food insecurity. T-tests (or welch two sample t-tests when groups had unequal variance) and chi-square analyses were used to investigate differences in baseline characteristics between the CBT-AD and standard of care groups.

Third, we used univariable linear regressions to investigate the association, at baseline, between each of the sociodemographic, medical, and psychiatric variables and overall cognitive functioning (as estimated by the global *T*-score). Initially, strength of associations were determined using Pearson and point-biserial correlation coefficients. Subsequently, variables significantly associated ($p < .05$) with global *T*-scores were entered into multivariable linear regression models to determine which best explained cognitive test performance. A backwards stepwise approach was used for model building, where the variables with the smallest *t*-value were sequentially removed from the model. Each time a variable was removed, the new model was compared to the previous model using a chi-square test to ensure that that removal had no significant effect on the model. For each model, Cook's *D* investigated influential outliers. We examined any point with a Cook's D over $4/n$, where n is the number of observations. Outliers were deleted from the analyses if the model was improved without them.

Fourth, to investigate the association, at baseline, between depression severity (as measured by HAM-D score) and performance within each cognitive domain (as measured by

the domain *T*-score), we used univariable linear regression modeling and Pearson and point-biserial correlations.

Fifth, to determine whether the CBT-AD treatment improved depression severity and cognitive test performance and whether improvements in depression severity were associated with improvements in cognitive test performance over time, we used linear mixed-effects modelling fit by maximum likelihood. The first model had HAM-D scores as an outcome to determine if, from baseline to follow-up, depression scores had improved significantly more in the group assigned to receive CBT-AD. We then built models with the global domain *T*-score and each cognitive domain *T*-score as a separate outcome variables to investigate whether, from baseline to follow-up, (1) cognitive test performance of participants assigned to the CBT-AD condition had improved significantly more than that of those assigned to the standard of care condition, and (2) improvement in HAM-D scores in both groups was associated with improvement in cognitive test performance at follow-up.

Results

Table 1 presents the sample's sociodemographic and clinical characteristics. Most participants were women, a statistic representative of the South African PWH population (George et al., 2019). isiXhosa was the primary language of almost all participants (93%). The sample's median monthly household income was USD100, 89% were unemployed, and 68% had experienced severe food insecurity.

Regarding educational characteristics, most participants (85%) had not completed high school (in South Africa, this is 12 years capped by a major exit examination); 13% of the sample self-reported that they could not read or write; and 69% had been held back at least one year due to poor academic performance.

Table 1

Sample Sociodemographic and Clinical Variables at Baseline: Descriptive Statistics (N = 105)

Variable	*M (SD)*	*f (%)*
Sociodemographic		
Sex (female)		76 (72.38%)
Age (yrs)	39.79 (9.14)	
Education (yrs completed)	9.30 (2.45)	
Monthly household income (ZAR)	1600 (0–2900) [a]	
HFIAS [b]	12.74 (6.90)	
ACTG SF-21	46.65 (16.18)	

Q-LES-Q	41.83 (12.85)	
Held back in school		72 (68.57%)
Literacy [c]		91 (86.67%)
Medical		
Log_{10} HIV viral load	3.56 (1.44)	
Current absolute CD4	248.49 (209.38)	
History of neurological events	-	37 (35.24%)
Vascular risk		16 (15.24%)
ART regimens		
Reinitiated		56 (53.85%)
Second		47 (45.19%)
Third		1 (0.96%)
HIV RNA viral suppression [d]		25 (23.81%)
Self-reported nadir CD4 count <100 cells/ml		68 (64.76%)
Psychiatric		
HAM-D	25.63 (7.10)	
High risk alcohol use [e]		30 (28.85%)
Past diagnosis of MDD		96 (93.20%)
History of recurrent MDD		22 (21.15%)

Note. [a]Median (interquartile range); [b]Higher score indicates greater food insecurity; [c]Percentage of participants who could read and write; [d]HIV RNA viral load < 400 copies/mL; [e]Indicated if AUDIT score > 20. ZAR = South African Rands; HFIAS = Household Food Insecurity Access Scale; ACTG SF-21 = Adult AIDS Clinical Trials Group SF-21; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; ART = antiretroviral therapy; HAM-D = Hamilton Rating Scale for Depression; MDD = major depressive disorder.

Regarding HIV disease variables, two-thirds of the sample reported a nadir CD4 count of below 100 cells/μL. Just over half of participants had been reinitiated on first-line treatment ART; 45% had been prescribed second-line ART.

Regarding other medical history, 35% of participants had a history of significant neurological events and 15% met the criteria for having significant cardiovascular disease risk factors.

Regarding psychiatric history, all participants had a primary diagnosis of current MDD, 93% of participants met criteria for a diagnosis of MDD once in the past and 21% had a history of recurrent MDD. The average HAM-D score fell within the 'severe depression' range (M = 25.63, SD = 7.10) at baseline (Zimmerman et al., 2013), with 61% of participants endorsing current suicidal ideation and/or a lifetime history of making a suicide attempt.

Regarding other psychiatric disorders (as per MINI diagnosis), 41% of participants met criteria for current alcohol use disorder, with the mean AUDIT scores indicating harmful alcohol consumption (Saunders et al., 1993). Finally, 8% of participants met criteria for panic

disorder, 6% for agoraphobia, 4% for post-traumatic stress disorder, 2% for social anxiety disorder, and 2% for substance use disorder. No participants met criteria for bipolar mood disorder, obsessive-compulsive disorder, or generalised anxiety disorder.

Regarding differences in baseline sociodemographic and clinical characteristics between the CBT-AD and standard of care group, there were no significant group differences in HAM-D scores (p = .197) and other baseline characteristics (ps > .056), except for Q-LES-Q scores (p = .013) which were significantly higher in the CBT-AD group (M = 46.37, SD = 11.22) compared to the standard of care group (M = 39.71, SD = 13.09). There were also no significant group differences in baseline global or cognitive domain T-scores (ps > .161). Viral non-suppression was an entry criterion for the CBD-AD group, whereas 34.72% of the standard of care group were virally suppressed at baseline.

Associations of Sociodemographic, Medical, and Psychiatric Variables with Cognitive Performance at Baseline

The results of the univariable associational analyses (measured using linear regression; see Table 2) showed that older age, fewer years of education, and greater food insecurity were significantly associated with lower global T-scores at baseline. There were no significant associations between global T-scores and any of the medical or psychiatric variables, including HIV disease variables and depression severity.

Table 2

Univariable Associations of Sociodemographic, Medical, and Psychiatric Variables with Global T-score at Baseline (N = 105)

Variable	Estimate	95% *CI*	*p*	*ESE*
Sociodemographic				
Age (yrs) [a]	-0.20	-0.33 – -0.07	.002**	-0.29
Sex (female) [b]	-0.23	-2.99 – 2.52	.867	-0.02
Education (yrs completed) [a]	0.64	0.15 – 1.13	.011*	0.25
Monthly household income (ZAR) [a, d]	< -.001	< -.001 – < .001	.699	-0.11
HFIAS [a, c]	-0.19	-0.36 – -0.01	.040*	-0.20
ACTG SF-21[a]	-0.02	-0.10 – 0.06	.577	-0.06
Q-LES-Q [a]	-0.06	-0.15 – 0.04	.242	-0.12
Held back in school [b]	0.09	-2.56 – 2.75	.944	0.01
Literacy [b]	3.06	-0.52 – 6.64	.093	0.16
Medical				
Log_{10} HIV viral load [a]	-0.17	-1.03 – 0.70	.703	-0.04
Current absolute CD4 [a]	< -.001	-0.01 – 0.01	.872	-0.02
History of neurological events [b]	-2.28	-4.82 – 0.26	.079	-0.17
Vascular risk [b]	-1.01	-4.44 – 2.41	.559	-0.06
ART regimens [b]				-0.06

Second vs. reinitiated	-0.25	-2.75 – 2.25	.845	
Third vs. reinitiated	-8.43	-21.19 – 4.33	.193	
Self-reported nadir CD4 count [b]	-0.76	-3.34 – 1.81	.557	0.06
Psychiatric				
HAM-D[a]	< .001	-0.18 – 0.17	.994	< -.001
High risk alcohol use [b, d, e]	2.33	-0.36 – 5.03	.089	0.19
Past diagnosis of MDD [b]	-0.04	-5.03 – 4.95	.988	0.14
History of recurrent MDD [b]	0.76	-2.29 – 3.80	.622	0.05

Note. [a]Continuous variable, therefore ESE calculated using Pearson's correlation coefficient; [b]Categorical variable, therefore ESE calculated using the point-biserial correlation coefficient; [c]Higher score indicates greater food insecurity; [d]High risk alcohol use indicated if AUDIT score > 20; [e]One participant removed from analysis because data value was an influential outlier (Cook's $D = 0.06$). 95% *CI* = 95% confidence interval; *ESE* = effect size estimate; ZAR = South African Rands; HFIAS = Household Food Insecurity Access Scale; ACTG SF-21 = Adult AIDS Clinical Trials Group SF-21; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; ART = antiretroviral therapy; HAM-D = Hamilton Rating Scale for Depression; MDD = major depressive disorder.
*$p < .05$. **$p < .01$. ***$p < .001$.

When building the multivariable linear regression models to determine the best model of baseline global cognitive performance in this sample, we entered the three significant variables individually associated with global-*T* score: age, education (years completed), and HFIAS score.

The final model (adjusted $R^2 = .10$, $p = .002$) included education and HFIAS score. For every year of education completed, global *T*-score increased by 0.62 points (CI: 0.08, 1.15; $p = .025$; $r = .25$), on average. For every one unit increase in HFIAS score, global *T*-score decreased by 0.20 points (CI: -0.38, -0.03; $p = .020$; $r = -.20$), on average.

The model was not significantly different from the fully specified model (adjusted $R^2 = .12$, $p = .083$), indicating a good model fit. Data from two participants were removed from the analyses because they contained influential outliers (Cooks' $D = 0.23$ and 0.21).

Association between Depression Severity and Cognitive Performance at Baseline

At baseline, depression severity was significantly associated with performance in the attention/working memory domain, with increasing depression severity related to worse attention/working memory. On average, for every one point increase in HAM-D score, the *T*-score in the Attention/Working Memory domain decreased by 0.25 points (CI: -0.45, -0.05; $p = .016$; $r = -.24$).

HAM-D score was not significantly associated with performance in any other cognitive domain: Motor (estimate = 0.08; CI: -0.23, 0.39; p = .615; r =.05); Information Processing Speed (estimate = -0.01; CI: -0.28, 0.27; p = .967; r = -.004); Verbal Fluency (estimate = 0.06; CI: -0.15, 0.28; p = .572; r = .06); Auditory-Verbal Learning and Memory (estimate = -0.03; CI: -0.30, 0.24; p = .810; r = -.02); Visuospatial Learning and Memory (estimate = -0.04; CI: -0.35, 0.26; p = .780; r = -.03); Executive Function (estimate = 0.19; CI: -0.09, 0.46; p = .177; r =.13).

Effects of CBT-AD Treatment on Depression Severity and Cognitive Performance Over Time

The first model investigated if, from baseline to follow-up, HAM-D scores had improved significantly more in the group assigned to receive CBT-AD than in the standard of care group. Analyses detected a significant Group x Timepoint interaction (estimate = -5.35; CI: -9.75, -0.96; p = .017), indicating that those in the CBT-AD group improved by an estimated 5.35 points more than those in standard of care group. Analyses also detected a significant main effect for Timepoint (estimate = -9.67; CI: -12.24, -7.10; $p < .001$), indicating that, in overall sample (i.e., regardless of group assignment) and on average, HAM-D scores improved by an estimated 9.67 points from baseline (M = 25.63, SD = 7.10) to follow-up (M = 13.96, SD = 9.28). Analyses detected no significant main effect for Group (estimate = -1.93; CI: -5.13, 1.27; p = .235).

