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The relationship between the combined effects of life-course trauma and HIV on cognition in rural South African adults: A secondary data analysis

By

Nkgodi Obed Kupa



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04 June 2024

DECLARATION

I Nkgodi Obed Kupa declare that this Thesis/Dissertation/Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science: Infectious Diseases Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University. _____ (Signature of candidate)_04_day of _June_ 20_24___in_Grahamstown.

Abstract

Background:

Lifecourse traumatic events (TE) refers to both childhood and adult trauma. Childhood TE refers to a spectrum and domains of adverse experiences occurring before the age of 18. Global and South African-based research suggests that life-course TE are associated with both physical and mental disorders including HIV and poor cognition (also referred to as neurocognitive impairment (NCI)). While data suggests that life-course TE, HIV and NCI are highly prevalent in South Africa and risk of NCI has been researched, little is known of the combined effect of life-course TE and HIV on NCI in adulthood. To fill the gap in the literature, I analysed data from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI), from rural Bushbuckridge (Mpumalanga province).

Study Aim

To examine the combined (interaction) effect of TE and HIV infection on the cognition of older adults in South Africa.

Methods:

I analysed (secondary) data from the HAALSI study. The main exposures analysed were: life-course TE and HIV-positive status. A pre-analysis phase consisted of several exploratory steps to define the exposure and outcome: First TE data which had been measured by the English Longitudinal Study of Aging (ELSA) life history questionnaire were examined. The main exposure variable was coded 1 if one experiences a TE and 0 otherwise from seven potential TE. NCI, the main outcome variable was defined based on measuring cognitive domains: orientation and memory. A score≥1.5 standard deviations (SD) below the mean of the baseline cognitive function distribution on the cognitive assessment (managing to know the date, day,

month and president) will mean no NCI while a score below the means some degree of NCI). The main outcome variable was cognition measured by the Oxford Cognitive Screener (OCS-plus). Based on the validation of Tablet-Based OCS-plus in HAALSI, OCS-Plus included nine brief tests measuring cognitive ability in nine different domains, including language, memory (intentional and incidental), and executive functioning (task switching-alternating jobs between tasks), attention (auditory), and praxis (doing things). A stand-alone application called OCS-Plus was developed using Matlab and Psychophysics Toolbox for Windows Surface Pro tablets. Further preparatory steps for the analysis included: the exposure variables (HIV status and composite trauma-defined as the presence of at least one trauma item-) were created as follows: 1. HIV status was categorized into HIV positive and negative and coded 1 and 0 respectively. 2. Composite trauma was coded 1 if ever experienced any of the seven trauma items and 0 if none were experienced. Four groups of participants were created by exposure status. These were: 1. HIV positive and also experienced TE. 2. HIV negative but experienced TE. 3. HIV positive but TE negative. 4. HIV negative and trauma negative. Descriptive statistics were calculated for both exposures and outcomes as well as relevant sociodemographic variables. Both unadjusted and adjusted logistic regression techniques were employed to examine the combined effect of life course TE and HIV on NCI in older adults. The adjusted logistic regression models were done: 1) handling HIV and composite trauma separately and 2) considering the interaction term of HIV and composite trauma. Variables such as education, employment status, age, nationality, gender, hypertension, stroke, HIV status, marital status and composite trauma were considered confounders and adjusted accordingly.

Results:

Of the 5,059 study participants recruited and residing in the Agincourt study area in Bushbuckridge, 65% of the study participants had experienced at least 1 TE, and the most

common trauma experienced were “ever experiencing severe financial hardship which was experienced by 58.74% of the participants, 39.73% whom “ever experienced a natural disaster” and 23.30% “ever experienced a death of a relative or friend” and the prevalence of NCI was 7% (n=352).. The median age of participants was 64 (IQR: 55-74) years; 53.07% of the study participants were females; 44.42% had no formal education, and 72.63% of the study participants were not working. In the multiple logistic regression model with the interaction term, the odds of having NCI decreased by 64% (AOR=0.36; 95%CI: 0.25-0.52) and 59% (AOR=0.41; 95%CI: 0.24-0.75) among those who had some primary school (1-7 years) and some secondary school (8+ years), respectively compared to those with no education. The odds of having NCI decreased by 98% (AOR=1.98; 95%CI: 1.05-3.72) among those who were not working compared to those employed. A one-year increase in age was associated with a 5% increase in the odds of having a cognitive impairment (OR=1.05; 95%CI: 1.04-1.07). Those who were married had 37% (OR=0.63, 95%CI: 0.47-0.84) reduced odds of having NCI compared to those who were married. Those without composite trauma had 90% (AOR=0.10; 95%CI: 0.07-0.15) reduced odds of having NCI compared to those who have composite trauma. Those who were HIV positive and had experienced composite trauma had an increased odds of 1.78 (95% CI: 1.04-3.04) of having NCI compared to those who are HIV negative and had not experienced composite trauma. In the interaction model, we found no association between HIV status, stroke, or hypertension and NCI. However, the results of the interaction model suggested a significant association between HIV and the composite trauma score on NCI.

Conclusions:

The results suggest that lifecourse TE and HIV infection influence NCI. The full HAALSI cohort could be employed to examine the effect of TE data collected at baseline and incident NCI at later waves.

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ABBREVIATIONS

ANI	Asymptomatic neurocognitive impairment
ACC	Anterior cingulate cortex
ACHD	Adults with congenital heart disease
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
CAPI	Computer-assisted personal interviews system
CCHD	Child congenital heart disease

CD4	Cluster differentiation type 4
CNS	Central nervous system
GBV	Gender-based violence
HAALSI	Health and Aging in Africa: A longitudinal study INDEPTH community in South Africa
HAART	High-active antiretroviral therapy
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive Deficits
HF	Heart failure
HIC	High-income country
HIV	Human immunodeficiency virus
HRS	Health and retirement study
KZN	KwaZulu-Natal
LIC	Low-income country
MDR-TB	Multi-drug resistant tuberculosis
MND	Mild neurocognitive deficits
MSM	Men who have sex with men
NCI	Neurocognitive impairment
OR	Odds ratio
PLWHA	People Living With HIV/AIDS
PTSD	Post-traumatic stress disorder
S.A	South Africa
SES	Socio-economic status
SSA	Sub-Saharan Africa

US HRS	United States Health and Retirement Studies
USA	United States of America
USHRS	United state health and retirement study
WHO	World health organization

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW.

Chapter 1 presents the introduction and literature review of the research report. The first part, the introduction consists of several sections including: 1.1.1. HIV /AIDS, comorbidities and Neurocognitive Impairment (NCI), 1.1.2. Epidemiology of NCI among people living with HIV (PLWHA), 1.1.3.Lifecourse traumatic events (TE), 1.1.4.Lifecourse TE and HIV/AIDS,1.1.5. NCI and TE among PLWHA.

Chapter 1 further presents a second part which consists of the literature review, problem statement, justification, research question, aim and objectives for this research report. The literature review consists of several sub-sections including: 1.2.1. Prevalence and correlates of NCI in the general population, 1.2.2. Prevalence and correlates of NCI among PLWHA, 1.2.3. The relationship between TE, HIV and NCI, 1.3. Problem statement, 1.4. Justification, 1.5. Research question, 1.6. Aim, 1.7. Objectives.

1.1. BACKGROUND

1.1.1. HIV/AIDS, COMORBIDITIES AND NEUROCOGNITIVE IMPAIRMENT (NCI)

The HIV/AIDS epidemic has impacted the Sub-Saharan African (SSA) region substantially over the last three decades. In the early twentieth century, HIV was believed to enter human populations through cross-species transmission of chimpanzee retroviruses that are found in western equatorial Africa. (1–3).

Currently, South Africa has the largest HIV epidemic in the world, with approximately 7.7 million People Living with HIV/AIDS (PLWHA). This absolute number suggests an HIV prevalence estimate of 20.4 % for South Africa (5). HIV/AIDS has been linked to both morbidity and mortality (3–5). Recent data from the SSA region suggest that the consequences of HIV/AIDS including virological failure and drug resistance have public health significance

potentially leading to drug-resistant mutations and reduced clinical benefit of HIV/AIDS treatment (3,6-7) .

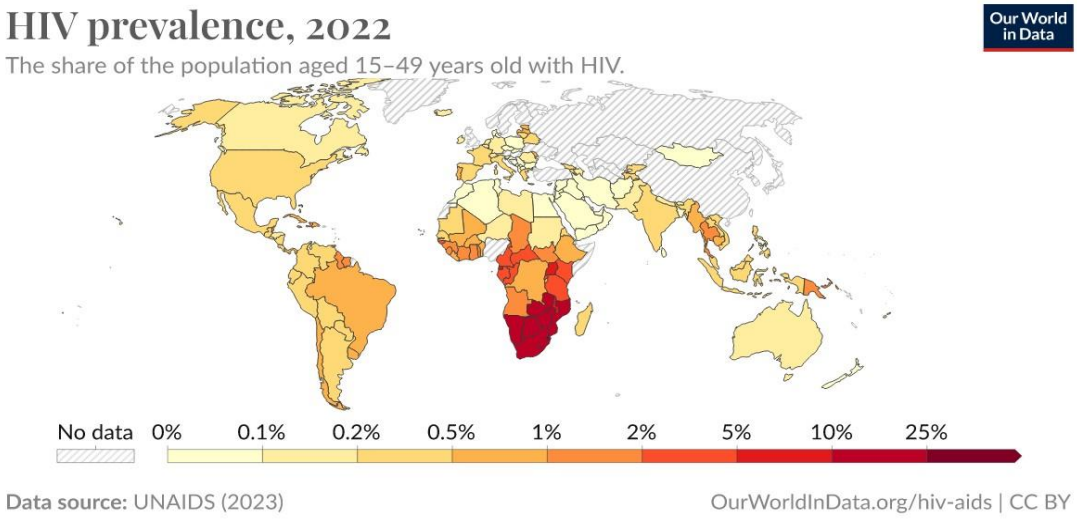


Figure 1 Adult HIV prevalence (15-49 years), 2022

Since the roll-out of Highly Active Antiretroviral Therapy (HAART), PLWHA have been living longer and therefore require attention for a range of comorbid diseases (8,9). These comorbid conditions include additional, comorbid infectious diseases such as tuberculosis (TB) and cryptococcal meningitis (11-12).

PLWHA can also experience comorbid non-communicable diseases (NCDs). For example, Mutagonda and colleagues examined comorbid non-communicable diseases among PLWHA in Tanzania with a focus on depression (12). Their results suggested a prevalence estimate of 11.8% of depression associated with the risk of additional NCD (including cancer and hypertension). A 2018 systematic review conducted by Osibogun and colleagues added to the evidence base of comorbidities among PLWHA suggesting a higher risk of biomarkers for cardiovascular disease among PLWHA who also had Hepatitis C virus (12).

Another example of a comorbid, non-communicable condition in PLWHA is that of NCI (13,14). NCI refers to impairment in the domains of cognition including executive function (which is the capacity to carry out appropriate activities and to prevent inappropriate actions in order to achieve a particular objective) (15). HIV Associated Neurocognitive Disorder (HAND) itself is considered on a spectrum from those who are completely asymptomatic and HAND-free to those who are 'asymptomatic but have neurocognitive impairment' (ANI), or 'mild neurocognitive deficit' (MND) (16). The furthest and most severe end of the spectrum is 'HIV-associated dementia' (HAD) where individuals may experience severe cognitive decline or impairment in the domains described above (17). These could then manifest as cognitive, behavioural, or motor disturbances (18,19).

