

NEUROCOGNITIVE OUTCOMES IN HIV AND CHILDHOOD TRAUMA

by

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Declaration

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ABSTRACT

It is well established that South African women are disproportionately affected by HIV/AIDS and gender based violence. Research to date has provided evidence for neurocognitive decline in individuals infected with HIV/AIDS and in individuals who have experienced early life trauma. However, many gaps remain in our knowledge about the neurocognitive profile of HIV and childhood trauma in South African women. The present study focused on the neurocognitive effects of HIV infection and childhood trauma, both separately and in combination in South African women. The primary aim of the study was to assess neurocognitive functioning in HIV-positive and matched HIV-negative controls, with and without a history of childhood trauma. Moreover, the study sought to assess the synergistic relationship between HIV and childhood trauma in influencing neurocognitive outcomes, a relationship which has not yet been investigated.

A neuropsychological battery sensitive to HIV-related impairments was administered to 83 HIV-positive and 47 matched HIV-negative women with histories of childhood trauma. A history of childhood trauma was assessed using the Childhood Trauma Questionnaire short form (CTQ-SF). Forty eight of the 83 HIV-positive women were exposed to childhood trauma. Among the control subjects, a total of twenty women were exposed to childhood trauma.

Findings of the present study revealed neurocognitive deficits in memory and executive functions. Results demonstrated significant HIV effects in memory (HVLT-R learning and delay trials), and executive functions (Halstead Category test). Similarly, a trauma

effect was evident in delayed recall (HVLTR delay). Moreover, results revealed a significant interaction effect between HIV status and trauma status on the WAIS-III Symbol Search Task, a task of psychomotor speed. However, HIV-negative controls with a history of childhood trauma scored the highest on this task. Although this finding was unexpected, it may suggest that psychomotor speed may not be a sensitive or discriminating test of childhood trauma in healthy adults.

The present study demonstrated evidence for HIV and trauma effects in the ability domains of learning and delayed recall and executive functions. Although the present study did not find evidence for a synergistic relationship between HIV and trauma, it did provide evidence for both HIV and trauma effects on neurocognition, a finding in keeping with previous studies. Future research should be prospective in nature and should better delineate the nature, severity, and temporal relationship of childhood trauma to neurocognitive outcomes, as well as the mediators and moderators of these outcomes.

OPSOMMING

Dit is alombekend dat Suid-Afrikaanse vroue buite verhouding swaar deur MIV/vigs en geslagsgebaseerde geweld getref word. Navorsing tot dusver lewer bewyse van neurokognitiewe verswakking by individue met MIV/vigs sowel as individue wat vroeg in hulle lewe reeds trauma ervaar het. Tog is daar steeds vele gapings in ons kennis oor die neurokognitiewe profiel met betrekking tot MIV en kindertrauma onder Suid-Afrikaanse vroue. Hierdie studie konsentreer op die neurokognitiewe uitwerking van MIV-infeksie en kindertrauma, afsonderlik sowel as gesamentlik, op Suid-Afrikaanse vroue. Die hoofdoel van die studie was om neurokognitiewe funksionering by MIV-positiewe vroue te bepaal en dit met gepaste MIV-negatiewe kontrolepersone te vergelyk, met én sonder 'n geskiedenis van kindertrauma. Daarbenewens wou die studie die sinergistiese verwantskap tussen MIV en kindertrauma in hul impak op neurokognitiewe uitkomstebepaal – 'n verwantskap wat tot dusver nog nie ondersoek is nie.

'n Neurosielkundige toetsbatterij wat gevoelig is vir MIV-verwante swakhede is onder 83 MIV-positiewe vroue en 47 gepaste MIV-negatiewe kontrolepersone met 'n geskiedenis van kindertrauma afgeneem. 'n Geskiedenis van kindertrauma is met behulp van die kort weergawe van die kindertraumavraelys (CTQ-SF) vasgestel. Agt-en-veertig van die 83 MIV-positiewe vroue is as kinders aan trauma blootgestel. Van die kontrolegroep het 20 vroue in hul kindertyd trauma beleef.

Die studie het neurokognitiewe tekorte in korttermyngeheue én uitvoerende funksies aan die lig gebring. Die resultate het 'n beduidende MIV-verwante uitwerking op

korttermyngeheue (hersiene Hopkins- verbale leer-en-vertragingstoets, oftewel HVLT-R) sowel as uitvoerende funksies (Halstead-kategorietoets) getoon. Eweneens het die studie op 'n duidelike traumaverwante uitwerking op herinneringsvermoë (HVLT-R-vertraging) gedui. Daarbenewens het die WAIS-II- (Wechsler-volwassene-intelligensieskaal) simboolsoekopdrag – 'n psigomotoriese spoedtoets – 'n beduidende wisselwerkingseffek tussen MIV-status en traumastatus getoon. Tog het MIV-negatiewe kontrolepersone met 'n geskiedenis van kindertrauma die beste in hierdie opdrag gevaar. Hoewel hierdie bevinding verrassend was, kan dit daarop dui dat psigomotoriese spoed dalk nie 'n gevoelige of diskriminerende toets van kindertrauma by gesonde volwassenes is nie.

Die studie het bewys gelever van MIV- en traumaverwante uitwerkings op korttermyngeheue en uitvoerende funksies. Hoewel die ondersoek nie bewyse van 'n sinergistiese verwantskap tussen MIV en trauma kon vind nie, het dit wél bevestig dat MIV en trauma neurokognitiewe werking beïnvloed – 'n bevinding wat in pas is met vorige studies. Toekomstige navorsing behoort ondersoekend te wees en die aard, felheid en tydgebondenheid van die verwantskap tussen kindertrauma en neurokognitiewe uitkomst, sowel as die mediator- en moderatorveranderlikes van hierdie uitkomst, beter te omskryf.

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LIST OF ABBREVIATIONS

CES-D: Center for Epidemiologic Studies Depression Scale

CTQ-SF: Childhood Trauma Questionnaire (Short Form)

CTQ-SA: Childhood Trauma Questionnaire: Sexual Abuse subscale

CTQ-PA: Childhood Trauma Questionnaire: Physical Abuse subscale

CTQ-EA: Childhood Trauma Questionnaire: Emotional Abuse subscale

CTQ-PN: Childhood Trauma Questionnaire: Physical Neglect subscale

CTQ-EN: Childhood Trauma Questionnaire: Emotional Neglect subscale

LEC: Life Events Checklist

DTS: Davidson Trauma Scale

CTS: Conflict Tactics Scale

AUDIT: Alcohol Use Disorders Identification Test

HDS: HIV Dementia Scale

IHDS: International HIV Dementia Scale

HVLT-R: Hopkins Verbal Learning Test Revised

BVMT-R: Brief Visuospatial Memory Test Revised

WAIS-III Digit Symbol: Wechsler Adult Intelligence Scale (Digit Symbol task)

WAIS-III Symbol Search: Wechsler Adult Intelligence Scale (Symbol Search task)

WMS-III Spatial Span: Wechsler Memory Scale (Spatial Span task)

WCST: Wisconsin Card Sorting Test

COWAT: Controlled Oral Word Association Test – FAS

PASAT: Paced Auditory Serial Addition Task

HCT: Halstead Category Test

GBV: Gender-based violence

IPV: Intimate partner violence

CSA: Child sexual abuse

CNS: Central nervous system

BBB: Blood brain barrier

DTI: Diffusion tensor imaging

FA: Functional anisotropy

MRI: Magnetic resonance imaging

fMRI: Functional magnetic resonance imaging

HIV: Human immunodeficiency virus

AIDS: Acquired immunodeficiency syndrome

ARV: Antiretroviral

ART: Antiretroviral therapy

cART: Combined antiretroviral therapy

HAART: Highly active antiretroviral therapy

NP: Neuropsychological

HAND: HIV-associated neurocognitive disorders

ANI: Asymptomatic neurocognitive impairment

MND: Mild neurocognitive disorder

HAD: HIV associated dementia

IADL: Instrumental activities of daily living

ADL: Activities of daily living

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INTRODUCTION

In the following chapter I will provide the rationale and significance for the present study. Thereafter, I will outline the aims and objectives of the present study, as well as the study hypotheses. Finally, I will provide an overview of all chapters presented in this dissertation.

1.1 *Introduction and significance*

According to the Joint United Nations Programme on HIV/AIDS (2010), an estimated 33.3 million individuals worldwide were living with HIV/AIDS by the end of 2009. Of these people living with HIV/AIDS, 2.6 million people globally were newly infected with HIV in 2009. An estimated 68% or 22.5 million live in Sub-Saharan Africa (UNAIDS, 2010). In South Africa, it is estimated that 5.63 million adults and children were infected with HIV and AIDS in 2009. Of these, 3.3 million were females (Department of Health, 2010). In light of these data, it is clear that women bear the brunt of this disease. A women's vulnerability is largely attributable not only to biological factors but also to socio-economic inequalities. Gender-based violence (GBV) is a common phenomenon in countries where the prevalence rate of HIV is also high. Studies conducted in developing countries such as South Africa and other African countries have reported high rates of GBV in both adults and children. This includes intimate partner violence (IPV), rape, and childhood abuse (Andersson, Cockcroft, & Shea, 2008; Jewkes, Penn-Kekana, Levin, Retsaka, & Schrieber, 2001; Kalichman & Simbayi, 2004). A recent study demonstrated that exposure to sexual and physical partner violence and gender power inequity in

relationships at baseline predicted incident HIV infections over 2 years of follow-up and therefore provides evidence for increased risk of HIV infection in young South African women who have experienced abuse (Jewkes, Dunkle, Nduna, & Shai, 2010).

Studies have shown that among persons who become HIV-positive, there is a high prevalence of previous traumatic life events such as a history of sexual or physical abuse (e.g. Bedimo, Kissinger, & Bessinger, 1997; Brady, Gallagher, Berger, & Vega, 2002; Whetten et al., 2006). Research has also suggested that HIV-infected women may face more current and past negative life events than men in developing parts of the world (Lipsitz et al., 1994).

A broad range of research has shown that HIV has significant brain and behavioural implications. Risk for significant brain involvement is highest in more advanced disease stages of HIV but subtle changes are also evident in medically asymptomatic individuals (Heaton et al., 1995). Research has demonstrated significant psychopathology (Myer et al., 2008; Olley, Seedat, & Stein, 2006; Olley, Zeier, Seedat, & Stein, 2005), neurocognitive dysfunction (Heaton et al., 2011; Joska et al., 2010), and brain morphological/metabolite abnormalities (Heyes et al., 2001; Jernigan et al., 1993) in HIV-infected individuals. Similarly, research has demonstrated significant implications for mental health (Afifi et al., 2008; Kessler et al., 2010), neurocognitive outcomes (Horner and Hamner, 2002; Majer, Nater, Lin, Capuron, & Reeves, 2010; Palmer et al., 1997), and neuroimaging outcomes (Bremner et al., 2003; Choi, Jeong, Rohan, Polcari, & Teicher, 2009) in victims of early life and adult trauma. In light of these findings, women living with HIV/AIDS, who also have a history of childhood trauma, and/or acute stress

or PTSD as an adult, may be especially vulnerable to psychiatric and neurocognitive dysfunction due to additive or interactional effects of HIV and childhood trauma.

Therefore, the impact of stress, more specifically childhood trauma, on the brain in the context of HIV remains mostly unclear. Given the high prevalence of these two conditions in South Africa, research in this area is warranted.

1.2 *Aims*

The present study investigated the behavioural and brain effects of childhood trauma and HIV infection among South African women.

The principal aim of the present study was to explore neurocognitive differences among HIV-positive women (with and without histories of childhood abuse) and HIV-negative women (with and without histories of childhood abuse). Embedded within this principal aim are the following objectives:

(i) To assess the individual effect of HIV on neurocognitive outcomes by means of a comprehensive international NP (neuropsychological) battery among HIV-positive women (with and without histories of childhood abuse), and matched HIV-negative women (with and without histories of childhood abuse).

(ii) To assess the individual effect of childhood trauma on neurocognitive outcomes by means of a comprehensive international NP battery among HIV-positive women (with

and without histories of childhood abuse), and matched HIV-negative women (with and without histories of childhood abuse).

(iii) To assess the combined effects of HIV and a history of childhood trauma on the neurocognitive outcomes among HIV-positive women (with and without histories of childhood abuse), and matched HIV-negative women (with and without histories of childhood abuse).

(iv) To assess the predictive ability of various behavioural measures on neurocognitive outcomes in these women. The behavioural measure included: traumatic life events, adult posttraumatic stress symptomatology, depression, alcohol use/dependence, and intimate partner violence (IPV). In addition to these behavioural measures, important demographic and clinical variables were also explored. These included: age, education, CD4 lymphocyte count, and viral load.

An additional aim of the present study was to conduct HIV-1 subtyping on all blood samples collected, in order to establish the predominant circulating viral clade among this cohort of infected women.

Lastly, the present study sought to investigate, by means of a systematic review, the mental health outcomes associated with HIV-infection and early life adversities.

1.3 *Study hypotheses*

Hypothesis 1: neurocognitive differences would be evident in women with HIV infection, in keeping with prior research, and in women with a history of childhood trauma (separately).

Hypothesis 2: a synergistic relationship between HIV and a history of trauma would be evident. Therefore, the study hypothesized that neurocognitive differences would be evident in the dually affected group (women who are both HIV-positive and victims of childhood abuse). This synergistic relationship with respect to impact on neurocognition has not been previously documented.

1.4 *Overview of chapters*

The second chapter provides an overview of the NeuroAIDS literature conducted worldwide. It specifically outlines the neurocognitive literature conducted in non-African countries, African countries, and South Africa. It focuses on studies conducted in HIV-infected individuals and individuals who have experienced early life or adult trauma.

The third chapter outlines the methods utilised in the present study, including the study design, the selection and categorisation of study participants, data collection instruments, and data analysis procedures. This chapter also includes a section on HIV clade sequencing and laboratory findings based on blood samples collected.

The chapter thereafter discusses the selection of the neurocognitive battery utilised in the present study. It also includes psychometric properties and details on normative data for these tests.

The fifth chapter provides a presentation of the neurocognitive findings of the present study. In order to address the supplementary study aim of mental health outcomes, this chapter also comprises a systematic review which was conducted and prepared for submission to an internationally accredited journal. The manuscript focuses on the mental health outcomes in HIV-infected individuals with a history of childhood maltreatment. Both psychiatric sequelae and neurocognitive impairments are common in victims of childhood trauma (Afifi et al., 2008; Choi et al., 2009; Johnson, 2004; Kaplow & Widom, 2007; Kessler et al., 2010; Majer et al., 2010; Palmer et al., 1997). Mental health and neurocognitive deficits are closely inter-linked, highlighting the importance of providing an overview of both these areas.

The sixth chapter provides a discussion and interpretation of the results found in the present study. It also includes a summary of principal findings, contributions to knowledge gaps and limitations of the present study.

The final chapter provides a conclusion, implications for practice, and directions for future research.

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BACKGROUND

2.1 *Introduction*

The following chapter provides an overview of key literature pertaining to the fields of NeuroAIDS and trauma. To begin with, the most recent global and local HIV/AIDS statistics are reported. The phenomenon of gender-based violence is discussed and studies reporting early life and adult trauma statistics are presented. Thereafter, various important discussions are presented regarding the central nervous system effects of HIV/AIDS, challenges with neuropsychological testing, and findings from previous studies assessing HIV-related neurocognitive outcomes. These findings are divided into the developed world, low to middle income countries outside of Africa, African countries, and then finally South Africa. Thereafter, the effects of trauma on the central nervous system are discussed and results from trauma focused neuropsychological studies are reported. The effects of depression and alcohol consumption are also briefly discussed. The constituent discussions presented in this chapter are pertinent to the field of neuropsychology and inform the topic of this dissertation overall.

2.2 *Global HIV/AIDS statistics*

According to the Joint United Nations Programme on HIV/AIDS (2010), an estimated 33.3 million individuals worldwide were living with HIV/AIDS by the end of 2009. Of these people living with HIV/AIDS, 2.6 million people globally were newly infected with HIV in 2009. Moreover, 1.8 million people globally died of AIDS in 2009 (UNAIDS, 2010).

Of all the people living with HIV/AIDS worldwide, an estimated 68% or 22.5 million live in Sub-Saharan Africa (UNAIDS, 2010). Moreover, according to these data, 1.8 million adults and children were newly infected and 1.3 million adults and children died from AIDS in 2009 in this region (UNAIDS, 2010). It is clear from these statistics that Sub-Saharan Africa carries the greatest burden of the pandemic (UNAIDS, 2010).

2.2.1 *HIV/AIDS in Southern Africa*

Results from the South African Department of Health Study indicate that the prevalence rate of HIV among pregnant women attending antenatal clinics across all nine South African provinces was 29.4% in 2009. The national HIV prevalence in the general population (aged 15-49 years) was 17.8% in 2009. In the Western Cape, the prevalence rate was estimated at 16.9%, with a prevalence of 17.9% in the Cape Town metropole region specifically. The overall provincial prevalence rate increased from 15.3% in 2007 to 16.9% in 2009 (Department of Health, 2010). It is estimated that 5.63 million adults and children were infected with HIV and AIDS in 2009. Of these, 3.3 million were females. The HIV prevalence in females aged 30-39 has increased substantially (6.0%) since 2006, with 29.3% in 2006 to 32.4% in 2008 and 35.4% in 2009 (Department of Health, 2010). An estimated 1.58 million South Africans aged 15 and older were in need of antiretroviral treatment in 2009 (Department of Health, 2010). Moreover, the report estimated 314 000 AIDS deaths in South Africa in 2009. It is clear that women bear the brunt of this disease. A women's vulnerability is largely attributable not only to biological factors but also to socio-economic inequalities.

2.3 *Gender-based violence and childhood trauma*

Gender-based violence (GBV) is a common phenomenon in countries where the prevalence rate of HIV is also high. GBV has been defined as a multifaceted phenomenon and can include physical, sexual and emotional violence and deprivation or neglect (Andersson et al., 2008). Studies conducted in developing countries such as South Africa and other African countries have reported high rates of GBV in both adults and children. This includes intimate partner violence (IPV), rape, and childhood abuse (Andersson et al., 2008; Jewkes et al., 2001; Kalichman & Simbayi, 2004).

Many definitions of childhood trauma exist. However, for the present study, given that the Childhood Trauma Questionnaire (Bernstein et al., 2003) was used to retrospectively assess childhood trauma, the trauma definitions provided by Bernstein and colleagues were adhered to. Bernstein et al. conducted an extensive review of the literature on child abuse and neglect. The CTQ is consequently a standardised measure, its factors were empirically derived, and it was validated against a structured interview for childhood trauma (CTI). According to Bernstein et al. (2003) sexual abuse is defined as “sexual contact or conduct between a child younger than 18 years of age and an adult or older person.” Physical abuse is defined as “bodily assaults on a child by an adult or older person that posed a risk of or resulted in injury.” Emotional abuse is defined as “verbal assaults on a child’s sense of worth or well-being or any humiliating or demeaning behaviour directed toward a child by an adult or older person.” Physical neglect is defined as “the failure of caretakers to provide for a child’s basic physical needs, including food, shelter, clothing, safety, and health care.” Emotional neglect is defined as

“the failure of caretakers to meet children’s basic emotional and psychological needs, including love, belonging, nurturance, and support.” (Bernstein et al., 2003).

There exists a broad body of literature examining GBV and revictimisation in the developed world. In an overview of women, trauma and HIV, Wyatt, Myers, & Loeb (2004) state that one out of every three girls is sexually abused by age 18 in the United States. High prevalence of childhood emotional (51.9%), physical (51.1%), and sexual (41.6%) abuse has been reported in HIV-positive individuals (Walton et al., 2011). However, few studies have assessed GBV in South Africa. Among the studies that have assessed this, high rates of GBV and revictimisation have been reported in South African women. Dunkle et al. (2004) collected data from 1395 women aged 16-44 years attending antenatal clinics in Soweto, South Africa. 55.5% of the sample reported physical/sexual partner violence, with 42.8% of these women reporting more than one incident. Adult sexual assault by non-partners was evident in 7.9% of the women. Child sexual assault was reported in 8.0% of the sample, with 7.3% of the women reporting forced first intercourse (Dunkle et al., 2004). A high rate of adult revictimisation was evident in those women who reported a history of child sexual assault, with 74.8% reporting physical/sexual partner violence and 15.6 reporting adult sexual violence by a non-partner (Dunkle et al., 2004). Similarly, Jewkes, Levin, Mbananga, & Bradshaw (2002) report on findings from the 1998 South Africa demographic and health survey. In a nationally representative sample consisting of 11 735 women aged 15-49 years, 153 of these women had been raped (forced or persuaded to have sex against their will) before the age of 15 years. It was also found that the largest group of perpetrators (33%) was school teachers

(Jewkes et al., 2002). Jewkes, Dunkle, Nduna, Jama, & Puren (2010) sought to describe the prevalence of adverse childhood experiences in a rural sample of South African youth aged 15-26. A total of 1367 males and 1415 females were recruited from 70 rural South African villages. High rates of adverse childhood experiences were documented among men and women before the age of 18. The adverse childhood experiences in women and men were as follows: physical punishment (89.3% and 94.4%), physical hardship (65.8% and 46.8%), emotional abuse (54.7% and 56.4%), emotional neglect (41.6% and 39.6%), and sexual abuse (39.1% and 16.7%). Incident HIV infections were more common in women who had experienced emotional abuse, sexual abuse, and physical punishment, respectively. Moreover, emotional neglect among women was significantly associated with depression, suicidality, alcohol abuse, and incident HSV2 (herpes simplex type 2 virus) infections (Jewkes et al., 2010).

Many studies have investigated the link between adverse childhood experiences such as physical and/or sexual abuse and HIV risk. The experience of childhood trauma may increase HIV infection risk indirectly by increasing high-risk behaviors or by interfering with HIV prevention choices (Arriola, Loudon, Doldren, & Fortenberry, 2005). For example, many of the outcomes associated with childhood trauma place individuals at increased risk of contracting HIV through behaviours such as transactional sex, unprotected sex, inability to negotiate condom use, alcohol and/or drug abuse, early onset of sexual activities, and multiple sex partners (Cohen et al., 2000; Meade, Kershaw, Hansen, & Sikkema, 2009; Mimiaga et al., 2009; Mosack et al., 2010; Wilson and Widom, 2008). In a recent study, Senn and Carey (2010) investigated adult sexual risk

behaviour in women with histories of childhood maltreatment. The sample included 414 women and results suggest that childhood sexual abuse (CSA) was uniquely associated with adult sexual risk behaviour. CSA was the best predictor of adult sexual risk behaviour above all other forms of maltreatment (physical and psychological abuse and neglect).

