Cognitive deficits in PWH with post-acute sequelae of SARS-CoV-2 infection

Abstract

The proposed study will focus on the investigation of the dual impact of HIV infection and post-acute sequelae (PASC) of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2 infection) on neurocognitive and psychiatric outcomes in South African adults. The specific aim of the proposed study is to investigate the longitudinal effects of HIV infection and post-acute sequelae of SARS-CoV-2 infection on cognitive functioning and psychiatric morbidity. The study will allow demonstration of feasibility to recruit HIV+ and matched HIV- individuals, with and without PASC. With data from the pilot study, we plan to apply for R01 funding to continue and expand the scope of this collaborative work to include larger samples in whom longitudinal neuromedical, neuropsychiatric, neurocognitive, and neuroimaging data will be collected. The proposed pilot study will be embedded as a sub-study in a larger NIH (NIAID) IeDEA-SA grant aimed at assessing the mental health of HIV-infected adults attending public sector health facilities in Cape Town. This pilot study will recruit a well-defined patient group of HIV-positive and HIV-negative adults attending five purposively selected public sector health facilities in Cape Town, representing ethnically diverse populations. To address the proposed research question, a longitudinal study design with a 6-month follow-up will be applied. The study will entail quantitative assessments of a cohort, comparing adults living with HIV with post-acute sequelae of SARS-CoV-2 infection to matched controls. Ninety HIV-positive adults (45 with PASC and 45 without PASC) and ninety HIV-negative adults (45 with PASC and 45 without PASC) will be recruited. All participants will undergo screening for PASC and neurocognitive and psychiatric assessments at baseline and at the 6-month follow-up. Initial goals will be to replicate neurocognitive abnormalities previously reported in the single-risk group, and to look for evidence of interaction in individuals who are both HIV+ and COVID-19 survivors with PASC. Such interactions could manifest as disproportionate neurocognitive dysfunction in the dually affected group. The proposal outlined here draws on the expertise of investigators from the HNRC at UCSD and Stellenbosch University's Department of Psychiatry. Dr Mariana Cherner (HNRC) directs the Interdisciplinary Research Fellowship in NeuroAIDS and is an investigator within the HIV Neurobehavioral Research Program. She has vast experience in adult neuropsychological assessment and a keen interest in culturally competent neuropsychological assessment, with a focus on HIV in resource-limited settings. The SA group (Drs Spies and Seedat) also has experience in longitudinal NeuroAIDS research. The current collaboration with Dr Cherner will be extremely important in developing local expertise in this area of research and in developing sustainable NeuroAIDS research capacity locally.

Background and Significance

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the pathogen responsible for the coronavirus disease-2019 (Covid-19) pandemic which has resulted in over 200 million confirmed infections and over 4 million deaths worldwide. Although SARS-CoV-2 manifests primarily with respiratory tract infections and flu-like symptoms, Covid-19 is now recognized as a multisystem disease often involving the nervous system (Roberts et al., 2020). Across the globe, a subset of patients who sustain an acute SARS-CoV-2 infection are developing a wide range of persistent symptoms that do not resolve over the course of

many months, including psychiatric, neuropsychiatric, and neurological symptoms. A wide range of symptoms affecting the cardiopulmonary, neurocognitive, and gastrointestinal systems, as well as effects on skin and eyes, and general pain, may persist in the post-acute phase and constitute a “long Covid” syndrome (Ladds et al., 2020; Lancet, 2020) which has also recently been called the syndrome of “post-acute sequelae of SARS-CoV-2 infection” (PASC) (Nalbandian et al., 2021). Around one in three people with symptomatic COVID-19 still experience symptoms 12 weeks after onset (Whitaker et al., 2021). Long Covid can be experienced by all age groups and not only those with acute severe disease. The debilitating symptoms are wide-ranging, multisystemic, and predominantly fluctuating or relapsing (Alwan, 2021). Some develop persistent and debilitating symptoms despite a relatively mild illness at onset, and they are known as Covid-19 “long haulers” (Callard & Perego, 2021; Carfì, Bernabei, & Landi, 2020; Goërtz et al., 2020).