The average HAM-D score for the CBT-AD group fell within the ‘severe depression’ range (M = 24.30, SD = 7.65) at baseline and within the ‘mild depression’ range (M = 9.31, SD = 7.91) at follow-up. The average HAM-D score for the standard of care group fell within the ‘severe depression’ range (M = 26.24, SD = 6.80) at baseline and within the ‘moderate depression’ range (M = 16.56, SD = 9.04) at follow- up (Zimmerman et al., 2013). Regarding percentage change, there was a 61.69% decrease in HAM-D scores in the CBT-AD group and only a 36.89% decrease in the standard of care group from baseline to follow-up.

The next set of models investigated whether, from baseline to follow-up, global and cognitive domain T-scores had improved significantly more in the group assigned to receive CBT-AD than in the standard of care group. This hypothesis was not confirmed, with analyses detecting no significant Group x Timepoint interaction (see Table 3).

Table 3

Effects of CBT-AD Treatment on Cognitive Performance Over Time: Linear mixed effects regression model (N = 105)

	Estimate	95% *CI*	*p*
Outcome = Motor domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-2.15	-6.54 – 2.25	.337
Timepoint (baseline versus follow-up)	3.67	1.97 – 5.36	< .001*
Group x Timepoint interaction	-0.94	-3.79 – 1.91	.516
Outcome = Information Processing Speed domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-1.07	-5.16 – 3.01	.605
Timepoint (baseline versus follow-up)	3.75	1.62 – 5.87	.001*
Group x Timepoint interaction	1.18	-2.40 – 4.76	.516
Outcome = Attention/Working Memory domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	0.30	-2.81 – 3.40	.850
Timepoint (baseline versus follow-up)	1.79	0.28 – 3.29	.020*
Group x Timepoint interaction	1.81	-0.72 – 4.35	.160
Outcome = Verbal Fluency domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-2.32	-5.59 – 0.94	.161
Timepoint (baseline versus follow-up)	1.71	-0.003 – 3.42	.049*
Group x Timepoint interaction	2.18	-0.69 – 5.06	.136
Outcome = Auditory-Verbal Learning and Memory domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-1.94	-6.17 – 2.29	.368
Timepoint (baseline versus follow-up)	5.01	2.98 – 7.04	< .001*
Group x Timepoint interaction	2.31	-1.10 – 5.72	.183
Outcome = Visuospatial Learning and Memory domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-1.02	-5.89 – 3.85	.679
Timepoint (baseline versus follow-up)	3.48	1.43 – 5.53	.001*
Group x Timepoint interaction	-0.14	-3.59 – 3.30	.934
Outcome = Executive Function domain *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-0.68	-4.76 – 3.41	.744
Timepoint (baseline versus follow-up)	3.13	0.66 – 5.60	.013*
Group x Timepoint interaction	-0.64	-4.82 – 3.54	.763
Outcome = Global *T*-score			
Predictors			
Group (CBT-AD versus standard of care)	-1.27	-3.87 – 1.34	.338
Timepoint (baseline versus follow-up)	3.37	2.58 – 4.16	< .001*
Group x Timepoint interaction	0.79	-0.54 – 2.12	.241

Note. HAM-D = Hamilton Rating Scale for Depression; CBT-AD = cognitive-behavioural therapy for adherence and depression.

*$p < .05$. **$p < .01$. ***$p < .001$.

Finally, we investigated whether baseline-to-follow-up improvement in HAM-D scores was associated with baseline-to-follow-up improvement in global and cognitive

domain *T*-scores. In these models, we adjusted for baseline-to-follow-up changes in viral suppression (viral suppression x Timepoint interaction).

Analyses detected no significant main effect for HAM-D score (-0.09 < estimates < 0.11; CIs: -0.30, 0.34; *ps* > .290) or significant HAM-D x Timepoint interaction (-0.14 < estimates < 0.13; CIs: -0.37, 0.38; *ps* > .179), except in the Attention/Working Memory domain.

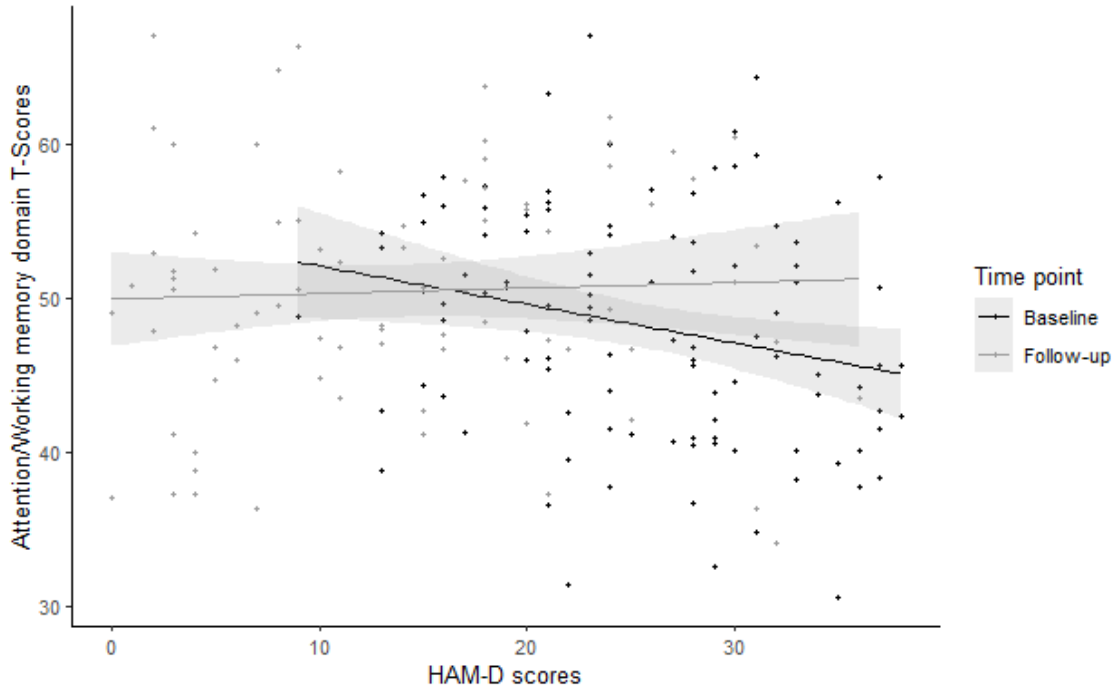
Regarding the Attention/Working memory domain, the analysis detected a significant main effect for HAM-D score (estimate = -0.24; CI: -0.39, -0.10; $p = .001$) and a significant HAM-D x Timepoint interaction (estimate = 0.23; CI: 0.05, 0.41; $p = .013$). Perusal of the data presented in Figure 2 suggests that this significant result may be accounted for by the fact that, at baseline, depression severity was associated with worse cognitive performance; however, at follow-up (i.e., when depression had improved), this association was much weaker and no longer statistically significant.

In this final set of models, the main effect for Timepoint (baseline versus follow-up) for all global and cognitive domain *T*-scores was not significant except in the cases of Global *T*-score (estimate = 3.07; CI: 0.76, 5.38; $p = .009$) and Verbal Fluency domain *T*-score (estimate = 5.10; CI: 0.33, 9.86; $p = .036$); for the other outcome variables, -2.68 < estimates < 5.45; CI: -6.79, 11.34; *ps* > .063.

Note that the main effect for viral suppression for all global and cognitive domain *T*-scores was not significant (-0.10 < estimates < 1.8; CIs: -3.99, 5.15; *ps* > .120), neither was the viral suppression x Timepoint interaction (-3.26 < estimates < 1.36; CIs: -6.17, 6.19; *ps* > .079).

Figure 2

Association between Depression Severity and Attention/Working Memory Domain Performance at Both Time Points (N = 105)



Note. HAM-D = Hamilton Rating Scale for Depression

Discussion

In this study, a sample of 105 incompletely ART adherent South African PWH with comorbid major depressive disorder, all of whom were from socioeconomically disadvantaged backgrounds, completed a baseline sociodemographic, psychiatric, and neuropsychological assessment. Some (n = 33) were then randomly assigned to a CBT-AD condition while the rest (n = 72) were assigned to standard-of-care treatment. Eight months post-baseline, 81 ($n_{\text{CBT-AD}}$ = 29) repeated the assessment.

Results indicated that, at baseline, participants with less education and more food insecurity delivered overall poorer performance on the cognitive test battery. At that timepoint, HIV disease factors and medical/psychiatric comorbidities were not significant predictors of global cognitive functioning; however, depression severity was significantly associated with poorer performance in the domain of attention/working memory. This significant effect in that cognitive domain was not present at follow-up, when the cohort overall was less depressed. Regarding this improvement in depression, it should be noted that depression improved significantly more in the group assigned to receive CBT-AD than those in the comparison group. For the CBT-AD group, depression improved from ‘severe’ to ‘mild’ and for the standard of care group, from ‘severe’ to ‘moderate’ (Zimmerman et al., 2013).

HIV disease factors might be expected to predict cognitive performance in a sample with poorly controlled viral replication: many previous studies have reported such associations (Ellis et al., 2011; Heaton et al., 2011; Jumare et al., 2018; Robertson et al., 2007; Sacktor et al., 2002; Starace et al., 2002). However, recent trends in the literature suggest that the effects of HIV on cognitive performance may be weaker than the effects of socioeconomic and psychosocial variables, especially in samples drawn from low- and middle-income countries (LMICs) or from socioeconomically disadvantaged populations (Cysique & Becker, 2015; Do et al., 2018; Dreyer et al., 2021b; Haddow et al., 2018; Maki et al., 2015; Vo et al., 2013; Winston et al., 2013).

One of these socioeconomic/psychosocial variables is level of educational attainment. The current data demonstrating its effects on cognitive performance are consistent with a longstanding and strong line of research indicating that individuals with lower levels of education perform more poorly on standardized cognitive tests than those with higher levels (Lenehan et al., 2015; Strauss et al., 2006).

However, data regarding the effects of the other significant socioeconomic/psychosocial variable in our analyses, food insecurity, are not as prevalent. This is despite the fact that food insecurity in LMICs is a significant problem (Crush et al., 2012). For instance, in South Africa 68–89% of people living in peri-urban communities outside Cape Town are estimated to have moderate-to-severe food insecurity (Battersby, 2011; Lee et al., 2021; Misselhorn & Hendriks, 2017). Beyond the obvious physical health implications, food insecurity has been associated with cognitive impairment (Gao et al., 2009; Koyanagi et al., 2019). It is unclear, however, whether the mechanism underlying this association is related to purely nutritional pathways or whether food insecurity is a proxy for broader structural inequalities that can affect cognitive performance via a host of complex social, educational, socioeconomic, and health pathways (Burch et al., 2016; Farah, 2017; Hobkirk et al., 2017; Nightingale et al., 2021; Watson et al., 2019; Weiser et al., 2009; Weiser et al., 2012; Weiser et al., 2011).

Despite reportedly high rates of food insecurity in LMIC-resident PWH (Anema et al., 2009), there are no studies that have investigated relations between food insecurity and cognitive performance among PWH. The current study showed that greater food insecurity is associated with weaker global cognitive performance in LMIC-resident PWH. Previous studies investigating this relationship in US-based samples of PWH found that food insecurity was associated with weaker global cognitive performance, more specifically,

poorer performance in the domains of motor function, information processing speed, and learning and memory (Hobkirk et al., 2017; Tamargo et al., 2021).