In addition, childhood trauma may directly increase the risk of HIV infection through sexual abuse. Injury and the tearing of tissue resulting from sexual violence may increase the likelihood of HIV infection (Johnson, 2004). However, most studies have been of a cross-sectional nature and in turn, temporal relationship and causality have been questioned. Jewkes et al. (2010) conducted a prospective cohort study assessing whether intimate partner violence (IPV) and relationship power inequity increased the risk of incident HIV infection in 1099 South African women. The study involved a longitudinal data analysis from a previously published cluster-randomised controlled trial undertaken in the Eastern Cape province of South Africa in 2002-2006. The women were aged 15-26 years, were HIV-negative at baseline and had at least one additional HIV test over 2 years of follow-up. The results demonstrated that 128 women acquired HIV during 2076 person-years of follow-up, which translates into an incidence of 6.2 per 100 person-years). Of the 325 women with low relationship power equity, 51 acquired HIV, compared with 73 of 704 with medium or high relationship power equity (Jewkes et al., 2010). 253 women reported more than one episode of IPV, of which 45 acquired HIV. The population attributable fractions were 13.9% for relationship power equity and 11.9% for IPV, respectively (Jewkes et al., 2010). The results support the hypothesis that

exposure to sexual and physical partner violence and gender power inequity in relationships at baseline predict incident HIV infections over 2 years of follow-up and therefore provides evidence for increased risk of HIV infection in young South African women who have experienced abuse. The results of this study highlight the need for HIV interventions specifically focusing on gender issues. Current interventions tend to be dominated by promotion of male condom use and more recently male circumcision, thereby providing little help to vulnerable women and children (Jewkes et al., 2010). Increased attention needs to be directed to how trauma may contribute to HIV risk and disease symptoms (Wyatt et al., 2004).

2.4 *HIV infection and the brain*

HIV not only invades the immune system but also the central nervous system (CNS) and is capable of penetrating the blood-brain barrier (BBB) early in the course of infection (Woods et al., 2009). Risk for a significant brain involvement is highest in the more advanced disease stages but subtle changes are also evident in medically asymptomatic individuals (Heaton et al., 1995). Increased impairments in the brain have been documented at each stage of the infection (CDC, 1993), with mild impairment evident in those in the medically asymptomatic stage of infection (Heaton et al., 1995). HIV is also frequently associated with structural and functional brain abnormalities. Frequent brain complications of HIV-1 infection include brain atrophy, dendritic loss, and neuronal injury (Heyes et al., 2001). Prior neuroimaging research has shown both morphological and brain metabolite abnormalities in HIV-infected individuals (Everall et al., 1999; Grant et al., 1987; Jernigan et al., 1993; Heyes et al., 2001; Schweinsburg et al., 2005).

More recently, diffusion tensor imaging (DTI) studies have been conducted in HIV-infected individuals. DTI is a relatively new technique used to measure white matter integrity using metrics such as fractional anisotropy (FA). DTI studies have suggested more sensitivity than conventional magnetic resonance imaging (MRI) methods in detecting subtle white matter abnormalities in infected persons. For example, abnormal FA was evident in the white matter of the frontal lobes and internal capsules of HIV patients (Pomara, Crandall, Choi, Johnson, & Lim, 2001). A more recent DTI study investigating HIV apathy in South African individuals revealed changes in white matter tracts in the medial prefrontal cortex (Hoare et al., 2010).

2.5 *HIV and neurocognition*

HIV can be highly neurovirulent and once in the CNS, it is frequently associated with neurocognitive disorders. In diagnosing and categorising HIV effects on the CNS, neuropsychological (NP) assessments remain the most important tools. This is especially the case in resource-limited settings, where modern neuroimaging technology is often unavailable (Robertson, Liner, & Heaton, 2009). Neurocognitive disorders are dependent on HIV disease stage and range from less severe to its worst form, HIV associated dementia (Grant, 2008). Collectively, these disorders are referred to as HIV-associated neurocognitive disorders (HAND). The most recent diagnostic nomenclature of HAND defined by the American Academy of Neurology (ANN) includes three syndromes, namely: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV associated dementia (HAD) (Antinori et al., 2007). According to Grant (2008), 30-60% of infected individuals manifest at least mild neurocognitive

disturbances. An individual would be diagnosed with ANI provided they demonstrate impairment in two or more cognitive domains. Diagnoses of MND and HAD require that the individual demonstrate impairment in two or more cognitive domains that results in disturbances of instrumental activities of daily living (IADLs) such as financial management, medication adherence, driving and employment (Woods et al., 2009). HAD is more common in late stages of infection and as can be expected, is associated with more pervasive and profound impairments (Grant, 2008). It has been estimated that the prevalence rates of HAD fall between 5% and 15%. Moreover, with increased use of combination antiretroviral therapies (cART), the incidence of HAD has declined as much as 50% (Sacktor et al., 2001). Although any cognitive ability can be compromised, it has been suggested that some are more common than others in HAND (Grant, 2008). Memory disturbances in particular tend to be most prominent, with individuals displaying impairments in learning and retrieval of information. Psychomotor slowing, disturbances with executive functions, and problems with attention are also frequent (Grant, 2008).

2.6 *Cross-cultural neuropsychological testing: challenges and developments*

Most neuroAIDS research to date has been conducted in developed countries such as the U.S., Europe, and Australia. Very little is known about the NP complications of HIV in the developing areas of the world (Heaton et al., 2008). Conducting NP assessments in resource-limited settings can be very challenging. The overwhelming disease burden in countries such as sub-Saharan Africa can confound the identification of HIV effects on the CNS, especially given the comorbidity of other diseases such as tuberculosis, hepatitis and malaria. These diseases have their own CNS effects (Robertson et al., 2009).

Moreover, justifying studies of this nature without some direct benefit to participants can be difficult, especially when funding is limited and when so many people are in need of HIV treatment. (Robertson et al., 2009). Other challenges include participant recruitment and retention, especially in cases where study participants are required to travel long distances or compromise work for participation. Finally, the lack of neurological and neuropsychological expertise in many developing countries also presents a challenge (Robertson et al., 2009).

“An even more fundamental question is whether Western NP tests will be valid in developing countries, where the people have very different educational, cultural, and linguistic backgrounds to those in the U.S., Europe and Australia.” (Heaton et al., 2008). In order to determine whether an HIV-infected individual is impaired in performance requires the availability of data gathered from large groups of healthy control subjects (i.e. norms). These subjects should not have any clinical condition known to influence the functioning of the brain (Grant, 2008). Although the process of norming has progressed, this still remains a major challenge in NP testing, especially in the developing world. It is imperative that norms take into account demographic variables known to influence test performance such as age, education, gender, and cultural factors. As discussed in Cherner et al. (2007), the general literature shows that both verbal and non-verbal cognitive tests are significantly influenced by demographic factors, with education and/or illiteracy playing a significant role (Ardila, 1995; Byrd, Jacobs, Hilton, Stern, & Manly, 2005; Manly et al., 1999). It has been suggested that performance based tasks specifically decline with advanced age. Therefore in determining whether a person with HIV may be

impaired due to their illness, one needs to consider the age of that person and select age equivalent norms (Grant, 2008).

Similarly, the effects of education are as noteworthy as that of age. Although non-verbal tests can also be affected by education, the most education sensitive tasks are those involving vocabulary, information, arithmetic, and comprehension (Grant, 2008). This highlights the challenge of NP testing in persons with low education levels or poor quality of education. In the United States, education until the age of 16 is compulsory, making normative studies representing the lowest levels of education (i.e. less than 9 years) very challenging and scarce (Cherner et al., 2007). The majority of NP tests have been normed to populations who are traditionally agreeable to research, such as university students or white persons of a higher socio-economic status. In turn, these norms may not display significant education effects and may result in the overdiagnosis of impairments in persons with low education levels (Cherner et al., 2007).

Therefore, applying these NP methods to developing countries where education levels may be lower or the quality of education poorer could confound the interpretation of test results. Culture, which includes race, ethnicity, and native language, also plays a prominent role on NP performance. For example, in the United States, worse test performance among African Americans has been observed in comparison to white persons with similar age and education levels (Manly, Jacobs, Touradji, Small, & Stern, 2002). Although all participants in this study had equal levels of education, Manly et al. (2002) suggest that quality of education may also play a prominent role. Therefore, the

development of African American norms for commonly used NP tests was necessary in order to decrease the over diagnosis of impairments in blacks living with HIV (Grant, 2008). Individuals from other cultural backgrounds may also perform worse on NP measures. For example, the degree of acculturation may influence test performance (Manly et al., 1998). Moreover, variable literacy in English may have a profound impact on test performance (Grant, 2008).

In light of these challenges, the need to develop standardised NP measures that are comparable and relevant in international settings has received increasing attention. Efforts have been made and continue to be made in translating and norming commonly used NP tests in HIV populations internationally (Cysique et al., 2007; Heaton et al., 2008; Kanmogne et al., 2010). Studies have been conducted in developing countries such as Africa, India, and China. The work conducted in China has demonstrated that US norms could be applied to modified versions of NP tests in China. Similar prevalence, severity, and patterns of impairment to Western studies were observed (Cysique et al., 2007; Heaton et al., 2008). The findings of these few studies conducted in developing countries will be discussed later in this chapter.

2.7 Neurocognitive effects of HIV infection in the developed world

A broad range of studies assessing the impact of HIV on the CNS have been conducted in the developed world, reaching as far back as 1987 (Grant et al., 1987). The most recent research is that of CHARTER (CNS HIV Antiretroviral Therapy Effects Research). It is an ongoing cohort study with over 1500 participants (Heaton et al., 2010; Heaton et al.,

2011). In 1995, Heaton et al. (1995) examined NP effects of the different successive stages of HIV infection. This study found increased rates of impairment at each stage of infection. Similarly, the CHARTER study found that neurocognitive impairment remained most common among people with a history of more severe HIV disease (Heaton et al., 2011). Woods, Moore, Weber, & Grant (2009) have discussed the cognitive profile of HAND in the developed world. The most affected cognitive domains reported (including longitudinal studies) are attention and working memory, learning and memory, motor skills, psychomotor speed, information processing, and executive functions (Grant et al., 1987; Heaton et al., 1995; Saykin et al., 1991; Tozzi et al., 2005).

The aim of the CHARTER study was to investigate the current prevalence of HAND in a large sample of individuals. A later study incorporating CHARTER data assessed HAND in pre-cART (combination antiretroviral therapies) and cART eras. 1555 HIV-infected adults in the cART era were recruited from 6 university clinics across the U.S. Results revealed that 52% of individuals were cognitively impaired. Three levels of comorbidity burden were also looked at (i.e. minimal to severe non-HIV risks for NP impairment). Higher rates of NP impairment were evident in groups with greater comorbidity burden (40%, 59%, and 83%). For the HAND diagnoses (ANN; Antinori et al., 2007), 33% met criteria for ANI, 12% for MND, and only 2% for HAD. Among the 843 participants with minimal comorbidities, history of low nadir CD4 cell count was a strong predictor of cognitive impairment. Compared with the remaining subsets (47%), the lowest impairment rate (30%) on cART was evident in those with suppressed plasma viral loads and nadir CD4 cell counts ≥ 200 cells/mm³. The study findings highlight that milder

forms of NP impairment remain predominant, even among those receiving cART with minimal comorbidity burden (Heaton et al., 2010).

It is largely unknown what impact cART has on HAND. A follow-up study examined impairment rates and predictors of impairment for the pre-cART (1988-1995) and cART eras (2000-2007). A total of 857 participants from the pre-cART era and 937 from the cART era were included. As previously demonstrated in the pre-cART era (Heaton et al., 1995), the CHARTER findings also provide evidence for increased impairment rates with successive disease stages, A, B, and C (CDC, 1993). Impairment rates include 25%, 42%, and 52% in the pre-cART era and in the cART era, 36%, 40%, and 45%, respectively. In the CDC-A (medically asymptomatic stage), NP impairment was more common in those on cART. A low nadir CD4 cell count predicted impairment in both eras. In the pre-cART era, degree of current immunosuppression, estimated duration of infection, and viral suppression of treatment in cerebrospinal fluid (CSF) were associated with impairment. Patterns of NP impairment were also different in both eras. In the pre-cART era, more deficits in the domains of motor skills, cognitive speed, and verbal fluency were evident. However, in the cART era, greater impairment in the domains of memory (learning) and executive functions were evident. The study findings highlight that mild NP impairment is common in all stages of infection, despite the use of cART. Moreover, the association of impairment with nadir CD4 across both eras suggests that earlier initiation of treatment may facilitate the prevention of HAND. Therefore, the timing of antiretroviral therapy (ART) initiation is of importance and should be closely examined in future clinical trials (Heaton et al., 2011).

The samples vary in all studies conducted in the developed world. However, from a recent review, it is clear that women have been under-represented in NP studies of HIV.

According to Maki and Martin-Thormeyer (2009) only 6 all-female case control studies have been conducted to date. All six studies were cross-sectional and compared HIV-positive and HIV-negative women. Of these studies, one did not find any significant differences in NP performance between infected and uninfected women (Stern et al., 1998). However, this finding was attributed to the NP battery utilised which may not have been adequately sensitive in the sample of asymptomatic women and to a small sample size. An increased risk for NP impairment was associated with psychological distress and older age in one study (Richardson et al., 2005). In another study, NP impairment was only evident in women with AIDS (Mason et al., 1998). Deficits were evident in the domains of psychomotor speed, verbal learning, and verbal recall. These deficits were not seen in the other groups (controls and asymptomatic infected women). Similarly, HIV-positive serostatus was a significant predictor of psychomotor speed in another study. Alcohol use and education were strong predictors of psychomotor slowing in this sample (Durvasula, Miller, Myers, & Wyatt, 2001). In another study, deficits in HIV-positive women were most evident on two measures of psychomotor speed. HIV-infected women performed worse than HIV-negative women (Richardson et al., 2002). The last study reported significantly worse performance on a measure of learning and delayed recall (HVLT-R) among infected women compared with controls (Maki et al., 2009). Moreover, alterations observed in HIV-positive women in an encoding and retrieval task (functional MRI) were associated with worse verbal memory.

In conclusion, the studies reviewed by Maki and Martin-Thormeyer (2009) demonstrate significantly higher rates of NP impairment among HIV-positive women compared to uninfected women, regardless of symptom status and with or without an AIDS diagnosis. Collectively these studies suggest that impairment is most common in the ability domain of psychomotor speed (Maki and Martin-Thormeyer, 2009).

2.8 *Neurocognitive effects of HIV infection in the developing world*

As discussed earlier in this chapter, very few studies assessing the neurocognitive effects of HIV infection have been carried out in the developing world. Given the challenges of cross-cultural NP investigations, there is a paucity of research in countries such as South Africa. Within different regions of the world, different subtypes (clades) of HIV exist. Each clade influences disease progression (Kiwanuka et al., 2008) and it has been suggested that these influences may vary between the different viral clades (Clifford et al., 2007). Clade B is predominant in the Western world where the majority of HIV NP studies have taken place. However, research has established that the dominant viral clade in South Africa is C (Sacktor et al., 2007). A study assessing viral clades in South Africa suggested that 89% of infected individuals in Cape Town are infected with clade C virus (Jacobs et al., 2009). Given the gross underrepresentation of studies in developing parts of the world, the clade specific manifestations of HIV in the brain are largely unknown.

2.8.1 *Neurocognitive effects of HIV infection in low to middle income countries outside Africa*

One of the very first studies to carry out a cross-cultural NP investigation was the WHO Neuropsychiatric AIDS Study (Maj et al., 1994). The study investigated neurocognitive functioning in HIV-negative, and asymptomatic and symptomatic seropositive individuals in five countries: Germany, Brazil, Kenya, Zaire (Congo), and Thailand. A Western developed NP battery assessing various ability domains was translated and successfully administered in all five languages. The results suggest increased risk of subtle cognitive disturbances in asymptomatic seropositive individuals. Increased global NP impairment was evident in asymptomatic HIV- positive individuals in Brazil and Zaire, compared to controls. An increased NP impairment was evident in symptomatic infected individuals compared to the controls in all sites (Maj et al., 1994). Moreover, among asymptomatic seropositive individuals, a significant education effect on NP performance was evident. In the two African countries, low education had a significant effect on NP performance in asymptomatic seropositive participants. Results also revealed increased functional impairment in IADL among symptomatic seropositive individuals compared with asymptomatic seropositive and HIV-negative individuals across all sites (Maj et al., 1994).

Research has suggested that clade C infections predominate in India (Gupta et al., 2007; Yepthomi et al., 2006). However, there is a paucity of research investigating the neurocognitive effects of this viral clade. Yepthomi et al. (2006) translated a battery of NP measures into two widely spoken languages in Southern India. The battery was

administered to 30 ART naïve seropositive individuals (median CD4 count of 97) and 30 age and education matched controls. Results demonstrated worse performance on tests of verbal and visual memory, motor skills, and cognitive flexibility/abstraction among seropositive individuals with low CD4 counts. Moreover, 56% of the patients with advanced disease demonstrated impairment in two cognitive domains (Yeptomhi et al., 2006).

Similarly, Gupta et al. (2007) assessed NP deficits in 119 ART naïve adults infected with clade C HIV. Results revealed that among the seropositive individuals, 60.5% demonstrated mild to moderate cognitive deficits in the domains of fluency, working memory, and learning and memory (Gupta et al., 2007). Moreover, it was found that the group of seropositive individuals with greater immunosuppression had greater impairment in visual working memory than individuals with better immune functioning (Gupta et al., 2007). It was found that 51% of HIV-positive patients demonstrated impairments in two cognitive domains. This finding is similar to that of Yeptomhi et al. (2006), who reported impairments in 56% in two cognitive domains in South India. It is worth noting that these findings are similar to those reported in ART naïve individuals infected with clade B virus in the Western world. This finding may suggest that the neurotoxicity is similar to that of viral clade B, however, further research is needed to establish this.

Cysique et al. (2007) conducted a pilot study comparing NP effects of HIV infection in Anhui China and the U.S. A NP battery commonly used in the U.S. was translated and

adapted to be culturally suitable to the Chinese population. The battery was administered to 28 HIV-positive individuals and 23 matched controls. In the U.S., the battery was administered to 39 HIV-positive and 31 control subjects. In the China group, HIV-infected individuals performed worse than control subjects on all NP measures, regardless of whether raw data or domain scaled scores were used in analyses. Results revealed medium HIV effect sizes for raw and scales scores (range .42 to .65) and the global scaled score (.55), respectively (Cysique et al., 2007). Significant country effects were also evident on two ability domains, namely: verbal fluency and speed of information processing, with the U.S. group obtaining higher scores on these domains. However, there were no significant country effects on the global NP score or on the remaining five NP domain scores. Moreover, there were no interaction effects between HIV and country. The results therefore suggest a robust and comparable HIV effect on NP performance in both countries (Cysique et al., 2007).

The second study conducted in China investigated the neurobehavioural effects of HIV infection in former plasma donors in rural China. This study was the first large scale attempt at estimating HAND within a major risk group in the rural part of Anhui province. A NP battery commonly used in the developed world was administered to 203 HIV-positive individuals and 198 former plasma donors. Among HIV-positive individuals, 46% were also infected with HCV. Demographically corrected norms (N = 141) were developed based upon individuals free of both infections. NP impairment was found in 34.2% of HIV-infected individuals, 39.7% of the co-infected individuals, and 12.7% of the uninfected control subjects. Results also revealed that individuals with

AIDS were more impaired (43%) than non-AIDS individuals (29%). Moreover, when examining all groups together, participants with NP impairment reported more cognitive complaints and decreased independence in everyday functioning (Heaton et al., 2008).

Following this, Cysique et al. (2010) examined cognitive decline over one year among HIV- infected former plasma donors in rural China. The sample consisted of 192 HIV- positive and 101 matched controls. Individuals on cART increased from baseline (56%) to follow-up (60.9%). Results suggested that 53 (27%) HIV-positive individuals developed significant cognitive decline compared with 5 (5%) HIV-negative individuals. AIDS status, lower nadir CD4 cell count, and worse processing speed predicted cognitive decline at baseline. At follow-up, cognitive decline was associated with lower current CD4 cell count and failure of viral suppression on cART. Cognitive decline was also associated with increased independence in activities of daily living (Cysique et al., 2010).

2.8.2 Neurocognitive effects of HIV infection in African countries

Wong et al. (2004) assessed neurological complications among 53 HIV-positive and 31 HIV- negative individuals in Uganda. The International HIV Dementia Scale (IHDS) and tests of verbal memory, psychomotor speed, motor skills, and functionality were administered. Result revealed that 54% of the sample had a CD4 count of less than 200 cells/mm³. HIV-infected individuals had greater functional impairment, impaired performance on the IHDS, verbal memory task, and motor skills task in comparison to HIV controls (Wong et al., 2004).

Following this, Sacktor et al. (2006) conducted a longitudinal study in Uganda assessing the effects of highly active antiretroviral therapy (HAART) on cognitive performance. The study evaluated NP test performance and functional performance in HIV-positive individuals after 3 and 6 months of HAART. Results from 23 patients revealed the mean CD4 count improved from 71 to 161 (3 months) and 222 (6 months), respectively. Moreover, improvements were evident in the HIV dementia stage, functionality, and in tests of psychomotor speed, verbal memory, and executive functions after 3 and 6 months of HAART (Sacktor et al., 2006). These results provide evidence for an improvement in neurocognitive and functional impairment in patients receiving HAART in sub-Saharan Africa.

Robertson et al. (2007) assessed NP performance in 110 HIV-positive patients in comparison to 100 HIV-negative control subjects in Uganda. Although efforts were made to match the two groups, the control group was younger, more highly educated, and contained fewer females. Results of ANCOVAs (covaried for education) revealed that the HIV-positive individuals performed worse on the mean NP z-score and on all individual tests except for those measuring motor skills. Significant group differences were evident on measures of attention, verbal learning and memory, speed of information processing, and executive functioning (Robertson et al., 2007). The authors conclude that the findings from this region where clades A and D predominate are in keeping with findings in the Western world where clade B is mostly found (Robertson et al., 2007).