Many coronaviruses are capable of altering the structure and function of the nervous system (Al-Obaidi et al., 2018; Michalicová, Bhide, Bhide, & Kováč, 2017). In Covid-19 patients worldwide, neurologic manifestations of varying severity have been reported in 36.4–82.3% of those hospitalized (Carfì et al., 2020; Ellul et al., 2020; Koralnik & Tyler, 2020; Mao et al., 2020; Romero-Sánchez et al., 2020). A recent study found that non-hospitalized Covid-19 “long haulers” experienced prominent and persistent “brain fog” and fatigue that affected their cognition and quality of life (Graham et al., 2021). Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients has led to questions of whether “brain fog,” with or without fatigue, might represent a mild form of post-Covid-19 encephalopathy (Liotta et al., 2020).

Cognitive impairment has been noted with or without fluctuations, including brain fog, which may manifest as difficulties with concentration, memory, receptive language and/or executive function (Heneka, Golenbock, Latz, Morgan, & Brown, 2020; Kaseda & Levine, 2020; Ritchie, Chan, & Watermeyer, 2020). A recent study found that SARS-CoV-2 patients performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population (Graham et al., 2021). Similarly, a study including patients hospitalized for complications of SARS-CoV-2 infection in non-intensive COVID units found that 5 months after hospital discharge, 42.1% had processing speed deficits, while 26.3% showed delayed verbal recall deficits and 21% presented with deficits in both processing speed and verbal memory (Ferrucci et al., 2021). Long-term cognitive impairment is well recognized in the post-critical illness setting, occurring in 20–40% of patients discharged from an ICU (Sakusic & Rabinstein, 2018).

In addition to evidence suggesting that a variety of acquired brain injuries stem from serious neurologic conditions related to the illness itself or its treatment, neurocognitive deficits are additionally likely to be complicated by psychiatric comorbidities (Kaseda & Levine, 2020). Research from past coronavirus outbreaks, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), indicate a high likelihood of psychiatric symptoms and disorders in COVID-19 survivors, most notably post-traumatic stress symptoms (PTSS) and post-traumatic stress disorder (PTSD) (A. M. Lee et al., 2007; S. H. Lee et al., 2019). In a cohort of 402 COVID-19 survivors in Italy 1 month after hospitalization, approximately 56% screened positive in at least one of the domains evaluated for psychiatric sequelae (PTSD, depression, anxiety, insomnia and obsessive-compulsive symptomatology) (Mazza et al., 2020). Post-COVID brain fog in critically ill patients with COVID-19 may evolve from mechanisms such as deconditioning or PTSD (Kaseda & Levine, 2020). Patients with neuropsychiatric sequalae such as anxiety, depression, sleep disturbances, PTSD, and fatigue following SARS-CoV-2 infection may also experience cognitive dysfunction.

Comorbidities, including those that involve immunosuppression, seem to be associated with higher risk of COVID-19 death (Williamson et al., 2020). However, little evidence exists on how HIV infection affects risk of poor outcomes from COVID-19 and prevalence data on SARS-CoV-2 in HIV are still very scarce. A large population-based cohort study in the Western Cape Province of South Africa found that among 536,574 HIV patients aged ≥20 years, 3978 were diagnosed with COVID-19 (Boulle et al., 2020). COVID-19 mortality risk among PLHIV was found to be double the risk of those without HIV (Boulle et al., 2020). High rates of cognitive disorders in antiretroviral-treated people living with HIV have been described worldwide (Alford & Vera, 2018; Winston & Spudich, 2020). With the cohort of people with HIV becoming increasingly older and having high rates of comorbidities and concomitant medication use, rates of cognitive disorders are likely to increase (Winston & Spudich, 2020). Data on HIV/SARS-CoV-2 co-infection is still scarce and to our knowledge, no studies have examined neurocognitive outcomes of people living with HIV with post-acute COVID syndrome.

The long-term impact of PASC through lingering neuropsychiatric manifestations may be substantial as the SARS-CoV-2 pandemic continues to escalate. Current understanding of cognitive sequelae of COVID-19 is still largely limited to individuals who required hospitalization and to our knowledge, there are currently no studies examining this in PLHIV. Given the paucity of studies examining the combined effects of HIV/SARS-CoV-2 co-infection, we seek to investigate whether worse neurocognitive and psychiatric outcomes could be expected in individuals dually affected by HIV and post-acute sequelae of SARS-CoV-2 infection. This possibility warrants further investigation.