Regarding associations between cognitive performance and depression, our analyses suggested that higher HAM-D scores (indicating greater depression severity) were associated with weaker performance in the domain of attention/working memory at baseline, when the sample's mean HAM-D score fell in the severely depressed range (Zimmerman et al., 2013). However, at follow-up, when the mean HAM-D score fell within the mild range, the association no longer met the threshold for statistical significance. This finding is consistent with several previous studies suggesting that more severe depression is associated with greater cognitive impairment (McDermott & Ebmeier, 2009; Shimizu et al., 2011), and, perhaps more notably, with Cysique et al. (2016), who found that global cognitive functioning was only impaired in PWH with chronic and clinically unstable depression. With specific regard to attention/working memory and depression in PWH, the literature is equivocal: Some studies report that comorbid depression impairs performance in this domain (Bragança & Palha, 2011; Fellows et al., 2013; Gibbie et al., 2006; Goggin et al., 1997; Harrison et al., 2017; Rubin et al., 2014), whereas others report no such relationship (Akolo et al., 2014; Bryant et al., 2015; Cysique et al., 2007; Haddow et al., 2018).

In our sample of PWH, depression severity was not associated with global cognitive performance or with performance in cognitive domains (e.g., information processing speed, verbal memory) that one might expect, based on previous studies, to be affected (see, e.g., Bryant et al., 2015; Fellows et al., 2013). The review by Rubin and Maki (2019) of 41 studies (most of them cross-sectional) examining associations between depression and cognition in PWH reported that the most reliably affected cognitive domains were motor function, information processing speed, learning and memory, and executive function. Only 3 of 8, cross-sectional studies that measured attention/working memory, found a relationship between depression and attention/working memory.

We posit that reasons for the discrepancy between our depression-cognition results and those of previous studies might arise from differing sample characteristics. Our participants were recruited from socioeconomically disadvantaged neighbourhoods, were all carrying a formal (via structured clinical interview) diagnosis of MDD on enrolment, with an average HAM-D score in range conventionally described as "severely depressed" (Zimmerman et al., 2013). Moreover, most of our participants (72%) were female. In contrast, most HIV-cognition research is conducted in high-income settings with samples that are frequently all- or majority-male, and with depression measured only using a cut-off score

on a symptom questionnaire such as the HAM-D or the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). In fact, of the 41 studies reviewed by Rubin and Maki (2019), only 5 used structured clinical interviews to diagnose current MDD. Symptom questionnaires are screening instruments for overall depressive symptomology. As such, they are not conclusively diagnostic and are therefore not as accurate as clinical interviews in diagnosing MDD (Subica et al., 2014). Moreover, the relationship between depression and cognition may be different in PWH with a confirmed current diagnosis of MDD, compared to those experiencing depressive symptoms (Cysique et al., 2016). Sex differences (Dreyer et al., 2021a; Rubin et al., 2019) and socioeconomic hardship (Watson et al., 2019) could also play a role in the relationship between depression and cognitive performance in PWH.

Few longitudinal studies have investigated the effects of depression severity on cognitive performance. Studies using similar longitudinal designs as ours to investigate associations between depression and cognitive performance over time have produced mixed results (Cysique et al., 2007; Gibbie et al., 2006; Grant et al., 2014; Heaton et al., 2015; Paolillo et al., 2020; Vo et al., 2013). Two large longitudinal studies, the Multicenter AIDS Cohort Study (MACS; Vo et al., 2013) and CHARTER Study (Grant et al., 2014; Heaton et al., 2015), found that a diagnosis of current MDD/higher depressive symptoms were associated with declines in cognitive functioning. Additionally, Paolillo et al. (2020) found that a high cumulative burden of depression over time was associated with a steeper decline in cognitive functioning, compared to a low cumulative burden of depression. Cysique et al. (2007) found that a new current episode of MDD in men with HIV, who did not meet criteria for MDD at baseline, was not associated with changes in cognitive functioning within a 2-year period. Another study reported that, although depression declined and scores in several cognitive domains improved over a 2-year follow-up period, there was no significant association between the two (Gibbie et al., 2006). The same study did, however, find a similar result to ours in observing that depression scores were significantly inversely correlated with working memory performance at baseline.

This is the first study to describe the effects of CBT-AD on cognitive performance. Although the treatment was more effective than standard of care at relieving depressive symptomatology (confirming results from the primary outcome paper; Safren et al., 2021), this improvement did not generalize to cognitive performance. It is possible that the cognitive effects of the CBT-AD intervention could not be detected because the size of the subgroup receiving the CBT-AD treatment was small, meaning that potential effects of the treatment on cognitive performance may have gone undetected. For instance, the larger CBT-AD trial (*N*

= 161; CBT-AD *n* = 80, standard of care *n* = 81), powered at medium effects (0.50) had >80% power to detect a between-group difference in cognitive performance at follow-up (Safren et al., 2021), whereas the current study only had 57% power to detect the same effect (Faul et al., 2007). Hence, results related to the effects of the intervention should be interpreted with caution.

The research presented here has several methodological limitations. First, the relatively small sample size means that the study may have been underpowered to detect potentially significant associations between various variables and cognitive performance. In addition, the findings drawn from this real-world clinical sample of PWH with depression and incomplete ART adherence who live in a socioeconomically disadvantaged setting in South Africa may not be generalisable to all samples of PWH with depression and incomplete ART adherence.

Conclusion

In this sample of people with HIV and incomplete ART adherence, recruited from socioeconomically disadvantaged settings in a low- or middle-income country, non-biological factors (educational level and food insecurity) were stronger predictors of global cognitive performance than the biological effects of HIV and other medical factors. This result, which emerged even in a group with poorly controlled HIV (i.e., whose brains would be especially vulnerable to biological effects of the infection), adds to the growing body of evidence that, in PWH, factors other than the disease are important determinants of cognitive performance. It is therefore imperative that future research collect information on socioeconomic factors when assessing cognitive performance in PWH—collecting such data will allow studies to reduce the potential for inaccurate interpretation of cognitive test scores and consequent overestimation of the prevalence of cognitive impairment in this population.

We also found that severe depression in this sample of PWH is associated with poorer cognitive performance in the domain of attention and working memory. Because the strength of this association became markedly weaker when the level of depression improved, we suggest that depression in such samples of PWH could be a potentially modifiable risk factor for those presenting with attention and working memory dysfunction. Because attention and working memory are the gateway to information acquisition and serve as a necessary foundation for higher-level cognitive functioning, improvement in cognitive performance in this domain may improve the overall functioning of PWH (Parsons & Rizzo, 2008).

Overall, factors associated with cognitive performance in this sample were likely not related to brain injury. It is important for clinicians to assess depression in PWH presenting

with cognitive difficulties, and for HIV researchers to collect information on psychosocial factors in their studies of cognitive impairment.

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Chapter 6

Cognitive Performance, as well as Depression, Alcohol Use, and Gender, predict Anti-Retroviral Therapy Adherence in a South African Cohort of People with HIV and Comorbid Major Depressive Disorder

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Description of the contribution of candidate and co-authors

AJD was the first author of this manuscript. This entailed leading the drafting, analyses and conceptualising. These data were collected as part of a larger research program for a randomised controlled trial of a cognitive-behavioral treatment for ART adherence and depression (CBT-AD), which involved JAJ, SAS, CO and JL. AJD developed and implemented the study protocol for the neuropsychological supplement project, with guidance from JAJ, LSA and KGFT. This involved writing the protocol, obtaining ethical approval, and ensuring ethical standards and procedures were followed, including protocol modifications, deviations and annual progress reports. AJD managed the daily running of the supplement project, including the finances, the care of the participants, overseeing the data collection and quality checking the data.

In this manuscript, AJD formulated the research questions, cleaned, analysed and interpreted the data, and wrote the manuscript. JAJ, SN and KGFT contributed to the manuscript by providing guidance, discussing ideas and reviewing drafts and JL provided

input into data management and analyses. All co-authors provided input, reviewed drafts and approved the final manuscript.

Current status Accepted for publication in AIDS and Behavior

Dreyer, A. J., Nightingale, S., Andersen, L. S., Lee, J. S., Gouse, H., Safren, S. A., O'Cleirigh, C., Thomas, K. G. F., & Joska, J. (in press). Cognitive Performance, as well as Depression, Alcohol Use, and Gender, predict Anti-Retroviral Therapy Adherence in a South African Cohort of People with HIV and Comorbid Major Depressive Disorder. *AIDS and Behavior*.

Abstract

Depression and cognitive impairment, which commonly coexist in people with HIV (PWH), have been identified as potential barriers to optimal antiretroviral therapy (ART) adherence. We investigated associations between cognitive performance, depression (as well as other sociodemographic, psychosocial and psychiatric variables) and ART adherence in a South African cohort of PWH with comorbid major depressive disorder (MDD). Cognitive performance and ART adherence were assessed at two time points 8 months apart ($N_{baseline}$ = 105, $N_{follow\text{-}up}$ = 81). Adherence was indicated by self-report, objective measures (Wisepill usage and plasma tenofovir-diphosphate levels), and HIV viral suppression. Mixed-effects regression models examined associations across both time points. Univariable models detected no significant associations between cognitive performance (globally and within-domain) and ART adherence. Multivariable modelling showed increased depression severity (β = -0.54, $p < .001$) and problematic alcohol use (β = 0.73, p = .015) were associated with worse adherence as measured subjectively. Being female (OR = 0.27, p = .048) and having better global cognitive performance (OR = 1.83, p = .043) were associated with better adherence as indicated by viral suppression. This study identifies poor global cognitive performance, as well as depression and problematic alcohol use, as potential barriers to optimal ART adherence in PWH and comorbid MDD. Hence, clinicians could consider assessing for cognitive deficits, depression, and problematic alcohol use, and should endeavour to provide the appropriate support so as to improve adherence.

Keywords: adherence; antiretroviral therapy; cognitive impairment; depression; HIV

Introduction

Antiretroviral therapy (ART) has revolutionised the treatment of people with HIV (PWH). It improves quality of life, reduces HIV-related morbidity and prevents onward transmission of the virus in adherent individuals with suppressed viral loads (Meintjes et al., 2017; Takuva et al., 2017). Despite these clear and considerable benefits, a significant proportion of PWH are incompletely ART adherent. In South Africa, which has the largest population of PWH (7.8 million) and the largest ART program in the world, incomplete ART adherence is a significant public health concern (UNAIDS, 2021).

One group of PWH identified as being at high risk of incomplete ART adherence are those with depression (Colibazzi et al., 2006; Gonzalez et al., 2011; Kacanek et al., 2010; Langebeek et al., 2014). Nel and Kagee (2013) found that South African PWH reporting non-optimal ART adherence were approximately three times more likely to report moderate-to-severe symptoms of depression than those reporting optimum adherence (Nel & Kagee, 2013).

Depression can also negatively affect cognitive test performance in PWH. The impairing effects of major depressive disorder (MDD) in PWH are typically observed in the domains of motor skills, information processing speed, attention and working memory, learning and memory, and executive function (Bragança & Palha, 2011; Fellows et al., 2013; Goggin et al., 1997; McDermott & Ebmeier, 2009; Rock et al., 2014; Rubin & Maki, 2019; Shimizu et al., 2011).

The literature further suggests that there are independent associations between cognitive performance and ART adherence in the general population of PWH (Sayegh et al., 2016). A systematic review (Lovejoy & Suhr, 2009) summarised this literature and found that impaired cognitive performance (globally and across domains) was associated with worse adherence in 9 of the 11 studies included in sample. The specific domains in which significant associations tend to be present include information processing speed, verbal fluency, attention/working memory, learning and memory, and executive function (Andrade et al., 2013; Caballero et al., 2019; Ettenhofer et al., 2010; Hinkin et al., 2002; Hinkin et al., 2004; Lovejoy & Suhr, 2009; Mark, 2011; Sayegh et al., 2016; Thaler et al., 2015).