The biological mechanism for the risk of NCI in PLWHA is as follows: The HI Virus enters the cells of the central nervous system (CNS) rapidly and there is a potential for neuro-inflammation or inflammation of the nervous tissue (20,21). HIV infection can damage neurons, and specialized brain cells carrying messages (22,23). In PLWHA, adult neurons may not regenerate or replace themselves due to the infection (24,25). A USA-based study by Liu and colleagues reported that damage to oligodendrocytes (cells in the CNS critical in providing insulation to the axons (i.e. the portion of neurons that carry nerve impulses)) was found to lead to neuronal injury and axonal demyelination, which may lead to neurological or cognitive impairment (26). Figure 2 below presents the HIV entering the brain. The reference for the figure is *(L Chang et al 2020: A Review of Preclinical and Clinical Studies)* (27).

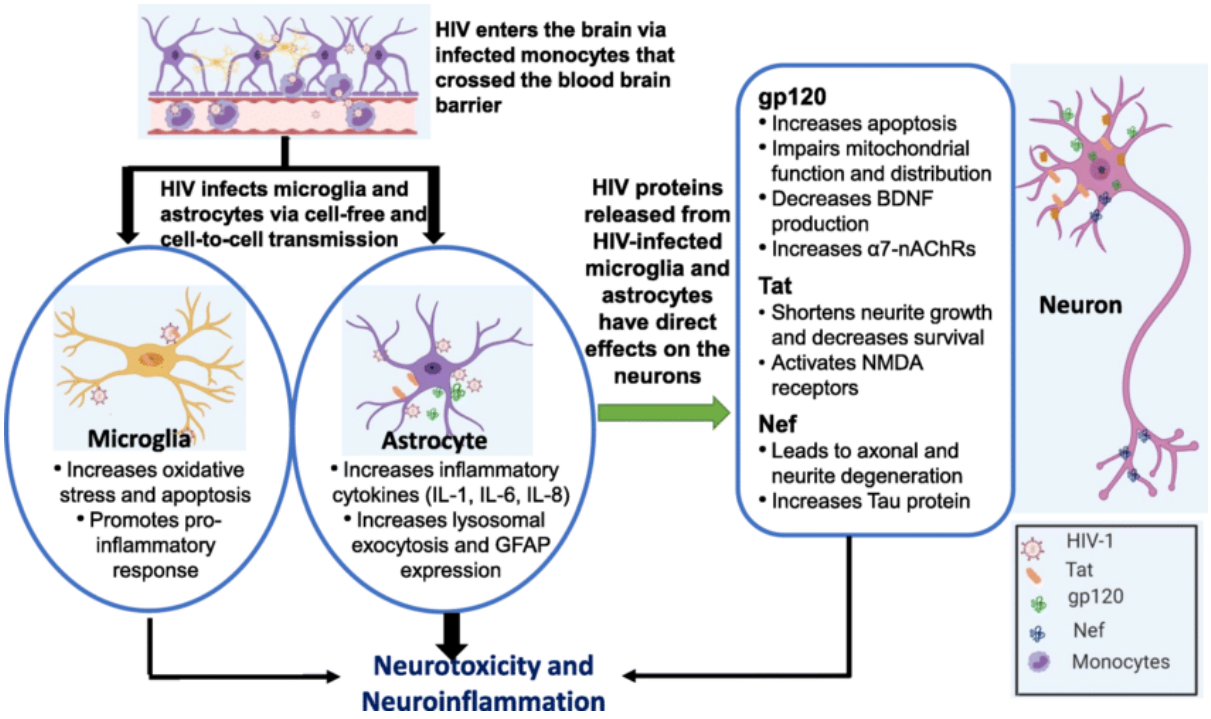


Figure 2 HIV virus entering the brain

Continuing focus on the African continent, a study published in 2020 of adults attending primary health care clinics in Zimbabwe by Nyamayaro and colleagues examined NCI among PLWHA (28). The study examined results from a comprehensive neuropsychological battery (administered by a trained neuro-psychologist). A comprehensive neuropsychological battery consists of tests to examine several domains of cognition including motor functioning, speed of information, executive functioning, working memory, learning, memory and verbal fluency. According to the study 49.7% of PLWHA had an estimated prevalence of NCI with only 26% of motor function being affected among PLWHA, and being the least affected. HIV-positive patients reported impairments in more than 50% of the memory and attention areas. In the same study, PLWHA NP tests were worse than HIV-negative control groups in terms of attention, speed of information processing, memory, and verbal fluency.

Also, PLWHA had 2.5 times higher risk of cognitive impairment than HIV-negative individuals, according to the study. The battery was also administered to an HIV-negative sample as a point of comparison (28).

Iswahyudhi and colleagues' study, conducted in Indonesia, discovered that among people aged 41-59, PLHWA with a nadir CD4 count < 200 cells/uL was linked to NCI. In the same study, it was observed that the majority of participants' antiretroviral contained efavirenz (86%), with a CPE score of < 92.5%. Additionally, the participants' cognitive impairment was found to be 47.3%, indicating that ART and nadir CD4 cell levels contribute to NCI (29).

According to Force and colleagues' cohort study, which included 31 individuals, all HIV patients had plasma viral loads of less than 50 copies/ml at baseline, and 78% of the HIV group had detectable HIV-RNA copies/ml when compared to patients without HIV using cerebrospinal fluid (CSF). Compared to 26% of those who failed the GDS (<0.5) and were linked to stable HAND, 71% of research participants demonstrated cognitive improvement using both the Frascati criteria and the Global Deficit Score (GDS). GDS fell from 1.4 in 13 HIV individuals to 0.8 in 18 patients without HIV.

When 22 patients with effective CPE ≥ 9 were compared to 9 patients with CPE < 9, NCI improved in the CPE ≥ 9 group in the control group. 15 non-improving patients and 16 patients with Frascati improvement were compared, and at baseline, ARV changes for improving patients were linked to a 38% vs. 0% reduction in the treatment burden from Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (a class of antiretroviral medications used to treat HIV) (30).

HIV infections are associated with NCI, as per the data cited above (17,31,32). However several additional exposures could modify or mediate the risk (33–35). These are elaborated further below in the section on the epidemiology of NCI below:

1.1.2. EPIDEMIOLOGY OF NCI AMONG PEOPLE LIVING WITH HIV (PLWHA)

The results of a systematic review and meta-analysis examining HAND globally suggest the following results for the epidemiology of NCI for specific regions: a prevalence of 31.5% using a global deficit score threshold 0.5 was estimated in the United Kingdom in a cross-sectional study of 248 participants on PLWHA and HIV negative MSM older than the age of 18 years, using an opportunistic sampling (sampling of patients at the time of routine clinic visits) from 2011-2013, with patients recruited regardless of symptoms, treatment and comorbidities (36). In the same study, every cognitive score was translated to age, sex, and education and the standardized Z-score normative means and standard deviations were applied. While in the USA, participants were drawn at baseline from the CNS HIV Anti-retroviral Therapy Effects Research (CHAPTER), which included 347 people according to the Frascati criteria, aged 18 years and above which were based on thorough assessments of neuromedical, neurocognitive, psychiatric, and functional abilities, a prevalence of 50.40% was estimated among asymptomatic neurocognitive impairment compared to 21.7% of neurocognitive normal in a 347 participants cohort study, with factors such as lower nadir CD4, Hepatitis C viral disease and substance abuse having effect on NCI (37). In a cross-sectional study conducted in five European outpatient clinics involving 448 HIV-positive patients over the age of 18, both computerized and pen-and-paper neuropsychological tests were used. A prevalence of 35% was reported and factors like university education were associated with lower NCI in patients with less severe depressive symptoms than in those without university education and who had some comorbid conditions (33).

In contrast to the US study, which selected study participants based on their baseline classification as asymptomatic neurocognitive impairment (ANI) and neurocognitive normal (NCN) by the Frascati criteria on comprehensive neuro-medical treatment, the study participants in the UK were routinely attending clinics for HIV care. In the UK, AIDS-defining illnesses, glucose, liver function tests, and specifics of neurological, cardiovascular, and psychiatric comorbidities have been examined, in contrast to the US where no individuals with severe confounding comorbidities that would preclude HAND diagnosis were included in the study. HIV-RNA viral load, HCV, and nadir CD4 cells have all been included in the investigations.

In terms of neurocognitive assessments, a thorough battery of tests covering seven cognitive domains—motor function, verbal fluency, learning, executive function, attention/working memory, speed of information and memory—was examined in the US as opposed to a study conducted in the UK that used pen and paper NP test batteries to assess five domains—psychomotor speed, verbal memory, working memory, and verbal fluency—using the controlled oral word association test (COWAT) and the category fluency test (CFT).

The Frascati criteria were used to diagnose ANI and NCN in the US. A computer-assisted international diagnostics interview was used to determine the diagnosis of mood disorders and substance use disorders both currently and in the past, while a modified Lauten and Brody instrumental activities of daily living scale was used in the UK to measure functional status. Every cognitive score test was translated into age, sex, and education-standardized Z-score in the UK by comparing its normative means and standard deviation to a Patient's Assessment of Own Functioning Inventory (PAOFI) score of three or higher, which denotes the presence of three or more cognitive symptoms.

An African based systematic review showed that prevalence estimate of 45.15% from the African continent suffer with NCI and gender (females) , no formal education, and unemployment are some of the factors that contributes to NCI, while a 49.6% from Asia also suffer NCI (18,33,36,37).

Individual studies suggest that age, education level, negative life events and chronic stressors are also associated with NCI in PLWHA (18,31,38–40). In addition, a USA based study by Palar and colleagues suggested that food insecurity internalized HIV stigma, and depressive symptoms are independently associated with poor HIV outcomes and may be interrelated among women living with HIV (41)

Among HIV-positive people in Sub-Saharan Africa receiving pre-ART (a period before receiving Antiretroviral therapy), prevalence estimates of NCI in the region is as high as 42.37%, with studies from Uganda estimating that adults with HIV pre-ART have an NCI prevalence estimate of 46.49%, while those on ART for more than six months have an NCI prevalence estimate of 30.39% (17).

1.1.3. LIFECOURSE TRAUMATIC EVENTS (TE)

Various forms of life-course TE, including abuse, neglect, and physical abuse are highly prevalent(42–44). A surveillance study from the USA 2011-2014 behavioural risk factor surveillance system in 23 states substantiates this statement. This study's nationally representative sample across 23 USA states reports that over 60 percent of participants reported experiencing at least one life-course TE while 20 percent of the sample had experienced 3 or more (45). According to Goddard and colleagues 2021, adverse childhood experiences (ACEs), also known as childhood TE are defined as childhood maltreatment, neglect, and traumatic events that have a long-term detrimental effect on teenagers and adult's health (46). A United Kingdom-based research study by Fisher and colleagues conducted in 2009 reported that

physical and sexual abuse was the most prevalent forms of childhood TE experienced among women (47). Compared to sexual abuse, physical abuse of women throughout childhood was revealed to be the most common kind of trauma in a 2019 Italian study by Comacchio and colleagues (48). A study by Sardinha and colleagues in 2022, found that in high-income, low-income, and middle-income countries, intimate partner violence among women has been linked to some form of TE during childhood (49).