The co-occurrence of neurocognitive deficits, neuropsychiatric and psychiatric sequalae, HIV infection, and PASC poses significant challenges to treating HIV. There are gaps in our knowledge about the effects of COVID-19 after the initial stages of infection, particularly in the context of HIV infection. The magnitude of the problem is not yet known, but given the number of individuals of all ages, including PLHIV, who have been or will be infected with SARS-CoV-2, the public health impact could be profound. To our knowledge, there are no other published studies investigating this research question, highlighting the innovative thrust of the proposed pilot study. Our focus on neurocognitive disorders and psychiatric outcomes in individuals dually affected by HIV and PASC aligns with the NIH HIV/AIDS research priorities, fitting under the high priority topic of clinical research to increase understanding of HIV-related comorbidities, coinfections, and complications. Moreover, this research aligns with the NIH's new PASC Initiative to fund and study the prolonged health consequences of SARS-CoV-2 infection.

Specific Aims

We propose to conduct a pilot study, in collaboration with the HNRC at UCSD, to explore the dual impact of HIV infection and post-acute sequelae of SARS-CoV-2 infection on neurocognition and psychiatric morbidity in South African adults. South Africa has been impacted severely by the coronavirus disease 2019 (COVID-19) pandemic. As of December 2021, over 2,9 million confirmed cases and over 89,000 deaths have been recorded. SARS-CoV-2 is recognized as a multisystem disease often involving the nervous system (Roberts et al., 2020). Symptoms following the acute phase often persist for several months and are identified as the syndrome of "post-acute sequelae of SARS-CoV-2 infection" (PASC) (Nalbandian et al., 2021). Neurologic manifestations of COVID-19, including cognitive sequelae have been documented but understanding of this is still largely limited to

individuals who required hospitalization (Ellul et al., 2020; Koralnik & Tyler, 2020; Mao et al., 2020; Romero-Sánchez et al., 2020). South Africa has the largest HIV epidemic in the world, with 7.8 million people with HIV (PWH), and over 5 million people receiving antiretroviral therapy (ART) (Joint United Nations Programme on HIV/AIDS (UNAIDS)., 2021). High rates of cognitive disorders in antiretroviral-treated people living with HIV have been described worldwide (Alford & Vera, 2018; Winston & Spudich, 2020). In South Africa, neurological manifestations of HIV (Anderson et al., 2020) and neurocognitive impairment over time has been demonstrated (Spies, Fennema-Notestine, Cherner, & Seedat, 2017). Understanding HIV-related comorbidities, coinfections, and complications is important in managing and treating HIV. To our knowledge, there are currently no studies examining cognitive function and psychiatric outcomes in HIV-infected COVID-19 survivors. Within the context of two colliding epidemics in South Africa, we seek to investigate whether worse neurocognitive and psychiatric outcomes could be expected in individuals dually affected by HIV and PASC. The study will allow demonstration of feasibility to recruit people with HIV with PASC. The specific aims of the proposed study are:

1. To investigate the longitudinal effects of HIV infection and PASC on cognitive functioning. We will assess neurocognition at baseline and at the 6-month follow-up period. We hypothesize that among PWH with PASC, there will be poorer cognitive function compared to matched controls, with these group differences maintained over time.
2. To investigate psychiatric outcomes and symptom severity among PWH and COVID-19 survivors. We will assess depression, anxiety, posttraumatic stress symptoms at baseline and at the 6-month follow-up period. We hypothesize that PWH and COVID-19 survivors have a higher prevalence of psychiatric disorders than HIV-negative persons and persons who did not have COVID-19.
3. To identify possible risk and resilience factors among PWH and COVID-19 survivors such as sociodemographic features and HIV and SARS-CoV-2 disease related variables (viral load, CD4 and antiretroviral adherence).

These preliminary data will make a novel contribution to HIV and SARS-CoV-2 research. With data from the pilot study, we plan to apply for R01 funding to continue and expand the scope of the collaborative study to include larger groups and a longer follow-up period.