An important note about that systematic review is that 10 of the 11 studies included in the sample were conducted in the United States, with the lone exception being an Italian study. Clearly, then, few studies investigating this question have been conducted in low- and middle-income countries, such as South Africa. Among these few studies, findings are

equivocal and methods may be suboptimal. For instance, whereas a study conducted in Malawi found no relationship between cognitive impairment and adherence (Kelly et al., 2014), another one conducted in Tanzania (Nyundo, 2022) found that impaired cognitive performance was a strong predictor of suboptimal adherence. However, this latter study used only the Montreal Cognitive Assessment (MoCA), a screening tool, to measure cognitive performance.

In addition to MDD and impaired cognitive performance, other sociodemographic, psychosocial, and psychiatric factors can affect ART adherence. Problematic alcohol use (Chander et al., 2006; Hendershot et al., 2009; Kekwaletswe et al., 2017; Morojele et al., 2014), increased food insecurity (Hong et al., 2014; Musumari et al., 2014; Singer et al., 2015; Weiser et al., 2014), younger age (Hinkin et al., 2002; Hinkin et al., 2004; Mujugira et al., 2016; Pillay et al., 2020), fewer years of education (Thaler et al., 2015), and being a woman (Andrade et al., 2013; Puskas et al., 2011) are associated with non-optimal ART adherence. Of note, however, is that studies conducted in South Africa have found that women are likely to have better ART adherence than men (Joseph Davey et al., 2018; Pillay et al., 2020).

In the HIV literature, medication adherence is measured using subjective behavioral reports and/or objective ART drug blood levels and pill-taking measures. Subjective reports, which involve reporting if ART was taken as recommended over a specified time interval, are used most commonly (Lovejoy & Suhr, 2009; Simoni et al., 2006). Objective measures, which are considered to be more accurate than self-report (Spinelli et al., 2020), include real-time electronic medication monitoring of pill-taking. Various forms of medication event monitoring system (MEMS) technology have been developed to measure adherence (Kerr et al., 2005). One example of such MEMS technology is the Wisepill box. Each time the pillbox is opened, a signal is transmitted to a web server logging the time and date, thus indicating that medication may have removed from the device at that point (Haberer et al., 2010; Lovejoy & Suhr, 2009).

Recent studies have reported on the use of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) as an objective biomarker of cumulative ART adherence (Castillo-Mancilla & Haberer, 2018). Due to its long intracellular half-life in red blood cells (17 days), TFV-DP can provide information about average adherence over the preceding 6–8 weeks (Anderson et al., 2018; Castillo-Mancilla et al., 2013). Because tenofovir disoproxil fumarate (TDF) forms the backbone of first-line (and some second-line) ART regimens in South

Africa, TFV-DP is a particularly useful measure of adherence in this context (Jennings et al., 2022).

Currently, there is no gold standard for measuring ART adherence (Kerr et al., 2005; Saberi et al., 2020). Although some consider MEMs to be such a standard (Lovejoy & Suhr, 2009; Paterson et al., 2002), others consider biological measures such as TFV-DP to be more accurate (Alcaide et al., 2017; Castillo-Mancilla & Haberer, 2018). Self-report can accurately measure adherence, although it may tend toward overestimation (Liu et al., 2001; Phillips et al., 2019; Simoni et al., 2006).

Most studies investigating the association between cognitive performance and adherence have used either self-report or MEMS (Caballero et al., 2019; Ettenhofer et al., 2010; Lovejoy & Suhr, 2009; Nyundo, 2022; Sayegh et al., 2016; Thaler et al., 2015). Of the studies reviewed above, one study measured adherence using pharmacy refill record (Andrade et al., 2013) and another used plasma ART concentrations (Kelly et al., 2014). To our knowledge, no study has investigated this relationship using TFV-DP in DBS.

Durable high ART adherence (> 80%) is necessary to achieve and maintain viral suppression (Bezabhe et al., 2016; Byrd et al., 2019). Hence, viral suppression is an indication of successful adherence. Of particular interest here is that viral suppression may be independently influenced by cognitive performance, depression, problematic alcohol use, and food insecurity (Aibibula et al., 2017; Gokhale et al., 2019; Mark, 2011; Vagenas et al., 2015).

In South Africa (and in other countries with a high burden of HIV), it is critical to identify predictors of ART adherence, especially in vulnerable groups of PWH (such as those with comorbid depression who are incompletely adherent). Such identification could facilitate solutions that can be targeted in a strategic manner to improve adherence and achieve viral suppression. The main aim of this study was to investigate whether, in an incompletely adherent South African cohort of PWH with comorbid MDD, cognitive performance was associated with ART adherence. We also investigated the associations of sociodemographic, psychosocial, and psychiatric factors with ART adherence. Among psychiatric factors, depression was of particular interest.

Method

Setting

The study procedures were part of a larger research program (Dreyer et al., 2022; Joska et al., 2020; Safren et al., 2021).

Participants were recruited at two primary care community clinics in Khayelitsha, a peri-urban community in Cape Town, South Africa. Khayelitsha was established in the mid-1980s under the apartheid regime's principles of racial segregation. As a consequence of this legacy, today almost all its residents are Black African and it is one of the poorest areas of Cape Town. Most adult residents speak isiXhosa as a first language, fewer than one-third of them have completed high school, and there are high levels of HIV infection, crime, and unemployment (Crush et al., 2012; Nleya & Thompson, 2009; Smit et al., 2016; Stern et al., 2017; City of Cape Town, 2013).

Participants

Participants were 105 PWH with comorbid MDD who had failed first-line ART (i.e., they had already been established as incompletely ART adherent). A subgroup of participants who were not virally suppressed (HIV RNA viral load > 400 copies/mL) at baseline (n = 72) were subsequently included in large randomised controlled trial of a cognitive-behavioural treatment for ART adherence and depression (CBT-AD; Joska et al., 2020; Safren et al., 2021). As part of the current study, an additional 33 participants who were not part of the trial were recruited. Of the total sample of 105 participants, 81 were assessed again 8 months later.

Inclusion criteria were (a) age ≥ 18 years; (b) HIV-seropositive status (confirmed via medical record); (c) current diagnosis of MDD as measured on the Mini International Neuropsychiatric Interview, Version 7.0 (MINI; Sheehan, 2014); and (d) having failed first-line ART, identified by the community clinic as not having collected ART for > 3 months.

We did not exclude participants with medical and psychiatric co-morbidities and/or other factors that could influence cognitive performance because we wanted our sample to be representative of the clinical population of interest (i.e., PWH with MDD who are incompletely ART adherent). Therefore, the only exclusion criteria were (a) active and untreated severe mental illness (e.g., psychosis or mania) that would interfere with participation, (b) inability or unwillingness to provide informed consent, and (c) lack of sufficient fluency in English or isiXhosa. Participants using antidepressants were eligible even if they met criteria for a current depressive episode; however, they had to have been on a stable antidepressant regimen and dose for at least 2 months.

All participants provided written informed consent. The study protocol was approved by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee and the University of Miami Institutional Review Board.

Materials

Measures of sociodemographic and psychosocial variables. Participants self-reported sociodemographic information (e.g., gender, age, highest level of education, monthly household income, primary language, and employment status). They also completed the Food Insecurity Access Scale (HFIAS; Coates et al., 2007), which measures household food insecurity.

Measures of HIV disease variables. HIV viral load and current CD4 cell counts were extracted from the medical records. If participants did not have recent (1-month) testing, blood samples for assay were collected using the COBAS AmpliPrep/TaqMan HIV-1 test (range: 20-10,000,000 copies/mL; Damond et al., 2007). ART regimens (i.e., reinitiated on first line, second line, or third line) were also extracted from the participant's medical record. Participants self-reported whether their nadir CD4 count had ever been below 100 cells/μL.

Measures of psychiatric variables. The MINI structured diagnostic interview (Sheehan, 2014) was used to (a) diagnose MDD during screening procedures, so as to establish eligibility for study participation, and (b) screen for the presence of psychiatric disorders that would disqualify individuals from participation. This interview was conducted by a psychiatric nurse and supervised by a clinical psychologist. We used the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) to identify high-risk alcohol use. High-risk alcohol use was defined using a cut-off score of > 20 on the AUDIT. This is the standard cut-off proposed by the World Health Organization (WHO) and suggests probable alcohol dependence (Babor et al., 1992). We used the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960; Williams et al., 2008) to assess depression severity.

Cognitive assessment. The battery comprised 12 standardized neuropsychological tests, each of which assessed performance in one of seven cognitive domains commonly affected by HIV (Grant, 2008). This battery of tests has been widely used in South African research (e.g., Gouse et al., 2022; Joska et al., 2011).

Cognitive domains and neuropsychological tests: *Executive functioning*: Color Trails Test 2 (CTT2) and Wisconsin Card Sorting Test (WCST); *Audioverbal learning and memory*: Hopkins Verbal Learning Test-Revised (HVLT-R); *Visuospatial learning and memory:* Brief Visuospatial Memory Test-Revised (BVMT-R); *Verbal fluency*: Category fluency test (animals; fruits and vegetables); *Attention/working memory*: Wechsler Memory Scale-Third

Edition (WMS-III) Spatial Span subtest and Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span subtest; *Information processing speed*: CTT1, WAIS-III Digit Symbol Coding subtest and WAIS-III Symbol Search; *Motor skills*: Grooved Pegboard Test (GPT) dominant (DH) and nondominant hand (NDH) and Finger Tapping Test DH and NDH.

Tests were administered in either English or isiXhosa, depending on the participant's preference, by a bilingual neuropsychology technician.

Measures of ART adherence.

Adherence questionnaires. We used two self-report adherence questionnaires, labelled here Self-Report Adherence 1 (SRA-1) and Self-Report Adherence 2 (SRA-2). Both ask the respondent to indicate if they took their ART as prescribed over the previous 2 weeks. In SRA-1, participants rated their adherence on a 6-point Likert-type scale with anchor points at very poor and excellent. In SRA-2, answers were recorded as a percent of time they were completely adherent, with 10 options ranging from 10% to 100%. Methods of rating adherence using time-frames of longer than 1 week have been shown to be more accurate than 1 week or 3 day time-frames (Lu et al., 2008).

Wisepill. The Wisepill adherence monitor (Wisepill Technologies, Cape Town, South Africa) is an electronic medication monitoring system that consists of a pill box container fitted with a GSM (Global System for Mobile Communication) communication chip. Wisepill holds approximately 30 large pills or 60 small pills in a two-compartment inner container and is powered by a 1,100 mA lithium polymer rechargeable battery (Great Power Battery Ltd, Hong Kong). Each time the device is opened, a cellular signal is sent and recorded in real-time on a web-based server. The data stored there are accessible to researchers via a secure Internet interface. Wisepill technology is a feasible way of monitoring ART adherence objectively and in real time (Bionghi et al., 2018; Haberer et al., 2010).

Tenofovir diphosphate (TFV-DP). For all participants in the study on ART with TDF as a backbone (e.g., most participants that were reinitiated onto the first line ART regimen were on tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV)), TFV-DP was measured in DBS. Blood was drawn by a nurse into a blood vial. A pipette was then used to extract 50 microliters of whole blood from the vial and fill five separate blood spots on the sampling paper (Whatman 903 ProteinSaver card). The card was dried for a minimum of 2 hours before being individually packaged in a plastic bag with desiccant. The cards were kept in a refrigerator for a maximum of 1 week, and then stored at -80˚C. An indirect method for the quantification of TFV-DP in 50 µl human DBS was developed and validated at the Clinical

Pharmacokinetic Laboratory in the UCT Division of Clinical Pharmacology. The assay involved a solid phase separation of tenofovir and TFV-DP, enzyme dephosphorylation of TFV-DP to tenofovir, followed by high performance liquid chromatography with tandem mass spectrometry detection of tenofovir (Stranix-Chibanda et al., 2021).