In their study of 13284 participants across low and middle-income countries (LMIC) from Indonesia, China, Bangladesh, and Sri Lanka, Fulu and colleagues, there was a significant difference in childhood TE prevalence between Indonesia and Papua New Guinea, with 59% of men in Indonesia having experienced trauma and 92% in Papua New Guinea. Further, they discovered that 2% and 25% of Indonesian men experienced physical and sexual abuse in Papua New Guinea, as compared to 44% of women in Sri Lanka and 84% in Papua New Guinea who experienced childhood TE (50). A Latin American study by Lanham and colleagues 2019, reported that there is a relationship between physical child abuse and women's experiences of violence as adults and children in different settings such as education, healthcare, police and other state institutions (51).

A USA-based study by Watson and colleagues reported that several negative experiences among PLWHA, physical assault, sexual abuse, poverty, unemployment, and childhood trauma are all quite prevalent. And these factors are known to have an adverse effect on the central nervous system (CNS), causing inflammation, disrupting brain function, and raising the likelihood of mental disorders and poor cognitive performance (52,53).

A recent sample recruited from Botswana, albeit not nationally representative (n=483) suggested that 21.1% of the sample had experienced one childhood trauma while 38.9% reported three or more childhood traumas (54). A South African study conducted in Soweto,

published in 2016, by Closson and colleagues, found that 99.7% of respondents reported having at least one potentially traumatic event (PTE). In addition, they discovered that over three-quarters (74%) of young people reported having experienced the death of a family member or close friend. Overall, the finding suggests that 7% of adolescent boys were likely to have experienced or perpetrated violence such as coercing someone to have sex with them, purposefully harming someone else (51%), and 76% witnessing an act of violence in the community (55). In addition, childhood TE has both short-term and long-term implications for health in adulthood, with both Sexual risk behaviours being likely to be reported by women and men who have experienced them, as well as being more likely to encounter or commit intimate partner violence (56).

In the World Mental Health Survey (WMHS), Kessler and colleagues analyzed different TE as well as the number of TE individual participant's experience. These analyses have aimed to predict the risk of post-traumatic stress disorder but could be used to examine a dose-response relationship (57). Interestingly, a distribution of TE in a 2017 analysis by Kessler and colleagues was found to be any one TE (25.8%) any two TE 18.0% and any three TE 12.9%(57)

In light of the literature cited above in relation to HIV-negative samples, one potential factor that could modify or mediate the risk of NCI in PLWHA (whose HIV infection likely places them at risk anyway) is life-course TE (58,59). This relationship between life-course TE and NCI is elaborated below in the chapter.

1.1.4. LIFECOURSE TE AND HIV/AIDS

There is a complex pathway between life-course TE and HIV both from the point of view of acquiring infection as well as accessing treatment once diagnosed HIV positive (60–62). For example, a Chinese study examining correlates of HIV infection among prisoners suggested participants who were HIV positive had experienced at least one childhood TE. This study

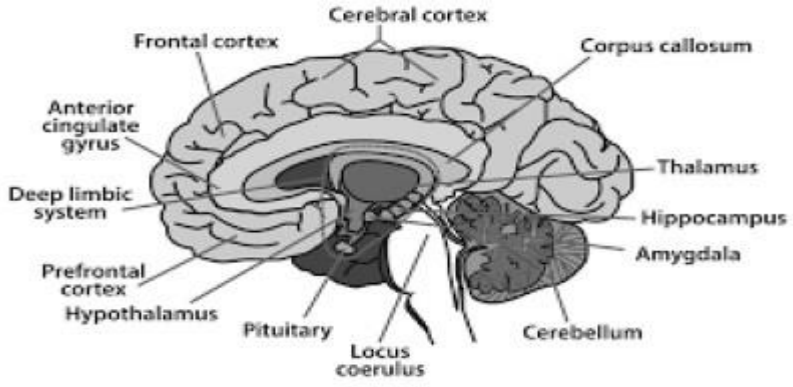
consisted of over 500 participants with several scales administered to examine both life-course TE and common and severe mental disorders (63). According to Whetten and colleagues 2012, in various U.S. samples, estimates of sexual and/or physical abuse of PLWHA varied from 30% to over 50% (64).

Moving to the African continent, a Ugandan-based sample recruited from one HIV clinic suggested that childhood TE was linked to major depressive disorder among adolescents with HIV(65). Further, a longitudinal study conducted in SA suggested that those who had suffered TE as children had a higher risk of getting HIV (61).

1.1.5. NCI AND TE AMONG PLWHA

Several studies have suggested that TE can be linked to NCI in the general (HIV-negative) population (68–70). The biological mechanisms for the pathways between TE and NCI suggest that stress experienced during infancy, childhood or adolescence can result in structural, functional or epigenetic changes in the areas of the brain responsible for cognition i.e. the temporal lobes and hippocampus (71). The affected brain regions in HIV-positive individuals with a history of lifecourse TE include the left frontal lobe, right anterior cingulate cortex, left hippocampal region, right amygdala, and left caudate (72,73).

Figure 3 below is a visual depiction of the regions of the brain potentially affected by TE.



Source of image: Neurobiology of trauma (Julie L Valentine, Brigham young university)

Figure 3 Regions of the brain potentially affected by TE

Furthermore, it has been noted that stress alters the central nervous system and neuroendocrine system, which can disrupt immune system function , impairing immunological responses (74). Prolonged stress in HIV-negative people is associated with anatomical and functional changes in the hippocampus and prefrontal cortex (75) and also decreases the capacity for working memory (76).

A more pronounced effect on these structural regions can be seen in women who have both HIV and childhood trauma, and those with weaker motor abilities, learning, language/fluency, abstraction/executive functioning, processing speed, and attention/working memory. In addition, the striatum, amygdala, corpus callosum, and anterior cingulate regions of the brain were smaller as a result of trauma-induced shrinkage of the hippocampal structure (77–79). In HIV-infected individuals, childhood TE may contribute to brain alterations and neurocognitive decline (61,72,73). Researchers working in the area of TE and NCI refer to the glucocorticoid-cascade hypothesis of ageing (80,81). This hypothesis stipulates that chronic stress over the life course can lead to an increase in cortisol which in turn can lead to atrophy in the hippocampus (the region of the brain implicated in learning and memory) (80,81).

Kapetanovic and colleagues 2022, in a USA-based study that enrolled 187 study participants, reported that interpersonal trauma (IPT) was prevalent among HIV-positive individuals. Additionally, they noted that attention/working memory test performance was higher in HIV-negative individuals without a history of IPT compared to HIV-positive individuals with IPT and that PLWHA had more losses in activities of daily living. They also noted that PLWHA had poor cortical thickness in numerous cerebral regions (82). The literature review section of the research report below further expands on the epidemiology of NCI among both HIV-positive and negative samples.

1.2: LITERATURE REVIEW

PUBMED, Springer, Elsevier, American Neurology journal, were searched extensively for studies of NCI among PLWHA who have experienced TE across their life course, central to the research question and as neuroaids emerged around 2008, we restricted our search from 2008 onwards. NCI, HIV, and PLWHA are abbreviations that replaced search phrases like Neurocognitive Impairment, Human Immunodeficiency Virus, and People Living with HIV and AIDS. To finish a search statement and restrict the search results, Boolean operators were applied. Some of the restrictions are full text, date period (less than five years of data), language (only papers published in English), and journal type (such as Google Scholar). We have limited our literature analysis by using quotation marks to look up specific phrases. The search was heavily reliant on keywords like HIV, cognition, and life course trauma.

Several studies were accessed and are presented under the following themes: 1. Prevalence and correlates of NCI in the general population. 2. NCI among PLWHA. 3. TE and NCI. 4. The combined effect of TE and HIV on NCI.

1.2.1. PREVALENCE AND CORRELATES OF NCI IN THE GENERAL POPULATION

Global and African-based research suggests that several illnesses and socio-demographic correlates may be associated with NCI among children and adults who are not HIV positive(83–85). For example, in a 2022 publication, Manly and colleagues presented a USA nationally representative analysis of the Health and Retirement Study (HRS). Their findings suggest that the prevalence of mild NCI and dementia vary by race, ethnicity, and socioeconomic status. In their study, they found that dementia (lack of mental abilities like thinking, remembering and reasoning), was more common among non-Hispanic black

individuals. Their findings also highlighted that black and Hispanic individuals have poor SES compared to non-Hispanic white individuals (86).

A USA based study by Portela-Parra and colleagues who published their study in 2019, found that exposure to economic challenges, such as growing up in poverty-stricken families, having a low SES, and experiencing food insecurity, has all been linked to an increased risk of cognitive impairment in the general adult population (87).

A Norwegian cross-sectional study that examined the relationship between motor and cognitive function after a stroke, discovered that mild stroke patients exhibited cognitive impairment. Cognitive dysfunction, executive dysfunction, and memory impairment have all been linked to impairments in grip strength and mobility. They also showed that, following a stroke, motor function is a strong predictor of cognitive deterioration (88).

Literature has been reviewed that focuses on education and age factors associated with NCI. In a Swedish study by Lovden and colleagues evaluating education and cognition in a lifespan but these analyses are yet to be duplicated on the African continent.

According to their findings, factors including family socioeconomic resources can have an impact on both educational success and cognitive development, and cognitive development is associated with being chosen for longer educational programs. They further reported that in early adulthood but also into late adulthood, it tends to affect individual differences in cognitive abilities (89).

1.2.2. PREVALENCE AND CORRELATES OF NCI AMONG PLWHA

Global and African-based studies have examined the prevalence and correlates of NCI among PLWHA, both adults and children (31,33,90). These studies span several years given that interest in the intersecting fields of HIV/AIDS and NCI seemed to emerge around 2008 (91,92).

For example, a meta-analysis published in 2020 by Wang and colleagues aimed to synthesize the global prevalence and burden of HAND and examined the prevalence of NCI in PLWHA. Findings indicate that low-income countries had a higher prevalence of HAND and mild neurocognitive disorder (MND) than middle- and high-income countries. When compared to males, females had a higher prevalence of HAND whereas MND and asymptomatic neurocognitive impairment (ANI) were similar when stratified by sex. In the same study (the meta-analysis), it was further reported that the prevalence of ANI was lower in studies with younger participants, whereas the prevalence of MND and HAND was higher in studies with younger participants (youngest being 21 years and oldest 70 years) (93).

Compared to the prevalence of MND, HAND was higher in participants with low CD4 counts. Correlates of the prevalence estimates of MND and HAND included the region i.e. SSA, higher in low-income countries, and lower in participants with higher CD4 counts (93).