Experimental Design and Methods

To prepare for larger grant submissions in the future, we wish to demonstrate feasibility by conducting a pilot study of PWH with post-acute sequelae of SARS-CoV-2 infection and matched controls. The proposed pilot study will be embedded as a sub-study in a larger NIH (NIAID) IeDEA-SA grant aimed at investigating the burden of mental health disorders among HIV-positive and HIV-negative adults, and COVID-19 survivors in South Africa. This study will provide a large epidemiological base to draw on, allowing us to recruit our HIV-COVID pilot sample entirely through this base. There are varying working definitions of PASC and these working definitions are likely to change as understanding of PASC and other post-COVID conditions increases. PASC is a research term coined by the NIH and will form the focus of NIH's RECOVER initiative. For the present study, we will align with the NIH and define PASC as the failure to recover from acute COVID-19, or those persistently symptomatic for > 30 days from onset of infection.

Design and participants

A longitudinal study design with a 6-month follow-up will be applied. The study will entail quantitative assessments of a cohort, comparing adults with HIV with post-acute sequelae of SARS-CoV-2 infection to matched controls. The sample for the pilot study will consist of men and women recruited through the larger IeDEA-SA grant study on mental health in HIV. The larger study will recruit a sample of 800 HIV-positive and 200 HIV-negative adults stratified by sex and age attending five purposively selected public sector health facilities in Cape Town, representing ethnically diverse populations. All participants will be screened for medical history. Participants will be excluded if they meet the following criteria: (a) a history of neurological disease (e.g. dementia, seizure disorders); (b) severe head injury resulting in loss of consciousness for more than 30 minutes; (c) prior neurological surgery; (d) a history of psychotic disorders; (e) a history of learning disorders (e.g., dyslexia) or Attention Deficit/Hyperactivity Disorder (ADHD); (h) current severe alcohol use disorder; (j) regular cannabis use in the last six months; (k) drug abuse in the last two years, excluding cannabis; (l) an inability to read or write in either English, Afrikaans, or isiXhosa and/or to give informed consent; and (m) formal education of fewer than seven years. From this stratified random sample, we aim to recruit 90 cases (with and without PASC) and 90 controls (with and without PASC; see sample breakdown in figure 1 in appendix).

Procedure

Ethical clearance for the parent study (IeDEA-SA) will be obtained from the Human Research Ethics Committee of the University of Cape Town Ethical clearance will be obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University. Once potential participants have consented to participate in the larger study, they will be asked for permission to be contacted by our study team to discuss participation in the proposed sub-study. Only study participants giving their consent to be contacted will be contacted to inform them about the study aims and procedures. Once participants have agreed to take part in the study, they will be requested to travel to Stellenbosch University (Tygerberg medical campus) on a single occasion for secondary screening and a neurocognitive assessment. Participants will be reimbursed for their transport costs to and from the study assessment. Participants will be tested using a battery of neuropsychological tests (aim 1). All assessments will be repeated at the 6-month follow-up. As part of their participation in the larger IeDEA-SA grant study on mental health in PWH, all participants will be assessed for psychiatric illness at baseline and 6-month follow-up. Refer to study timeline in appendix. We will have access to these data to assess psychiatric outcomes in our sample (aim 2). See figure 2 in appendix.

Measures

(1) Demographic and clinical variables

A demographic questionnaire asking for age, sex, ethnicity, country of origin, education, relationship status, employment, household income, household size, and number of children will be administered. Current and nadir CD-4 cell count, HIV viral load, antiretroviral status, and COVID-19 routine data will be recorded.

(2) Neuromedical Evaluation

Blood samples will be obtained for measurement of viral loads and CD-4 cell counts. The blood draw will be conducted by a research nurse appointed to the study.