Procedure

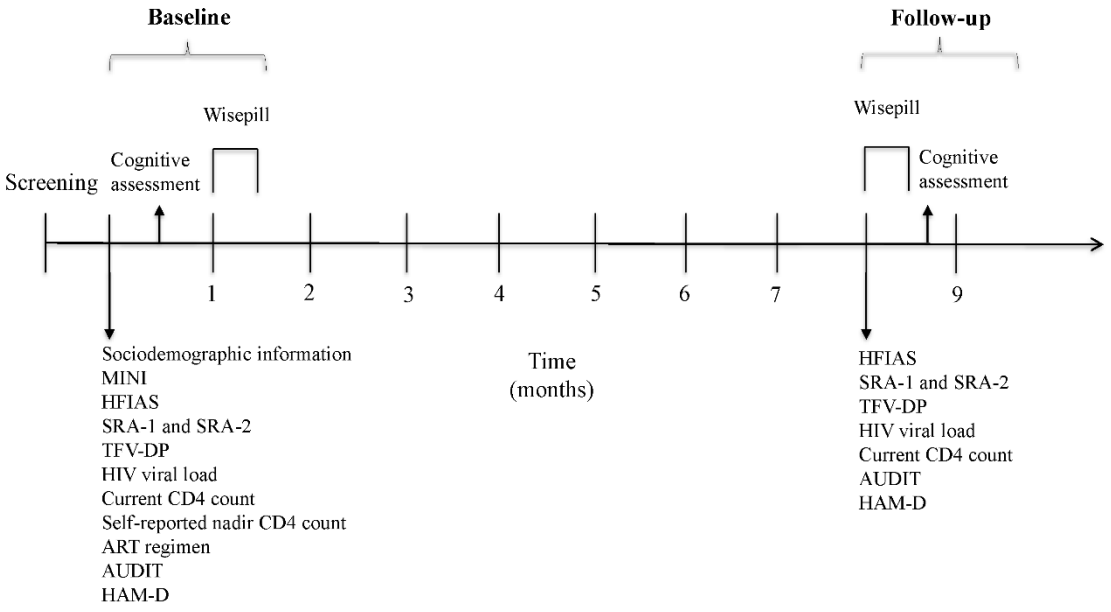
Figure 1 shows the study timeline and procedures at each time point.

Individuals who remained eligible for study participation after the screening procedures were scheduled for two baseline visits (approximately 2 weeks apart). During the first baseline visit, participants completed measures of sociodemographic, psychosocial, HIV disease, and psychiatric variables. Adherence was measured using the self-report adherence questionnaires and blood was drawn for the DBS sample. During the second baseline visit, participants completed the cognitive assessment. After the set of baseline visits, the 72 participants included in the trial were randomised to receive a CBT-AD treatment or comparison condition described by Joska et al. (2020) and Safren et al. (2021). Participants received the Wisepill box at the study visit that they were randomised.

All participants were scheduled for another two follow-up visits 8 months post-baseline. At those visits, they first completed the same measures of psychosocial, HIV disease, psychiatric variables, and ART adherence measures as at baseline and then completed the same cognitive test battery.

Figure 1

Timeline of Study Procedure



Note. MINI = Mini International Neuropsychiatric Interview; HFIAS = Household Food Insecurity Access Scale; SRA-1 and SRA-2 = Self-Report Adherence 1 and Self-Report Adherence 2; TFV-DP = Tenofovir diphosphate; ART = antiretroviral therapy; AUDIT = Alcohol Use Disorders Identification Test; HAM-D = Hamilton Rating Scale for Depression.

Data Management and Statistical Analysis

Deriving outcome variables.

Cognitive outcomes. We derived 15 separate outcome variables from the neuropsychological test data. Outcomes for the domain of *executive functioning* were CTT2 completion time (in seconds) and WCST perseverative errors; for *audioverbal learning and memory*, HVLT-R total across the three immediate recall trials and total on the delayed recall trial; for *visuospatial learning and memory*, BVMT-R total across the immediate recall trials and total on the delayed recall trial; *for verbal fluency*, category fluency test total number of animals and total number of fruits and vegetables named in 1 minute; *for attention/working memory*, WMS-III Spatial Span subtest total raw score, WAIS-III Digit Span subtest total raw score, and CTT1 completion time (in seconds); *for information processing speed*, WAIS-III Digit Symbol Coding subtest total raw score and WAIS-III Symbol Search total raw score;

and for *motor skills*, GPT DH and NDH completion time (in seconds) and Finger Tapping Test DH and NDH completion time (in seconds).

The raw scores for each of these outcomes were converted to demographically corrected *T*-scores ($M = 50$, $SD = 10$) before statistical analysis of the cognitive data. Normative standards for the tests were based on raw control data collected in previous studies conducted by the UCT HIV Mental Health Research Unit (Joska et al., 2011; Paul et al., 2014; Robbins et al., 2018). Data was provided on personal request from co-authors JJ (oral communication, November 2017) and HG (oral communication, June 2018). These data were collected between 2008 and 2016 from healthy community-dwelling individuals ($N = 233$) who presented at the same community clinics in Khayelitsha from which the current sample was recruited. Hence, the control sample and the current sample of HIV seropositive participants were similar across key demographic (age, ethnicity, language, education), psychosocial, and socioeconomic characteristics. In the control data studies, all participants (1) were HIV seronegative, (2) were aged ≥ 18 years, and (3) had ≥ 5 years of formal education. Exclusion criteria for the sample were (1) major psychiatric conditions, (2) neurological disease that could affect brain integrity, (3) lifetime history of head injury resulting in loss of consciousness >30 min, and (4) current substance use disorder.

We used the control data to calculate demographically corrected *z*-scores, using standard regression-based norming processes. The *z*-scores were then converted to *T*-scores. If participants had *z*-scores greater than 5 SD below the mean, the conversion to a *T*-score resulted in negative *T*-score. In these cases, we assigned a score of zero, the lowest possible *T*-score to maintain the clinical significance of such poor performance. Cognitive data were summarised into domain and global *T*-scores. Domain *T*-scores were calculated by taking the average of *T*-scores of the cognitive outcomes within each domain. Global *T*-score was calculated by taking the average across-domain *T*-scores.

ART adherence outcomes. The outcome variables for ART adherence are SRA-1 and SRA-2, Wisepill, TFV-DP and HIV viral suppression. The raw scores from SRA-1 and SRA-2 were used as outcome variables for self-reported adherence. TFV-DP was recorded as a continuous variable of fmol/punch. A correction factor was applied for the TFV-DP per 50 µL to convert to fmol/3-mm punch, as these units have been used in previous studies (e.g., Jennings et al., 2022).

Regarding Wisepill, a dose was counted as "taken" if the pill box was opened within 2 hours of the prescribed time. We calculated a percent of doses taken by dividing the number of times the box was opened by the number of prescribed doses over a 2-week period,

following each of the time points (i.e., baseline and follow-up). Some participants had their follow-up cognitive assessment closer to the 12-month follow-up in the larger trial. For these participants we recorded percentage Wisepill use over the 2 weeks preceding the 12-month follow-up visit. Wisepill data was only available for the participants included in the trial (n = 72).

HIV viral suppression was defined at plasma viral load < 400 copies/mL, which was the threshold of viral breakthrough in a similar population of PWH in Cape Town (Jennings et al., 2022).

Inferential analyses. We used R version 4.1.2 (2021-11-01) and RStudio version 2021.09.0 to complete all inferential analyses, with the threshold for statistical significance set at $\alpha = .05$.

Before beginning the analyses that allowed investigation of the study's major aims, we (a) calculated sample descriptive statistics for baseline values of the relevant variables, (b) calculated sample descriptive statistics for ART adherence outcomes at baseline and at follow-up, and (c) conducted a principal component analysis (PCA) with a varimax rotation to create composite variables from the measures of ART adherence. Specifically, we ran a PCA using SRA-1, SRA-2, Wisepill, and TFV-DP to determine the components the measures loaded onto so that we could combine the measures to create composite ART adherence variables. For an item to be retained in a component, it needed to have a factor loading > 0.4 and no higher loading on another factor. Creating a composite of adherence measures is recommended to more accurately measure adherence and, in this case, helped determine whether the various measures of ART adherence were measuring the same construct (Kerr et al., 2005; Liu et al., 2001). Viral suppression was retained as its own outcome variable because of its value as a commonly used and important clinical indicator.

Our first major analysis investigated univariable associations between cognitive performance and ART adherence at both time points. Here, linear mixed-effects regression models featured as predictors each of the domain *T*-scores and global *T*-score and as outcomes each ART adherence composite variable and viral suppression. We also included a random intercept for participants to account for multiple observations (i.e., that the same individual completed each measure twice, at baseline and at follow-up). Analyses included data from both time points to increase statistical power.

Our second major analysis used linear multivariable mixed effects regression modelling to determine the measured variables most strongly associated with incomplete ART adherence at both time points. Again, data from both time points were included analyses

to increase statistical power. There were three separate models: one for each ART adherence composite variable, and one for HIV viral suppression. In the fully specified models, we entered the following as fixed effects: sex (male versus female), age, education (years completed), HFIAS score (as an estimate of food insecurity), AUDIT score (above versus below the cut-off score [≥ 20] for high-risk alcohol use), global *T*-score (as an estimate of cognitive performance), and HAM-D score (as an estimate of depression symptomatology). We also included a random intercept for participants to account for multiple observations (i.e., that the same individual completed each measure twice, at baseline and at follow-up). Each model was built using a backwards stepwise approach, starting with the fully specified model and sequentially dropping variables that were not contributing to the model. Each time a variable was removed, the new model was compared to the previous model using a chi-square test to ensure that the removal did not affect the model negatively.

We investigated statistical assumptions and outliers for all regression-based analyses. Influential outliers were investigated using Cook's distance. We investigated any point > 4/*n*, where *n* is the number of observations. Outliers were removed from the analyses if the model improved without them. An Intraclass Correlation Coefficient (ICC) > 0.10 was considered high and indicated a multilevel analysis was relevant (Musca et al., 2011).

Results

Descriptive Statistics

Table 1 presents the sample's sociodemographic and clinical characteristics. Most participants were women, which is typical of the South African PWH population (George et al., 2019). isiXhosa was the primary language of most participants (93%). The sample's median monthly household income was 1600 ZAR (100 USD). Most participants (85%) had not completed high school (in South Africa, this is 12 years capped by a major exit examination), 89% were unemployed, and 68% had experienced severe food insecurity. Participants had all been identified by the community clinic as failing first line ART and therefore were either reinitiated on first line or placed on second- or third line ART regimens. All participants had a primary diagnosis of current MDD and the average HAM-D score was within the 'severe depression' range (Zimmerman et al., 2013) at baseline.

Table 1

Sociodemographic and Clinical Variables at Baseline: Descriptive Statistics (N = 105)

Variables	*M* (*SD*)	*f* (%)
Sociodemographic and psychosocial		
Sex (female)		76 (72.38%)
Age (yrs)	39.79 (9.14)	
Education (yrs completed)	9.30 (2.45)	
Monthly household income (ZAR)	1600 (0–2900) [a]	
HFIAS [b]	12.74 (6.90)	
HIV disease		
Log_{10} HIV viral load	3.56 (1.44)	
Current absolute CD4	248.49 (209.38)	
ART regimens		
Reinitiated		56 (53.85%)
Second		47 (45.19%)
Third		1 (0.96%)
Self-reported nadir CD4 count <100 cells/ml		68 (64.76%)
Psychiatric		
HAM-D score	25.63 (7.10)	
High risk alcohol use [c]		30 (28.85%)
Cognitive Performance by Domain (*T*-score)		
Motor skills	46.53 (11.32)	
Information Processing Speed	46.36 (9.83)	
Verbal Fluency	50.40 (7.86)	
Attention and Working Memory	43.50 (9.87)	
Audioverbal Learning and Memory	50.00 (11.10)	
Visuospatial Learning and Memory	48.17 (7.53)	
Executive Functioning	43.17 (9.96)	
Global Cognitive Performance (*T*-score)	46.87 (6.34)	

Note. [a] Median (interquartile range); [b] Higher score indicates greater food insecurity. [c] High risk alcohol use indicated if Alcohol Use Disorders Identification Test (AUDIT) score > 20. *M* (*SD*) = mean (standard deviation); ZAR = South African Rands; HFIAS = Household Food Insecurity Access Scale; ART = antiretroviral therapy; HAM-D = Hamilton Rating Scale for Depression

Table 2 presents descriptive statistics for the ART adherence outcomes at both baseline and follow-up.