In another U.S.A-based study, Clark and colleagues 2023, were the nadir CD4 levels (497-947 cells/uL) of study participants who ranged in age from 21 to 70 were examined, and substances like alcohol and drugs (opiates and cocaine) were evaluated, reported that participants who tested positive for HIV revealed greater frequencies of threat exposures from adverse childhood experiences, while rates of deprivation (a lack of anticipated social and cognitive stimulation) did not differ. They further found that HIV-positive status was associated with neuropsychiatric symptoms e.g. depression, anxiety and apathy (94). Studies with a high proportion of participants on antiretroviral therapy (ART) had a lower prevalence of HAND (95–97). ANI and mild neurocognitive disorder (MND) accounted for about 88% of all forms of HAND (93). Some studies suggested that a high proportion of female participants experienced a higher prevalence of HAND (98–100). Furthermore, it was found that persons with low levels of nadir CD4 count (200 cells/mm3) and those living in South America and the Caribbean had greater

rates of HAND and ANI among HIV-positive adults with factors such as neurological examination and the measured HIV viral load taken into consideration (93).

In a 2014 study by Grant and colleagues in the USA, it was found that, although ANI, is the most common form of HAND in the ART era, does not interfere with daily functioning (37). In another USA based study by Fellows and colleagues 2014, specifically in the areas of executive functioning, learning, and memory, NCI was found to be widespread among PLWHA, with a prevalence estimate ranging from 15 to 55% (101). Further patients with ANI were at an increased risk of progressing to symptomatic impairment (37). It was well documented that age was associated with worse global neuropsychological performance (an18-minute cognitive test battery includes seven subtests standardized worldwide and translated into several languages) both in the general population and in PLWHA (102,103).

Goodkin and colleagues found that among HIV-positive adults, episodic memory and motor function with advanced HIV infection were more vulnerable to the aging-related progression of NCI in a cohort research that included 5086 participants who were 18 years of age and above (102).

In a systematic review and meta-analysis in Sub-Saharan Africa, conducted in 2013, Habib and colleagues found that the NCI burden was 42.37% for HIV-positive adults not on ART, compared with 30.39% for HIV-positive on ART (17). Further studies have found that patients in Sub-Saharan Africa commonly had more advanced symptomatic infections with severe immunosuppression with anemia, worsening performance status, wasting, and decreased CD4 cell counts (104,105).

In an Ethiopian study by Wubetu and colleagues 2021, it was estimated that 41% of HIV-related NCI had been diagnosed, 35.1% of them suffered from mild NCI, 5.2% from moderate impairments, and 0.7% from severe impairments. It was further reported in the same study that

compared to younger (20-39 years) participants, who had a 1.06% risk of developing an HIV-associated NCI diagnosis, older (60-64 years) participants had a 6% higher chance. According to Wubetu and colleagues, their justification could be because of HIV-associated neurocognitive impairment, which could be made worse by the effects of brain aging (106). Another study conducted by Ramlall and colleagues in South Africa in 2020 suggests that individuals with MDR-TB have NCI, which is associated with HIV co-infection, long hospital stays, lower education, and older age (50-59 years) (107).

In a rural sample in South Africa, Joska and colleagues examined the prevalence of both HIV and NCI among older adults (60 years – 80+ years). The study recruited a sample of 1388 in the rural Eastern Cape region of South Africa. According to their findings, research participants who tested positive for HIV were more likely to be younger, less educated, unmarried, and to have a lower BMI.

It was further found that dementia was likely among HIV-positive individuals, and that screened dementia was among younger people and those without HIV and older age. Joska and colleagues also found that, as a result of the constellation of 'legacy effects' (pre-treatment, HIV-associated neuropathology, ongoing low-grade inflammation, and ART-associated neurotoxicity), dementia prevalence was found to increase with HIV status while low levels of education and depression also contributed to dementia (108).

1.2.3. THE RELATIONSHIP BETWEEN TE, HIV AND NCI

NCI as an outcome is complex with several, possible exposures linked to its onset and presentation as the literature cited above has suggested.

Clinical depression and post-traumatic stress disorder (PTSD) have both also been linked to NCI manifesting as decreased judgment, memory, and concentration (109). In a USA military cohort of males living with HIV (MLWH), Deiss and colleagues 2019 reported that PTSD

symptoms were widespread among PLWHA and they were linked to a decline in autobiographical memory. They also reported that there is a link between PTSD and NCI, and that those with a lifetime history of PTSD had a six-fold higher likelihood of receiving an NCI diagnosis than those without a history of PTSD (52). Given that TE and its consequences are related to HIV and to NCI, it seems plausible that studies may found a relationship between TE, HIV and NCI.

In a South African-based longitudinal study examining the effects of childhood trauma and HIV on neurocognitive functioning by Spies and colleagues in 2017, findings suggest that a correlation has been found between linguistic fluency and executive functioning as a result of childhood trauma and HIV, which may negatively impact the cognitive ability of South African women (60). In a separate study by Spies and colleagues in 2020 it was found that verbal fluency, and attention deficits due to HIV were all linked with possible TE and stressful life events, and HIV-positive and HIV-negative males with and without previous trauma experiences all showed impaired working memory, reaction time, and motor function, as well as overall NCI (72).

A systematic review focusing on low and middle-income countries by Spies and colleagues in 2020, it was found that the most likely impacts of potentially traumatic or stressful experiences (PTE) and stressful life events (SLE) are poor memory and executive function and significant risk factors for NCI in HIV-positive individuals include exposure and exposure to SLE and/or PTSD (72).

Another South African study by Roomaney and colleagues published in 2022 examined gene-environment interactions, specifically dopamine transport and metabolism which are known to impact NCI. Their study which recruited a relatively small sample size (n= 64 HIV-positive women and *n* = 49 HIV-negative comparison group) found that childhood TE had an adverse

effect on global cognition scores and that HIV-seropositivity was linked to noticeably worse follow-up ratings (110).

Furthermore, a study by Grant and colleagues published in 2014 reported that childhood TE and HIV status have a significant impact on global cognitive scores and that HIV-cognitive scores and HIV-positive individuals with childhood TE were associated with poor global cognitive function (37). In accordance with their results, the study further highlighted the detrimental consequences that childhood TE may have on PLWH's cognitive performance as found by previous studies (60,111).

A study by Watson and colleagues 2019, where 70% of men living with HIV, found that, in six cognitive domains, individuals with lower socioeconomic status, in some ways also a stressor or indication of adversity performed worse and were more likely to suffer from HIV-associated NCI (52).

According to Walton and colleagues 2011, in HIV-positive people, significant rates of childhood emotional (51.9%), physical (51.1%), and sexual (41.6%) abuse during childhood have been reported (112). Literature suggests that rape, childhood TE and intimate partner violence could also be linked to the onset of NCI (49,50,67). A clinical study found that impairment of daily living activities, chronic HIV infection for more than five years, poor drug compliance, co-existing medical conditions, neurological disease history, plasma HIV-1 RNA loads of between 1.7log10 and 3log10 copies/ml, comorbid infection with opportunistic diseases, and psychological factors such as negative life events, as well as high-level stress correlated with HIV-associated neurocognitive disorders (22).

As per the studies above, it seems that TE during childhood or adulthood could be important to examine in relation to NCI. Further, the above literature review suggests that there is a paucity of studies on trauma in relation to NCI on the African continent (113). In Sub-Saharan

Africa, studies that examined childhood TE and HIV's effects on NCI were not specifically focused on the combined effects of lifecourse trauma and HIV on NCI in South Africa or any African country (114).

There is a growing need for extensive research in Sub-Saharan Africa to discover ways to prevent NCI, potentially through the lens of life-course TE (115). Both gender-based violence and life-course trauma in rural areas make it important to study the possible causes of NCI and life-course trauma among PLWHA and HIV- negative populations (116). Most low- and middle-income countries, especially those in Sub-Saharan Africa, know little about the effects of life course trauma and HIV on NCI (117). Considering the high prevalence of HIV, inequality, and low levels of education, South Africa may display distinct patterns of childhood TE and HIV on cognitive functioning and provide new insights into risk and protective factors for the development of cognitive decline and provide effective psychotherapy to people affected by these factors (118).

2.2. PROBLEM STATEMENT

NCI in PLWHA can impact the quality of life (111,119). According to a systematic review by Spies and colleagues 2020, it was found that studies in the USA have shown a significant link between TE and NCI among PLWHA. A military cohort study of 200 military beneficiaries aged 18-50 years, Deiss and colleagues reported 19% of NCI among military personnel living with HIV, Watson and colleagues reporting 39,3% of NCI among PLWHA compared to a 27.4% with HIV negative, while in an African continent, only few studies were reported with significant link between trauma and NCI among PLWHA (72). An African-based genetic study by Roomaney and colleagues 2022, reports that, compared to HIV-negative participants, 78% of HIV-positive women reported experiencing any form of childhood trauma before the age of 18, versus 36.7% of HIV-negative participants. The findings of the studies suggest a strong association between HIV infection and lifecourse TE (110). Our work aims to fill a gap and is

an epidemiological study with a larger sample than the genetic studies mentioned above. The current study also focuses on a rural area where there may be different variables associated with the outcome of interest.

There is a growing need for extensive research in Sub-Saharan Africa to discover ways to prevent and treat NCI and life-course TE. The growing number of gender-based violence in rural areas makes it important to study the possible causes of Neurocognitive Impairment and Childhood TE among HIV-positive and negative populations (116). A comprehensive prevention or treatment plan can be developed by epidemiologists, psychologists, and clinicians only after finding out what the possible causes of NCI and life-course trauma are among HIV positives and negatives (120).

My study will fill the gap left by studies cited above that focus on only females. My study analyses data in the Enhlanzeni district in the Bushbuckridge region of Mpumalanga, where most villagers are dependent on social grants for their survival compared to some studies that had been in urban settings (121). In this study, secondary data analysis will be conducted on 5,059 (2345 men and 2714 women) data; therefore, the data from a primary study will be used for analysis. There is a large sample size in this classic epidemiological study to minimize the margin of error and control the risk of reporting false negatives and false positives (38).

As a means of contributing to the existing knowledge about NCI and childhood trauma, this study will make use of a more statistical approach such as univariate and bivariate analysis. For example, the study cited above by Roomaney and colleagues consisted of a sample of 113 women between the ages of 18 and 50 years, which is a smaller sample size (110). For our study, we enrolled 6281 at the start of the project and completed the study with 5,059 study participants who were eligible to be in the study, and this is a bigger sample size appropriate for epidemiological studies (38,110).

2.3. JUSTIFICATION

Individuals with HIV are significantly affected by the disease both mentally and socially (122). Understanding the relationship between life-course trauma and HIV on NCI may lead to interventions that improve quality of life (60). Most low and middle-income countries, especially those in Sub-Saharan Africa, know little about the effects of life-course trauma and HIV on NCI (117). Considering the high prevalence of HIV, inequality, and low levels of education, South Africa may display distinct patterns of life-course trauma and HIV on cognitive functioning and provide new insights into risk and protective factors for the development of NCI and provide effective treatments to people affected by these factors (118).

2.4. RESEARCH QUESTION

1) What is the individual contribution of HIV status and life-course TE on NCI among adults from rural South Africa in the HAALSI study (waves 2) adjusting for potential confounders?
2) What is the combined (interaction) effect of life-course trauma and HIV on NCI in rural South African adults?