(3) Assessment of post-acute sequelae of SARS-CoV-2 infection

As part of the larger study, participants will be assessed using the C4R questionnaire (Oelsner et al., 2021), providing limited information on COVID-19 recovery and persistent symptoms. In order to document PASC in-depth, an adapted version of the Covid 19 Yorkshire Rehab Screen (C19-YRS) (O'Connor et al., 2021; Sivan, M; Halpin, SJ; Gee, 2020) will be used to assess for symptoms of long Covid. As a measure of functional status following COVID-19 infection, we will administer the Post-COVID-19 Functional Status (PCFS) Scale (Klok et al., 2020). SARS-CoV-2 antibody status will be tested in the larger study at the recruitment visit and will be used to confirm previous SARS-CoV-2 infection. However, antibody status will not be the sole inclusion criterion. Given that rapid antibody tests may not be a reliable marker of previous infection and that antibodies could also be detected in vaccinated individuals, we aim to confirm prior SARS-CoV-2 infection by requesting that participants provide proof of a prior positive PCR test result, where possible. However, given that a participant may be asymptomatic while infected with SARS-CoV-2, not all participants who test positive for antibodies will have a positive PCR test result. If the participant has been vaccinated against SARS-CoV-2, we will regard the positive antibody result as an indication of prior infection with the virus rather than antibodies from vaccination. We will screen all participants for previous SARS-CoV-2 infection on a case-by-case basis using the above-mentioned approach. We will also screen all participants for PASC, irrespective of a positive antibody test result or a previous positive PCR test result.

(4) Psychiatric Assessment

Mental health outcomes of interest include depression, anxiety, and posttraumatic stress symptoms. As part of the larger IeDEA-SA grant study, all participants will undergo screening for psychiatric illness at baseline and 6-month follow-up with the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998), Patient Health Questionnaire (PHQ)-9), Generalized Anxiety Disorder 7-item scale (GAD-7), and the PTSD Checklist for DSM-5 (PCL-5).

(5) Neurocognitive Assessment

All participants will undergo longitudinal neuropsychological testing using a comprehensive test battery (International HIV Neurobehavioral Research Centre battery). These assessments will be conducted by a research nurse who received standardized training and certification in the administration and scoring of the Battery. The Battery is available in English, Afrikaans, and isiXhosa. Instructions for the NC battery were translated into Afrikaans and isiXhosa using standard techniques of forward and back translation in South Africa as part of our previous work (Spies, Fennema-Notestine, Archibald, Cherner, & Seedat, 2012; Spies et al., 2017). See figure 3 in appendix for details on NP Battery.

Data Analysis

AIM 1: Regression analysis will be performed to identify demographic characteristics significantly affecting the raw neurocognitive (NC) scores for each test. The raw scores for each NC test will be converted into normally distributed scaled scores. A multiple fractional polynomial (MFP) method will be used to generate predicted test scores for each participant. The demographic variables that account for significant variance in raw test scores (i.e., age,

education, gender, and NC test language) will be entered into this MFP model to control for the variance in NC performance accounted for by these characteristics. Residual scores will be calculated by subtracting the predicted scaled scores of each participant from their respective scaled scores. The residual scores will subsequently be converted to demographically corrected T-scores. To estimate the severity of cognitive impairment at baseline at 6-month follow-up, demographically corrected T-scores (as determined by newly developed South African norms (Cilliers, M; Suliman, S; Kidd, M; Franklin, D; Cherner, M; Heaton, R; Spies, G; Seedat, 2021) will be converted to deficit scores. These scores will be converted as follows: 0 (T-score ≥40) = normal cognition; 1 (T-score 35-39) = mild NC impairment; 2 (T-score 30-34) = mild-to-moderate NC impairment; 3 (T-score 25-29) = moderate NC impairment; 4 (T-score 20-24) = moderate-to-severe NC impairment; and 5 (T score <20) = severe NC impairment. A Global Deficit Score (GDS) will subsequently be determined by averaging the deficit scores across all tests. Global neurocognitive impairment will be assigned to participants with a GDS ≥ .50. For pre- post comparisons of the 4 groups, mixed model ANOVA will be conducted with participants as random effect. HIV (positive/negative), PASC (present/absent) and time (baseline, 6 months) will be included as fixed effects. Normality will be assessed by inspecting normal probability plots, and post hoc analysis will be done using Fisher Least Significant Difference (LSD) testing.