Table 2

ART Adherence measures at Baseline and Follow-up: Descriptive Statistics

	Baseline			Follow-up		
Variables	*n*	*M* (*SD*)	*f* (%)	*n*	*M* (*SD*)	*f* (%)
SRA-1	103	2.33 (1.42)		80	3.60 (1.33)	
SRA-2 (%)	104	60.54 (30.58)		80	80.07 (20.50)	
Wisepill (%)	70	67.70 (31.67)		51	51.09 (38.78)	
TFV-DP (fmol/punch)	48	634.75 (521.88)		39	669.20 (526.64)	
HIV viral suppression [a]	105		25 (23.81%)	81		40 (49.38%)

Note. [a] HIV RNA viral load < 400 copies/mL. SRA = self-report adherence; TFV-DP = Tenofovir diphosphate. *M* (*SD*) = mean (standard deviation).

ART Adherence Composite Variables

The PCA resulted in a two-factor solution that explained 82% of the variance. Based on this analysis, all four ART adherence measures were retained. The two self-report variables loaded onto one component (Eigenvalue = 1.875; factor loadings were SRA-1 = 0.964 and SRA-2 = 0.956), which explained 47% of the variance. Wisepill and TFV-DP loaded onto another component (Eigenvalue = 1.406; factor loadings were Wisepill = 0.823 and TFV-DP = 0.850), which explained 35% of the variance.

Hence, we created two separate composite variables for the ART adherence measures: The first is the Self-Report Adherence Composite (composed of SRA-1 and SRA-2), and the second is the Objective Adherence Composite (composed of Wisepill and TFV-DP). We calculated values for each of these composite variables by multiplying the values for each of the original ART adherence outcome variables by the factor loadings and adding them together.

Univariable Associations between Cognitive Performance and ART Adherence

Analyses detected no significant associations between any of the cognitive performance predictor variables (each of the domain *T*-scores and the global *T*-score) and any of the ART adherence outcome variables (Self-Report Adherence Composite, Objective Adherence Composite, viral suppression; see Table 3).

Table 3

Univariable Associations between Cognitive Performance and ART Adherence

	Outcome Variables											
	Objective Adherence Composite (n = 96)				Self-Report Adherence Composite (n = 105)				Viral suppression (n = 104)			
Predictor Variables	*est*	*CI*	*t*	*p*	est	*CI*	*t*	*p*	*OR*	*CI*	*z*	*p*
Domain *T*-scores												
Motor skills	-0.00	-0.02 – 0.01	-0.27	.785	0.01	-0.02 – 0.03	0.68	.500	1.03	0.99 – 1.08	1.53	.125
Information Processing Speed	-0.00	-0.02 – 0.01	-0.50	.617	0.00	-0.02 – 0.03	0.31	.756	1.04	0.99 – 1.09	1.63	.103
Verbal Fluency	-0.00	-0.02 – 0.02	-0.04	.967	0.01	-0.02 – 0.05	0.80	.427	1.03	0.97 – 1.09	1.00	.319
Attention and Working Memory	0.01	-0.02 – 0.03	0.54	.586	0.02	-0.02 – 0.05	0.89	.376	1.49	0.97 – 2.28	1.82	.069
Audioverbal Learning and Memory	-0.01	-0.03 – 0.00	-1.53	.129	0.02	-0.01 – 0.05	1.48	.141	1.03	0.99 – 1.08	1.45	.148
Visuospatial Learning and Memory	-0.00	-0.02 – 0.01	-0.34	.738	0.01	-0.02 – 0.03	0.68	.495	1.02	0.98 – 1.05	0.88	.382
Executive Functioning	-0.02	-0.03 – -0.00	-1.98	.050[a]	0.02	-0.01 – 0.05	1.35	.179	1.01	0.97 – 1.05	0.53	.598
Global *T*-score	-0.09	-0.26 – 0.07	-1.10	.272	0.20	-0.08 – 0.47	1.38	.168	1.08	0.99 – 1.16	1.82	.068

Note. Est = estimate, CI = confidence interval. [a] Data from one participant were removed from the analyses because the value was an influential outlier (Cook's D = 0.06).

Multivariable Modelling of ART adherence

Self-Report Adherence Composite. The final model included the HAM-D and AUDIT variables as fixed effects. For every one unit increase in HAM-D score, this adherence composite score decreased by 0.54 points (CI: -0.78, -0.30; t = -4.43; $p < .001$; r = -0.27) on average across both time points. For participants with AUDIT scores ≥ 20 (i.e., those reporting high-risk alcohol use), this adherence composite score was 0.73 points lower (CI: -1.31, -0.15; t = -2.47; p = .015; r = -0.21), on average across both time points, compared to participants with AUDIT scores < 20.

For this final model, the marginal R^2 was .13, indicating that these fixed effects explained 13% of the variance in the outcome.

We used several measures to determine the model's robustness. The ICC was .24, which supports the use of a linear mixed model. The conditional R^2 was .34, which also confirms the importance of having a random effect for participant in the model (i.e., 34% of the variance in the outcome was explained by this random effect). Another indication of the model's robustness is that the final model (AIC = 730.69) was significantly better than the null model (AIC = 751.00; $\chi^2 = 24.31$; $p < .001$).

Objective Adherence Composite. The final model included only age as the fixed effect, which was not statistically significantly associated with this adherence outcome (estimate = 0.16; CI: -0.01, 0.32; t = 1.87; p = .064, r = .16). The marginal R^2 was .02, indicating that this fixed effect explained 2% of the variance in the outcome.

Again, we used several measures to determine the model's robustness. The ICC was .16, which supports the use of a linear mixed model. The conditional R^2 was .18, which also confirms the importance of having a random effect for participant in the model (i.e., 18% of the variance in the outcome was explained by this random effect). The final model (AIC = 473.50) was not significantly better than the null model (AIC = 472.11; $\chi^2 = 3.39$; p = .066).

HIV viral suppression. Results for this model (a binary logistic multivariable mixed effects regression model) are reported in Table 4. The final model included sex, age, HAM-D score, and global T-score as fixed effects.

Analyses indicated that both sex and global T-score were statistically significant. On average across both time points, female participants were 0.27 times more likely than male participants to be virally suppressed. For every one-unit increase in global T-score, the odds of the participant being virally suppressed increased by 1.83.

For this final model, the marginal R^2 was 0.15, indicating that the fixed effects explained 15% of the variance in the outcome.

The ICC for this model was .45, which supports the use of a mixed effects model. The conditional R^2 was .53, which also confirms the importance of having a random effect for participant in the model (i.e., 53% of the variance in the outcome was explained by this random effect). Another indication of the model's robustness is that the final model (AIC = 230.33) was significantly better than the null model (AIC = 240.02; $\chi^2 = 17.69$; $p = .001$).

Table 4

HIV Viral Suppression Across Both Time points: Final binary mixed effects regression model

Fixed Effect	Odds ratio	*CI*	*z*	*p*
Sex (male versus female)	0.27	0.07 – 0.99	-1.98	.048*
Age (years)	1.79	0.99 – 3.24	1.94	.053
HAM-D score	0.61	0.36 – 1.02	-1.87	.062
Global *T*-score	1.83	1.02 – 3.29	2.03	.043*

Note. HAM-D = Hamilton Rating Scale for Depression; CI = confidence interval.

*$p < .05$.

Discussion

The main aim of this study was to investigate associations between cognitive performance and ART adherence in a South African cohort of PWH with comorbid MDD. We also investigated associations between ART adherence and a set of sociodemographic, psychosocial, and psychiatric variables. Among the psychiatric variables, depression was of primary interest.

Univariable analyses indicated that neither global nor within-domain cognitive performance were significantly associated with any ART adherence outcome. Multivariable models showed that global cognitive performance was not significantly associated with ART adherence (measured both subjectively and objectively). However, when controlling for depression severity and education level, better global cognitive performance (and being female) was significantly associated with greater probability of being virally suppressed.

One might have expected, based on results reported by previous studies, that poor cognitive performance in individual cognitive domains would have been significantly associated with worse ART adherence, regardless of whether the outcome was measured subjectively or objectively (Andrade et al., 2013; Ettenhofer et al., 2010; Hinkin et al., 2002; Hinkin et al., 2004; Lovejoy & Suhr, 2009; Mark, 2011). For instance, impaired executive functioning can make medication management more challenging, and impaired learning and

memory can result in difficulties remembering to take medication (Ettenhofer et al., 2010; Lovejoy & Suhr, 2009).

One explanation for our non-significant univariable results might involve sample characteristics: Participants in our sample were (at baseline, at least) diagnosed with MDD, whereas participants in previous studies that found significant associations were not reported as experiencing such psychiatric illness. The presence of depression may modify relations between cognitive performance and ART adherence given that there are independent associations between depression and cognitive performance (Bragança & Palha, 2011; Fellows et al., 2013; Goggin et al., 1997; McDermott & Ebmeier, 2009; Rock et al., 2014; Rubin & Maki, 2019; Shimizu et al., 2011) and between depression and ART adherence (Colibazzi et al., 2006; Gonzalez et al., 2011; Kacanek et al., 2010; Langebeek et al., 2014; Nel & Kagee, 2013).

This speculation is supported by results from the multivariable models. Global cognitive performance was significantly associated with viral suppression in a multivariable model that controlled for depression severity and education level. In other words, when not controlling for these factors (as in the univariable models), the presence of MDD and low levels of education (on average, the sample had only completed 9 years of education) may have masked the significance of the association between overall cognitive performance and viral suppression. However, when the statistical controls are put in place, the significant association is revealed.

Considering our finding that global cognitive performance was significantly associated with ART adherence as indicated by viral suppression but that it was not significantly associated with the other measures of ART adherence (i.e., by either the other objective or the subjective indices), it may be that the measures that we used in fact measure slightly different aspects of adherence within the same general construct. More specifically, viral suppression is more properly considered an outcome of successful ART adherence, rather than a measure of adherence (Republic of South Africa National Department of Health, 2019; UNAIDS, 2021). Also, viral suppression likely reflects cumulative optimal adherence over a relatively long timeframe (Stöhr et al., 2013; Supervie et al., 2016), whereas our other measures provide more current indications of adherence (we took Wisepill reports over a 2-week period and TFV-DP and self-report outcomes at two discrete time points). In other words, what our results imply is that poor cognitive performance may be associated with historical poor adherence, as indicated by viral suppression, but may not be associated with recent incomplete adherence (as measured by self-report, Wisepill, and TFV-DP).

Increased depression and problematic alcohol use were significant predictors of worse self-reported ART adherence. This finding is consistent with previous research showing that, independently, depression (Colibazzi et al., 2006; Gonzalez et al., 2011; Kacanek et al., 2010; Langebeek et al., 2014; Nel & Kagee, 2013) and problematic alcohol use (Chander et al., 2006; Hendershot et al., 2009; Kekwaletswe et al., 2017; Magidson et al., 2017; Morojele et al., 2014) predict incomplete adherence in PWH.