Contrasting results were found in a study conducted in Ethiopia (Clifford et al., 2007). The sample consisted of 73 HIV infected untreated individuals and 87 HIV-negative controls closely matched on demographic characteristics. All patients were assessed for cognitive and motor functioning. No significant group differences were evident for the timed gait, grooved pegboard, task learning, or animal naming tasks. However, poorer performance on the finger tapping speed in the dominant hand was evident for HIV-positive individuals and this was significantly associated with HIV viral load (Clifford et al., 2007). One limitation of this study was the limited test battery. However, a strength of this study was the closely matched groups on important demographic characteristics. Additionally, the authors suggest that the viral clade C (predominant in Ethiopia) may be less neurotropic than that of viral clade B. This possibility that clade C may have less neurotropism than clade B requires further investigation.

Lawler et al. (2010) conducted a pilot study to determine the prevalence of NP impairment in 120 HIV-positive individuals selected from an outpatient clinic in Gaborone, Botswana. The IHDS was used to assess NP impairment, using a cut-off score of 9.5. Performance on the IHDS was also compared with performance on tests of processing speed and verbal learning/memory. Results revealed that despite 97.5% of patients were on HAART, 38% met criteria for dementia on the IHDS. Moreover, a significant association between NP impairment and performance on the tests of processing speed and verbal learning/memory was evident. Age affected processing speed and performance on the IHDS. However, the level of education significantly influenced performance on all three cognitive measures. The effects of depression and

CD4 counts were also investigated but results revealed no significant association between these variables and NP impairment (Lawler et al., 2010).

In Cameroon, Kanmogne et al. (2010) conducted a pilot study assessing HAND in 44 HIV-infected and 44 matched uninfected individuals. A battery of 19 NP measures was administered to the sample to determine the NP effect of HIV infection on seven ability domains. Results of the pilot study revealed that HIV-infected individuals performed worse overall, when looking at the global mean z score. Moreover, HIV-positive individuals performed worse on the domains of speed of information processing, psychomotor speed, working memory, and executive functions. In those individuals with AIDS, performance was worse compared to those with less advantaged disease (Kanmogne et al., 2010).

2.8.3 *Neurocognitive effects of HIV infection in South Africa*

In looking at South Africa specifically, there is a paucity of research assessing NP performance and impairment in HIV-infected individuals. Three published studies have assessed HAND to date. As discussed earlier, many studies have utilised the IHDS to screen for dementia. However, there is an urgent need to more accurately test for HAND in South Africa. The IHDS may be of limited utility due to varying sensitivity and specificity. The use of NP tests is more suitable, but norms are not readily available (Singh et al., 2010).

Singh et al. (2010) sought to derive normative scores for two commonly used NP tests, namely the Trail-Making Test (parts A and B) and the Digit Span Test (forward and backward). In order to assess memory and recall, the memory component of the IHDS scale was used. The study demonstrated that these three tests can easily be administered in ART clinics in South Africa. The majority of the participants were female (84.9%). The average age was 28.5 years and 10 years of education. Results demonstrated that older adults performed worse. There were also gender effects but these were not uniform across all the tests. Women performed better than men on the Trails B and backward Digit Span task. This study is the first in South Africa to recommend a brief and easily administered battery of standardised NP tests, while providing locally relevant population norms to assess HAND in this country (Singh et al., 2010).

Joska, Fincham, Stein, Paul, & Seedat (2010) examined the clinical correlates of HAND in 536 patients attending HIV clinics in Cape Town, South Africa. All participants were receiving care at the clinics. The mean age of the participants was 33.98 years and 73.3% were female. The majority of the sample (54.9%) had an education level of greater than or equal to 10 years. 68.1% were Black and 27.8% were of mixed race (Coloured), with the majority being Xhosa speaking (62.7%). The mean CD4 count was 273 cells/mm³, ranging from 2 cells/mm³ to 1433 cells/mm³. Less than half the sample (47.8%) was on ART. In order to screen for HAND, the HIV Dementia Scale (HDS) was used. Ganasen, Fincham, Smit, Seedat, & Stein (2008) have demonstrated that the HDS is a sensitive screening measure for frank dementia in ART settings in South Africa. The HDS demonstrated 80% sensitivity and 80% specificity in the abovementioned study. The

results of the study carried out by Joska et al. (2010) revealed 23.5% of cognitive impairment in the sample, using a cut-off of ≤ 10 on the HDS. It is worth noting that 35.8% reported alcohol abuse and 7.5% reported drug abuse. Moreover, 30.6% met PTSD caseness. Demographic and clinical variables such as older age, low education, PTSD and alcohol abuse among those with many months since diagnosis was associated with HAND. This study highlights the effects of HIV on the CNS and the need for routine screening for co-morbid mental illnesses (Joska et al., 2010).

Joska et al. (2010) conducted another investigation into HAND in patients commencing ART in Cape Town, South Africa. The sample consisted of 283 HIV-infected individuals attending primary health care facilities. Of the 283 individuals originally screened, 170 completed the full assessment. The mean age was 29.5 years and the majority were female (74%) and Xhosa speaking (89%). The mean education level was 10 years. The median CD4 cell count was 168 cells/mm³. A battery of commonly used NP tests sensitive to HIV effects in international settings was used to assess neurocognitive functioning. This battery was selected to make the findings comparable. The battery was adapted and translated to be locally suitable by local neuropsychologists. The battery consisted of tests from the following domains: attention, learning and memory, motor, psychomotor speed, executive functions, and language. In order to establish impairment, data from 51 HIV uninfected individuals were used to generate z-scores. The NP battery, and a neuromedical and functional assessment allowed the participants to be categorised into one of four HAND categories defined by the ANN (Antinori et al., 2007). These classifications were discussed previously in this chapter. They include: no impairment,

ANI, MND, and HAD. Results revealed that more than half (94) had at least mild peripheral neuropathy. Of the 170 individuals, 43 (25%) met criteria for HAD, while 72 (42%) had MND, and 15 (9%) met criteria for ANI. A total of 40 (24%) individuals were cognitively unimpaired. Patients with HAD tended to have lower education, to be older, and to have lower CD4 cell counts. There seemed to be more men in the HAD group, however, this did not reach statistical significance. Multivariate analyses revealed that level of education and male gender were predictive of HAD. Lower CD4 cell count was not associated with HAD status, although a trend was evident. The study provides preliminary evidence for high prevalence of HAND in South Africa where HIV clade C is predominant (Joska et al., 2010).

2.9 *Trauma and the brain*

Just as HIV invades the CNS and results in significant brain involvement, an increasing number of studies have also identified stress-related structural, functional, and metabolite alterations. Research has demonstrated changes in the brains of individuals who have suffered adverse childhood events, such as abuse (e.g. Bremner et al., 1997; Bremner et al., 2003; Choi et al., 2009; Cohen et al., 2006; De Bellis, Keshavan, Spencer, & Hall, 2000; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Teicher et al., 2004; Vythilingam, Heim, Newport, & Miller, 2002) or intimate partner violence (e.g. Fennema-Notestine, Stein, Kennedy, Archibald, & Jernigan, 2003; Seedat, Videen, Kennedy, & Stein, 2005). These alterations include structural abnormalities in the hippocampus, temporal gyrus, fornix, limbic, basal ganglia, supratentorial cranial vaults, and corpus callosum regions. Functional abnormalities include failure of hippocampal

activation. Metabolite alterations include lower *N*-acetylaspartate/creatine ratio in the anterior cingulate, and higher anterior cingulate choline/creatine volumes.

2.10 *Trauma and neurocognition*

Prior research investigating stressful life events, acute stress, and PTSD has found evidence for impaired cognitive functioning. For example, there is evidence for deficits in memory and executive functions among individuals with PTSD (Clark et al., 2003; Jelinek et al., 2006; LaGarde, Doyon, & Brunet, 2010). Sources of PTSD in the aforementioned studies included mainly serious accidents and assaults. An association between small hippocampal volumes and cognitive impairment (memory deficits in particular) in subjects with PTSD has also been demonstrated (Bremner et al., 1995; Bremner, 2006; Heim and Nemerhoff, 2009). Sources of PTSD in the aforementioned studies included mainly combat related PTSD and childhood abuse. In a review of 19 studies, Horner and Hamner (2002) report impairment in attention or immediate memory (or both) in 16 studies assessing PTSD patients. The majority of studies focused on combat related PTSD, with only a handful (five studies) assessing non-combat related PTSD. Only one of the five studies focused on childhood abuse. Methodological problems such as comorbidity burden, substance abuse, and histories of neurological injury were present in many studies, thereby contributing to confounding. Isaac, Cushway, & Jones (2006) have reviewed studies reporting episodic memory impairments in PTSD patients and have also reported widely varying results. Bremner (1999) has suggested that excessive levels of cortisol released during severe stress may result in damage to the hippocampus and thereby cause memory impairments. Although some

studies have found evidence for neurocognitive deficits in individuals with PTSD, some studies have not (Twamley, Hami, & Stein, 2004; see reviews by Horner and Hamner, 2002; Isaac et al., 2006). Results, therefore, vary widely among PTSD studies conducted to date.

Studies examining the cognitive performance of individuals exposed to traumatic events early in life are limited and have, too, been inconsistent. In a study assessing sexually abused children, Palmer et al. (1997) reported profound impairment in intellectual development, language, and psychomotor speed. However, in two recent studies comparing trauma exposed and non-exposed children and adolescents, trauma exposure was not associated with poorer performance in intelligence (Saigh, Yasik, Oberfield, Halamandaris, & Bremner, 2006) or memory and learning (Yasik, Saigh, Oberfield, & Halamandaris, 2007). Moreover, in a study assessing verbal learning deficits among women with a history of childhood abuse, although traumatised women reported higher levels of psychological distress, they did not differ significantly in verbal learning compared to controls (Jelicic, Geraerts, & Merckelbach, 2008). On the other hand, Choi et al. (2009) investigated the brain involvement in young adults exposed to parental verbal abuse (PVA), which constitutes a form of emotional abuse. The study included 16 subjects, of which 12 were female. DTI revealed reduced FA in three regions of the brain in subjects with a history of high-level exposure to PVA. Verbal IQ and Verbal Comprehension Index (VCI) were assessed using the WAIS-III. Results revealed that reduced FA in the left superior temporal gyrus was significantly correlated with Verbal IQ and VCI in young adults exposed to PVA (Choi et al., 2009). Given the lack of

studies, Majer et al. (2010) sought to assess the association between childhood trauma exposure and cognitive function in healthy adults. The study was a pilot study with a sample of 47 healthy adults. The type and severity of childhood trauma was assessed using the CTQ. The results revealed that specific subscales on the CTQ were associated with cognitive function among these healthy adults. An association between the emotional abuse and impaired spatial working memory was evident. Moreover, the physical neglect subscale correlated with impaired spatial working memory. The results therefore provide evidence that emotional abuse and physical neglect may be associated with memory deficits in adults (Majer et al., 2010). The authors conclude that future prospective studies are required to provide more information on the causal relationship between childhood trauma and cognitive impairment.

Research has demonstrated an increased risk of HIV-related morbidity and mortality, and poorer cognitive functioning among individuals who have a history of childhood trauma, acute stress, and PTSD (Leserman et al., 2005; Leserman et al., 2007). Stressful life events have been shown to influence executive functions, attention, and processing speed in HIV-positive men (Pukay-Martin, Cristiani, Saveanu, & Bornstein, 2003). The sample in this study included HIV-positive and HIV-negative subjects, however, neurocognitive deficits were only evident in those trauma survivors who were HIV-positive. For HIV-positive subjects, negative life stressors were related to poor performance on measures of executive functions, attention, and processing speed. Positive life events resulted in better cognitive performance on these measures (Pukay-Martin et al., 2003).

2.11 *HIV, trauma, and neurocognition*

To my knowledge, there are currently no published studies investigating the additive effects of HIV and childhood trauma on the CNS in women. These constructs have been investigated separately as outlined earlier in this chapter, however, no studies have investigated the possible additive effects of HIV and trauma on the brain. As discussed, HIV has been shown to have a significant effect on the CNS. Research has also demonstrated similar stress-related effects on the brain. Therefore, women living with HIV/AIDS, who also have a history of childhood trauma, and/or acute stress or PTSD as an adult, may be especially vulnerable to psychiatric and neurocognitive dysfunction due to the additive or interaction effects of HIV and childhood trauma. Therefore, the impact of stress, more specifically childhood trauma, on the brain in the context of HIV remains mostly unclear. Given the high prevalence of these two conditions in South Africa, research in this area is warranted.

2.12 *Depression and alcohol abuse*

The mental health outcomes of HIV-infected individuals have been well documented to date. Research suggests a significant burden of mental illness in individuals living with HIV/AIDS, both globally and in the developing world. Mental illnesses documented in HIV-infected individuals include predominantly substance use, anxiety, and mood disorders (Evans et al., 2002; Lipsitz et al., 1994; Myer et al., 2008; Olley et al., 2003; Olley, Seedat, Nei, & Stein, 2004; Olley et al., 2005; Olley et al., 2006; The WHO World Mental Health Survey Consortium, 2004). Depression is the most comorbid psychiatric disorder found among HIV-positive individuals, with prevalence rates as high as 50%

(Ciesla and Roberts, 2001). Moreover, it has been suggested that HIV disease progression may be hastened by mental disorders such as depression and anxiety (Antelman et al., 2007; Boarts, Sledjeski, Bogart, & Delahanty, 2006; Farinpour et al., 2003; Leserman et al., 1999; Lesserman et al., 2007). Mental health symptoms in HIV infected individuals begin either shortly after the receipt of an HIV-positive diagnosis or during the course of the disease (Olley et al., 2006). This suggests that psychiatric sequelae may be associated with the receipt of a positive diagnosis or with other factors encountered during the course of the illness. Individuals infected with HIV often suffer from psychiatric disorders like depression and anxiety due to a number of reasons. Some of these reasons include: adjusting to an HIV diagnosis, living with a highly stigmatised chronic and life-threatening illness, anticipating and receiving news on disease progression, and witnessing the death of friends and family (Collins, Holman, Freeman, & Patel, 2006; Green & Smith, 2004; Myer, Seedat, Stein, Moomal, & Williams, 2009; Myer et al., 2009). The development of these disorders is also influenced by the direct effect that HIV has on the central nervous system (Myer et al., 2009). Similarly, research suggests the long-term mental health outcomes of childhood maltreatment include predominantly substance, anxiety, and mood disorders (Afifi et al., 2008; Kaplow and Widom, 2007; Kessler et al., 2010).

Given that psychiatric disorders are common among HIV-positive individuals and survivors of childhood trauma, comorbid depression and/or alcohol abuse may have independent or additive effects on the CNS. In HIV-negative individuals, depression has been shown to be associated with NP deficits in attention, learning and memory,

psychomotor speed, and executive functions (Woods et al., 2009). Although, the effect of depression on neurocognition in HIV has been researched, studies have failed to identify significant additive effects of depression and HIV on cognition (Grant et al., 1993).

In a study designed to investigate HIV-associated affective and cognitive disorders, Starace et al. (2002) found that the prevalence of cognitive impairment (17.9%) and of depressive symptomatology (15.5%) were prominent. In a recent study in Uganda, Nakasujja et al. (2010) investigated depression and cognition among HIV-infected individuals who were initiating HAART. The sample consisted of 102 HIV-infected individuals and 25 controls. The CES-D was administered to assess depressive symptomatology. The IHDS and a battery of NP measures assessed cognitive functioning. Results of the study revealed that higher depression scores on the CES-D (> 16) were evident in the HIV-infected group compared to matched HIV-uninfected controls. The HIV-infected individuals had higher likelihood of cognitive impairment than HIV-negative counterparts. Out of 102 HIV-infected individuals, 40 were identified with both depression and cognitive impairment. Castellon et al. (2006) assessed components of depression in HIV infection and their differential relationship to NP functioning. A total of 247 HIV-infected individuals completed a NP battery and the Beck Depression Inventory (BDI). A principal components analysis revealed three factors, namely: Self-Reproach (SR), Mood-Motivation Disturbance (MM), and Somatic Disturbance (SOM). Analyses assessing the relationship between NP functioning and each of these factors revealed that the MM factor was most associated with several ability domains. These domains included verbal memory, executive functioning, and motor

speed. The study suggests that specific items on depression rating scales may be more indicative of CNS dysfunction than others (Castellon et al., 2006). Depression has also been shown to uniquely predict everyday functioning among cognitively impaired HIV-positive individuals. Heaton et al. (2004) assessed the impact of NP impairment on everyday functioning among 267 HIV-infected individuals. Among the 267 HIV-positive individuals, 99 were classified as cognitively impaired. Deficits among those who were impaired included deficits in learning (68%), abstraction/executive functioning (54%), attention/working memory (53%), and motor functioning (47%). Results revealed that compared to unimpaired controls, those with NP impairment performed significantly worse on all laboratory measure of everyday functioning. Multivariate modeling revealed that impairment on the functional battery and depression were unique predictors of poorer treatment outcomes, reduced medication adherence, and everyday functioning. Therefore, the study provides evidence of an independent effect of depression on the level of everyday functioning among HIV-infected individuals (Heaton et al., 2004).

Earlier NP studies of alcohol dependence/abuse in the context of HIV were confounded by the inclusion of individuals who were dependent on multiple substances (Woods et al., 2009). However, it is now more recognised that heavy drinking and HIV may have adverse additive effects on cognition. Research has demonstrated evidence for an interaction effect between alcohol and HIV on NP functioning in the areas of selective attention (Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum, & Sullivan, 2005), verbal reasoning and auditory processing (Green, Saveanau, & Bornstein, 2004), and psychomotor speed (Durvasula, Myers, Mason, & Hinkin, 2006).

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METHODS

3.1 *Research design*

The present study was a cross-sectional descriptive study and utilized a quantitative methodological framework. The sample consisted of two case groups and two control groups. The present study was embedded within a larger prospective case-control study.

3.2 *Participants*

The sample comprised HIV-positive women with and without histories of childhood trauma and HIV-negative controls with and without histories of childhood trauma. The present study made use of convenience sampling. One hundred and thirty South African women were recruited from HIV clinics / infectious diseases units (IDUs) within primary health care facilities in the Boland, Khayelitsha, and Tygerberg Eastern health districts of the Western Cape region. A total of 8 primary health care facilities were recruited from. One hundred and forty seven women were initially screened, of which 130 had neurocognitive assessments. Their mean age was 29.6 (SD = 7.0, range 18 to 50 years). These community health facilities provide treatment for HIV and other sexually transmitted infections (STIs). The clinics also provide a voluntary counselling and testing (VCT) service to patients. Although some of these facilities are responsible for the administration of antiretroviral treatment (ARVs) to patients who are in need of such treatment, the majority (83.3%) of HIV-positive women included in the present study were ARV naïve, with only 15.5% of patients receiving antiretroviral treatment.

All HIV-positive women were receiving care and HIV medications through the respective clinics when they were recruited into the study. Their HIV status was confirmed through their clinic doctor/counselor. All control subjects were recruited once they had been for VCT and a negative status could be confirmed. A total of eight control subjects were recruited from their communities due to difficulties with recruitment from the respective clinics. In these cases, HIV serological testing was performed to confirm their HIV status. The blood was drawn by the study nurse and each subject participated in pre and post test counselling conducted by the study doctor. This HIV serology testing was conducted by the Department of Virology, University of Stellenbosch.

The following inclusion criteria were applied in the present study: (a) willing and able to provide written and informed consent, (b) between the ages of 18 and 65 years, (c) able to read and write English or Afrikaans at a minimum of the 5th grade level, (d) psychotropic-naïve, and (e) medically well enough to undergo neuropsychological testing.

Exclusion criteria for the present study included: (a) women with a current or past history of schizophrenia, bipolar disorder, or any other psychotic disorder as defined on the M.I.N.I.-Plus (Mini International Neuropsychiatric Interview), (b) current (12 month) history of substance or alcohol dependence or abuse, (c) women with significant head injury which was defined as a head injury resulting in loss of consciousness for more than 24 hours, (d) women with current seizure disorders of any cause, (e) control participants with current / chronic use of medication for a medical illness (e.g. hypertension, diabetes etc.), (f) history of opportunistic CNS (central nervous system) infections or neoplasms,

(g) a diagnosis of hepatitis, and (h) current use or use within the past month of any psychotropic medication.

A total of 6 women (4 HIV+ and 2 HIV-) reported previous head injuries. Four of these were open head injuries, of which three were due to motor vehicle accidents (MVAs) and one was due to domestic violence. Two women reported closed head injuries, one due to a MVA and one due to a fall. None of these women reported being unconscious or suffering from any subsequent sequelae.

All women (HIV+ and matched HIV- women) were categorised according to whether or not they met the criteria for childhood trauma using the Childhood Trauma Questionnaire Short Form (CTQ-SF) (Bernstein et al., 2003). Therefore, the four groups consisted of HIV-positive women with and without a history of childhood trauma and HIV-negative women with and without a history of childhood trauma. The five subscales of the CTQ-SF each consist of 5 items with scores ranging from 5 to 25. A sixth summary score assesses overall trauma with scores ranging from 25 to 125 with higher scores indicating higher levels of childhood trauma (score of 25-31 = no trauma, score of 41-51 = low to moderate, 56-68 = moderate to severe, and 73-125 = severe to extreme). Participants were categorised as having a history of childhood trauma if they had a score of 41 or higher on the CTQ-SF. The HIV-negative women were as closely matched to the HIV-positive women on variables such as age and education. Below is a breakdown of the number of participants recruited in each of the four groups.

Sample breakdown (N = 130)

	HIV-positive	HIV-negative
With childhood trauma	48	20
Without childhood trauma	35	27

3.3 *Procedures*

The present study formed part of a larger genetics and neuroimaging study running at the Department of Psychiatry, University of Stellenbosch. The larger study involves a prospective case-control study. The present study focused on the neurocognitive data derived from the baseline phase of the larger study. The protocol for the present study and the study as a whole was approved by the Health Research Ethics Committee (institutional review board) of the Faculty of Health Sciences, Stellenbosch University (reference number: N/07/07/153). Approval to recruit participants was also obtained from the chiefs of relevant hospitals and clinics, the Western Cape Department of Health, and City Health. The study preparations began in February 2008 and participants were screened and assessed from July 2008 to July 2010.

Participants were recruited by the researcher (research psychologist) and a research assistant. Moreover, doctors, nurses and counsellors at the relevant health facilities assisted with patient referrals. The study was explained by the research psychologist and/or the research assistant to individual participants, in a private setting. Potential participants were invited to take part and were informed of the following: (1) the nature and purpose of the present study, (2) any potential risks or benefits associated with

participation, (3) confidentiality and anonymity related to participation, (4) that participation was entirely voluntary, and (5) they could refuse participation at any time or withdraw anytime without any consequences. With their approval, participants were screened either face to face or telephonically. If inclusion criteria were met, a formal interview was scheduled. Participants were given the opportunity to ask questions and thereafter, were required to sign an informed consent form.