AIM 2: We will estimate the unweighted prevalence of psychiatric disorders and binominal 95% confidence intervals (CI) stratified by age, sex, ethnicity, HIV status, Sars-Cov-2 antibody status, and history of COVID-19.

AIM 3: We will construct linear regression models to assess whether sociodemographic features and clinical features of HIV (viral load, CD4 and treatment retention), and COVID-19 are associated with cognitive function at baseline and 6 months.

Data Management and Utilisation

Ethical Considerations

We will follow the data and safety monitoring guidelines in accordance with the Stellenbosch University Health Research Ethics Committee (HREC) and regulatory guidelines. We will obtain approval of study protocol and consent from the HREC on an annual basis and will submit all protocol amendments and modifications for HREC approval prior to implementation. Ethical principles will be upheld throughout the research process.

Data and record safety/confidentiality

All research project personnel have completed training in the protection of human research subjects in accordance with Good Clinical Practice (GCP) guidelines and carry our research in accordance with ICH (International Conference on Harmonization) guidelines and local IEC/IRB requirements. In addition, all personnel who will be involved with participants will complete Human Research Protection Training and Conflict of Interest Training.

The pilot study will be embedded as a sub-study in a larger NIH (NIAID) IeDEA-SA grant aimed at assessing the mental health of HIV-infected adults attending public sector health facilities in Cape Town. Participants will be recruited by the parent study team and the study team will only follow up with those who agree to be contacted for the sub-study. All research subjects will be allowed to make an informed decision on whether they want to participate in the study or not. The details of this study will be explained to participants. The voluntary

nature of the study will be emphasised, and participants will be assured that they can withdraw from the study at any time without negative repercussions. Finally, research participants will have the right to privacy, anonymity, and confidentiality. To safeguard privacy of participants, a unique study number will be allocated to participants to identify them. This number will be the same for the parent and the sub-study. Data will be saved on central computers and will be analyzed by authorised researchers, with oversight from the study PI (Dr Spies). Identifying information will be protected and can only be accessed by the research team. As part of the parent study, participants' unique health ID (a number that is used by health care providers in the Western Cape Province to identify patients) will be shared with an authorised officer from the Western Cape Provincial Health Data Centre who will extract the health-related data from central computers for each participant. Each participant's personal details and the link between personal data and the study number will only be accessible by members of the local study team.

All data collected in this study will be treated as confidential. To maintain anonymity and confidentiality, no details that could link a respondent or their organisation to the study will be disclosed in the reporting of study findings.

Data management

Demographic, clinical, and psychiatric data will be captured using self-report questionnaires. Cognitive data will be captured using a series of pencil and paper and computer tasks (see neurocognitive battery in Appendix for more details). A trained study research nurse and research assistant, with oversight from the study PI will be responsible for data collection. All data will be captured in IBM Statistical Package for the Social Sciences (SPSS). The study PI will be responsible for data management and quality checking. Stellenbosch University's research data management regulations will be strictly adhered to: http://www.sun.ac.za/english/research-innovation/Research-Development/Documents/Policies%20and%20Guidelines/ENGLISH/RDM_Regulations_English_01_12_2020.pdf

Electronic data

All electronic files (e.g., databases, spreadsheets, etc.) containing identifiable subject information will be password protected. Any computers hosting such files will be encrypted and have a password to prevent access by un-authorized users. Furthermore, for systems not running Windows, a password-protected screen saver will be installed and configured to activate five minutes after the computer has been idle. If subject data are to be exchanged with others, the data will be coded. Any information that is exported to spreadsheets or statistical software will not contain subject identifying data.

Data and sample sharing plan

Sharing of data generated by this study will be carried out in several different ways. The final dataset will include self-reported demographic and behavioural data from the subjects and longitudinal cognitive data from neurocognitive assessments. The final dataset will be stripped of identifiers prior to release for sharing and we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual

participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

In addition, we anticipate that data will be shared through presentation at national and international scientific meetings. It is expected that the investigators and collaborators on this project will be active participants in these meetings and share the data with scientists interested in similar research. In addition, data will as far as possible be shared through publications in Open Access journals (dependent on the availability of funding), in which the scientist retains copyright on the published material and in other high-quality peer-reviewed journals providing free-online access to all published content with a 6-month lag period following publication. This will greatly expand general access to our findings.