Being female was significantly associated with increased chances of being virally suppressed. This finding is consistent with other South African studies suggesting that women have better ART adherence than men (Heestermans et al., 2016; Joseph Davey et al., 2018; Pillay et al., 2020). In South Africa, men with HIV are less likely to access and remain linked to HIV care (Braitstein et al., 2008; Osler et al., 2020). Several mechanisms may explain this gender disparity, including the prioritisation of maternal and child health services in the South African public health systems and gender differences in health-seeking behaviour (Osler et al., 2020).

We acknowledge the following limitations of the study design. First, the relatively small sample size means the study may have been underpowered to detect potentially significant associations between, for instance, within-domain cognitive performance and ART adherence, or between any of the predictors and objectively measured ART adherence. Second, we did not apply corrections for multiple comparisons. Third, because viral suppression assesses HIV treatment efficacy and is not simply an outcome of successful ART adherence, non-suppression may indicate viral resistance to ART rather than incomplete adherence (Spinelli et al., 2020). Fourth, we cannot infer a causal direction in the relationship between adherence and cognitive performance. Although we imply above that poor cognitive performance leads to poor adherence, the opposite relationship between cognition and adherence (i.e., incomplete ART adherence resulting in worse HIV disease which in turn causes more cognitive impairment) has been reported by others (Ettenhofer et al., 2010). The relationship between cognitive performance and viral suppression may also relate to unidentified confounding factors associated both with better cognitive performance and better HIV management. For example, better cognitive performance may be reflective of less food insecurity, better quality of education, and other psychosocial variables, all of which may also facilitate better self-management of HIV infection and, ultimately, higher rates of viral suppression.

Conclusion

The results from our mixed-effects regression models indicated that, in this incompletely adherent sample of PWH with comorbid MDD, lower levels of cognitive performance were associated with HIV viral non-suppression. Men were also less likely than women to be virally suppressed. Finally, participants with more severe depression and high-risk alcohol use self-reported worse ART adherence, although this pattern of data was not replicated in objective markers of adherence.

Because successful ART adherence is crucial to improving the lives of PWH, preventing HIV-related mortality, and reducing new infections, it is vital to identify barriers to optimal adherence in groups of PWH identified as being at high risk for incomplete adherence. This endeavour is particularly important in South Africa, which has the largest population of PWH and the largest ART program in the world (UNAIDS, 2021). Current adherence interventions in our setting are primarily aimed at addressing depressive symptoms (e.g., Safren et al., 2021) and problematic alcohol use (e.g., Belus et al., 2020; Magidson et al., 2021) – none target cognitive underperformance. Interventions aimed at improving adherence and achieving successful HIV suppression in vulnerable cohorts of PWH should explore cognitive screening and practical forms of cognitive rehabilitation.

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Chapter 7

General Discussion

This chapter summarises and integrates the results of the five studies that form the core of this thesis, thus providing a synthesis and discussion of the main findings, including the research, clinical, and policy implications. At the end of the chapter, I discuss the overall strengths and limitations of the thesis and present the overall conclusion.

The overarching aim of the thesis was to explore the sociodemographic and psychosocial determinants of cognitive performance in people with HIV (PWH). To achieve this aim, I undertook five separate investigations: (1) a review of published literature examining sex differences in the cognitive performance of people with HIV (PWH) ; (2) an original empirical study examining if there were significant sex differences in the cognitive performance of a sample of PWH attending community clinics in Khayelitsha, a peri-urban community in Cape Town, South Africa; (3) an original empirical study examining how much variation in prevalence rates of HIV-associated cognitive impairment within a sample of South African PWH was due to the method used to define that impairment, and which of those methods correlated best with MRI biomarkers of HIV-related brain pathology; (4) an original empirical study examining the contribution of sociodemographic and psychosocial variables, as well as HIV-disease factors and other medical and psychiatric comorbidities, to cognitive performance in the same sample of PWH described in (2) above; and (5) an original empirical study examining associations between cognitive performance, as well as sociodemographic, medical and psychiatric variables, and antiretroviral therapy (ART) adherence in the same sample of PWH described in (2) above. Hence, this thesis reported findings from five separate journal manuscripts.

Summary of Individual Manuscript Findings

Study 1 was a systematic review and meta-analysis of published studies containing data comparing the cognitive performance of women with HIV (WWH) against that of men with HIV (MWH). After a thorough literature search and study evaluation process, 11 studies were included in the systematic review and 6 in the meta-analysis. The major finding was that there were no significant differences in the global cognitive performance of WWH and MWH, although WWH performed significantly more poorly than MWH in the domains of psychomotor coordination and visuospatial learning and memory. An important secondary finding was that, where studies did detect significant differences in the cognitive performance of WWH and MWH, these were likely due to sex-based variation in educational and psychiatric characteristics among study samples.

Study 2 investigated sex differences in the cognitive performance of a South African sample of PWH. Participants (N = 105) had been recruited into a larger research program

whose centerpiece was a randomised controlled trial of a cognitive-behavioral treatment for ART adherence and depression (CBT-AD). This sample of PWH had incomplete ART adherence and comorbid major depressive disorder (MDD), and had been recruited from socioeconomically disadvantaged backgrounds. We assumed that sex differences were more likely to manifest in a sample with these characteristics than in the general population of PWH, and hence this presented an ideal opportunity to investigate such differences. Additionally, these sample characteristics allowed exploration of the biological (i.e., HIV disease and other medical factors), psychiatric (i.e., depression severity and high-risk alcohol use), and psychosocial (e.g., level of education and food insecurity) effects on cognitive performance within each of the WWH and MWH groups separately. The major findings were that (a) there were no significant differences in cognitive performance between WWH and MWH, both globally and within individual cognitive domains; (b) fewer years of education, illiteracy, and greater food insecurity were independently associated with lower cognitive performance in WWH but not MWH; and (c) years of educational attainment and degree of food insecurity were the strongest predictors of cognitive performance in WWH. The conclusion was that sex differences in cognitive performance in PWH are not universal and that, where they do exist, they are likely due to sample characteristics that may represent broader societal inequalities rather than true biological differences.

Study 3 applied 20 different quantitative methods of determining cognitive impairment to neuropsychological data from a South African sample of 148 PWH. Across-method analyses detected wide variation in rates of cognitive impairment (20–97%). In other words, the method used to define cognitive impairment determined how many individuals within the sample were classified as impaired. Moreover, cognitive impairment defined by any method was not correlated to neuroimaging biomarkers of HIV-associated brain injury.

Study 4 investigated the sociodemographic, medical, and psychiatric variables associated with cognitive performance in the same sample of PWH as described in Study 2 (i.e., the sample that was a part of the larger research program involving the CBT-AD randomised controlled trial). The study also investigated whether, from pre-intervention baseline to follow-up post-intervention (8-months post-baseline), depression and cognitive performance improved significantly more in participants assigned to the CBT-AD condition than in those assigned to a standard-of-care condition. Finally, analyses sought to capture the magnitude of association between post-intervention improvements in depression and cognitive performance. The major findings were that (a) fewer years of education and greater food insecurity were the strongest predictors of baseline global cognitive performance; (b) at

follow-up depression, but not cognitive performance, had improved significantly more in the CBT-AD group than in the comparison group; and (c) more severe depression was associated with poorer cognitive performance in the domain of attention and working memory at baseline, but the strength of this association became markedly weaker when the level of depression in the overall sample improved at follow-up. An important note here is that no variables directly indexing brain injury were significantly associated with global cognitive performance, at either baseline or follow-up.

Study 5 used data from the same sample of PWH as described in Study 2 and in Study 4 to investigate associations of ART adherence (as measured by both self-report and objective measures, as well as HIV viral suppression) with cognitive performance and other psychiatric and sociodemographic variables. Mixed effects regression models identified poor global cognitive performance as a potential barrier to achieving HIV suppression, and indicated that, independent of cognitive performance, men were less likely than women to be virally suppressed. Additionally, participants with more severe depression and high-risk alcohol use self-reported worse ART adherence, although this pattern of data was not replicated when using objective markers of adherence.

Main Thesis Findings

Three main findings emerged from the five studies contained in this thesis.

Main Finding 1

The first main finding is that global cognitive test performance in PWH is more strongly influenced by non-biological (mainly psychosocial) factors, such as educational level and food insecurity, than by factors related directly to HIV-associated brain injury. Evidence for this main finding emerged from Study 1, Study 2, Study 3, and Study 4. Study 1, the systematic review and meta-analysis, showed that where sex differences in cognitive performance of PWH do exist, they seem to be driven by sociodemographic and psychiatric characteristics, such as education attainment and depression severity, rather than by HIV-disease variables. In other words, in studies sampling from populations with stark differences in male-female educational attainment and depression severity, WWH might perform more poorly than MWH, whereas in studies sampling from populations with more gender equality along those divisions one might not observe such sex differences in cognitive performance. Consistent with those results and speculation, Study 2 and Study 4 found that fewer years of education and greater food insecurity were the strongest predictors of poor cognitive performance within both the entire sample of PWH and the subgroup of WWH. HIV disease variables and medical/psychiatric comorbidities were not significant predictors of global

cognitive performance in this sample of PWH, even though all participants had comorbid MDD and poorly controlled HIV (i.e., a sample whose brains would be especially vulnerable to biological effects of the infection). Study 3 found a lack of association between cognitive impairment (defined using 20 different methods) and neuroimaging outcomes of HIV-related brain injury. This result again implies that test performance in PWH may be better explained by non-biological factors than by factors related directly to HIV-associated brain injury. Note that these study results are based on the assumption that structural and diffusion MR metrics are valid indices of HIV effects on the brain and the associated effects on brain integrity.

Overall, this major finding from the studies presented in this thesis suggests that factors other than HIV disease are important determinants of cognitive performance in PWH and that PWH might perform poorly on cognitive testing for a range of non-biological reasons. This suggestion is consistent with a growing body of evidence indicating that socioeconomic and psychosocial variables strongly predict cognitive performance, especially in samples drawn from low- and middle-income countries (LMICs) or from socioeconomically disadvantaged populations (Cysique & Becker, 2015; Do et al., 2018; Haddow et al., 2018; Maki et al., 2015; Vo et al., 2013; Winston et al., 2013). The other side of this coin, naturally, is the conclusion that the effects of HIV disease itself on cognitive performance may be less influential. Of course, HIV-associated brain injury may still affect some individuals and sub-groups of PWH.

An important implication of this major finding for the field is that a rigidly quantitative approach to diagnosing cognitive impairment (i.e., classifying impairment based purely on neuropsychological test performance) may be misleading, especially in situations where researchers might want to ascribe poor performance on those tests directly to the effects of HIV disease. As the studies in this thesis show, there are likely to be multiple reasons underlying the poor performance of PWH on cognitive tests and, furthermore, there is likely to be a strong influence of psychosocial and socioeconomic factors on that performance in some populations of PWH. For the most part, tests themselves are agnostic as to the causes of poor performance, and hence HIV neuropsychology studies must, in a much more regular and reliable fashion than is currently the case, consider and control for non-biological factors that can influence test scores.[1]

[1] Many variables not measured in this thesis (and rarely measured at all in HIV neuropsychology studies) could also contribute to poor cognitive performance in vulnerable individuals (e.g., those with low-quality education, poor access to resources, childhood trauma, and chronically high stress

One way to consider and control for those factors is to compare the cognitive performance of PWH to that from well-matched comparison samples. However, even though the studies presented here followed this path, psychosocial variables (e.g., level of education and food insecurity) still had a distinct and significant influence on cognitive performance.

Another possible solution is to use tests, and associated normative data, appropriate for local contexts (e.g., resource-limited settings with high HIV burden and populations, such as that in South Africa, with vast linguistic, sociocultural, and socioeconomic diversity; Gouse, 2021; Robbins et al., 2013; Watts & Shuttleworth-Edwards, 2016). However, developing such tests and collecting such normative data is a resource-heavy task and is not especially prioritized by policymakers in LMICs such as South Africa.