All assessments took place at the University of Stellenbosch. Participants were required to attend assessments on two separate occasions (no more than 7-9 days apart) in order to minimise fatigue. At the first visit, participants underwent the following procedures: (1) a physical examination, (2) recording of vital signs and a blood draw, (3) a neuropsychiatric interview using the Mini International Neuropsychiatric Interview, M.I.N.I.-Plus (Sheehan et al., 1998), and (4) completion of a battery of self-report instruments. The blood drawn from participants was for CD4 lymphocyte and viral load measurements and genetics assays for the parent study. The study nurse was responsible for the drawing of blood and the physical examination was performed by a resident doctor at the Department of Psychiatry. The National Health Laboratory Service (NHLS) situated at Tygerberg hospital were responsible for CD4 lymphocyte and viral load measurements. Genetic assaying for the parent study took place at the Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Stellenbosch University. The neuropsychiatric interview was conducted by the researcher (research psychologist). Moreover, all participants were monitored and assisted with the

completion of the self-report instruments by the researcher and a research assistant. The duration of the first visit was 2-2 ½ hours.

At the second visit participants underwent the following procedures: (1) a neuropsychological assessment using the HIV Neurobehavioral Research Center's [HNRC] international battery and (2) Magnetic Resonance Imaging (MRI) using the Siemens 3T Magnetom scanner housed at the Cape Universities Brain Imaging Center (CUBIC) at the Faculty of Health Sciences, Stellenbosch University. All neurocognitive assessments were conducted by the researcher who was trained and certified in administering the neurocognitive battery. Participants underwent the neuroimaging assessment as part of the parent study. The duration of the second visit was 3½ - 4 hours. Each participant received an amount of ZAR 150 cash as a travel reimbursement to the University. In addition, each participant received a shopping voucher to the value of ZAR 100 as a token of gratitude for taking part in the study.

3.4 *Instruments*

All interviews were administered in either English or Afrikaans. All self-report instruments and the neurocognitive battery were translated and back translated into Afrikaans.

A description and presentation of the psychometric properties of each instrument included in the present study is presented next.

3.4.1 *Demographics questionnaire*

A demographics questionnaire was created and included demographic information on age, education, ethnicity, home language, marital status, annual household income, and employment status.

3.4.2 *The MINI-International Neuropsychiatric Interview Plus (M.I.N.I.-Plus)*

The M.I.N.I. is a short structured diagnostic interview and was developed jointly by psychiatrists and clinicians to assess the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, APA, 1994) and ICD-10 (International Classification of Diseases) current and lifetime psychiatric disorders (Sheehan et al., 1998). The M.I.N.I. has an administration time of approximately 15 minutes and is useful in both clinical and research settings. The M.I.N.I. - Plus is one of the family interviews developed from the M.I.N.I. and takes approximately 45-60 minutes to administer. The M.I.N.I.-Plus requires limited training and was designed for use in research settings. The interview includes 23 disorders, including modules for somatization disorders. Two validation studies were conducted to test the validity of the M.I.N.I. and the agreement with the SCID-P (Structured Clinical Interview for the DSM-III, Patient version) and the CIDI (Composite Interview Diagnostic Interview). A version of the M.I.N.I. that included several lifetime diagnoses that are now confined to the M.I.N.I.-Plus was used in these validation studies. Good results were obtained when M.I.N.I. diagnoses were compared with both the SCID-P and the CIDI. Kappa values were good or very good for the M.I.N.I. diagnoses, with only three values falling below 0.50. Kappa values ranged from 0.43-0.84, respectively. In comparing the M.I.N.I. with the CIDI, sensitivity was 0.70 or greater for all but four

values. Specificities and negative predictive values were 0.70 or higher for all of the diagnoses. In comparing the M.I.N.I. with the SCID-P, sensitivity was 0.70 or greater for all but three values. Specificities and negative predictive values were 0.85 or higher for all of the diagnoses. Good to excellent reliability has also been established. All of the kappa values for interrater reliability were above 0.75, and the majority (70%) were 0.90 or higher. Moreover, good test retest reliability has been established, with 61% of the values above 0.75. In summary, the validation results of the M.I.N.I. were very positive, with good to excellent validity and reliability in elucidating symptom criteria (Sheehan et al., 1998).

3.4.3 *The Childhood Trauma Questionnaire – Short Form (CTQ-SF)*

The Childhood Trauma Questionnaire (Bernstein et al., 1994) measures the frequency of abuse and neglect in childhood and adolescence. The original version consisting of 70 items was developed with adults. However, the questionnaire has been modified for use down to 12 years of age (Ohan, Myers, & Collett, 2002). The questionnaire functions as well with adolescents as it does with adults (Ohan et al., 2002). An advantage of using the CTQ in adolescent samples is its ability to detect ongoing abuse and not just past abuse as in the case of adults.

The most recent modification is the CTQ-SF (Bernstein et al., 2003). This version was developed to provide a brief, reliable, and valid assessment of a broad range of traumatic childhood experiences. The CTQ-SF is a standardised, retrospective 28-item measure of childhood emotional abuse, physical abuse, sexual abuse, emotional neglect and physical

neglect. The CTQ-SF includes a three-item minimization/denial validity scale that was developed to detect the underreporting of maltreatment. Most of the items measure the occurrence of abuse and neglect (“When I was growing up, someone tried to touch me in a sexual way, or tried to make me touch them”). However, a few of the items are subjective (“When I was growing up, I believe that I was sexually abused”). The original 70-item version was validated in an adult sample of drug or alcohol dependent patients. High internal consistency was reported for the five sub-scales (0.79-0.94). Good test-retest reliability and convergence validity was demonstrated (Bernstein et al., 1994). The psychometric properties of the CTQ-SF were examined with four diverse samples consisting of adult substance abusing patients and adolescent psychiatric inpatients (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Bernstein et al., 2003). The reliability of the five CTQ-SF sub-scales ranged from $\alpha = .61$ to $\alpha = .95$. A reliability coefficient of $\alpha = .95$ for the full version of the scale has been demonstrated, indicating high internal consistency. Good test-retest reliability of .88 over a 2- to 6- month interval has been demonstrated. A moderately high convergent validity has been found between the self-report CTQ and an observer-rated interview of childhood trauma, the Childhood Trauma Interview (CTI). In the adolescent sample, convergent validity has been supported by moderate correlations between CTQ sub-scales and therapists’ ratings of abuse and neglect. Moreover, correlations between the CTQ and therapists’ scores were higher for the same forms of maltreatment than for different forms of maltreatment, suggesting evidence for divergent validity (Ohan et al., 2002). In the adolescent sample, females scored higher than males on the sexual and emotional abuse sub-scales (Bernstein et al., 1997). Although unknown, this finding could be indicative of increased

occurrence of abuse, increased perception of abuse, or increased willingness to reveal abuse among females (Ohan et al., 2002). Scores on the CTQ range from 5 to 25 for each of the abuse types. Each item comprises a likert scale ranging from 1 (“never true”) to 5 (“very often true”). A total score for the 25 items is obtained, with the lowest possible score being 25 and the highest possible score being 125. Higher scores indicate more severe levels of abuse or neglect (score of 25-31 = no trauma, score of 41-51 = low to moderate, 56-68 = moderate to severe, and 73-125 = severe to extreme). The CTQ-SF is a quick and easy to use screening method for maltreatment that could be more difficult to assess during a clinical interview. Individuals may under report abuse, therefore, using the CTQ may facilitate dialogue about ongoing abuse or abuse histories (Bernstein et al., 1997). The internal reliability coefficients of the CTQ-SF in the study sample are reported in the results chapter.

3.4.4 *The Revised Conflict Tactics Scale (CTS-2)*

The CTS-2 is a widely used instrument for identifying domestic violence in dating, cohabiting, or marital relationships. The instrument has scales to measure victimisation and perpetration of three strategies often used in partner conflicts, namely: physical assault, psychological aggression, and negotiation. The CTS-2 also includes scales to measure injury and sexual coercion. All CTS-2 scales have sub-scales for less severe and more severe behaviours (Straus, Hamby, Boney-McCoy, & Sugarman, 1996). Scoring of the CTS-2 can be complex as multiple scoring techniques are possible. However, a commonly used method in research is the prevalence method. A dichotomous variable (0-1) is created, with a score of 1 assigned if one or more of the violent acts in the scale

occurred. Initial psychometric properties of this instrument demonstrated good internal consistency: negotiation ($\alpha = .86$), psychological aggression ($\alpha = .79$), physical assault ($\alpha = .86$), sexual coercion ($\alpha = .87$), and injury ($\alpha = .95$) (Straus et al., 1996). Internal consistency reported in forty-one articles ranged from $\alpha = .34$ to $\alpha = .94$, with an average of $\alpha = .77$. It is notable however, that low reliability coefficients occurred when the behaviour under measurement occurred minimally or was absent in some samples (Straus, 2007). The scale has demonstrated temporal consistency, with good test-retest reliability coefficients ranging from .49 to .90, with an average of .72 (Straus, 2007). Finally, there is evidence of construct and discriminant validity (Straus et al., 1996; Straus, 2007).

3.4.5 *The Center for Epidemiological Studies Depression Scale (CES-D)*

The CES-D (Radloff, 1977) is a 20-item widely used self-report instrument designed to measure depressive symptomatology. The scale was specifically designed to measure depressive symptomatology in the general population, unlike previous depression scales which have been predominantly used in clinical populations. The CES-D emphasises the affective component of depressive symptomatology, namely depressed mood. Each item comprises a likert scale ranging from 0 to 3. A total score for the 20 items is obtained, with the lowest possible score being 0 and the highest possible score being 60. Higher scores are indicative of more severe depression. A seriously depressed person would be expected to experience many of the symptoms but not necessarily all of them (Radloff, 1977). Good internal consistency has been demonstrated, with reliability coefficients of $\alpha = .85$ in the general population and $\alpha = .90$ in a patient sample. Moderate test-retest

reliability has been demonstrated, ranging from .45 to .70. Moreover, discriminant validity has been established, with CES-D scores discriminating well between inpatient and general population samples and discriminating moderately between levels of severity within patient groups (Radloff, 1977).

3.4.6 *Life Events Checklist (LEC)*

The LEC is a widely used measure of exposure to potentially traumatic events. It was developed in order to facilitate the diagnosis of posttraumatic stress disorder (PTSD). One of the LEC's unique features is that it enquires about various types of exposure to each potentially traumatic event (Gray, Litz, Hsu, & Lombardo, 2004). Therefore, the LEC elicits whether the participant experienced, witnessed, or learned of the traumatic event, a feature that other traumatic event measures do not possess. Participants rate their experience of each traumatic event listed on a likert scale. Higher scores are indicative of the experience of more traumatic life events. The LEC has demonstrated reasonable temporal stability over a 7 day interval. In assessing reliability of the instrument as a measure of direct trauma exposure, only one item failed to meet conventional standards of reliability. All other item kappa coefficients were above .50, with seven items demonstrating kappa coefficients of .60. The mean reported kappa coefficient for the measure was .61 and the test retest correlation was .82 (Gray et al., 2004). A moderately high convergent validity has been found between the LEC and an established psychometrically sound measure of traumatic life events, the Traumatic Life Events Questionnaire (TLEQ) (Gray et al., 2004).

3.4.7 *Davidson Trauma Scale (DTS)*

The DTS is a widely used 17-item self-report and was developed closely to the symptom definitions of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, DSM-IV (American Psychiatric Association, 1994). The instrument measures symptoms of PTSD on frequency and severity scales (Davidson et al., 1997). The items are categorised according to the criteria set out in the DSM-IV: criteria B (intrusive re-experiencing) criteria C (avoidance and numbness) and criteria D (hyperarousal). For each item, the participant rates the frequency and severity during the previous week on 5-point (0 to 4) scales, with the lowest possible score being 0 and the highest possible score being 136. Higher scores are indicative of more PTSD symptoms (Davidson et al., 1997). The DTS has demonstrated good internal consistency ($\alpha = .99$) and test-retest reliability over a 2-week interval, with a coefficient of .86. For the frequency items alone, the internal consistency was $\alpha = .97$ and $\alpha = .98$ for the severity items (Davidson et al., 1997). Moreover, good concurrent, convergent, divergent, and predictive validity have been established (Davidson et al., 1997).

3.4.8 *Alcohol Use Disorders Identification Test (AUDIT)*

The AUDIT is a widely used 10-item screening tool covering the domains of alcohol consumption, drinking behaviour, and alcohol related problems. A unique feature of the AUDIT is its ability to identify problem drinking in its milder stages and to detect individuals with dangerous or destructive alcohol consumption before dependence or permanent damage has occurred (Saunders et al., 1993). Responses to each item are scored from 0 to 4, with the lowest possible score being 0 and the highest possible score

being 40 (Saunders et al., 1993). In a sample screened with the AUDIT, a screening score of 8 produced 92% sensitivity and 94% specificity. Moreover, a screening score of 10 produced 80% sensitivity and 98% specificity. The validity of the AUDIT was established using external reference groups of alcoholics and non-drinkers. Of the alcoholics, 99% had a score of 8 or more and 98% had a score of 10 or more, demonstrating that the AUDIT performed well with this sample. (Saunders et al., 1993). The AUDIT has demonstrated good internal consistency, with a median alpha of .83 (range .75 to .97). Moreover, there is evidence for good temporal reliability, and construct and criterion validity of the AUDIT (Reinert and Allen, 2007).

3.5 HNRC Neuropsychological Test Battery

The neuropsychological battery was compiled by the HIV Neurobehavioral Research Center (HNRC). The battery consisted of 17 individual test measures assigned to ability areas thought to be especially vulnerable to effects of HIV on the brain. The HNRC neuropsychological battery is discussed in more detail in the next chapter.

3.6 Statistical Analyses

All statistical procedures were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 18) and Statistica (version 10). Frequencies (*f*), percentages (%), means (*M*), standard deviations (*SD*), and ranges were calculated for all independent variables. Pearson's and Spearman's correlation statistics were used to correlate demographic characteristics, clinical variables, and self-report data with neuropsychological data. HIV and Childhood trauma interaction effects on

neuropsychological performance were analysed using an Analysis of Covariance (ANCOVA) with age and education as covariates. A multiple regression analysis was performed on those neuropsychological tests that were significant in the ANCOVA. Self-report instruments and demographic and clinical variables were entered into the analysis to determine whether or not they could explain variance in the significant dependent variables. Finally, a best subsets regression analysis was conducted in order to determine which predictors needed to be included in the model. These predictors were put into the model in order to determine the amount of variance they could explain. All were two-tailed and significance was set as $p < .05$.

3.7 *HIV-1 subtyping*

HIV-1 is genetically diverse, consisting of 9 subtypes, 2 sub-subtypes, approximately 43 circulating recombinant forms (CRFs) and numerous unique recombinant forms (URFs). A comprehensive understanding and detailed description of HIV clades is an important factor in the diagnosis, treatment, and prevention of HIV-1 (McCutchan, 2006). The six most predominant strains have been identified as subtypes A, B, C, D, and recombinants CRF01_AE and CRF02_AG (McCutchan, 2006). Globally, subtype C is spread mainly via heterosexual contact. This is especially the case in Southern Africa and India (Jacobs et al., 2009). In a recent South African study, the majority of sequences ($n = 320$) were subtyped as C (89.0%). Other subtypes detected were subtype A (3.1%), subtype B (6.8%), and one each of subtypes F1, G, U, and a CH recombinant (Jacobs et al., 2009). The implications that this genetic diversity has for HIV-1 evolution and vaccine development remains undetermined and widely debated. There is therefore a need to

continuously investigate the HIV-1 epidemic and to detect the various circulating subtypes (Jacobs et al., 2009).

Increased debate has been centered on the neurotoxicity unique to each genetic clade. HIV-associated neurocognitive disorders (HAND) are a consequence of HIV-1 infection and occur across all genetic clades. It has been suggested that HIV subtypes may possess different biological properties, influencing clinical outcome and HIV-associated cognitive impairment (Sacktor, Nakasujja, Robertson, & Clifford, 2007). Research has provided evidence for lower incidence of neurological impairment among individuals infected with clade C in sub-Saharan Africa and India (Clifford et al., 2007; Gupta et al., 2007; Yephthomi et al., 2006). In light of this, many studies have sought to test this hypothesis and have concluded that subtype C is less neurotoxic than that of other clades, especially clade B (Constantino, Huang, Zhang, Wood, & Zeng, 2011; Mishra, Vetrivel, Siddappa, Ranga, & Seth, 2008; Rao et al., 2008).

EDTA blood samples were collected from all participants in the present study and the HIV-1 subtyping methods and results are described below.

3.7.1 RNA extraction and PCR amplification of partial gag gene

HIV-1 RNA was extracted from the plasma using the QIAamp Viral RNA kit (Qiagen GmbH, Hilden, Germany) and the QIAcube automated extraction system, according to manufacturer's instructions. Isolated RNA was stored at -70°C until used for PCR reactions.

Reverse transcriptase polymerase chain reaction (RT-PCR) amplification was done on a 484-bp fragment of the *gag* gene (HXB2 nucleotides 1237–1721) using the Access RT-PCR kit (Promega, Madison, WI, USA) and methods previously described (Swanson, Devare, & Hackett, 2003).

Briefly, 5 μ l of RNA was used in a reaction volume of 50 μ l containing 40pmol/ μ l primers; 0.2mM dNTPs; 1mM MgSO₄; AMV/ *Tfl* 5X reaction buffer; 1 Unit AMV reverse transcriptase and 1 Unit *Tfl* DNA polymerase. The GeneAmp 9700 PCR system (Applied Biosystems, Foster City, California, USA) was used with the following cycling parameters: one cycle of reverse transcription at 48°C for 45 minutes, one cycle of denaturation at 94°C for 2 minutes, forty cycles of denaturation at 94°C for 30 seconds, primer annealing at 53°C for 30 seconds, primer extension at 72°C for 1 minute, followed by a cycle of final primer extension at 72°C for 10 minutes.

For nested PCR, 3 μ l of the pre-nested PCR product was used with the GoTaq Flexi PCR kit (Promega, Madison, WI, USA) and 40pmol/ μ l of primers. The 50 μ l PCR reaction contained 0.2mM dNTPs; 1.5 mM MgCl₂; 1 U of Taq DNA polymerase in GoTaq Flexi buffer. The cycle parameters were one cycle of denaturation at 94°C for 2 minutes, forty cycles of denaturation at 94°C for 30 seconds, primer annealing at 53°C for 30 seconds, primer extension at 68°C for 1 minute, followed by one cycle of final primer extension at 68°C for 7 minutes.

Amplified PCR products were separated on 1% agarose gels, stained with ethidium bromide (Promega, Madison, Wisconsin, USA) and visualized using the UVitec (Cambridge, UK) gel documentation system.

The PCR products were stored at 4°C until used for sequencing reactions.

3.7.2 *DNA sequencing*

The PCR products were purified before sequencing reactions were done by degrading single-stranded DNA and diphosphates using *Exonuclease 1* and Shrimp alkaline phosphatase (Amersham Pharmacia Biotech., NJ) respectively.

All PCR products were sequenced on both strands using the BigDye Terminator v3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, California, USA) and run on an ABI Prism 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA), according to manufacturer's instructions.

After the chromatograms were analysed, overlapping fragments were assembled, validated and exported as a text file in fasta format, using Sequencher 4.10.1 (Gene Codes Corporation, Ann Arbor, MI).

3.7.3 *Phylogenetic analysis*

The REGA HIV-1 subtyping Tool Version 2.0 was initially used to identify HIV-1 subtypes (<http://dbpartners.stanford.edu/RegaSubtyping>). Multiple alignments and phylogenetic analysis were implemented using Geneious v5.4.3

(<http://www.geneious.com>). Briefly, the *gag* sequences obtained, were aligned with the 2008 dataset of HIV-1 reference sequences obtained from the Los Alamos National Laboratory (LANL) HIV Database (<http://www.hiv.lanl.gov>), using Clustal X version 1.81 (Thompson, Gibson, Plewniak, Jeanmougin & Higgins, 1997). These alignments were verified manually in Geneious version 5.4.3 before further analysis.

A maximum likelihood tree with the nearest-neighbor-interchange (NNI) heuristic method was constructed with the PHYML plugin (Guindon & Gascuel, 2003), and the GTR (General-time-reversible) substitution model. The transition / transversion ratio was fixed and both the proportion of invariable sites and the Gamma distribution parameter were estimated. The tree was optimized for tree topology, branch length and substitution rate. The reliability of the branching and clustering pattern was estimated using approximate likelihood ratio test (aLRT) statistics.

The jumping profile Hidden Markov Model (jpHMM) tool for HIV-1 recombinant detection (<http://jphmm.gobics.de>), was also used to identify HIV-1 subtypes (Zhang et al., 2006) and the HIV BLAST tool was used to find sequences most similar to each of our outlier sequences (http://www.hiv.lanl.gov/content/sequence/BASIC_BLAST/basic_blast.html).

3.8 *Results of HIV-1 subtyping*

3.8.1 *PCR amplification and sequencing*

Gag PCR were done on the RNA of 85 patient samples of which 70 were PCR positive and 15 PCR negative. Of the 15 PCR negative samples, 8 had a viral load of less than 1000 and 3 were lower than the detection limit (LDL) of the assay. In three of the PCR positive samples, no readable sequences could be obtained. A summary of the results are shown in Table 1.

3.8.2 *Phylogenetic analysis*

Analysis with the REGA online tool indicated that the majority of the sequences could be classified as HIV-1 subtype C, however for 7 sequences this classification was not supported by bootstrap analysis.

The result of the ML phylogenetic analysis of the partial gag gene is shown in Figure 1. The majority of the samples clustered with HIV-1 subtype C. The sequence from sample TB037-09 had a very long branch, indicating possible variability. The sequence from PT049-09 was an outlier to subtype C on this tree.

Sequences were further evaluated with the jpHMM HIV tool, a probabilistic generalisation of the jumping alignment approach. Because recombination breakpoints identified by jpHMM were found to be significantly more accurate than breakpoints defined by traditional methods based on comparing single representative sequences (Schultz et al., 2006; Zhang et al., 2006), we used this approach to identify recombinants. Using this tool we identified two possible recombinants, TB037-09 and PT049-09.