In accordance with the FAIR guidelines (Wilkinson et al., 2016) and in compliance with rules of good scientific practice, data will be stored and shared with the public via the Open Science Framework https://osf.io/ upon publication of the study findings (Foster, & Deardorff, 2017), which will allow permanent access to the data via a globally unique and persistent identifier. We will share raw data of all study variables (excluding email addresses) as well as scripts needed to replicate the analyses. Thus, data will be anonymous, not allowing the identification of individual participants.

Risks and Benefits

Risks

This study is low risk to participants and there will not be any major risks or costs associated with taking part in this study. We do not anticipate any adverse events, serious adverse events, injuries, or other medical problems requiring insurance cover related to the parent study or sub-study. The potential risks expected include loss of confidentiality, a small risk that participant may experience psychological distress related to collection of information on mental health, substance use, and HIV status. Study personnel will be trained to identify participants experiencing psychological distress and refer them appropriately for care at the site.

Benefits

Direct benefits

A direct benefit from participating in this study is the potential improvement in health care. Specifically, participants may benefit from the identification and management of mental health and substance use disorders and HIV disease as part of the IeDEA-SA parent study. As part of the sub-study, participants may benefit from the identification and management of PASC in those living with HIV. In both studies, patients requiring immediate management will be referred to the appropriate services at the study sites or to another facility, as required.

Indirect benefits

There are important indirect benefits of participating in this study. Specifically, these include identification of appropriate mental health screening tools (parent study) and appropriate screening for PASC (sub-study) for use in public health care programmes, particularly for patients living with HIV and those diagnosed with Covid-19. This will potentially result in the increased availability of a standardised, broadly implementable screening and management platform. Thus, potentially improving health outcomes for study participants and beyond.

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APPENDIX

Timeframe

Study Activities	**Year 1** (2022)				**Year 2** (2023)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Ethics and training								
Data collection (baseline)								
Analyses (baseline data)								
Data collection (6-month follow-up)								
Analyses (6-month follow-up)								
Report writing and data dissemination								

Figure 1: Sample breakdown (N = 180)

Cases (N = 90)	**Controls (N = 90)**
45 = HIV+ COVID - 45 = HIV+ with PASC	45 = HIV- COVID- 45 = HIV- with PASC

PASC = post-acute sequelae of SARS-CoV-2 infection

Figure 2: Participant assessment information

Session	**Procedure**	**Duration**
1 (Baseline)	Pre-screening for eligibility, signing of informed consent form, demographic and clinical information, blood sample collection	Approximately 30 minutes
1 (Baseline)	PASC screening	Approximately 30 minutes
1 (Baseline)	Neurocognitive assessment	Approximately 2 - 2½ hours
2 (6-month follow-up)	Follow-up screening, signing of informed consent form, demographic and clinical information, blood draw	Approximately 30 minutes
2 (6-month follow-up)	PASC screening	Approximately 30 minutes
2 (6-month follow-up)	Neurocognitive assessment	Approximately 2 - 2½ hours

PASC = post-acute sequelae of SARS-CoV-2 infection

Figure 3: HNRC International Neurobehavioral Battery and Ability Domains

Brief Visuospatial Memory Test, Revised	Learning and Delayed Recall
Hopkins Verbal Learning Test, Revised	Learning and Delayed Recall
Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol test	Speed of Information Processing
Wechsler Adult Intelligence Scale-III (WAIS-III) Symbol Search test	Speed of Information Processing
Trail Making Test A	Speed of Information Processing
Paced Auditory Serial Addition Test	Attention/Working Memory
Wechsler Memory Scale-III Spatial Span	Attention/Working Memory
Wisconsin Card Sorting Test (computer version)	Abstraction/Executive Function
Color Trails (Test 1 and 2)	Abstraction/Executive Function
Stroop Color and Word Test	Abstraction/Executive Function
Halstead Category Test (computer version)	Abstraction/Executive Function
Controlled Oral Word Association Test	Language
Category Fluency (Animals, Action)	Language
Grooved Pegboard Test (both hands)	Motor Function
Hiscock Digit Memory Test	Screening for effort