Possibly the most radical solution to this problem is to move away from the rigidly quantitative approach to cognitive assessment that characterizes most HIV neuropsychology studies and to instead use a more flexible approach: taking a detailed history, using structured and/or semi-structured interviewing techniques, and adapting test administration and interpreting test scores bearing in mind the individual test-taker's context and background. Using this approach requires much more involvement of clinical judgement to determine whether the individual's performance is indicative of cognitive impairment. Of course, this method of assessment is much more typical of what one finds in clinical neuropsychological practice than in most research studies—the relative lack of objectivity and standardization can be enemies of replicability. It is also important to note that an approach to evaluating cognitive impairment which relies on well-trained neuropsychologists to perform clinical assessments is not feasible in the vast majority of LMICs where the largest group of PWH reside. The challenge for HIV neuropsychology studies, therefore, is to find ways to incorporate useful aspects of clinical practice into their research designs. This endeavour is a vital to ensure study findings are applicable and relevant to clinical practice, and subsequently the lives of PWH.

Another implication of this major thesis finding relates more broadly to the way that formal diagnostic criteria for HIV-associated cognitive impairment have been developed and are expressed. Most current criteria rely exclusively on rigid quantitative interpretations of neuropsychological test performance. For example, according to the HIV-associated neurocognitive disorder (HAND) criteria (Antinori et al., 2007), a diagnosis of asymptomatic

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levels). Factors such as culture and language are also known to influence performance on cognitive tests (Ferrett et al., 2014; Strauss et al., 2006).

neurocognitive impairment (ANI) is made if cognitive performance is ≥ 1 SD below the normative mean. Similarly, a diagnosis of global impairment according to the global deficit score (GDS) criteria (Carey et al., 2004) is made purely on the basis of low scores on cognitive tests.

Study 3's findings showed that imaging biomarkers of HIV brain injury were not associated significantly with HIV-associated cognitive impairment as defined by any of 20 different neuropsychological methods. Of import here, of course, is that the criteria used by all of those methods were based purely on cognitive test scores. In other words, none of the currently published neuropsychological criteria for defining cognitive impairment in PWH accurately defined HIV-associated cognitive impairment in a South African cohort. Others have also highlighted the limited diagnostic accuracy of these criteria (see, e.g., Gates & Cysique, 2016; Gisslén et al., 2011; Meyer et al., 2013; Underwood et al., 2018), as well as the need for updated (i.e., relevant and accurate) criteria for defining cognitive impairment in diverse global populations of PWH (see, e.g. Ciccarelli, 2020; Meyer, 2022; Saloner & Cysique, 2017).

One of the consequences of a lack of diagnostic accuracy is that it hampers research investigating underlying biomarkers for HIV-associated cognitive impairment and the development of therapeutic intervention. Another consequence is that research studies might be overestimating the prevalence of HIV-associated cognitive impairment. Such overestimation, given that it implies that PWH are at much higher risk of developing cognitive difficulties than they actually are, can be stigmatizing and anxiety-provoking for those individuals (Nightingale et al., 2014).

Naturally, the consequences of this lack of diagnostic accuracy will be most pronounced in settings where the burden of HIV is greatest. Given that those settings also tend to be resource-limited contexts, such as those that characterize much of sub-Saharan Africa, it is imperative that HIV researchers recognize the urgent need for new methods of diagnosing HIV-associated cognitive impairment.

The work presented in this thesis can help inform these new methods in two ways. First, it is clear from the results described above that a diagnosis of cognitive impairment should not be based purely on test performance. Instead, it should only be made after conducting a thorough clinical evaluation (including a detailed history taking) alongside a neuropsychological assessment. Second, the assessment should consider the individual's sociodemographic and socioeconomic background and the potential influence of these variables on cognitive test performance.

Emerging from these findings and our clinical observations, our research group has emphasized the need to develop new criteria for cognitive impairment in PWH. Recent publications have proposed ways toward that end (see, e.g., Nightingale et al., 2021). Additionally, I have been involved in an International HIV-Cognition Consortium that aims to develop new consensus criteria for cognitive impairment in PWH (see, e.g., Nightingale et al., 2022). This globally representative group has almost half of its members based in LMICs and includes academics and clinicians from a range of disciplines (neurology, psychiatry, neuropsychology, and HIV/infectious disease), as well as representatives from the PWH community. This group has been meeting since November 2021 to work towards a new framework for diagnosing cognitive impairment in PWH. One of its guiding principles is that updated criteria are essential to advance HIV research and to improve clinical care for PWH. Furthermore, it operates under the imperative that series of empirical research studies will be required to validate these new diagnostic criteria.

Main Finding 2

The second main finding of this thesis, evidence of which emerged from Study 1 and Study 2, is that the oft-mooted sociodemographic influence of sex on cognitive performance in PWH was not observed consistently. This finding is congruent with those reported in many previously published research studies (e.g., Behrman-Lay et al., 2016; Faílde Garrido et al., 2013; Robertson et al., 2004; Sibanda-Kunda et al., 2015). Although several other studies do report worse cognitive performance in WWH than MWH (e.g., Burlacu et al., 2018; Maki et al., 2018; Qiao et al., 2019; Wei et al., 2020), an important implication of this main finding of the thesis is that sex differences in the cognitive performance of PWH are not found universally, and that therefore clinicians and researchers need not be concerned that all WWH will present with greater cognitive impairment than all MWH.

Where significant sex differences in cognitive performance do exist, they may present in the domains of psychomotor coordination, visuospatial learning, and visuospatial memory, although the effects are relatively small and may be explained (at least partially) by sex-based variation in sociodemographic and psychiatric characteristics.

Therefore, another equally important implication is that where sex differences favouring MWH are observed, they may be driven by persistent issues of gender inequality (such as the high rates of trauma and greater prevalence/severity of MDD in women) that contribute to the differential vulnerability of WWH to cognitive impairment. These broader societal issues should be at the forefront of public policy and national healthcare decision making.

Main Finding 3

The third main finding of this thesis is that poor global cognitive performance may be a barrier to optimal ART adherence, in that PWH and MDD with lower cognitive performance were more likely not to be virally suppressed. This finding is an important one, for South Africa to achieve the 95-95-95 goals. The clinical implication of this finding is that assessing for cognitive impairment among PWH and providing appropriate support could help achieve viral suppression in patients with depression and non-optimal adherence to ART.

The findings of this thesis, evidence of which emerged from Study 1 and Study 2, that were discussed earlier on in this chapter, suggest that education level is protective, and food insecurity is injurious to, cognitive functioning in PWH and MDD. Research interventions aimed at improving adherence to HIV treatment and achieving successful HIV suppression in vulnerable cohorts of PWH should explore food insecurity interventions and other practical forms of cognitive rehabilitation. At public policy levels, addressing larger psychosocial issues, such as food insecurity and low education attainment, may also help improve cognitive performance in PWH, which could consequently have the beneficial by-product of improving rates of viral suppression in PWH and assist in achieving the 95-95-95 goals to end the HIV epidemic.

Thesis Strengths and Limitations

This thesis has several methodological strengths and limitations.

Thesis Strengths

First, the samples contained in this thesis are understudied and underrepresented within the global HIV literature on account of the following characteristics: (a) the thesis studies included majority-female samples and were conducted in South Africa, a LMIC, whereas most HIV studies include majority-male samples and are conducted in high-income countries (such as the United States and United Kingdom); (b) three of the studies contained in this thesis are centred on a distinct and clinically important sample of PWH with incomplete ART adherence, comorbid MDD and a background of socioeconomic disadvantage – a key population at higher risk for HIV-related morbidities and onwards transmission of the virus; (c) in the sample of PWH and comorbid MDD, all individuals with medical and psychiatric comorbidities were included in the study to ensure results were relevant to a real-life population of PWH, whereas such individuals are often excluded from HIV neuropsychology research studies.

Second, this thesis collected participant information not routinely gathered in HIV

neuropsychology studies: psychosocial data (e.g., income, food insecurity), and information on medical (e.g., neurological, and cerebrovascular risk factors) and school performance history (e.g., whether they had ever been held back or repeated a year in school, whether they were fully literate). One such variable, food insecurity, surfaced as one of the strongest predictors of cognitive performance, showing the importance of measuring variables not commonly investigated in studies.

Third, the scope of this thesis benefitted from being part of a larger research program which allowed access to resources and data that perhaps would not have been available and accessible in a stand-alone doctoral research project.

Thesis Limitations

First, despite the benefits mentioned above regarding being part of a larger research program to investigate the first, third and fourth research aims of the thesis (presented in Study 2, Study 4 and Study 5), a limitation of this set-up was that the study design of these studies were constrained by the already-established aims and methods of the broader study, the randomised-controlled trial for CBT-AD (Joska et al., 2020; Safren et al., 2021). This broader study was already recruiting participants when I developed the protocol for the supplement study that collected the neuropsychological data for this doctoral thesis. This constraint resulted in a limitation in the number of participants recruited and a complex dataset. For instance, Study 2 would have benefitted from having more MWH ($N = 29$) and Study 5 would have benefitted from having more participants in the CBT-AD group ($N = 33$). To address the sample size limitations, we recruited the additional $N = 33$ participants that were not part of the trial, and which resulted in a slightly more complex dataset (i.e., these participants were virally suppressed at baseline).

Second, following on from this point, the samples included in this thesis all had relatively small sample sizes and therefore the individual studies may not have had sufficient power to detect statistically significant effects. For instance, Study 2, may not have had sufficient statistical power to detect significant sex differences in cognitive performance considering the relatively small number of MWH included in the study. Similarly, in Study 2 and Study 5, it is possible that there was not enough statistical power to detect significant associations between cognitive performance and certain individual variables measured in the study that are known to influence cognitive performance (e.g., history of neurological events or vascular risk). Similarly, even though this thesis collected participant information not routinely gathered in HIV neuropsychology studies, it is not an exhaustive list of potential predictors of cognitive performance. Bigger studies with much larger sample sizes, preferably

with longitudinal designs, are needed to really determine the relative contribution and causal nature of all variables associated with cognitive performance in PWH.

Regarding follow-up sample size, although we successfully achieved an 80% retention rate from baseline to follow-up in Study 4 and Study 5, due to the COVID-19 lockdown restrictions, we closed the study prematurely in March 2020 and were unable to conduct follow-up assessments for five participants.

Third, the findings were drawn from the samples of PWH attending the primary care clinics in a peri-urban community in Cape Town, South Africa and therefore may not be generalisable to all samples of PWH. Similarly, the findings that were drawn from the samples of PWH with MDD and incomplete ART adherence, may not be generalisable to all samples of PWH.

Conclusion

The studies presented in this doctoral thesis generated results that might be distilled into three main findings. First, diagnosing cognitive impairment in PWH based purely on cognitive test scores does not accurately reflect HIV-related brain injury. In the absence of a clinical history and the nuance of clinical judgment, a diagnosis of cognitive impairment may be inaccurate because cognitive test performance is strongly influenced by non-HIV factors, including psychosocial and socioeconomic variables. Second, sex differences in PWH cognitive performance are not universal. In studies that do detect such differences, this manifestation may be attributed to sample characteristics that may represent broader societal inequalities rather than true biological differences. Third, poor cognitive performance may be a barrier to achieving viral suppression in PWH.

The implications of these three main findings, for both science and practice, are numerous. One implication is that the field should develop updated and refined criteria for diagnosing cognitive impairment in PWH. The development of such criteria, and their widespread employment in research studies, is essential for the field to progress. Another implication is that larger psychosocial issues, particularly those contributing to gender inequality, need to be addressed. For instance, interventions aimed at relieving food insecurity may be beneficial to PWH. Addressing these broader social issues will help improve cognitive performance in PWH, minimize sex-based differences in cognitive performance, and may improve ART adherence in PWH who are also managing depression.

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