2.5. AIM

This study aims to determine the combined (interaction) effect of life-course TE and HIV infection on the NCI of adult South Africans using the Health And Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) study

2.6. OBJECTIVES

1) To describe the socio-demographic characteristics and the most common cognitive symptoms experienced by adults from rural South Africa after experiencing life-course TE in the HAALSI study (wave 2)
2) To describe the individual contributions of HIV status and trauma on NCI among adults from rural South Africa in the HAALSI study (waves 2) adjusting for potential confounders.
3) To estimate the adjusted combined (interaction) effects of lifecourse trauma and HIV status on NCI among adults from rural South Africa in the HAALSI study waves (2)

CHAPTER 3: METHODS

Chapter 3 presents the methods of the primary and secondary study of the research report. The first part, an overview of the primary study consists of several sections including: 3.1.1. Primary study design, 3.1.2. Primary study settings and Population, 3.1.3 Primary study aim, 3.1.4 Data Collection and Sampling Methods

The second part, an overview of the secondary study consists of several sections including: 3.2.1. The study population of the current secondary study, 3.2.2. Data management, 3.2.3. Data analysis

This study is a cross-sectional study design based on Wave 2 of the HAALSI cohort study.

3.1 OVERVIEW OF THE PRIMARY STUDY

3.1.1 STUDY DESIGN

HAALSI is a prospective cohort of adults over the age of 40 in the Agincourt sub-district of Mpumalanga province. Thus far, there have been 4 phases of data collection in HAALSI resulting in what epidemiologists refer to as 4 waves.

3.1.2 STUDY SETTING AND POPULATION

The primary study is conducted in the Agincourt sub-district in Mpumalanga province in South Africa. This study examined the health and ageing experience of 5,059 adults 40 years and older (40-77 years) in an INDEPTH community in South Africa (HAALSI) and found an 86% response rate (121). In line with the structure of the United States Health and retirement studies (US-HRS), HAALSI represents approximately 116,000 individuals living in Mpumalanga province, north-eastern South Africa, in the Agincourt Health and Socio-demographic Surveillance System Census(121). Men and women aged 40 and over were recruited in the

cohort amounting to a total of 5,059 (2345 men and 2714 women) (123). The study participants were recruited from 2014-2015, with wave 2 of the study starting from 2014 and completing in 2015 with exposure and outcome variables measured in 2015.

3.1.3. STUDY AIM

The primary study is an interdisciplinary study aiming to longitudinally monitor social, economic and biological risks for chronic health conditions such as cardiovascular diseases, cognitive functioning and dementia. The cohort has focus on communicable and non-communicable diseases, in a random sample of adults in Agincourt South Africa(121).

3.1.4. DATA COLLECTION AND SAMPLING METHODS

Several previous published studies have examined HAALSI data(118,121). In November 2014 and November 2015, the team interviewed sampled individuals at home and collected data through Computer Assisted Personal Interview system (CAPI). A total of 6281 men and women were selected and 5059 completed home interviews, resulting in a response rate of 85,9%. Out of the 5059 participants enrolled, 391 (6%) patients were ineligible to participate due to death or migration out of the surveillance area before interviews (123). Among the remaining 5890 eligible participants, 353 (6%) could not be located, 48 (1%) were unable to participate and 430 (7%) refused to participate. The phone number, address, and vital status of each participant are verified each year by phone or home visits at the beginning of the year. Through bi-annual contacts, HAALSI participants who had died were identified and reported for verbal autopsy (VA), and the probable cause of death was determined using Inter VA-4 (121).

Measures

In-person interviews with qualified fieldworkers from the local area were conducted with all study participants at their homes (118,121). The majority of the HAALSI study's metrics are aligned with those employed in the HRS and its other international partner studies of aging, and they have been modified where necessary for cultural and linguistic relevance (118). Specific measures for the secondary study are presented below. Household wealth index was measured as house hold quintiles, quintile 1(poorest), quintile 2 (average), quintile 3 (richest).

Primary study data collection was based on a questionnaire and the known HIV status of participants. The questionnaires asked respondents to rate their own health, function, pain and discomfort, cognition, interpersonal relationships, sleep, energy, and general health. Hypertension was defined as a measured mean systolic blood pressure >140 mmHg or mean diastolic blood pressure >90 mmHg, or controlled blood pressure with self-reported use of hypertension medication, while stroke was self-reported. HIV status was determined through HIV enzyme-linked immunosorbent assays on dried blood spots (124)

To guarantee the appropriateness, comprehension, and reliability of the interview items, all study materials underwent back- and forward translations from English to the regional Shaangan language (xiTsonga). They were also pilot tested with a random sample of people who were not included in the HAALSI sample (118).

3.2. DESCRIPTION OF THE SECONDARY STUDY

3.2.1. STUDY POPULATION

The study population included HIV-positive and HIV-negative people who have experienced childhood TE, aged > 40 years of age or elderly people residing in healthcare facilities. Study participants were selected from the HAALSI Wave 2. The analytical samples were selected as follows: Wave 2 data were from a 2019 baseline wave of HAALSI, study participants of 5,059

in a cohort study were already known and captured, participants with known HIV status were part of the ongoing study, OCS-plus was used to interview the participants with life-course trauma experiences questions, data from a sub-sample aged 40–115 years were selected within age- and sex-strata, lastly the study participants who refused to answer certain questions were dropped).

3.2.2. DATA MANAGEMENT

An ethics waiver from the Human Research Ethics Committee (the University of the Witwatersrand, Faculty of Health Sciences) was applied, and protocol for analysing open access data. The data for this study were received from the gatekeepers in Excel format and imported into Stata/SE 17 for management, cleaning and in August 2022, I attended a workshop at the WITS rural health research unit (Agincourt) with the HAALSI team to develop skills for analysing the data.

Variables for analysis

Outcome: Neurocognitive impairment (NCI)

Cognitive function in line with the definition of NCI used the Oxford Cognitive Screen (OCS)-plus, a tablet-based test for evaluating NCI that was created for use in low-literacy and low-income environments, such as the Agincourt sub-district, it was used for the assessment in this study (124). With no literacy or numeracy requirements, the OCS-plus employed visual and auditory clues to perform the cognitive assessment tasks (118). NCI was measured as orientation and participants had told the: correct date, month, year and current president. The outcome variable was coded 1 if one experiences a life-course TE and 0 otherwise, NCI was defined based on orientation and memory. A score≥1.5 standard deviations (SD) below the mean of the baseline cognitive function distribution on the cognitive assessment (managing to

know the date, day, month and president) will mean non-cognitive impairment while a score below the mean means otherwise.

Exposure: TE and HIV

The primary measure of exposure for NCI was TE that have ever been experienced during the study participants' life course. The measure of TE were translated and to ensure validity and reliability, xiTsonga the local language, was back-translated from English (125). The TE ever experienced during one 'lifetime were grouped into twelve categories:

Table 1: TE ever experienced during one's lifetime.

1). Ever experiencing a natural disaster
2).Ever experiencing a life-threatening serious physical attack
3). Ever been the victim of sexual abuse
4).Ever been a victim of sexual abuse
5). Having parents unemployed for over 6 months
6). Ever experiencing parents fighting or arguing
7). Parents on substance abuse
8). Ever experience physical abuse by parents
9). Ever witnessed death in non-combat
10). Ever witnessed the death of relative or friend
11). Ever provided long-term care to disabled
12). Ever experienced severe financial hardship

Two parameterizations, a simple count of how many TE an individual has experienced and binary variables(yes/no) for exposure to different types of events were used (57). These binary variables took a value of 1 if the individual had experienced an event and 0 if they had not. A

composite trauma (defined as the presence of at least one trauma item) variable was generated from all the trauma questions asked and coded if ever experienced any of the seven trauma items and 0 if none were experienced.

The exposure variables HIV status was categorised into HIV positive and negative and coded 1 and 0 respectively.

Potential confounders

Aspects of society's sociodemographic makeup that are thought to be related to the possibility that a person has had TE with the outcome of NCI are as listed in the table below:

Table 2: Socio-demographic factors

1). Sex (male/female),
2). Country of birth (RSA, Mozambique,),
3). HIV status (positive, negative)
4). Lifecourse trauma (yes, no)
5). Age: 40-49, 50-59, 60-69, 70-79, 80+
6). Education: No formal education, primary (1-7 years), secondary (8-11 years), some secondary education (12 years+)
7). Household composition: Living alone, living 1 other person, living in 3-6 person household, living in 7+ person household
8). Household wealth Index: Quintile 1(poorest), Quintile 2-4 (average), Quintile 5 (richest)
9). Marital status (married, unmarried)
10). Employment status (employed: full-time or part-time), not working, homemaker

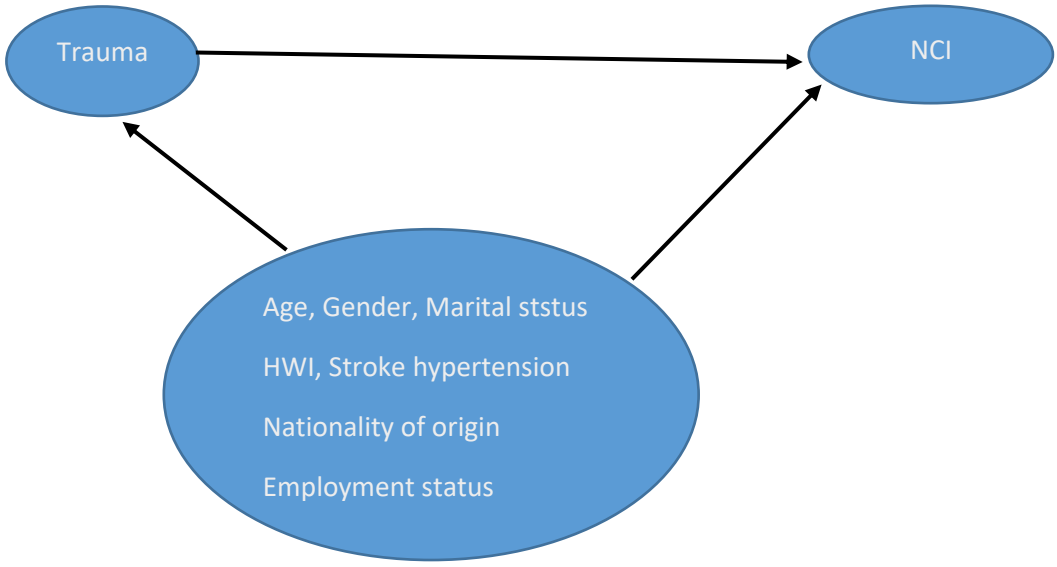
11). Hypertension (measured mean systolic blood pressure >140 mmHg or mean diastolic blood pressure >90 mmHg, or controlled blood pressure with self-reported use of hypertension medication) (yes. no)
12). Stroke (yes. no)

Stroke and hypertension were conceptualized as potential confounder as they are associated with the exposure (HIV and life-course trauma) and outcome (NCI).

3.3. DATA ANALYSIS

A Directed Acyclic Graph (DAG) was drawn to conceptualize the role of exposure variables and how they impact NCI.