The jpHMM tool indicated that TB037-09 was a possible HIV-1 subtype C recombinant (Figure 2). This sequence was 502 bp in length, but the first 126 bp was a region of uncertainty. The graph showing the posterior probabilities of the subtype at each sequence position calculated by jpHMM indicated that TB037-09 could be a possible BC recombinant. This online tool also indicated that PT049-09 was a possible subtype D, but the posterior probability was very low. Both these sequences should be further investigated using full genome sequencing. The BLAST tool indicated that both these samples were related to subtype C.

Table 1. Gag PCR results and REGA subtyping (N = 85).

Participant ID	CD4 count	Viral load	Gag PCR	REGA subtype	Bootstrap support
KC00208	232	2000	Positive	C	98
PM00308	217	3600	Positive	C	76
PM00408	Not done	2800	Positive	C	99
TG00508	810	4000	Positive	C	98
CS00608	165	1800000	Positive	C	Not supported
CD00708	Not done	6200	Positive	C	98
ZS00808	575	180	Positive	C	97
YS01008	699	12000	Positive	C	98
SR01208	390	190	Positive	C	99
NM01308	886	1800	Positive	C	100
PM01408	400	3400	Positive	C	98
LN01508	579	Lower than detectable limit	Negative	Negative	Negative
VG01608	538	51	Negative	Negative	Negative
PS01708	600	50	Positive	C	100
ST01808	628	7900	Positive	C	98
MN01908	456	6500	Positive	C	99
MH02008	257	98000	Positive	C	Not supported
ND02108	360	1900	Positive	C	96
FG02308	160	29000	Positive	C	Not supported
SM02408	121	7500	Positive	C	83
SK02508	680	Lower than detectable limit	Positive	C	97

Participant ID	CD4 count	Viral load	Gag PCR	REGA subtype	Bootstrap support
NM02608	392	21000	Positive	C	100
WJ02708	320	52000	Positive	C	97
BM02808	256	180000	Positive	C	94
TP02908	690	2000	Positive	C	Not supported
EF03108	268	1800	Positive	C	100
NK03208	780	920	Positive	C	81
NY03308	300	830	Positive	C	89
XM03408	156	Lower than detectable limit	Positive	No sequence	No sequence
NJ03509	240	1200	Positive	C	99
ND03608	340	690000	Positive	C	93
TB03709	374	1600	Positive	C	100
PM03809	270	200	Positive	C	97
NJ03909	416	2500	Positive	C	99
ZP04009	148	320000	Positive	C	99
GN04109	458	20000	Positive	C	96
TM04209	519	270	Positive	C	100
MD04509	845	7400	Positive	C	98
JK04709	304	2400	Negative	Negative	Negative
NP04809	489	1100	Positive	No sequence	No sequence
PT04909	157	84000	Positive	C	96
AS05209	229	Lower than detectable limit	Negative	Negative	Negative

Participant ID	CD4 count	Viral load	Gag PCR	REGA subtype	Bootstrap support
SN05509	354	16000	Positive	C	100
NF05609	321	16000	Positive	C	95
SB06709	400	1000	Negative	Negative	Negative
PM06809	777	2600	Positive	No sequence	No sequence
BM07209	589	Lower than detectable limit	Negative	Negative	Negative
LM08109	195	7900	Positive	C	Not supported
NM08209	377	37000	Positive	C	97
NG08309	414	19000	Negative	Negative	Negative
RG08409	491	570	Positive	C	99
NN08709	163	160000	Positive	C	91
TG08809	364	8600	Positive	C	100
TB08909	535	1800	Positive	C	99
NM09009	72	180000	Positive	C	94
MN09109	478	22000	Positive	C	96
NS09209	1053	78	Positive	C	99
PK09309	587	27	Negative	Negative	Negative
TM09809	690	61000	Positive	C	100
MT10009	1529	12000	Positive	C	100
CM10309	218	100000	Positive	C	95
AZ111-10	490	8000	Positive	C	85
BD112-10	508	20000	Positive	C	100
HN113-10	275	5900	Negative	Negative	Negative

Participant ID	CD4 count	Viral load	Gag PCR	REGA subtype	Bootstrap support
NM114-10	572	45000	Positive	C	90
BL115-10	586	7200	Positive	C	100
PK116-10	347	230000	Positive	C	100
NN117-10	411	22000	Positive	C	97
NS118-10	703	330000	Positive	C	96
ZN119-10	333	11000	Positive	C	99
ZM120-10	206	220	Negative	Negative	Negative
NS121-10	111	210000	Positive	C	99
ZN122-10	668 (113)*	350	Positive	C	99
AQ123-10	48	19000	Positive	C	Not supported
ZN124-10	228 (121)*	2400	Positive	C	Not supported
BM125-10	35	150	Negative	Negative	Negative
ZM126-10	60	3200000	Positive	C	96
VN127-10	46	4800	Positive	C	100
ET133-10	162	120	Negative	Negative	Negative
VZ134-10	282	10	Negative	Negative	Negative
LN135-10	46	Lower than detectable limit	Positive	C	97
BS139-10	231	29000	Positive	C	98
NN140-10	124	100000	Positive	C	95
AN141-10	286	260000	Negative	Negative	Negative

Figure 2. Posterior probabilities of the subtypes at each sequence position (original sequence positions) calculated by jpHMM.

Figure 2a.

Sequence #29: >TB037-09_Gag

This sequence is related to subtype(s): C

Fragment Start Position	Uncertainty Region Start - End	Breakpoint Interval Start - End	Fragment End Position	Fragment Subtype
Position in the original sequence [pred_recombination], [recombination_incl_UR_and_BPI], [UR_and_BPI]				
1	1 - 126	-	502	C
Position based on HXB2 numbering [pred_recombination] [recombination_incl_UR_and_BPI] [UR_and_BPI]				
1229	1229 - 1355	-	1731	C

Genome map (based on [HXB2 numbering](#))

Note:

- Numbers in the above figure denote intervals for recombination breakpoints based on HXB2 numbering.
- The uncolored regions denote missing information due to input fragment sequence.
- The gray regions denote missing information due to uninformative subtype models (subtype: N/A).
- The sequence regions of less than 10 nucleotides long are too short to be mapped onto the genome map.

Posterior probabilities of the subtypes (based on [HXB2 numbering](#))

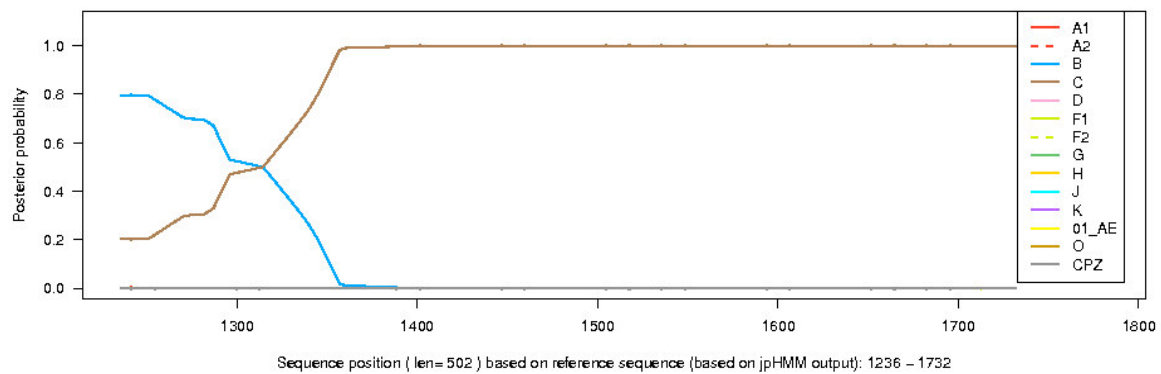
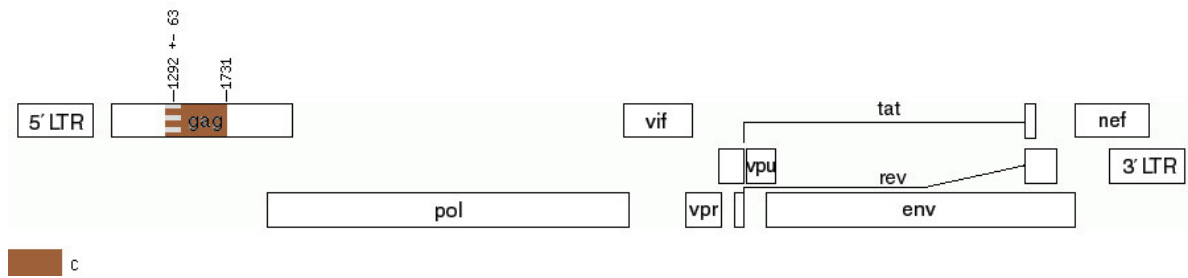


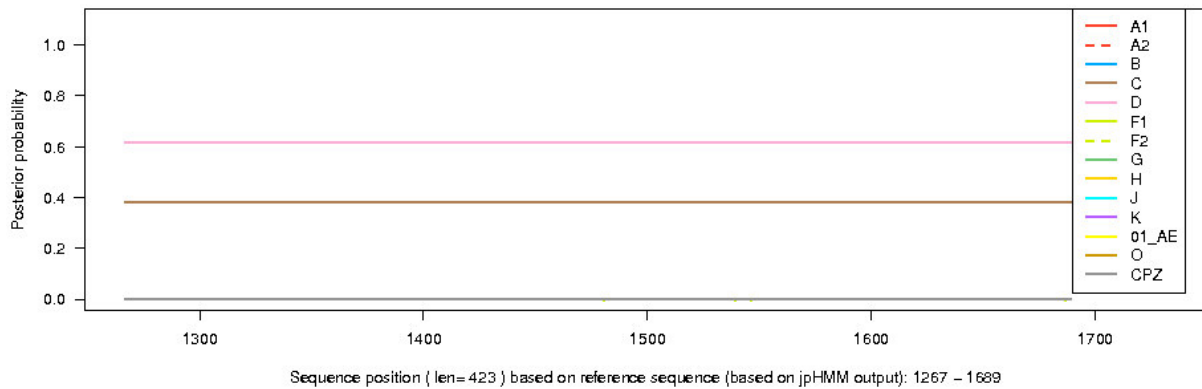
Figure 2b.

Sequence #36: >PT049-09_Gag

This sequence is related to subtype(s): D

Fragment Start Position	Uncertainty Region Start - End	Breakpoint Interval Start - End	Fragment End Position	Fragment Subtype
Position in the original sequence [pred_recombination], [recombination_incl_UR_and_BPI], [UR_and_BPI]				
1	1 - 423	-	423	D
Position based on HXB2 numbering [pred_recombination] [recombination_incl_UR_and_BPI] [UR_and_BPI]				
1267	1267 - 1689	-	1689	D

Genome map (based on [HXB2 numbering](#))



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THE HNRC NEUROPSYCHOLOGICAL BATTERY

The HIV Neurobehavioral Research Center (HNRC) is dedicated toward increased understanding of how HIV and other diseases affect the human nervous system. Their core research focus (local, national, and international) is on the prevention, diagnosis and treatment of HIV-related diseases as they affect the brain and nervous system. The center began in 1989 and since then, they have made successive changes in their neuropsychological battery. These changes were made to streamline the battery and to make it more specific. This resulted in a neuropsychological battery that was sensitive to HIV-related impairments, had demographically corrected norms, and in many instances had alternate forms available for increased sensitivity across multiple visits (Woods et al., 2004).

Although norms for the non-Hispanic White population were available through research done at the HNRC, it became evident that the use of such norms resulted in the overdiagnosis of neurocognitive impairment in minority groups. This was first observed in African Americans (Manly et al., 1998). As a result, research was conducted in order to develop a comprehensive manual of demographically corrected norms for African Americans. By applying correct norms, it became evident that the apparently higher rate of neuropsychological (NP) impairment in African Americans was not valid. Since then, the HNRC has placed increased emphasis on understanding the course of HIV neurocognitive impairment in international environments. Efforts to develop norms for Spanish-speaking Hispanics are underway. In addition, the HNRC has become involved

in NP methods development for use in resource-limited settings. Projects are running in countries such as Brazil, India, China, and Africa. A pilot study in China using a translated HNRC battery provided evidence that the selected NP battery can be adapted for use in international populations across a broad range of educational levels (Cysique et al., 2007). Similar adaptations are underway in India and Brazil. The HNRC neurobehavioral battery is therefore being used in HIV settings worldwide, including resource limited settings where educational levels may differ. In light of this cross-cultural application, the HNRC neurobehavioural battery is a very useful resource to utilise, even in settings where demographically corrected norms are not yet available.

The neuropsychological battery consisted of 17 individual test measures assigned to ability areas thought to be especially vulnerable to effects of HIV on the brain. These tests and ability domains are presented in table 1 on the next page.

Table 1 HNRC Neuropsychological Testing Battery

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

4.1 *Hiscock Digit Memory Test*

The Hiscock Digit Memory Test (Hiscock and Hiscock, 1989) is a forced-choice test designed to detect poor effort. A series of digits is presented on a stimulus card to the participant for five seconds and then removed. After a delay, the participant is shown a response card containing two number sequences printed side-by-side. One of the number sequences matches the sequence shown on the stimulus card. The subject is asked to show the number sequence that was shown previously. The delay intervals are 5, 10, and

15 seconds long, with a total of 12 stimuli per section. This test is simple and easy to administer and has demonstrated good performance even in patients with significant dementia (Hiscock and Hiscock, 1989).

4.2 *Hopkins Verbal Learning Test-Revised (HVLT-R)*

The HVLT-R (Benedict, Schretlen, Groninger, & Brandt, 1998) is a brief measure of verbal learning and memory. The test has six alternate forms, thus minimising practice effects and making it ideally suited to repeated testing. This test provides information on a subject's ability to learn and immediately recall verbal information across trials, as well as the ability to retain, reproduce, and recognise this information after a delay. A total of twelve words are read out to the subject over three trials at 2 second intervals. All responses are recorded verbatim. There are three semantic categories consisting of four words each. These semantic categories include: animals, human dwellings, and precious stones. The subject is required to recall as many words as possible from the list in any desired order after each trial. A 20-minute delay follows the administration of the first three trials, after which the subject is asked to recall the list once more. Subjects are then read a list of 24 words, one at a time, and are asked to answer "yes" if the word appeared in the original list and to reject 12 nontarget words by responding "no." Words in this recognition task consist of words originally read (12), words in the same semantic class (6), and words unrelated (6). For the purpose of the present study, appropriate modifications were made to the HVLT-R. It was decided that words such as "emerald" "sapphire" and "opal" from the precious stone semantic category would not be culturally suited to this South African sample. The precious stones category was therefore replaced

with vegetables (bean, lettuce, corn, and potato). Original normative data for the HVLT-R were derived from a sample of 1179 normal volunteers. In addition, test-retest (range .55 to .78) and interform reliability have been established, suggesting the HVLT-R has acceptable reliability and that the test forms are equivalent for learning and delayed recall. Moreover, discriminant validity has been established (Benedict et al., 1998).

4.3 *Brief Visuospatial Memory Test – Revised (BVMT-R)*

The BVMT-R provides a measure of immediate recall, learning rate, as well as delayed recall and recognition for visuospatial information. The test has six alternate forms, thus minimising practice effects and making it ideally suited to repeated testing. Each stimulus form consists of six two-dimensional geometrical figures or shapes printed in a 2 x 3 matrix. The display is presented for ten seconds, after which the subject is requested to reproduce as many of the figures as possible in their correct location on a blank sheet of paper. There are three trials and a 25-minute delay trial. Following these trials is a recognition trial in which subjects are shown 12 designs, one at a time, and asked to respond “yes” if the design appeared in the original matrix. The recognition trial consists of six target shapes and six nontarget shapes. An optional copy trial can be administered in order to rule out poor performance due to graphmotor or visuospatial impairment. Subjects are given the stimulus sheet and requested to copy the designs. Normative data for the BVMT-R were derived from a sample of 588 normal volunteers. Good interrater reliability has been established, with reliability coefficients ranging from .96 to .97 for the three learning trials, .97 for total recall, and .97 for delayed recall. Test-retest

coefficients range from .60 for trial one to .84 for trial 3. Moreover, construct validity has been demonstrated (Benedict, 1997).

4.4 *The Colour Trails Test (CTT)*

CTT (D'Elia, Satz, Uchiyama, & White, 1994) is based on the use of coloured circles and universal sign language symbols. CTT measures abstraction/executive functioning. For CTT 1, subjects are required to connect numbered circles in sequential order with a pencil as fast as they can. All odd numbered circles have a pink background and all even numbered circles have a yellow background. For CTT 2, subjects are required to draw lines between coloured circles in sequential order as fast as they can, while alternating between two colours, pink and yellow. Each number is presented twice, one with a pink background and one with a yellow background. The CTT is not influenced by knowledge of the alphabet, thus making it a culturally fair option to the Trails Making Test which relies on knowledge of the alphabet. CTT normative data were derived from 1528 normal healthy volunteers. The temporal stability of the CTT has been established, with test-retest coefficients of .64 for CTT 1 and .78 for CTT 2. Content and convergent validity have been established (D'Elia et al., 1994). Moreover, CTT 1 and 2 has been shown to be sensitive to the subtle cognitive impairment associated with HIV-1 (D'Elia et al., 1994).

4.5 *Stroop Colour and Word Test*

The Stroop test (Golden and Freshwater, 1998) is a test of both speed of information processing and executive functioning. The test consists of three pages the subject is required to read through as quickly as possible, namely: word reading, colour naming and

colour-word interference. Each page consists of 100 words presented in 5 columns of 20 items. The word naming task consists of the words “RED”, “GREEN” and “BLUE” printed in black ink. The colour naming task consists of XXX printed in red, green or blue. The colour-word interference page consists of the words from the word reading page printed in colours from the colour naming page. The two pages were blended item for item and in no case do the word and the colour it is printed in match one another. Normative data were derived from a sample of 300 normal volunteers. The reliability of the Stroop test has been shown to be highly consistent across different versions of this test (Golden and Freshwater, 1998). Test-retest reliability has been established covering periods from 1 minute to 10 days, with coefficient ranging from .73 to .89 (Golden and Freshwater, 1998).

4.6 *Wechsler Adult Intelligence Scale-III (WAIS-III)*

The WAIS-III Digit Symbol and Symbol Search tests are performance tasks measuring adult intelligence (Wechsler, 1997). Digit symbol is a test of psychomotor speed, concentration and graphomotor abilities which requires the participant to match symbols to numbers as quickly as possible, using a visual reference. The time limit is 120 seconds and the total score reflects the number of symbols correctly drawn. Symbol search requires attention, concentration and psychomotor speed. Respondents are required to scan two groups of symbols visually and determine if either of the two target symbols matches any of the five symbols appearing to the right of the target symbols. The subject is required to complete as many items as possible in a 120 second time period. Original normative data for the WAIS-III were derived from a sample of 2454 individuals. The

WAIS-III has demonstrated good test-retest reliability with coefficients ranging from .88 to .94. In addition, face, content, criterion-related and convergence validity have been established (Wechsler, 1997).

4.7 *Grooved Pegboard*

Grooved pegboard (Klove, 1963) is a test of fine motor coordination and speed. Subjects are required to place 25 small metal pegs into holes on a metal board. All pegs look alike and have a ridge on one side, which corresponds to a notch in each hole on the board. Subjects are asked to put the pegs into the holes as fast as they can, first using the dominant hand and then using the non dominant hand. The total time for each hand is recorded. Normative data was been derived in 1482 individuals. High test-retest reliability coefficients with intervals of 4-24 months have been demonstrated (.67 to .86).

4.8 *Trail Making Test A*

The Trail Making Test A (Reitan and Davison, 1974) is a measure of psychomotor speed, attention and cognitive sequencing. Subjects are asked to connect in ascending order a series of randomly arranged circles numbered from 1 to 25 as quickly as possible. Normative data were derived from 1212 individuals. Test-retest reliability coefficients have ranged from low (.46) to high (.94).

4.9 *WMS-III Spatial Span*

The WMS-III Spatial Span (Wechsler, 1997) is a test of working memory. The Spatial Span test taps a subject's ability to hold a visual-spatial sequence of locations in working

memory and then reproduce the sequence. In the first part of the test, the examiner points to a series of blocks at one second per block and the examinee is required to replicate an increasingly long series of visually presented spatial locations in the same order. In the second part of the test, the subject is required to repeat the process but this time in the reverse order. Two trials for each sequence length are administered. The test is discontinued if the subject scores 0 for both items in a sequence. The normative data were derived from 1250 individuals. The Spatial Span has demonstrated adequate (.70 to .79) internal consistency, generalisability coefficients and test-retest coefficients.

4.10 *Halstead Category Test – Computerised version*

The Halstead Category Test (Halstead, 1947) is a 208-item test of categorisation and frontal lobe executive functioning. The subject is shown a series of geometrical figures that represent a number between 1 and 4. The subject is required to figure out which number each design represents, and then to push down on the corresponding number (keys labeled 1-4) on the keyboard. The test is divided into seven subtests and within each subtest, the idea or principle used to find the correct answer never changes. The principle only changes between subtests, never within them. Therefore, the test requires the subject to deduct a principle through response-contingent feedback, to use the principle while it remains effective, and to abandon the principle when it no longer is effective (Strauss, Sherman & Spreen, 2006). Normative data were derived from 1212 individuals. High internal consistency for the 208-item version have been demonstrated, with $\alpha = .95$ for the total score. Reliability for subtest I and II were unacceptable (.46 and

.65) but high for the remaining subtests (.77- .95). Test-retest reliability coefficients have ranged from .60 to .90 (Strauss et al., 2006).

4.11 *Wisconsin Card Sorting Test (WCST) – Computerised version*

The WCST is a 64-item measure of executive function that required planning, use of feedback, and maintaining and shifting cognitive sets. Participants are required to match a card that appears at the bottom of a computer screen to one of four stimulus cards at the top of the screen. The stimulus cards are all different colours and have different shapes on them. The card that subjects are required to match to one of the stimulus cards varies in colour, geometric shape, and number. The participant receives feedback regarding correct and incorrect responses. Normative data were derived from 899 normal subjects. Test-retest reliability coefficients ranging from .37 to .72 have been reported (Strauss et al., 2006).

4.12 *Paced Auditory Serial Addition Task (PASAT)*

PASAT (Gronwall, 1977) is a 50-item test of speed of information processing. In this test, a series of randomised digits is serially presented via recording. Subjects are required to add the current number to the number that preceded it and respond with the answer out loud. The number of correct responses is recorded. Original normative data are based on a sample of 80 individuals. PASAT has demonstrated high internal consistency $\alpha = .90$. Test retest coefficients are excellent, ranging from .73 to .96.