Confounders relationship



Effect modification

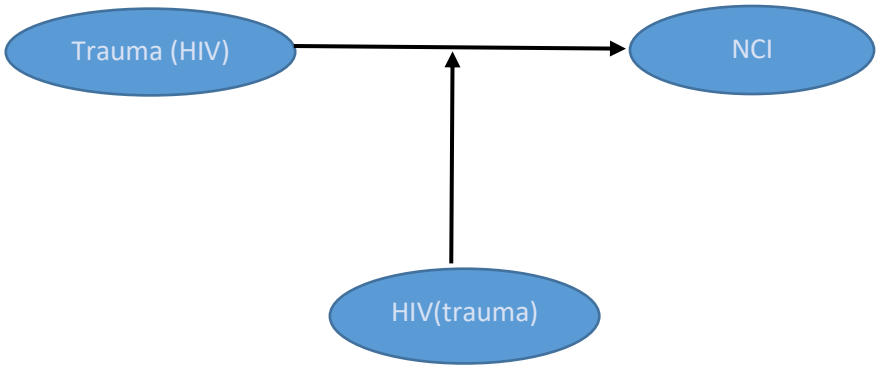


Figure 4 Directed Acyclic Graph (DAG) of variables conceptualized for examining causal relationships

Data analysis techniques employed are elaborated as per each objective presented below:

Objective 1: *To describe the socio-demographic characteristics and the most common cognitive symptoms experienced by adults from rural South Africa after experiencing childhood TE in the HAALSI study (wave 2)*

Descriptive statistics were calculated to summarise the categorical variables for objective 1 using frequencies and proportions. Median age was calculated in the study as the data were not normally distributed and the graphs (bar charts and pie charts) were drawn to give a pictorial view of the data.

Objective 2: *To describe the individual contribution of HIV status and trauma on NCI among adults from rural South Africa in the HAALSI study (waves 2) adjusting for potential confounders*

A bivariate analysis was conducted to examine the association between NCI with HIV status and life-course TE using the Chi-square test. Childhood TE and HIV status are both explanatory variables which were assessed to look at their relationship with the outcome

variable (cognitive impairment). Combining the effects of two variables, each variable, life-course TE and HIV status were examined in the model individually to understand their contribution.

Univariate logistic regression was employed to estimate the unadjusted measures of association (Odds ratio) and the corresponding 95% confidence interval. A stepwise–forward and backwards- variable selection was employed to select the variable of interest to consider in the final adjusted logistic regression model. The apriori selection of variables was conducted to guide the selection of variables in the model based on literature and not only statistical significance (126,127). The interaction between HIV and life-course TE was investigated in the adjusted model. The measures of association were reported as adjusted odds ratio (AOR) and their associated 95%CI. The likelihood ratio test was used to select the better model. The model post-estimation was done using the area under the curve (ROC) approach. Significance will be set at 5%.

Objective 3: *To estimate the adjusted combined (interaction) effects of life-course TE and HIV status on NCI among adults from rural South Africa in the HAALSI study wave 2.*

First, a bivariate analysis was conducted to examine the association between cognitive impairment with HIV status and life-course TE interaction terms using a Chi-square test. Life-course TE and HIV status are both explanatory variables which were assessed to look at their relationship with the outcome variable (cognitive impairment). Combining the effects of two variables, each variable, childhood trauma and HIV status were run on the model individually to understand their contribution.

Univariate logistic regression was used to estimate the unadjusted measures of association (Odds ratio) and the corresponding 95% confidence interval. A stepwise–forward and

backwards- variable selection was conducted to select the variable of interest to consider in the final adjusted logistic regression model. The apriori selection of variables was done to guide the selection of variables in the model based on literature and not only statistical significance.

The interaction between HIV and life-course TE was investigated in the adjusted model. The model adjusted for education, employment status, age, nationality of origin, marital status, composite trauma, HIV status and composite trauma. The measures of association were reported as adjusted odds ratio (AOR) and their associated 95%CI. The likelihood ratio test was used to select the better model. The model post-estimation was done using the area under the curve (ROC) approach. Significance will be set at 5%.

CHAPTER 4: RESULTS

Chapter 4 presents the results of the research report. The first part consists of several sections including 4.1. Introduction, 4.2. Socio-demographic and health characteristics of the analytical sample, 4.3. Bivariate analysis, 4.4. Results of the univariate model, 4.5. Results of the adjusted logistic regression model, 4.6. Results of the Interaction model: logistic regression

4.1. INTRODUCTION:

In this chapter, the results of the study are presented.

4.2. SOCIO-DEMOGRAPHIC AND HEALTH CHARACTERISTICS OF THE ANALYTICAL SAMPLE

The sociodemographic characteristics of the HAALSI population and socioeconomic conditions are presented in Table 3 followed by an explanatory text below.

Table 3 Socio-demographic characteristics of the analytical sample

Characteristics	**Categories**	**Frequencies**	**Percentages (%)**
Gender	Male Females No response	1,658 2,216 302	39.70 53.07 7.23
Education	No formal education Some primary school (1-7 years) Some secondary school(8+ years) No response	1,855 1,439 872 10	44.42 34.46 20.88 0.24
Employment status	Employed (full or part-time) Not working Homemaker No response	690 3,033 442 11	16.52 72.63 10.58 0.26
Age	Median (IQR): 64 (55-74)		
Household wealth index	Poorest Average	2,044 1,803	48.95 43.18

	Richest	329	7.88
Nationality of origin	RSA Mozambique No response	2,896 1,277 3	69.35 30.58 0.07
Marital Status	Married Unmarried No response	2,006 2,167 3	48.04 51.89 0.07
Hypertension	Yes No No response	1,578 2,551 47	37.79 61.09 1.13
HIV Status	Positive Negative No response	1,724 2,441 11	41.28 58.45 0.26
Stroke	Yes No No response	28 4,064 84	0.67 97.32 2.01

Of the 5,059 study participants recruited and residing in the Agincourt study area in Bushbuckridge, the median age of the participant was 64 (IQR: 55-74) years; 53.07% of the study participants were females; 44.42% had no formal education, and 72.63% of the study participants were not working. Most participants were poor (48.49%); 69.4% were South African nationals and 51.89% were unmarried. Regarding health, 37.79% of the participants were hypertensive, 41.28% of the study participants were HIV-positive, and 0.67% had experienced a stroke.

The lifecourse TE ever experienced in the HAALSI population is presented in Table 2 on the next page followed by an explanatory text below.

Table 4: Lifecourse TE ever experienced by the sample

Characteristics	Categories	Frequencies	Percentages (%)
Ever experience a natural disaster	Yes No No response	1,659 2,250 267	39.73 53.88 6.39
Ever experienced life-threatening incidents	Yes No No response	888 3,020 268	21.26 72.32 6.42
Ever been the victim of a serious physical attack	Yes No No response	245 3,664 267	5.87 87.74 6.39
Ever been a victim of sexual abuse	Yes No No response	59 3,849 268	1.41 92.17 6.42
Parents unemployed for over 6 months	Yes No No response	637 3,263 276	15.25 78.14 6.61
Ever experienced parents arguing or fight	Yes No No response	473 3,410 293	11.33 81.66 7.02
Parents of substance abuse	Yes No No response	391 3,509 276	9.36 84.03 6.61
Ever experienced physical abuse by parents	Yes No No response	452 3,452 272	10.82 82.66 6.51
Ever witnessed death in non-combat	Yes No No response	693 3,214 269	16.59 76.96 6.44
Ever witnessed the death of a relative or friend	Yes No No response	973 2,934 269	23.30 70.26 6.44
Ever provided long-term care to disabled	Yes No	483 3,424	11.57 81.99

	No response	269	6.44
Ever experience severe financial hardship	Yes No No response	2,453 1,454 269	58.74 34.82 6.44
Number of trauma Items	0 1 2 3 4 5 6 7	1,771 911 761 581 439 297 169 130	35.01 18.01 15.04 11.48 8.68 5.87 3.34 2.57

The most common type of TE experienced was people experiencing severe financial hardship at 58.74%. Further findings suggest that 39.73% have ever experienced a natural disaster, followed by 35.01% who had composite trauma, 23.30% who ever witnessed the death of a relative or friend, 16.59% of the participants witnessed death in non-combat, 15.25% whose parents have been unemployed for over 6 months, 11.33% ever experienced parents argue or fight, 11.57% ever provided long term care to disabled, 10.82% ever experienced physical abuse by parents, 9.36% who parents are on substance abuse, 5.87% who have ever been victims of serious physical attack and 1.41% who have been victims of sexual abuse.

Figure 5 below presents the number of TE experiences by the participants. For most participants who had trauma experiences, 18.01% of participants reported experiencing one trauma item, while 15.04% experienced two trauma items.

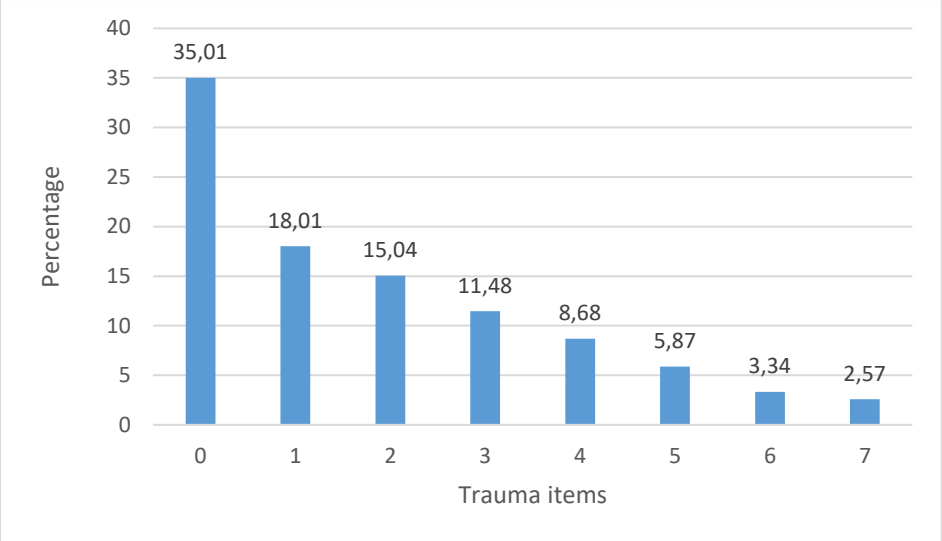


Figure 5: Distribution of the numbers of TE experienced

4.3. BIVARIATE ANALYSIS

The prevalence of NCI was 7% (n=352). The bivariate analysis of the analytical sample is presented in Table 5 followed by an explanatory text below.

Table 5: Bivariate analysis of the analytical sample

Characteristics	**Categories**	**No NCI**	**NCI**	***p*-value**
		n(%)	**n(%)**	
Gender	Male Females	1527(92.10) 2034(91.79)	131(7.90) 182(8.21)	0.724
Education	No formal education Some primary school (1-7 years) Some secondary school(8+ years)	1577(85.01) 1375(95.55) 852(97.71)	278(14.90) 64(4.45) 20(2.29)	**<0.0001**
Employment status	Employed (full or part-time) Not working Homemaker	676(97.97) 2712(89.42) 415(93.89)	14(2.03) 321(10.58) 27(6.11)	**<0.0001**
Age Mean (SD) Median (IQR)	 Mean: ±65.16;SD(12.59) (IQR): 64 (55;74)	 64.2 (12) 64 (55-74)	 75.04 (14.1) 64 (55-74)	 **<0.0001** **<0.0001**

Household wealth index	Poorest Average Richest	1874(91.68) 1635(90.68) 304(92.40)	170(8.32) 168(9.32) 25(7.60)	0.417
Nationality of origin	RSA Mozambique	2696(93.09) 1114(87.24)	200(6.91) 163(12.76)	**<0.0001**
Marital Status	Married Unmarried	1764(87.94) 2046(94.42)	242(12.06) 121(5.58)	**<0.0001**
Hypertension	Yes No	1451(91.95) 2323(91.06)	127(8.05) 228(8.94)	0.322
HIV Status	Positive Negative	1516(87.94) 2289(93.77)	208(12.06) 152(6.23)	**<0.0001**
Stroke	Yes No	22(78.57) 3718(91.49)	6(21.43) 346(8.51)	**0.015**
Composite trauma	Yes No	671(75.48) 3,142(95.59)	218(24.52) 145(4.41)	**<0.0001**

Participants without formal education had the highest proportion of NCI (n=274; 14.9%) compared to other levels of education and this was statistically significant (p-value=<0.001). Those who were not working had the highest NCI compared to other employment status groups (n=321, 10.58%) and this was statistically significant (p-value=<0.001). Participants from Mozambique had higher risk of NCI than SA nationals (n=163, 12.76%) and this was statistically significant (p-value=<0.001). Married participants had a NCI of 12.06% (n=242) compared to unmarried participants and this was statistically significant (p-value=<0.001). HIV-positive participants had the highest proportion of cognitive impairment (n=208, 12.06%) compared to HIV-negative participants, and this was statistically significant (p-value=<0.001).

Participants with stroke had the highest proportion of NCI (n=6, 21.43%) compared to those without stroke and this was statistically significant (p-value=<0.001). Participants who had experienced composite trauma had the highest proportion of NCI (n=218, 24.52%) compared to those without composite trauma, and this was statistically significant (p-value=<0.001).

4.4. RESULTS OF THE UNIVARIATE MODEL

In the univariate logistic regression model, the factors associated with cognitive impairment were found to be the level of education, employment status, age, nationality, marital status, HIV status, stroke and composite trauma.

The odds of having NCI increased by 74% (OR=0.26, 95%CI: 0.19-0.35) and 87% (OR= 0.13,95%CI: 0.08-0.21) among those who had some primary school (1-7 years) and some secondary school(8+ years), respectively compared to those with no education. The odds of having cognitive impairment increased by 5.71 (95%CI: 3.32-9.82) and 3.14 (95%CI: 1.62-6.05) among those who were not working and those who were homemakers, respectively compared to those employed. A one-year increase in age was associated with a 7% increase in the odds of having a cognitive impairment (OR=1.07; 95%CI: 1.06-1.08).

Mozambique nationals had an increased odds of 1.97 (95%CI: 1.58-2.45) of having NCI compared to SA nationals. Those who were married had 57% (OR=0.43, 95%CI: 0.34-0.54) reduced odds of having cognitive impairment compared to those who were married. Those who were HIV positive had an increased odds of 2.06 (95%CI: 1.06-2.57) of having NCI compared to those who are HIV negative. Those who had a stroke had an increased odds of 2.93% (95%CI: 1.18-7.27) of having cognitive impairment compared to those without stroke. Those who do not have composite trauma had 86% reduced odds of having NCI compared to those who had composite trauma (OR=0.14; 95%CI; 0.11-0.18).

Table 6: Logistic regression analysis examining predictors of NCI

The table below presents the univariate, bivariate and interaction results

Characteristics	**Categories**	**Univariate Analysis**		**Adjusted Analysis**		**Interaction model**	
		OR(95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Gender	Male Females	1(base) 1.04(0.82-1.31)	 0.724	1(base) 0.96(0.73-1.26)	 0.799	1(base) 0.96 (0.73-1.27)	 0.815
Education	No formal education Some primary school (1-7 years) Some secondary school(8+ years)	1 (base) **0.26(0.19-0.35)** **0.13 (0.08-0.21)**	 **<0.0001** **0.001**	1 (base) **0.36 (0.25-0.52)** **0.43(0.24-0.75)**	 **<0.0001** **0.003**	1(base) **0.36 (0.25-0.52**) **0.41 (0.23-0.73)**	 **<0.0001** **<0.0001**
Employment status	Employed (full or part-time) Not working Homemaker	1 (base) **5.71 (3.32-9.82)** **3.14 (1.62-6.05)**	 **<0.0001** **0.001**	1 (base) **1.99 (1.06-3.74)** 1.19 (0.56-2.50)	 **0.031** 0.645	1(base) **1.98 (1.05-3.72)** 1.14 (0.54-2.42)	 **0.033** 0.715
Age		**1.07 (1.06-1.08)**	**<0.0001**	**1.05 (1.04-1.07)**	**<0.0001**	**1.05 (1.04-1.15)**	**<0.0001**
Household wealth index	Poorest Average Richest	1 (base) 1.13 (0.90-1.41) 0.90 (0.58-1.40)	 0.274 0.660	1 (base) 1.08 (0.82-1.43) 0.96 (0.56-1.64)	 0.572 0.903	1(base) 1.07 (0.81-1.41) 0.95 (0.56-1.16)	 0.612 0.860
Nationality of origin	RSA Mozambique	1 (base) **1.97 (1.58-2.45)**	 **<0.0001**	1 (base) **1.46 (1.09-1.95)**	 **0.009**	1(base) **1.45 (1.08-1.93)**	 **0.011**
Marital Status	Unmarried Married	1 (base) **0.43 (0.34-0.54)**	 **<0.0001**	1 (base) **0.63 (0.47-0.84)**	 **0.002**	1(base) **0.63 (0.47-0.84)**	 **0.002**
Hypertension	No Yes	1 (base) 1.12 (0.89-1.40	 0.322	1 (base) 0.86 (0.47-1.49)	 0.331	1(base) 0.86 (0.64-1.15)	 0.325
HIV Status	Negative Positive	1 (base) **2.06 (1.65-2.57)**	 **<0.0001**	1 (base) 1.08 (0.82-1.42)	 0.559	1(base) 0.79 (0.533-1.17)	 0.252
Stroke	No Yes	1 (base) **2.93 (1.18-7.27)**	 **0.020**	1 (base) 2.62 (0.72-0.84)	 0.142	1(base) 2.67 (0.72-9.85)	 0.138
Composite trauma	No Yes	1 (base) **0.14 (0.11-0.17)**	 **< 0.0001**	1 (base) **0.14 (0.11-0.18)**	 **<0.0001**	1(base) **0.10 (0.07-0.15)**	 **<0.0001**
HIV Status# Composite trauma	No Yes					1(base) **1.78 (1.04-3.04)**	 **0.034**

4.5. RESULTS OF THE ADJUSTED LOGISTIC REGRESSION MODEL.

In the adjusted logistic regression model, the factors found to be associated with NCI were the level of education, employment status, age, nationality, marital status and composite trauma. The model was adjusted for education, employment status, and age, nationality of origin, marital status, composite trauma, gender, household wealth index, hypertension, HIV status, and stroke, HIV status and composite trauma.

After adjusting for other factors stated above, the odds of having NCI decreased by 64% (AOR=0.36; 95%CI: 0.25-0.52) and 53% (AOR=0.43; 95%CI: 0.24-0.75) among those who had some primary school (1-7 years) and some secondary school (8+ years), respectively compared to those with no education. After adjusting for other factors stated above, the odds of having cognitive impairment increased by 99% (AOR=1.99; 95%CI: 1.06-3.74) among those who were not working compared to those employed. After adjusting for other factors stated above , a one-year increase in age was associated with a 5% increase in the odds of having NCI (OR=1.05; 95%CI: 1.04-1.07).

After adjusting for other factors stated above, Mozambique nationals had an increased odds of 1.46 (95%CI: 1.09-1.95) of having NCI compared to SA nationals. Adjusting for other factors stated above, those who were married had 37% (OR=0.63, 95%CI: 0.47-0.84) reduced odds of having NCI compared to those who were married. Adjusting for other factors stated above, those who are HIV positive had an increased odds of 1.08 (95% CI: 0.82-1.42) of having NCI compared to those who are HIV negative. When adjusting for strokes, as a potential confounding variable, those who had had a stroke had an increased odds of 2.66 (95% CI: 0.72-0.84) of NCI compared to those without stroke. Very intriguing are the results mentioned above. Vasculopathy, coagulopathy, cardioembolism, and opportunistic infection are a few of the ways that HIV infection can lead to stroke, according to a study by Benjamin and colleagues

(128). Nonetheless, there is a good chance that the incidence of HIV infection and stroke will often overlap.

Adjusting for other factors stated above the odds of having NCI decreased by 86% (AOR=0.14 95%CI: 0.11-0.18) among those with composite trauma compared to those without composite trauma.

4.6. INTERACTION MODEL: LOGISTIC REGRESSION

In the adjusted logistic regression model with an interaction HIV-trauma term, the factors associated with NCI were the level of education, employment status, age, nationality, marital status, composite trauma and the HIV-trauma interaction.

Adjusting for other factors, the odds of having NCI decreased by 64% (AOR=0.36; 95%CI: 0.25-0.52) and 59% (AOR=0.41; 95%CI: 0.24-0.75) among those who had some primary school (1-7 years) and some secondary school (8+ years), respectively compared to those with no education. Adjusting for other factors, the odds of having NCI increased by 98% (AOR=1.98; 95%CI: 1.05-3.72) among those who were not working compared to those employed. Adjusting for other factors, a one-year increase in age was associated with a 5% increase in the odds of having a cognitive impairment (OR=1.05; 95%CI: 1.04-1.07).

Adjusting for other factors, Mozambique nationals had an increased odds of 1.45 (95%CI: 1.08-1.93) of having NCI compared to SA nationals. Adjusting for other factors, those who were married had 37% (OR=0.63, 95%CI: 0.47-0.84) reduced odds of having cognitive impairment compared to those who were married. Adjusting for other factors, those without composite trauma had 90% (AOR=0.10; 95%CI: 0.07-0.15) reduced odds of having NCI compared to those who have composite trauma. Adjusting for other factors, those who were HIV positive and had experienced composite trauma had an increased odds of 1.78 (95% CI:

1.04-3.04) of having NCI compared to those who are HIV negative and had not experienced composite trauma.

Conclusion

5,059 study participants were recruited from the Agincourt area, the median age of the participants was 64 (IQR: 55-74) years; 53.07% were females; 72.63% of the study participants were not working. 37.79% of the participants were hypertensive, 41.28% were HIV-positive, and 0.67% had experienced a stroke. People experiencing severe financial hardship were 58.74% and this was the highest number of people experiencing Traumatic Events. A bivariate analysis showed that the prevalence of NCI was 7%, and participants without formal education had the highest proportion of NCI (n=274; 14.9%) compared to other levels of education and this was statistically significant (p-value=<0.001).

Those who were not working had the highest NCI compared to other employment status groups (n=321, 10.58%) and this was statistically significant (p-value=<0.001). HIV-positive participants had the highest proportion of cognitive impairment (n=208, 12.06%) compared to HIV-negative participants, and this was statistically significant (p-value=<0.001).