4.13 *Controlled Oral Word Association Test (COWA) and Category Fluency Test*

The COWA is a test of verbal fluency using the letters F, A, and S. Subjects are required to say as many words as possible that begin with the letters F, A, and S, excluding proper names and different forms of the same word. The subject is allowed 60 seconds per letter to generate words. Performance is measured by the total number of correct responses.

The Category Fluency test is similar and is a test of verbal fluency. Subjects are asked to say as many words as possible that belong to a specified category. The categories include animals and actions. Perseverations and intrusions are recorded. Metanorms for FAS totals were derived from 17 625 individuals and Category fluency from 768 individuals.

High internal consistency for FAS has been demonstrated, $\alpha = .83$ and test-retest coefficients tend to be high for FAS, with .74 after an interval of five years (Strauss et al., 2006).

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RESULTS

5.1 *Demographic characteristics of the sample*

The sample consisted of 130 women attending community health facilities located in the Cape metropole and Winelands regions of the Western Cape Province, South Africa. Of the 130 participants, 83 (64%) were HIV-positive and 47 (36%) were HIV-negative. Forty eight of the 83 HIV-positive women were exposed to childhood trauma. Among the control subjects, a total of twenty women were exposed to childhood trauma. The participants were, on average, 30 years of age ($M = 29.6$, $SD = 7.0$). The age of the women ranged from 18 to 50 years. The majority of the women (96%) identified themselves as Black, and 4% identified themselves as Coloured. The majority (88%) were Xhosa speaking. The majority (93%) of the women identified themselves as being right handed, with only 7% of women reporting left handedness. Over half of the sample was single (71%) and more than a fifth were married or cohabiting (22.1%). In terms of educational level, most women (95%) had an educational level greater than grade eight. Less than a quarter (24%) of the sample completed high school, with only 3% of the sample reporting some form of education after high school. More than half of the sample was unemployed (65%), and 39% of women were breadwinners. The majority (79%) of the sample reported a combined household income of less than R10 000.00 per annum, with 16% of the sample reporting a combined household income of between R10 000.00-R20 000.00 per annum.

Demographic characteristics are summarised in table 1.

5.2 *Clinical characteristics of the HIV-positive sample*

The mean CD4 lymphocyte count among HIV-positive women was 405 cells/mm³, with a minimum of 35 and a maximum of 1529 cells/mm³. The mean HIV viral load was 105169.5 copies/ml, ranging from below the detectable limit to 3,200 000 copies/ml. There was no significant difference between groups based on CD4 lymphocyte count and viral load ($p > .05$). The predominant HIV clade was subtype C, with 64 (76%) carrying this strain of HIV. The majority of women were antiretroviral therapy (ART) naïve, with only 13 (15.5%) women on antiretroviral treatment. The impact that this ART use may have had on the neurocognitive findings is considered in the discussion chapter. These clinical characteristics are presented in table 2 and 3.

Psychiatric disorders were assessed using the M.I.N.I.-Plus. The commonest disorder was major depression (MDD) with a total of 33 women reporting current or past episodes. Suicidality was common with 24 women presenting with low, medium, and high levels of suicidality. Posttraumatic stress disorder (PTSD) was evident in 2 cases. The psychiatric disorders endorsed are presented in table 11.

5.3 *Internal consistency of self-report instruments*

A reliability analysis revealed very good internal consistency among the self-report instruments used in this sample of women. The alpha coefficients for the instruments were as follows: Conflict Tactics Scale (CTS) = .92, Childhood Trauma Scale (CTQ) = .79, Centre for Epidemiologic Studies Depression Scale (CES-D) = .95, Life Events

Checklist (LEC) = .84, Davidson Trauma Scale = .97, and Alcohol Use Disorders Identification Test (AUDIT) = .84.

5.4 *Correlations between demographic, clinical, and neurocognitive variables*

Pearson's correlation coefficients were calculated to determine the nature of any relationships between demographic and clinical variables and the dependant variables (neurocognitive variables). The demographic variables included age and education and the clinical variables selected included CD4 lymphocyte count and viral load. These results are summarised in table 4.

5.4.1 *Age*

Significant correlations were found between age and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = .46, p < .01$), Grooved Pegboard [non-dominant hand] ($r = .39, p < .01$), COWAT ($r = -.17, p < .05$), Category fluency [Animals] ($r = -.22, p < .01$), PASAT ($r = -.27, p < .01$), Trails A ($r = .26, p < .01$), Color trails 1 ($r = .20, p < .05$), Color Trails 2 ($r = .19, p < .05$), WAIS-III Digit symbol ($r = -.51, p < .01$), WAIS-III Symbol search ($r = -.41, p < .01$), WMS-III Spatial Span ($r = -.28, p = .01$), BVMT-R ($r = -.40, p < .01$), BVMT-R delay trial ($r = -.36, p < .01$), and Stroop colour word incongruent condition ($r = -.37, p < .01$).

A similar analysis was run using HIV-negative controls only (without childhood trauma). The mean age in this group ($n = 27$) was 25.07. Significant correlations were found between age and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = .51, p < .01$), COWAT ($r = -.40, p < .05$), Category fluency [Animals] ($r = -.59,$

$p < .01$), Trails A ($r = .39, p < .05$), WAIS-III Digit symbol ($r = -.57, p < .01$), and WAIS-III Symbol search ($r = -.46, p < .05$).

5.4.2 Education

Significant correlations were found between education and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = -.26, p < .01$), COWAT ($r = .36, p < .01$), Category Fluency [Animals] ($r = .29, p < .01$), Category Fluency [Actions] ($r = .35, p < .01$), PASAT ($r = .35, p < .01$), Trails A ($r = -.20, p < .05$), Colour Trails 1 ($r = -.20, p < .05$), WAIS-III Digit Symbol ($r = .38, p < .01$), WAIS-III Symbol Search ($r = .37, p < .01$), WMS-III Spatial Span ($r = .25, p < .01$), BVMT-R ($r = .34, p < .01$), BVMT-R [delay trial] ($r = .36, p < .01$), HVLT-R ($r = .27, p < .01$), HVLT-R [delay trial] ($r = -.27, p < .01$), Halstead Category Test ($r = -.42, p < .01$), Stroop word naming ($r = .24, p < .01$), and Stroop Colour naming ($r = .19, p < .05$).

A similar analysis was run using HIV-negative controls only (without childhood trauma). The mean age in this group ($n = 27$) was 25.07. Significant correlations were found between education and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = -.396, p < .05$), WAIS-III Digit Symbol ($r = .49, p < .01$), WAIS-III Symbol Search ($r = .40, p < .05$), WMS-III Spatial Span ($r = .54, p < .01$), BVMT-R ($r = .49, p < .01$), BVMT-R [delay trial] ($r = .62, p < .01$), HVLT-R [delay trial] ($r = -.57, p < .01$), and Halstead Category Test ($r = -.45, p < .05$).

5.4.3 *CD4 lymphocyte count*

No significant correlations were found between CD4 lymphocyte count and any of the neurocognitive variables ($p > .05$).

5.4.4 *Viral load*

No significant correlations were found between HIV viral load and any of the neurocognitive variables ($p > .05$).

5.5 *Correlations between self-report instruments and neurocognitive variables*

Pearson's correlation coefficients were calculated to determine the nature of any relationships between various self-report instruments (independent variables) and neurocognitive variables. The self report instruments included: Childhood Trauma Questionnaire, Centre for Epidemiologic Studies Depression Scale, Life Events Checklist, Davidson Trauma Scale, and Alcohol Use Disorders Identification Test. These results are summarised in table 5.

5.5.1 *Childhood Trauma Questionnaire*

Childhood trauma scores for the sub-scales and total scale have been summarised in table 7. Significant correlations were found between the CTQ and the following neurocognitive variables: Grooved Pegboard [non-dominant hand] ($r = .19, p < .05$), Trail Making Test A ($r = .19, p < .05$), WAIS-III Digit Symbol ($r = -.26, p < .01$), and Stroop word naming ($r = -.19, p < .05$).

5.5.2 *Centre for Epidemiologic Studies Depression Scale*

Significant correlations were found between the CES-D and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = .22, p < .01$), Grooved Pegboard [non-dominant hand] ($r = .31, p < .01$), Category fluency [Actions] ($r = -.19, p < .05$), PASAT ($r = -.19, p < .05$), Color trails 1 ($r = .23, p < .01$), WAIS-III Digit symbol ($r = -.20, p < .05$), WAIS-III Symbol search ($r = -.21, p < .05$), WMS-III Spatial Span ($r = -.25, p < .01$), BVMT-R ($r = -.17, p < .05$), BVMT-R delay trial ($r = -.22, p < .05$), and Stroop word naming ($r = -.18, p < .05$).

5.5.3 *Life Events Checklist*

No significant correlations were found between the LEC total score and any of the neurocognitive variables ($p > .05$).

5.5.4 *Davidson Trauma Scale*

A significant correlation was found between the DTS and Colour Trails 1 ($r = .17, p < .05$).

5.5.5 *Alcohol Use Disorders Identification Test*

A significant correlation was found between the AUDIT and Trail Making Test A ($r = -.20, p < .05$).

5.5.6 *Conflict Tactics Scale*

Spearman's correlations were computed to determine the nature of any relationships between the Conflict Tactics sub-scales and neurocognitive variables.

5.5.6.1 *Emotional Negotiation sub-scale* (items 1, 13, 39)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Category Fluency [Actions] ($r = -.20, p < .05$), WAIS-III Digit Symbol ($r = .17, p < .05$), and WAIS-III Symbol Search ($r = .18, p < .05$).

5.5.6.2 *Cognitive Negotiation sub-scale* (items 3, 59, 77)

A significant correlation was found between this sub-scale and the Category Fluency Test [Animals] ($r = -.19, p < .05$).

5.5.6.3 *Minor Psychological Aggression sub-scale* (items 5, 35, 49, 67)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Category Fluency [Actions] ($r = -.27, p < .01$), Color Trails 1 ($r = -.18, p < .05$), and BVMT-R [delay] ($r = -.18, p < .05$).

5.5.6.4 *Severe Psychological Aggression sub-scale* (items 25, 29, 65, 69)

Significant correlations were found between this sub-scale and the following neurocognitive variables: COWAT ($r = -.22, p < .01$), Category Fluency [Actions] ($r = -.27, p < .01$; $r = -.18, p < .05$), Trails A ($r = .20, p < .05$), Stroop Colour Naming ($r = -.25, p < .01$), and Stroop Colour Word incongruent condition ($r = -.18, p < .05$).

5.5.6.5 *Minor Physical Assault sub-scale* (items 7, 9, 17, 45, 53)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Category Fluency [Animals] ($r = -.18, p < .05$), WAIS-III Digit Symbol ($r = .18, p < .05$), and HVLTR ($r = .21, p < .05$).

5.5.6.6 *Severe Physical Assault sub-scale* (items 21, 27, 33, 37, 43, 61, 73)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Grooved Pegboard [dominant hand] ($r = -.18, p < .05$), PASAT ($r = .20, p < .05$), Trail Making A ($r = -.18, p < .05$; $r = .19, p < .05$), and WAIS-III Symbol Search ($r = .18, p < .05$).

5.5.6.7 *Minor Sexual Coercion sub-scale* (items 15, 51, 63)

Significant correlations were found between this sub-scale and the following neurocognitive variables: PASAT ($r = .21, p < .05$), Trail Making A ($r = .25, p < .01$), WAIS-III Digit Symbol ($r = .22, p < .05$), BVMT-R ($r = .19, p < .05$), BVMT-R [delay] ($r = .24, p < .01$), Halstead Category Test ($r = -.22, p < .01$), and WCST ($r = -.19, p < .05$).

5.5.6.8 *Severe Sexual Coercion sub-scale* (items 19, 47, 57, 75)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Grooved Pegboard [non-dominant hand] ($r = .18, p < .05$), COWAT ($r = -.17, p < .05$), Trails A ($r = .18, p < .05$), WAIS-III Symbol Search

($r = .18, p < .05$), WCST ($r = -.19, p < .05$), and Stroop Colour Word incongruent condition ($r = -.17, p < .05$).

5.5.6.9 *Minor Injury sub-scale* (items 11, 71)

No significant correlations were found between this sub-scale and any of the neurocognitive variables ($p > .05$).

5.5.6.10 *Severe Injury sub-scale* (items 23, 31, 41, 55)

Significant correlations were found between this sub-scale and the following neurocognitive variables: Grooved Pegboard [non-dominant hand] ($r = -.17, p < .05$), COWAT ($r = -.17, p < .05$), HVLT ($r = .17, p < .05$; $r = .18, p < .05$), and the Halstead Category Test ($r = .18, p < .05$).

5.6 *Analysis of Covariance (ANCOVA) of neurocognitive variables*

Univariate tests of significance using HIV status and childhood trauma as predictors were conducted. Age and education z scores were calculated from all neurocognitive raw scores and grouped in neuropsychological (NP) ability domains and a global NP score. The ability domains included: motor, verbal fluency, working memory, speed, learning, recall, and executive functions. The global score consisted of the average of all the NP ability domains. Results revealed no HIV or childhood trauma effects on any of the other ability domains except the recall domain. A significant HIV effect was evident for the recall domain, which consists of the HVLT-R and BVMT-R delay recall trials ($F = 4.19, p < .05$).

Univariate tests of significance using HIV status and childhood trauma as predictors and age and education as covariates were conducted on all NP raw data. Age and education were significantly correlated with most neuropsychological tests. Moreover, given that the control group was significantly younger and more educated than the cases, age and education were included as covariates. The results are summarised below and illustrated in table 8.

5.6.1 *The effect of HIV on neurocognitive outcomes*

Significant HIV effects were evident for the following neurocognitive tests: HVLT-R [total learning] ($F = 7.16, p < .01$), HVLT-R [delay] ($F = 13.0, p < .01$), and the Halstead Category test ($F = 4.77, p < .05$). No additional significant HIV effects were evident for the remaining neurocognitive variables ($p > .05$).

5.6.2 *The effect of childhood trauma on neurocognitive outcomes*

A significant childhood trauma effect was evident on the HVLT-R [delay trial] ($F = 4.90, p < .05$). No additional significant trauma effects were evident for the remaining neurocognitive variables ($p > .05$).

5.6.3 *The interactive effect of HIV and childhood trauma on neurocognitive outcomes*

A significant interaction effect was evident of the WAIS-III Symbol Search task ($F = 5.00, p < .05$). No additional significant interactive effects were evident for the remaining neurocognitive variables ($p > .05$).

5.7 *Summary of univariate findings*

In summary, univariate tests of significance on neuropsychological (NP) domain scores demonstrated only one HIV effect. This was evident for the memory recall domain.

Univariate tests of significance on NP raw data and using age and education as covariates demonstrated significant HIV effects in memory and executive functions. A significant trauma effect was evident in memory recall. Finally, a significant HIV and trauma interaction effect was evident for psychomotor speed.

5.8 *Multiple Regression Analysis*

A multiple regression analysis was conducted on the neurocognitive variables that were significant in the univariate tests of significance. These variables included the WAIS-III Symbol Search, HVLTR, HVLTR [delay trial] and the Halstead Category Test.

Predictor variables included in the regression model included HIV status, age, education, CTQ total score, DTS total score, and the CES-D total score.

The results are summarised in table 9.

5.8.1 *WAIS-III Symbol Search*

Results of the regression analysis revealed that HIV status, $\beta = 0.27$, $t(123) = 0.21$, $p = 0.84$, Age, $\beta = -0.41$, $t(123) = -4.52$, $p = 0.00$, Education, $\beta = 1.95$, $t(123) = 3.86$, $p = 0.00$, CTQ, $\beta = 0.04$, $t(123) = 1.12$, $p = 0.26$, DTS, $\beta = -0.02$, $t(123) = -0.83$, $p = 0.40$, and CES-D, $\beta = -0.02$, $t(123) = -0.40$, $p = 0.68$ could significantly account for 29.0% of the variance in WAIS-III Symbol Search, $F(6,123) = 8.19$, $p = 0.00$.

5.8.2 *HVLT-R*

Results of the regression analysis revealed that HIV status, $\beta = -2.36$, $t(123) = -2.83$, $p = 0.00$, Age, $\beta = -0.01$, $t(123) = -0.27$, $p = 0.78$, Education, $\beta = 0.85$, $t(123) = 2.76$, $p = 0.00$, CTQ, $\beta = -0.01$, $t(123) = -0.15$, $p = 0.87$, DTS, $\beta = -0.01$, $t(123) = -0.32$, $p = 0.74$, and CES-D, $\beta = 0.04$, $t(123) = 1.37$, $p = 0.17$ could significantly account for 14% of the variance in HVLT-R, $F(6,123) = 3.59$, $p = 0.00$.

5.8.3 *HVLT-R Delay Trial*

Results of the regression analysis revealed that HIV status, $\beta = -1.32$, $t(123) = -3.69$, $p = 0.00$, Age, $\beta = 0.01$, $t(123) = 0.63$, $p = 0.52$, Education, $\beta = 0.32$, $t(123) = 2.40$, $p = 0.02$, CTQ, $\beta = -0.01$, $t(123) = -0.65$, $p = 0.51$, DTS, $\beta = 0.00$, $t(123) = 0.01$, $p = 0.98$, and CES-D, $\beta = 0.01$, $t(123) = 0.35$, $p = 0.72$ could significantly account for 17% of the variance in HVLT-R delay trial, $F(6,123) = 4.33$, $p = 0.00$.

5.8.4 *Halstead Category Test*

Results of the regression analysis revealed that HIV status, $\beta = 10.4$, $t(123) = 2.23$, $p = 0.02$, Age, $\beta = -0.09$, $t(123) = -0.28$, $p = 0.77$, Education, $\beta = -7.85$, $t(123) = -4.5$, $p = 0.00$, CTQ, $\beta = 0.08$, $t(123) = 0.62$, $p = 0.53$, DTS, $\beta = 0.00$, $t(123) = 0.06$, $p = 0.94$, and CES-D, $\beta = -0.06$, $t(123) = -0.35$, $p = 0.72$ could significantly account for 22% of the variance in HCT, $F(6,123) = 5.73$, $p = 0.00$.

5.9 *Best Subsets Regression Analysis*

A best subsets regression analysis was conducted on all the neurocognitive variables using demographic and clinical characteristics and self-report instruments as predictor variables. The results are summarised in table 10.

5.9.1 *WAIS-III Symbol Search*

Results of the best subsets regression analysis revealed that Age, $\beta = -0.36$, $t(123) = -4.49$, $p = 0.00$, Education, $\beta = 1.88$, $t(123) = 3.98$, $p = 0.00$, CTQ sexual abuse, $\beta = 0.25$, $t(123) = 1.99$, $p = 0.04$, CES-D, $\beta = -0.06$, $t(123) = -1.69$, $p = 0.09$, CTS emotional negotiation, $\beta = 2.35$, $t(123) = 1.92$, $p = 0.06$ and CTS minor physical assault, $\beta = 4.18$, $t(123) = 2.52$, $p = 0.01$ could significantly account for 35.0% of the variance in WAIS-III Symbol Search, $F(6,123) = 11.1$, $p = 0.00$.

5.9.2 *HVLT-R*

Results of the regression analysis revealed that HIV status, $\beta = -2.29$, $t(123) = -3.09$, $p = 0.00$, Education, $\beta = 0.74$, $t(123) = 2.56$, $p = 0.01$, AUDIT, $\beta = 0.10$, $t(123) = 1.36$, $p = 0.17$, CTS minor psychological aggression, $\beta = -1.36$, $t(123) = -1.63$, $p = 0.10$, CTS minor physical assault, $\beta = 2.48$, $t(123) = 2.36$, $p = 0.01$, and CTS severe injury, $\beta = 2.55$, $t(123) = 1.86$, $p = 0.06$ could significantly account for 22% of the variance in HVLT-R, $F(6,123) = 5.95$, $p = 0.00$.

5.9.3 *HVLT-R Delay Trial*

Results of the regression analysis revealed that HIV status, $\beta = -1.20$, $t(123) = -3.85$, $p = 0.00$, Education, $\beta = 0.28$, $t(123) = 2.19$, $p = 0.02$, CTS cognitive negotiation, $\beta = 0.79$, $t(123) = 2.36$, $p = 0.01$, CTS minor sexual coercion, $\beta = -1.48$, $t(123) = -2.57$, $p = 0.01$, CTS minor injury, $\beta = -0.69$, $t(123) = -1.08$, $p = 0.07$, and CTS severe injury, $\beta = 1.48$, $t(123) = 2.51$, $p = 0.01$ could significantly account for 26% of the variance in HVLT-R delay trial, $F(6,123) = 7.24$, $p = 0.00$.

5.9.4 *Halstead Category Test*

Results of the regression analysis revealed that HIV status, $\beta = 7.64$, $t(123) = 1.82$, $p = 0.07$, Education, $\beta = -7.10$, $t(123) = -4.28$, $p = 0.00$, CTQ physical abuse, $\beta = -0.57$, $t(123) = -1.38$, $p = 0.17$, CTQ emotional neglect, $\beta = 0.84$, $t(123) = 1.94$, $p = 0.05$, CTS emotional negotiation, $\beta = -6.32$, $t(123) = -1.47$, $p = 0.14$, and CTS minor sexual coercion, $\beta = -9.22$, $t(123) = -1.58$, $p = 0.16$ could significantly account for 28% of the variance in HCT, $F(6,123) = 7.88$, $p = 0.00$.

5.9.5 *Grooved Pegboard Dominant Hand*

Results of the regression analysis revealed that Age, $\beta = 0.88$, $t(123) = 6.08$, $p = 0.00$, Education, $\beta = -2.29$, $t(123) = -2.82$, $p = 0.01$, CTS emotional negotiation, $\beta = -7.28$, $t(123) = -2.74$, $p = 0.01$; $\beta = 5.16$, $t(123) = 2.13$, $p = 0.03$, CTS severe psychological aggression, $\beta = -4.5$, $t(123) = -1.53$, $p = 0.13$, and CTS minor sexual coercion, $\beta = 5.61$, $t(123) = 2.49$, $p = 0.01$ could significantly account for 34% of the variance in Grooved Pegboard (dominant hand), $F(6,123) = 10.6$, $p = 0.00$.

5.9.6 *Grooved Pegboard Non-dominant Hand*

Results of the regression analysis revealed that Age, $\beta = 0.75$, $t(123) = 4.78$, $p = 0.00$, CES-D, $\beta = 0.24$, $t(123) = 3.35$, $p = 0.00$, CTS emotional negotiation, $\beta = -6.77$, $t(123) = -2.65$, $p = 0.01$, CTS severe psychological aggression, $\beta = 8.34$, $t(123) = 2.27$, $p = 0.02$, CTS minor physical assault, $\beta = -8.77$, $t(123) = -2.98$, $p = 0.00$, and CTS minor sexual coercion, $\beta = 5.75$, $t(123) = 2.35$, $p = 0.01$ could significantly account for 34% of the variance in Grooved Pegboard (non-dominant hand), $F(6,123) = 10.5$, $p = 0.00$.