Participants with stroke had the highest proportion of NCI (n=6, 21.43%) compared to those without stroke and this was statistically significant (p-value=<0.001). In our univariate model, the odds of having NCI increased by 74% (OR=0.26, 95%CI: 0.19-0.35) and 87% (OR= 0.13,95%CI: 0.08-0.21) among those who had some primary school (1-7 years) and some secondary school(8+ years), respectively compared to those with no education.

In our interaction model, after adjusting for other factors, the odds of having NCI decreased by 64% (AOR=0.36; 95%CI: 0.25-0.52) and 59% (AOR=0.41; 95%CI: 0.24-0.75) among those who had some primary school (1-7 years) and some secondary school (8+ years), respectively compared to those with no education

CHAPTER 5: DISCUSSION, LIMITATIONS AND RECOMMENDATIONS

Chapter 5 presents the discussion, limitations, and conclusion of the research report. The first part, the discussion consists of several sections including a reflection of the most salient of the findings reported above as well as a comparison to previous studies. The second part of this chapter consists of several sections including 5.2. Strengths, 5.3. Limitations, 5.4. Recommendations. This secondary analysis aimed to examine the combined (interaction) effect of life-course TE and HIV infection on the NCI of adult South Africans using the HAALSI data.

5.1.1. REFLECTION OF THE SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE

The high levels of little formal education and unemployment (44.42%) and 72.63% (respectively) are not surprising and are parallel to national South African estimates that have been reported over time. The 2001 General Population Census suggested that over 30% of South Africans over the age of 15 had not completed Grade 7. A decade later, a 2011 National statistics report had reported that, there is a higher prevalence estimate of Africans aged 60 years and older who do not have formal education, with black South Africans making up about 40% of this group (129). Another S.A based study by Rosenberg and colleagues in 2020, reported that 46% of the population had no formal education, and 42% were illiterate (130). With regard to the high rates of unemployment found in this sample, there is also parallel with national estimates. A 2022 paper by Shah suggested that more than 30% of South African households do not have working adults (131).

5.1.2. THE RELATIONSHIP BETWEEN HIV, TRAUMA AND NCI

In the multiple logistic regression with the interaction term, the odds of having NCI decreased by 64% (AOR=0.36; 95%CI: 0.25-0.52) and 59% (AOR=0.41; 95%CI: 0.24-0.75) among

those who had some primary school (1-7 years) and some secondary school (8+ years), respectively compared to those with no education. These findings are not surprising and have been corroborated by previous studies particularly in a setting such as S.A where literacy level is very low. These finding were corroborated by a previous study by Humphreys and colleagues in 2016 which reported that stronger educational levels are protective of NCI and that age-related associates such as attainment, intelligence and mental stimulations with education contribute to stronger NCI (124). Interestingly, in younger (20-35 years) HIV positive Zambians it was reported that higher education was also said to have protective effects against NCI deficits as well as for the particular cognitive domains of executive functioning, learning, and information processing speed (132). The odds of having NCI increased by 98% (AOR=1.98; 95%CI: 1.05-3.72) among those who were not working compared to those employed. In a 2015 review by Vance and colleagues, a conceptual framework for the benefits of employment on health was proposed. These benefits included social engagement and relations, attaining new skills, routine and structure, meaning and income. Further this review references Vance and colleagues (2011) who propose that unemployment allows for unfocused time, constrained income and risk of depression which could also lead to NCI (133).

Further, my findings are in line with a study by Madhavan and colleagues which reported that unemployment in middle-aged women has adversely contributed to NCI. Additionally, they found that several characteristics may function as a buffer between unemployment's impact on middle-aged women's cognitive capacities and One such important issue is the concerned women's work and family background (134).

In an S.A based study by Ssonko and colleagues in 2023 in a memory clinic in Groote Schuur Hospital, Cape Town, they suggested that the mean age at diagnosis of dementia was 72.4 years and that this differed by sub-types (135). In another study conducted by Kobayashi and

colleagues in the same HAALSI study, it was found that the risk of cognitive decline was significantly higher among adults between the ages of 70 and 74 (38).

A one-year increase in age was associated with a 5% increase in the odds of having NCI (OR=1.05; 95%CI: 1.04-1.07. This finding is consistent with previous literature on the effect of age on NCI. A Zambian based study by Kabuba and colleagues found that cognitive reserve, a protection against NCI was more apparent in younger (20-35 years) participants compared to older participants with more years of education.

In my study, those without composite trauma had 90% (AOR=0.10; 95%CI: 0.07-0.15) had reduced odds of having NCI compared to those who have composite trauma. This finding are in line with previous studies, which found that life-course events such as financial hardship, physical abuse, the death of a spouse or partner, and stress were all significantly associated with worse neurocognitive performance and functional declines(136,137) . Those who were HIV positive and had experienced composite trauma had an increased odds of 1.78 (95% CI: 1.04-3.04) of having NCI compared to those who are HIV negative and had not experienced composite trauma**.** These finding are in line with a several previous studies who may have used different measures for composite TE but conceptually had similar findings: a synthesis of findings by Spies and colleagues revealed that exposure to potentially traumatic events (PTEs) and stressful life events (SLEs) was associated with a significant increase in cognitive impairment among HIV-positive adults, and the most likely outcomes being memory impairments and executive function impairments (60,72).

In the interaction model, we found no association between HIV status, stroke, or hypertension and NCI. These findings are not in line with results from other studies. According to a study by Lo Coco and colleagues 2016, stroke is a significant contributor to cognitive decline and has been linked to the onset of both Alzheimer's disease and vascular dementia (138). Another

study conducted in 2018 by Tang and colleagues indicated that there is a trend toward considerable decline in cognitive test scores in stroke survivors, as well as evidence of cognitive stability and improvement (139). Our findings are not in line with the previous research, this might be due to reporting bias during data collection in the form of interviews.

The lack of inclusion of the majority of comorbid conditions linked to HIV, such as diabetes, tuberculosis, cardiovascular disease, and hepatitis diseases (HPC & HPB), in the model, may be the cause of HIV and other comorbidities on NCI becoming non-significant. Additionally, the non-significance of the multivariable model may have been impacted by patients missing information regarding their nadir CD4 and whether or not they were on ART during data analysis. It is assumed that the study participants might have not reported that they encountered stroke during their lives or the manner in which the questions were administered. It is also assumed that perhaps stroke was mild and did not affect NCI. As a result of reporting bias during interview-based data collection, our findings do not agree with those of the prior research. It is considered that either the way the study participants were questioned or whether they had ever experienced a stroke may not have been disclosed or there is also a possibility that the stroke was moderate and had no impact on NCI.

5.2. MARITAL STATUS

In the interaction model analysis, marital status was associated with NCI. Our studies show that those people who are married had 63%, AOR= 0.63 (95% CI: 0.47-0.84) decreased odds of developing NCI compared to unmarried people. In an Ethiopian study by Wubetu and colleagues 2021, there was no association between marital status and NCI (106). In a study conducted in Zimbabwe by Nyamayaro and colleagues 2020, they also reported no association between marital status and NCI (28). In a South African-based study by Kobayashi and colleagues 2021, they found that there is an association between NCI and marital status (not

married), whereas Zhi-Chao Chen and colleagues 2021 found a positive association between marital status (long-term divorced, separated and widowed) and NCI in a Chinese cross-sectional study observed (140). We find it difficult to reflect on what could be presented by marriage. There may be unmeasured confounders in relation to married participants or perhaps it is a chance finding.

5.3. STRENGTHS

The study's strengths include a big sample size, representation of a variety of age groups, the low-income population it studied in rural South Africa, and its extensive in-person survey. Weights were utilized in the primary study to reduce any bias that could be introduced into estimations between waves, mortality, and dropout. We additionally demonstrated that HIV status and composite trauma together (interaction) are linked with NCI, which is a significant strength given that most of the researchers have not assessed HIV/trauma interactions in predicting NCI.

These findings help improve our comprehension of how HIV, life-course trauma, and NCI interact. These studies also added to the body of knowledge regarding the critical function that school attainment plays an important role in the slowing of NCI.

5.4. LIMITATIONS

Although every effort has been made to resolve study limitations, there are still a few that deserve to be mentioned. The primary study has focused on various waves, specifically waves 1, 2, and 3 in that order. We only used wave 2 data in our analysis for a cross-sectional study. Since the study is a secondary data analysis, physical participation in data collection was not done, making it impossible to disclose a bias in the study from the study participants because some of the data depended on self-reported information. Another drawback was that some variables, like the household wealth index, could not be properly aggregated since various

people define wealth differently. In rural areas like the Bushbuckridge, people might not have formal jobs but may still have livestock as a source of wealth.

Numerous coexisting illnesses that may affect NCI were not examined in this study, including the existence of tuberculosis, myocardial infarction, tobacco usage, and alcohol intake. There was no evaluation of the HIV viral load severity at the onset of infection or at the time ART was started. This could be a drawback since research indicates that HIV enters through the central nervous system. The study's exclusion of participants' information regarding their use of antiretroviral therapy (ART) at study inception constituted a limitation, given current research indicating that patients who begin ART exhibit enhanced cognitive functioning and reduced viral loads are associated with improved NCI.

It should be noted that the samples were not nationally representative and that the results only pertained to the sample sites. However, a high response rate was reported, thus these discrepancies are unlikely to have an impact on our analysis and conclusion. Life-course traumas like ever experiencing sexual abuse or ever having parents on substance abuse may not have been as widely reported as they should have been, especially among men. Another drawback was that, at the time of sampling and enrolment, South Africa did not have a universal test and treat policy for HIV care, which would have improved NCI and slowed the transmission of infection among all infected people.

5.5. RECOMMENDATIONS

We recommend that longitudinal studies in the future investigate NCI in this context between HIV-positive and TE persons and that assessment instruments be further developed to make them more suitable for this and comparable contexts. Our goal is to provide healthcare practitioners with useful advice on how to manage cognitive impairment in those living with HIV and those who have experienced traumatic experiences, based on the results of this study.

Furthermore, our objective is to pinpoint areas of incomplete understanding and emphasize avenues for further investigation, examining innovative approaches for cognitive restoration. By tackling these goals, the research hopes to advance knowledge of the relationship between TE, HIV, and NCI and offer helpful advice on how to treat cognitive problems in TE survivors.

CHAPTER: 6. CONCLUSION

In this population-based representative study of older adults in the rural area of the Bushbuckridge region in South Africa, we observed no association between HIV status, stroke, and hypertension on NCI in the interaction model. Our analysis demonstrated a strong association between HIV and composite trauma on NCI. Despite huge challenges for people living in informal settlements, where poverty, gender inequality, and lack of access to service delivery are high, it is found that some of these factors independently shape HIV-risk behaviour among people (66). These studies add knowledge to existing research on life-course trauma and NCI in a low-literate and low-income society, especially in a region with many social issues such as low SES, low education, unemployment, high HIV prevalence, and GBV. This study highlights concerns over the long-term health repercussions of trauma suffered throughout childhood and adulthood, as well as its impact on NCI, particularly in rural South African populations with limited access to medical services. Strong intervention is therefore required for mental health challenges, HIV-positive individuals and those with co-morbid diseases, with a focus on cognition, social problems, and medication adherence among diseased people to reduce the burden of disease.

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