5.9.7 *COWAT*

Results of the regression analysis revealed that Education, $\beta = 2.65$, $t(123) = 4.34$, $p = 0.00$, CTQ physical neglect, $\beta = 0.29$, $t(123) = 1.43$, $p = 0.15$, CTS severe psychological aggression, $\beta = -3.89$, $t(123) = -1.65$, $p = 0.10$; $\beta = -4.69$, $t(123) = -2.63$, $p = 0.01$, CTS minor sexual coercion, $\beta = 5.58$, $t(123) = 2.02$, $p = 0.04$, and CTS minor injury, $\beta = 3.50$, $t(123) = 1.86$, $p = 0.06$ could significantly account for 24% of the variance in COWAT, $F(6,123) = 6.29$, $p = 0.00$.

5.9.8 *Category Fluency (Animals)*

Results of the regression analysis revealed that Age, $\beta = -0.09$, $t(123) = -2.47$, $p = 0.01$, Education, $\beta = 0.66$, $t(123) = 3.10$, $p = 0.00$, CTS cognitive negotiation, $\beta = -1.08$, $t(123) = -2.08$, $p = 0.01$; $\beta = 1.03$, $t(123) = 1.56$, $p = 0.12$, CTS minor psychological aggression, $\beta = 1.23$, $t(123) = 1.84$, $p = 0.06$, and CTS minor sexual coercion, $\beta = -1.09$, $t(123) = -1.95$, $p = 0.05$ could significantly account for 21% of the variance in Category Fluency (Animals), $F(6,123) = 5.52$, $p = 0.00$.

5.9.9 *Category Fluency (Actions)*

Results of the regression analysis revealed that Education, $\beta = 1.05$, $t(123) = 4.17$, $p = 0.00$, CTQ sexual abuse, $\beta = 0.08$, $t(123) = 1.17$, $p = 0.24$, CTS emotional negotiation, $\beta = -2.64$, $t(123) = -3.26$, $p = 0.00$; $\beta = 1.86$, $t(123) = 2.43$, $p = 0.02$, CTS minor psychological aggression, $\beta = -1.22$, $t(123) = -1.57$, $p = 0.11$ and CTS severe psychological aggression, $\beta = -1.46$, $t(123) = -1.59$, $p = 0.11$ could significantly account for 26% of the variance in Category Fluency (Actions), $F(6,123) = 7.27$, $p = 0.00$.

5.9.10 *PASAT*

Results of the regression analysis revealed that Age, $\beta = -0.30$, $t(123) = -2.70$, $p = 0.01$, Education, $\beta = 2.19$, $t(123) = 3.37$, $p = 0.00$, CTQ emotional neglect, $\beta = -0.42$, $t(123) = -2.10$, $p = 0.03$, CTQ physical neglect, $\beta = 0.48$, $t(123) = 1.75$, $p = 0.08$, CTS minor physical assault, $\beta = 4.44$, $t(123) = 1.99$, $p = 0.04$, and CTS minor sexual coercion, $\beta = 6.03$, $t(123) = 2.62$, $p = 0.01$ could significantly account for 26% of the variance in PASAT, $F(6,123) = 7.28$, $p = 0.00$.

5.9.11 *Trails A*

Results of the regression analysis revealed that Age, $\beta = 0.65$, $t(123) = 2.89$, $p = 0.00$, CTQ physical neglect, $\beta = 1.14$, $t(123) = 2.54$, $p = 0.01$, CTS minor psychological aggression, $\beta = -9.72$, $t(123) = -2.50$, $p = 0.01$, CTS severe psychological aggression, $\beta = 16.0$, $t(123) = 2.98$, $p = 0.00$, CTS minor physical assault, $\beta = -9.02$, $t(123) = -2.18$, $p = 0.03$, and CTS minor sexual coercion, $\beta = 12.4$, $t(123) = 3.56$, $p = 0.00$ could significantly account for 27% of the variance in Trails A, $F(6,123) = 7.64$, $p = 0.00$.

5.9.12 *Colour Trails 1*

Results of the regression analysis revealed that Age, $\beta = 0.42$, $t(123) = 1.91$, $p = 0.06$, CES-D, $\beta = 0.31$, $t(123) = 3.02$, $p = 0.00$, LEC, $\beta = -0.95$, $t(123) = -2.09$, $p = 0.04$, CTS minor psychological aggression, $\beta = -9.69$, $t(123) = -2.54$, $p = 0.01$, CTS severe psychological aggression, $\beta = 8.38$, $t(123) = 2.34$, $p = 0.02$, and CTS severe injury, $\beta = -10.0$, $t(123) = -1.69$, $p = 0.09$ could significantly account for 21% of the variance in Colour Trails 1, $F(6,123) = 5.39$, $p = 0.00$.

5.9.13 *Colour Trails 2*

Results of the regression analysis revealed that Age, $\beta = 1.25$, $t(123) = 2.45$, $p = 0.02$, LEC, $\beta = -2.17$, $t(123) = -2.04$, $p = 0.04$, CTS cognitive negotiation, $\beta = -13.0$, $t(123) = -1.65$, $p = 0.10$, CTS minor physical assault, $\beta = -30.0$, $t(123) = -2.86$, $p = 0.00$, CTS minor sexual coercion, $\beta = 14.23$, $t(123) = 1.77$, $p = 0.07$, and CTS minor injury, $\beta = 30.8$, $t(123) = 2.96$, $p = 0.00$ could significantly account for 15% of the variance in Colour Trails 2, $F(6,123) = 3.50$, $p = 0.00$.

5.9.14 *WAIS-III Digit Symbol*

Results of the regression analysis revealed that Age, $\beta = -0.85$, $t(123) = -6.47$, $p = 0.00$, Education, $\beta = 3.31$, $t(123) = 4.39$, $p = 0.00$, CTQ physical neglect, $\beta = -0.81$, $t(123) = -3.08$, $p = 0.00$, CTS minor psychological aggression, $\beta = 4.24$, $t(123) = 1.86$, $p = 0.06$, CTS severe psychological aggression, $\beta = -5.27$, $t(123) = -1.69$, $p = 0.09$, and CTS minor physical assault, $\beta = 6.37$, $t(123) = 2.33$, $p = 0.02$ could significantly account for 46% of the variance in WAIS-III Digit Symbol, $F(6,123) = 17.2$, $p = 0.00$.

5.9.15 *Spatial Span*

Results of the regression analysis revealed that Age, $\beta = -0.10$, $t(123) = -2.72$, $p = 0.01$, Education, $\beta = 0.47$, $t(123) = 2.07$, $p = 0.03$, CTQ emotional abuse, $\beta = 0.09$, $t(123) = 1.88$, $p = 0.06$, CES-D, $\beta = -0.05$, $t(123) = -2.83$, $p = 0.01$, LEC, $\beta = 0.16$, $t(123) = 2.06$, $p = 0.04$, and CTS emotional negotiation, $\beta = 1.44$, $t(123) = 2.48$, $p = 0.01$ could significantly account for 24% of the variance in Spatial Span, $F(6,123) = 6.31$, $p = 0.00$.

5.9.16 *BVMT-R*

Results of the regression analysis revealed that Age, $\beta = -0.38$, $t(123) = -5.04$, $p = 0.00$, Education, $\beta = 1.59$, $t(123) = 3.67$, $p = 0.00$, CTQ physical abuse, $\beta = 0.20$, $t(123) = 1.98$, $p = 0.04$, CTS minor physical assault, $\beta = 4.25$, $t(123) = 2.75$, $p = 0.01$, CTS severe physical assault, $\beta = -5.58$, $t(123) = -2.57$, $p = 0.01$, and CTS minor sexual coercion, $\beta = -3.30$, $t(123) = -2.80$, $p = 0.01$ could significantly account for 33% of the variance in BVMT-R, $F(6,123) = 10.2$, $p = 0.00$.

5.9.17 *BVMT-R (Delay trial)*

Results of the regression analysis revealed that HIV status, $\beta = -0.70$, $t(123) = -1.41$, $p = 0.15$, Age, $\beta = -0.10$, $t(123) = -3.20$, $p = 0.00$, Education, $\beta = 0.61$, $t(123) = 3.36$, $p = 0.00$, CTS minor psychological aggression, $\beta = -1.25$, $t(123) = -2.34$, $p = 0.02$; $\beta = 1.48$, $t(123) = 3.06$, $p = 0.00$, and CTS severe physical assault, $\beta = -1.35$, $t(123) = -1.62$, $p = 0.10$ could significantly account for 32% of the variance in BVMT-R (delay trial), $F(6,123) = 9.51$, $p = 0.00$.

5.9.18 WCST

Results of the regression analysis revealed that Education, $\beta = -1.51$, $t(123) = -1.75$, $p = 0.08$, CTQ physical neglect, $\beta = -0.57$, $t(123) = -1.82$, $p = 0.07$, DTS, $\beta = 0.06$, $t(123) = 1.84$, $p = 0.06$, CTS minor psychological aggression, $\beta = 3.36$, $t(123) = 1.34$, $p = 0.18$; $\beta = -4.93$, $t(123) = -1.81$, $p = 0.07$, and CTS minor physical assault, $\beta = -5.87$, $t(123) = -2.08$, $p = 0.04$ could significantly account for 11% of the variance in WCST, $F(6,123) = 2.5$, $p = 0.03$.

5.9.19 Stroop Word Naming

Results of the regression analysis revealed that Education, $\beta = 2.56$, $t(123) = 2.38$, $p = 0.02$, CTQ physical abuse, $\beta = -0.46$, $t(123) = -1.77$, $p = 0.07$, CES-D, $\beta = -0.13$, $t(123) = -1.48$, $p = 0.13$, AUDIT, $\beta = 0.63$, $t(123) = 2.18$, $p = 0.03$, CTS minor physical assault, $\beta = -6.21$, $t(123) = -1.84$, $p = 0.06$, and CTS severe injury, $\beta = 9.07$, $t(123) = 1.81$, $p = 0.07$ could significantly account for 16% of the variance in Stroop word, $F(6,123) = 3.94$, $p = 0.00$.

5.9.20 Stroop Colour Naming

Results of the regression analysis revealed that CTQ physical abuse, $\beta = -0.57$, $t(123) = -2.71$, $p = 0.01$, LEC, $\beta = 0.51$, $t(123) = 1.66$, $p = 0.09$, AUDIT, $\beta = 0.48$, $t(123) = 2.19$, $p = 0.02$, CTS emotional negotiation, $\beta = 6.01$, $t(123) = 2.49$, $p = 0.01$, CTS severe psychological aggression, $\beta = -8.20$, $t(123) = -3.56$, $p = 0.00$, and CTS minor sexual coercion, $\beta = -3.62$, $t(123) = -1.65$, $p = 0.09$ could significantly account for 20% of the variance in Stroop Colour Naming, $F(6,123) = 5.12$, $p = 0.00$.

5.9.21 *Stroop Colour Word Incongruent Condition*

Results of the regression analysis revealed that Age, $\beta = -0.35$, $t(123) = -3.48$, $p = 0.00$, CTQ emotional neglect, $\beta = -.023$, $t(123) = -1.54$, $p = 0.12$, CTS cognitive negotiation, $\beta = 3.89$, $t(123) = 2.37$, $p = 0.01$, CTS severe psychological aggression, $\beta = -5.14$, $t(123) = -3.05$, $p = 0.00$, CTS minor physical assault, $\beta = 4.64$, $t(123) = 2.19$, $p = 0.03$, and CTS minor sexual coercion, $\beta = -2.63$, $t(123) = -1.69$, $p = 0.09$ could significantly account for 21% of the variance in Stroop Colour Word, $F(6,123) = 5.52$, $p = 0.00$.

5.10 *Summary of multivariate analyses*

Two multivariate regression analyses were conducted to determine the predictive ability of a combination of independent variables. The neurocognitive tests were selected from significant univariate analyses. These tests comprise the HVLT-R, the Halstead Category Test, and the WAIS-III Symbol Search task. Independent variables used in the model included: HIV status, age, education, childhood trauma (CTQ), depression (CES-D), alcohol dependence/abuse (AUDIT), traumatic life experiences (LEC) and adult posttraumatic stress symptoms (DTS). A multiple regression analysis showed that the model could significantly account for 29.0% of the variance in WAIS-III Symbol Search, 14% in the HVLT-R learning trial, 17% in the HVLT-R delay trial, and 22% in the Halstead Category Test. A best subsets regression analysis was conducted in order to determine the best model of predictors for each of these dependent variables. Results revealed that the models chosen could predict 22% in HVLT-R, 26% in HVLT-R delay, 28% in the Halstead Category Test, and 46% in the WAIS-III Symbol Search task, respectively.

Table 1. *Demographic Characteristics of the Sample (N = 130)*

	N	f	(%)	M	SD	Range
Participants	130		(100)			
		83	(64)			
		47	(36)			
Gender	130		(100)			
Age (years)	130		(100)	29.6	7.0	18-50
Ethnicity	130		(100)			
		125	(96)			
		5	(4)			
Home language	130					
		115	(88)			
		6	(5)			
		4	(3)			
		5	(4)			
Handedness	130					
		121	(93)			
		9	(7)			
Marital status	130					
		93	(71)			
		26	(19.8)			
		3	(2.3)			
		4	(3.1)			
		3	(2.3)			
		1	(0.8)			
Education	130			10.7	1.2	7-14
		7	(5)			
		123	(95)			
		94	(71)			
		31	(24)			
		4	(4)			
Employment	130		(100)			
		46	(35)			
		84	(65)			
Breadwinner	130		(100)			
		51	(39)			
		79	(61)			
Annual household income	130		(100)			
		103	(79)			
		21	(16)			
		1	(1)			
		2	(2)			
		1	(1)			
		2	(2)			

Table 2. *Clinical Characteristics of the HIV-positive Sample (n = 83)*

	N	f	(%)	M	SD	Range
CD4 lymphocyte count	83		(64)	405	259.8	35-1529
< 200 cells/mm ³		18	(13.8)			
> 200 cells/mm ³		65	(50.2)			
Viral load	83		(64)	105169.5	407459.5	Below the detectable limit - 3,200 000 cells/mm ³
Below the detectable limit		6	(4.6)			
HIV Clade	83		(64)			
Clade C		64	(76)			
Negative		15	(18)			
No sequence		1	(1.2)			
Possible recombinant sequence		3	(3.6)			
Antiretroviral treatment						
Yes		13	(15.5)			
No		70	(83.3)			

Table 3. *Demographic and Clinical Characteristics of the HIV & Trauma Groups*

Variable		HIV-positive without childhood trauma (n = 35)	HIV-positive with childhood trauma (n = 48)	HIV-negative without childhood trauma (n = 27)	HIV-negative with childhood trauma (n = 20)
Mean age (SD)		31.5 (6.03)	31.7 (6.85)	25.0 (5.72)	27.7 (7.72)
Mean Education (SD)		10.6 (1.26)	10.5 (1.23)	11.4 (0.93)	10.6 (1.34)
Mean CD4 count		684	601	N.A.	N.A.
Mean Viral load		40425	528046	N.A.	N.A.
HIV Subtype C (N)		25	39	N.A.	N.A.
On ART (N)		9	4	N.A.	N.A.
Handedness (N)	Left	2	2	3	2
	Right	33	46	24	18
Ethnicity (N)	Black	33	47	25	20
	Coloured	2	1	2	0
Marital status (N)	Single	23	32	23	15
	Married	9	8	4	5
Home language (N)	Xhosa	32	42	24	17
	Afrikaans	2	2	2	0
	English	1	3	0	0
Employed (N)		20	32	18	14
Breadwinner (N)		16	23	6	6
Annual household income (N)	< R10 000	25	38	21	19

N.A = Not Applicable

Table 4. *Pearson's Correlations between Demographic and Clinical Characteristics and Neurocognitive variables (N = 130)*

Dependent variables	Age	Education	CD4 count	Viral load
Pegs (dominant hand)	< .01	< .01	0.67	0.41
Pegs (non-dominant hand)	< .01	0.06	0.58	0.17
COWAT (FAS)	< .05	< .01	0.82	0.70
Category Fluency (Animals)	.01	< .01	0.58	0.89
Category Fluency (Actions)	0.43	< .01	0.51	0.78
PASAT	.01	< .01	0.21	0.44
Trails A	< .01	< .05	0.42	0.70
Color Trails 1	< .05	< .05	0.29	0.09
Color Trails 2	< .05	0.11	0.35	0.32
Digit Symbol	< .01	< .01	0.46	0.99
Symbol Search	< .01	< .01	0.82	0.84
Spatial Span	< .01	< .01	0.83	0.19
BVMT-R	< .01	< .01	0.93	0.65
BVMT-R (delay)	< .01	< .01	0.95	0.98
HVLT-R	0.13	< .01	0.35	0.93
HVLT-R (delay)	0.27	< .01	0.82	0.87
HCT	0.25	< .01	0.68	0.39
WCST	0.44	0.08	0.51	0.40
Stroop Word	0.35	< .01	0.40	0.64
Stroop Color Naming	0.13	< .05	0.41	0.70
Stroop Color Word	< .01	0.22	0.50	0.34

Table 5. *Pearson's Correlations between Independent and Dependent variables**(N = 130)*

Dependent variables	CTQ	CES-D	DTS	LEC	AUDIT
	Total	Total	Total	Total	Total
Pegs (dominant hand)	0.18	< .01	0.07	0.95	0.32
Pegs (non-dominant hand)	< .05	< .01	0.06	0.73	0.42
COWAT (FAS)	0.64	0.11	0.19	0.37	0.37
Category Fluency (Animals)	0.30	0.36	0.60	0.39	0.28
Category Fluency (Actions)	0.62	< .05	0.16	0.39	0.40
PASAT	0.39	< .05	0.53	0.32	0.51
Trails A	< .05	0.08	0.60	0.56	< .05
Color Trails 1	0.32	< .01	< .05	0.11	0.30
Color Trails 2	0.31	0.35	0.57	0.15	0.65
Digit Symbol	< .01	< .05	0.19	0.76	0.26
Symbol Search	0.49	< .05	0.11	0.75	0.30
Spatial Span	0.82	< .01	0.09	0.17	0.76
BVMT-R	0.56	< .05	0.65	0.93	0.21
BVMT-R (delay)	0.47	< .05	0.30	0.87	0.45
HVLT-R	0.65	0.99	0.76	0.48	0.39
HVLT-R (delay)	0.21	0.22	0.29	0.29	0.40
HCT	0.10	0.11	0.23	0.79	0.97
WCST	0.45	0.44	0.09	0.58	0.73
Stroop Word	< .05	< .05	0.47	0.97	0.18
Stroop Color Naming	0.19	0.20	0.87	0.43	0.09
Stroop Color Word	0.13	0.16	0.50	0.69	0.09

Table 6. *Descriptive Statistics of Self-report Instruments (N=130)*

Scale	Subscale	Mean	SD	Minimum	Maximum
CTQ total		46.3	16.4	25	96
	Physical abuse	8.20	5.09	5	25
	Physical neglect	9.24	3.55	5	21
	Sexual abuse	6.93	4.52	5	25
	Emotional abuse	10.2	5.73	5	25
	Emotional neglect	11.7	4.92	5	25
CES-D total		13.6	15.3	0	60
LEC total		4.80	3.41	0	18
DTS total		21.5	31.3	0	116
AUDIT total		2.87	4.65	0	24

Table 7. *Childhood Trauma Questionnaire Scores (N = 130)*

		Physical Abuse	Sexual Abuse	Emotional Abuse	Emotional Neglect	Physical Neglect	Total Score
HIV-negative without childhood trauma	Min	5.00	5.00	5.00	5.00	5.00	25.00
	Max	10.00	7.00	11.00	13.00	12.00	40.00
	M	5.51	5.07	6.11	8.37	7.03	32.1
	SD	1.34	.384	1.86	2.37	1.91	4.04
HIV-positive without childhood trauma	Min	5.00	5.00	5.00	5.00	5.00	25.00
	Max	9.00	9.00	12.00	19.00	13.00	40.00
	M	5.40	5.17	5.91	8.82	6.85	32.1
	SD	1.14	.746	1.80	3.14	2.03	4.44
HIV-positive with childhood trauma	Min	5.00	5.00	5.00	6.00	5.00	41.00
	Max	25.00	25.00	25.00	25.00	19.00	89.00
	M	10.2	9.14	13.1	14.7	11.00	58.2
	SD	5.58	6.03	5.26	4.68	3.18	10.9
HIV-negative with childhood trauma	Min	5.00	5.00	7.00	7.00	7.00	41.00
	Max	25.00	21.00	25.00	23.00	21.00	96.00
	M	11.8	7.20	16.0	14.1	12.1	61.3
	SD	6.73	4.92	5.39	4.94	3.73	15.0

Table 8. *Analysis of covariance (N = 130)*

Dependent variables	HIV		Child-hood trauma		HIV* Child-hood trauma	
	F	p	F	p	F	p
Pegs (dominant hand)	0.45	0.51	0.18	0.67	2.04	0.16
Pegs (non-dominant hand)	0.42	0.52	0.33	0.57	1.79	0.18
COWAT (FAS)	0.95	0.33	3.49	0.06	0.03	0.87
Category Fluency (Animals)	0.60	0.44	0.79	0.37	0.03	0.86
Category Fluency (Actions)	0.03	0.86	0.96	0.33	0.62	0.43
PASAT	0.04	0.83	1.73	0.19	0.01	0.93
Trails A	0.02	0.88	0.73	0.39	0.09	0.77
Color Trails 1	0.45	0.50	0.04	0.84	0.01	0.98
Color Trails 2	0.03	0.87	0.27	0.60	0.09	0.76
Digit Symbol	0.12	0.73	3.38	0.07	0.22	0.64
Symbol Search	0.01	0.92	5.04	< .05	5.00	< .05
Spatial Span	0.50	0.48	2.46	0.12	1.00	0.32
BVMT-R	0.02	0.88	0.91	0.34	0.18	0.67
BVMT-R (delay)	1.08	0.30	0.99	0.32	0.57	0.45
HVLT-R	7.16	< .01	0.33	0.57	0.68	0.41
HVLT-R (delay)	13.0	< .01	4.90	< .05	0.99	0.32
HCT	4.77	< .05	0.18	0.67	0.79	0.38
WCST	0.15	0.69	0.75	0.39	0.84	0.36
Stroop Word	0.14	0.71	2.27	0.13	0.13	0.71
Stroop Color Naming	0.00	0.96	0.05	0.81	0.01	0.90
Stroop Color Word	1.04	0.31	1.57	0.21	0.51	0.48

Table 9. *Summary of Multiple Regression Analysis (N = 130)*

DV	Predictor	R ²	ΔR ²	β	p
WAIS-III Symbol Search		0.29	0.25		< .01
	HIV Status			0.27	0.84
	Age			-0.41	< .01
	Education			1.95	< .01
	CTQ			0.04	0.26
	DTS			-0.02	0.40
	CES-D			-0.02	0.68
HVLТ-R		0.15	0.11		< .01
	HIV Status			-2.36	< .01
	Age			-0.01	0.78
	Education			0.85	< .01
	CTQ			-0.01	0.88
	DTS			-0.01	0.75
	CES-D			0.04	0.17
HVLТ-R (Delay)		0.17	0.13		< .01
	HIV Status			-1.32	< .01
	Age			0.01	0.53
	Education			0.32	< .05
	CTQ			-0.01	0.52
	DTS			0.00	0.99
	CES-D			0.01	0.72
HCT		0.22	0.18		< .01
	HIV Status			10.4	< .05
	Age			-0.09	0.77
	Education			-7.85	< .01
	CTQ			0.08	0.53
	DTS			0.00	0.95
	CES-D			-0.06	0.73

Table 10. *Best Subsets Regression Analysis (N = 130)*

DV	Predictor	R ²	ΔR ²	β	p
WAIS-III Symbol Search		0.35	0.32		< .01
	Age			-0.36	< .01
	Education			1.88	< .01
	CTQ sexual abuse			0.25	< .05
	CES-D			-0.06	0.09
	CTS emotional negotiation			2.35	0.06
	CTS minor physical assault			4.18	< .05
HVLTR		0.22	0.18		< .01
	HIV status			0.74	< .01
	Education			0.28	< .05
	AUDIT			0.07	0.17
	CTS minor psychological aggression			0.83	0.10
	CTS minor physical assault			1.05	< .05
	CTS severe injury			1.37	0.07
HVLTR (Delay)		0.26	0.22		< .01
	HIV status			-1.20	< .01
	Education			0.27	< .05
	CTS cognitive negotiation			0.79	< .05
	CTS minor sexual coercion			-1.48	< .05
	CTS minor injury			-0.69	0.07
	CTS severe injury			1.47	< .05
HCT		0.28	0.24		< .01
	HIV status			7.64	0.07
	Education			-7.10	< .01
	CTQ physical abuse			-0.56	0.17
	CTQ emotional neglect			0.84	0.05
	CTS emotional negotiation			-6.32	0.14
	CTS minor sexual coercion			-9.22	0.12
Pegs (dominant hand)		0.34	0.31		< .01
	Age			0.88	< .01
	Education			-2.29	< .05
	CTS emotional negotiation			-7.28	< .05
	CTS emotional negotiation			5.16	< .05
	CTS severe psychological aggression			-4.53	0.13
	CTS minor sexual coercion			5.61	< .05
Pegs (non-dominant hand)		0.34	0.31		< .01
	Age			0.74	< .01
	CES-D			0.24	< .01
	CTS emotional negotiation			-6.77	< .05
	CTS severe psychological aggression			8.34	< .05
CTS minor physical assault			-8.69	< .01	

	CTS minor sexual coercion			5.75	< .05
COWAT (FAS)		0.24	0.19		< .01
	Education			2.65	< .01
	CTQ physical neglect			0.29	0.15
	CTS severe psychological aggression			-3.89	0.10
	CTS severe psychological aggression			-4.69	< .05
	CTS minor sexual coercion			5.58	< .05
	CTS minor injury			3.50	0.06
Category Fluency (Animals)		0.21	0.17		< .01
	Age			-0.09	< .05
	Education			0.66	< .01
	CTS cognitive negotiation			-1.80	< .05
	CTS cognitive negotiation			1.03	0.12
	CTS minor psychological aggression			1.23	0.07
	CTS minor sexual coercion			-1.09	0.05
Category Fluency (Actions)		0.26	0.23		< .01
	Education			1.05	< .01
	CTQ sexual abuse			0.08	0.24
	CTS emotional negotiation			-2.64	< .01
	CTS emotional negotiation			1.86	< .05
	CTS minor psychological aggression			-1.22	0.12
	CTS severe psychological aggression			-1.46	0.11
PASAT		0.26	0.23		< .01
	Age			-0.30	< .05
	Education			2.19	< .01
	CTQ emotional neglect			-0.42	< .05
	CTQ physical neglect			0.48	0.08
	CTS minor physical assault			4.44	< .05
	CTS minor sexual coercion			6.03	< .05
Trails A		0.27	0.24		< .01
	Age			0.65	< .01
	CTQ physical neglect			1.14	< .05
	CTS minor psychological aggression			-9.72	< .05
	CTS severe psychological aggression			16.0	< .01
	CTS minor physical assault			-9.02	< .05
	CTS minor sexual coercion			12.4	< .01
Colour Trails 1		0.21	0.17		< .01
	Age			0.42	0.06
	CES-D			0.31	< .01
	LEC			-0.95	< .05
	CTS minor psychological aggression			-9.69	< .05

	CTS severe psychological aggression	8.38	< .05
	CTS severe injury	-10.0	0.09
Colour Trails 2		0.15	0.10
			< .01
	Age	1.25	< .05
	LEC	-2.17	< .05
	CTS cognitive negotiation	-13.0	0.10
	CTS minor physical assault	-30.0	< .01
	CTS minor sexual coercion	14.2	0.08
	CTS minor injury	30.8	< .01
Digit Symbol		0.46	0.43
			< .01
	Age	-0.85	< .01
	Education	3.31	< .01
	CTQ physical neglect	-0.81	< .01
	CTS minor psychological aggression	4.24	0.06
	CTS severe psychological aggression	-5.27	0.09
	CTS minor physical assault	6.37	< .05
Spatial Span		0.35	0.32
			< .01
	Age	-0.10	< .05
	Education	0.47	< .05
	CTQ emotional abuse	0.09	0.06
	CES-D	-0.05	< .05
	LEC	0.16	< .05
	CTS emotional negotiation	1.44	< .05
BVMT-R		0.33	0.30
			< .01
	Age	-0.38	< .01
	Education	1.59	< .01
	CTQ physical abuse	0.20	< .05
	CTS minor physical assault	4.25	< .05
	CTS severe physical assault	-5.58	< .05
	CTS minor sexual coercion	-3.30	< .05
BVMT-R (Delay)		0.32	0.28
			< .01
	HIV status	-0.70	0.15
	Age	-0.10	< .01
	Education	0.61	< .01
	CTS minor psychological aggression	-1.25	< .05
	CTS minor psychological aggression	1.48	< .01
	CTS severe physical assault	-1.35	0.10
WCST		0.11	0.06
			< .05
	Education	-1.51	0.08
	CTQ physical neglect	-0.57	0.07
	DTS	0.06	0.07
	CTS minor psychological aggression	3.36	0.19
	CTS minor psychological aggression	-4.93	0.07
	CTS minor physical assault	-5.87	< .05

Stroop word		0.16	0.12		< .01
	Education			2.56	< .05
	CES-D			-0.13	0.07
	AUDIT			0.63	< .05
	CTS minor physical assault			-6.21	0.07
	CTS severe injury			9.07	0.07
Stroop Colour Naming		0.20	0.16		< .01
	CTQ physical abuse			-0.57	< .05
	LEC			0.51	0.09
	AUDIT			0.48	< .05
	CTS emotional negotiation			6.01	< .05
	CTS severe psychological aggression			-8.20	< .01
	CTS minor sexual coercion			-3.62	0.09
Stroop Colour Word		0.21	0.17		< .01
	Age			-0.35	< .01
	CTQ emotional neglect			-0.23	0.13
	CTS cognitive negotiation			3.89	< .05
	CTS severe psychological aggression			-5.14	< .01
	CTS minor physical assault			4.64	< .05
	CTS minor sexual coercion			-2.63	0.09

Table 11. *M.I.N.I.-Plus diagnoses (N = 130)*

Psychiatric Diagnosis	N	%
MDE current	10	7.6
MDE past	22	16.8
MDE with melancholic features	1	0.8
Low Suicidality	12	9.2
Medium Suicidality	1	0.8
High Suicidality	11	8.4
Lifetime panic disorder	1	0.8
Posttraumatic stress disorder (PTSD)	2	1.5
Generalised anxiety disorder (GAD)	1	0.8
Body dysmorphic disorder	1	0.8
Premenstrual dysphoric disorder	2	1.5

5.11 Given the high comorbidity burden among HIV-positive individuals and victims of childhood maltreatment, the researcher sought to investigate the mental health outcomes in HIV-positive victims of childhood maltreatment. The next part of this chapter comprises a systematic review which was conducted and prepared for submission to an internationally accredited journal. The manuscript focuses on the mental health outcomes in HIV-infected individuals with a history of childhood maltreatment.

**MENTAL HEALTH OUTCOMES IN HIV AND CHILDHOOD MALTREATMENT:
A SYSTEMATIC REVIEW**

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Abstract

Background Alarming high rates of childhood maltreatment have been documented in HIV-positive men and women in both the developed and developing world. In addition, mental disorders such as substance, mood, and anxiety disorders are highly prevalent in both HIV-infected individuals and victims of childhood maltreatment separately. However, there is a paucity of research investigating the mental health outcomes associated with childhood maltreatment in the context of HIV infection.

Objectives The present systematic review assessed mental health outcomes in HIV-positive individuals who were victims of childhood maltreatment.

Methods A systematic search of all retrospective, prospective, or clinical trial studies assessing mental health outcomes associated with HIV and childhood maltreatment. The following online databases were searched: PubMed, Social Science Citation Index, and the Cochrane Library (the Cochrane Central Register of Controlled Trials and the Cochrane Developmental, Psychosocial and Learning Problems, HIV/AIDS, and Depression, Anxiety and Neurosis registers).

Results We identified 34 studies suitable for inclusion. A total of 14 935 subjects were included in these studies. A variety of mixed mental health outcomes were reported. The most commonly reported psychiatric disorders among HIV-positive individuals with a history of childhood maltreatment included: substance abuse, major depressive disorder, and posttraumatic stress disorder. An association between childhood maltreatment and poor adherence to antiretroviral regimens was also reported in some studies.

Conclusion Childhood maltreatment may lead to significant adult psychopathology and poorer adherence to antiretroviral medications in HIV-infected individuals, which may complicate HIV disease. The experience of childhood maltreatment may also increase HIV

transmission by increasing high-risk behaviors, such as substance abuse and multiple sex partners, or by disabling HIV prevention choices.

Keywords: HIV/AIDS, childhood maltreatment, psychiatric morbidity, depression, anxiety, substance abuse.

Introduction

Gender-based violence (GBV) is a common phenomenon in countries where the prevalence rate of HIV is also high. GBV has been defined as a multifaceted phenomenon and can include physical, sexual and emotional violence and deprivation or neglect (Andersson, Cockcroft, & Shea, 2008). Studies conducted in developing countries such as South Africa and other African countries have reported high rates of GBV in both adults and children. This includes intimate partner violence (IPV), rape, and childhood abuse (Andersson et al., 2008; Jewkes, Penn-Kekana, Levin, Ratsaka, & Schrieber, 2001; Kalichman & Simbayi, 2004). Childhood maltreatment has been defined in many different ways. However, for the present review, childhood maltreatment included emotional, physical, and sexual abuse and emotional and physical neglect.

According to Bernstein et al. (2003) sexual abuse is defined as “sexual contact or conduct between a child younger than 18 years of age and an adult or older person.” Physical abuse is defined as “bodily assaults on a child by an adult or older person that posed a risk of or resulted in injury.” Emotional abuse is defined as “verbal assaults on a child’s sense of worth or well-being or any humiliating or demeaning behaviour directed toward a child by an adult or older person.” Physical neglect is defined as “the failure of caretakers to provide for a child’s basic physical needs, including food, shelter, clothing, safety, and health care.” Emotional neglect is defined as “the failure of caretakers to meet children’s basic emotional and psychological needs, including love, belonging, nurturance, and support.” (Bernstein et

al., 2003). Although women are more vulnerable and regarded as particularly at risk for abuse, men are also victims of rape and childhood maltreatment.

Many studies have investigated the link between adverse childhood experiences such as physical and/or sexual abuse and HIV risk. The experience of childhood maltreatment may increase HIV infection risk indirectly by increasing high-risk behaviors or by interfering with HIV prevention choices (Arriola, Loudon, Doldren, & Fortenberry, 2005). For example, many of the outcomes associated with childhood maltreatment place individuals at increased risk of contracting HIV through behaviours such as transactional sex, unprotected sex, inability to negotiate condom use, alcohol and/or drug abuse, early onset of sexual activities, and multiple sex partners (Cohen et al., 2000; Meade, Kershaw, Hansen, & Sikkema, 2009; Mimiaga et al., 2009; Mosack et al., 2010; Wilson & Widom, 2008). In addition, childhood maltreatment may directly increase the risk of HIV infection through sexual abuse. Injury and the tearing of tissue resulting from sexual violence may increase the likelihood of HIV infection (Johnson, 2004). Studies have also found that childhood maltreatment is strongly associated with adult revictimization which can further increase the risk for HIV among women (Arriola et al., 2005).

The mental health outcomes of HIV-infected individuals have been well documented to date. Research suggests a significant burden of mental illness in individuals living with HIV/AIDS, both globally and in the developing world. Mental illnesses documented in HIV-infected individuals include predominantly substance use, anxiety, and mood disorders (Evans et al., 2002; Lipsitz et al., 1994; Myer et al., 2008; Olley et al., 2003; Olley, Seedat, Nei, & Stein, 2004; Olley, Zeier, Seedat, & Stein, 2005; Olley, Seedat, & Stein, 2006; The WHO World Mental Health Survey Consortium, 2004). Moreover, it has been suggested that HIV disease progression may be hastened by mental disorders such as depression and anxiety (Leserman et al., 1999).

Similarly, research suggests the long-term mental health outcomes of childhood maltreatment include predominantly substance, anxiety, and mood disorders (Afifi et al., 2008; Kessler et al., 2010). Interestingly, Kaplow and Widom (2007) followed 496 individuals with neglect, physical and sexual abuse prior to the age of 12 into adulthood. Their research suggests that an earlier onset of maltreatment predicted more symptoms of anxiety and depression in adulthood, while controlling for gender, race, current age and reports of other abuse. Later onset of maltreatment was predictive of more behavioral problems in adulthood (Kaplow & Widom, 2007). In a review of child sexual abuse, Johnson (2004) outlines a number of child and adult psychological and behavioural consequences of child sexual abuse. These include substance use disorders, and anxiety and mood disorders, amongst others (Johnson, 2004).

While many studies have focused on mental health outcomes in childhood maltreatment and HIV separately, there is a paucity of research investigating childhood maltreatment and HIV in combination, and the associated mental health outcomes in dually affected men and women. HIV-infected women may face more current and past negative life events than men in developing parts of the world (Lipsitz et al., 1994) and this may lead to significant adult psychopathology and poor adherence to antiretroviral medications (Mugavero et al., 2006; Cohen et al., 2004). In light of this, it is evident that HIV-positive individuals, women in particular, are vulnerable to risk factors associated with abuse, and abuse-related changes in behavioural functioning, which may complicate HIV infection. A systematic assessment and summary of the available evidence is therefore warranted in order to add to the available evidence for both clinical and research decision making.

Methods

Search Strategy and selection criteria

We searched the electronic databases PubMed, Social Science Citation Index, the Cochrane Library (The Cochrane Central Register of Controlled Trials: CENTRAL) and the Cochrane Developmental, Psychosocial and Learning Problems, HIV/AIDS, and Depression, Anxiety and Neurosis registers in August 2010. No limit on the time period was applied to the search in order to avoid omission of relevant studies. Reference lists of articles identified through database searches and bibliographies of systematic and non-systematic review articles were examined to identify further relevant studies. We included all English language, original research (retrospective and prospective studies) and clinical trials reporting mental health outcomes of childhood trauma in HIV-positive individuals. The population included adult men and women already infected with HIV/AIDS who experienced childhood maltreatment prior to 18 years of age. We excluded systematic and non-systematic review articles and studies of no direct relevance to the comprehensive search. A combination of the following search terms was used: (Childhood abuse in HIV-infected individuals SAME mental health impact) OR (childhood abuse and HIV SAME mental health impact). No filters were included to ensure that all relevant papers were retrieved.

An initial search of titles was undertaken by the reviewer (GS). Studies were included irrespective of sample size and period of follow-up. Titles and abstracts of studies that appeared relevant were then assessed to determine whether they met the inclusion criteria. Abstracts that did not meet the inclusion criteria were rejected. The reviewer assessed full texts of articles that appeared to meet the inclusion criteria of the present study. Information was extracted regarding population characteristics and sample size, study design, outcomes measured and results. No exploration of publication bias was undertaken and it was not possible to conduct a sensitivity analysis for the current review article due to the fact that no meta-analyses were conducted.

Table 1. Summary of thirty four (n = 34) articles selected for review.

First author (year of publication)	N (HIV +/-)	Setting and main characteristics of population	Age range/ average age in years	Study design	Methods (measurement of exposure and outcomes)	Summary of outcomes	Main findings
(1) Holmes (1997).	95 (95/0).	United States. 95 HIV seropositive men. The majority were Caucasian men (67%). Sexual practices were homosexual/ bisexual in 87 (92%) subjects.	37.2.	Quantitative cross-sectional survey design.	Sociodemographic and sexual abuse histories were obtained. Standardised Clinical Interview for the DSM- III-R (SCID) was used to identify Psychoactive Substance Use Disorder (PSUD).	(1) Psychoactive Substance Use Disorder. (2) Increased risk of IVDU.	Nineteen (20%) subjects had sexual abuse histories. Reported first abuse occurred at a mean age of 8.1 years. Fifty- five (58%) subjects met the criteria for a diagnosis of PSUD at some time in their lifetime and nine (9%) currently met diagnostic criteria. Men with histories of sexual abuse did not exhibit a significantly increased risk of PSUD by lifetime or currently. When rates were examined by type of administration method, men with reported histories of sexual abuse did show a significantly increased risk of lifetime injection drug use (IVDU).
(2) Masten (2007).	49 (49/0).	United States.	42.5.	Baseline survey for a coping	Participants were individually screened at baseline using a	(1) Full criteria for PTSD.	All participants reported some form of sexual abuse history before the

		49 gay or bisexual HIV-positive men with childhood sexual abuse histories. The majority were African-American men.		group Intervention trial.	structured clinical interview assessing: demographics, sexual abuse history, depression, posttraumatic stress and risk to self or others.		age of 18, with 90% reporting unwanted penetrative anal sex. The average participant age at first abuse was 8.9 years. Most reported more than one abusive experience and frequently had a prolonged abuse exposure. 21 men (42.9%) met criteria for PTSD.
⁽³⁾ Myers (2006).	147 (147/0).	United States. 147 HIV-positive women. The majority were African-American (n = 79).	40.	Baseline survey for a risk reduction Intervention trial.	Childhood sexual abuse: Revised Wyatt Sex History Questionnaire (WSHR-R). PTSD: PTSD diagnostic module of the University of Michigan version of the Composite International Diagnostic Interview. Trauma-related sexual symptoms were assessed with the Trauma Symptom Inventory. Depression was assessed with the CES-D.	(1) More PTSD symptoms in those abused by a family member or by both a family and non-family member.	18% of the women reported one or more less severe sexual abuse incidents. 40% experienced one severe incident, including attempted or completed oral, anal, or vaginal sex, and digital penetration. 18% experienced one severe and one or less severe incidents, and 24% experienced two or more severe incidents. 34% of the women reported being abused by a perpetrator that was not a family member. 43% reported abuse by a family member, and 24% experienced being abused by both intra- and inter-familial

							perpetrators. The mean number of sexual abuse incidents was 1.8, with a range of 1 to 6 incidents, and on average, the abuse continued for 2 years. The relationship to perpetrator was a significant predictor of PTSD symptoms, with more PTSD symptoms among those who reported intrafamilial abuse or both intrafamilial and extra familial abuse compared to those who reported only experiencing extra familial abuse.
⁽⁴⁾ Paxton (2004)	457 (299/158).	United States. 65.4% of the sample was HIV-seropositive. The majority of the sample was African-American.	36.1.	Quantitative cross-sectional survey design.	Alcohol and drug abuse/dependence, depression, and panic disorder: subscales of the University of Michigan Revised Short Form of the Composite International Diagnostic Inventory (UM-CIDI). Posttraumatic stress symptoms: revised 17-item short form clinical checklist. Select items from the Revised Wyatt Sex History Questionnaire (WSHQ-	(1) PTSD symptoms. (2) Substance abuse. (3) Risky health behaviours. (4) Chronic stress. (5) History of psychiatric disorders.	HIV-positive women were more likely to report a history of childhood sexual abuse. Moreover, these women were more likely to report posttraumatic stress, risky health behaviours, substance abuse, chronic stress, and psychiatric history than HIV-negative counterparts.

					R) measured exposure to sexual and other lifetime trauma.		
⁽⁵⁾ Roy (2003).	149 (149/0).	United States. 149 HIV positive substance dependent patients. There were more males than females in the sample and the majority were African-American.	42.1 (suicide attempters) and 46.3 (non-attempters).	Quantitative cross-sectional survey design.	Structured Clinical Interview for DSM-IV: depression. The Eysenck Personality Questionnaire (EPQ) assessed neuroticism, extraversion, and psychoticism. The CTQ assessed for childhood abuse and neglect.	(1) Suicidality. (2) Substance dependence. (3) Lifetime depressive disorder. (4) High neuroticism scores.	66 (44.3%) had attempted suicide and 83 (55.7%) had not. Significantly more of those who had attempted suicide were female. Of the 66 patients, 51 who had attempted suicide had a primary substance dependence diagnosis. Significantly more of the patients who had attempted suicide had a lifetime history of a depressive episode. HIV positive patients who had attempted suicide had significantly higher scores on the CTQ for childhood emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. HIV positive attempters also had significantly higher neuroticism scores on the EPQ.
⁽⁶⁾ Sikkema (2008).	247 (247/0).	United States. 130 women and 117 men with a	42.3.	A randomized controlled behavioral intervention	A structured interview assessed depression, posttraumatic stress, and risk to self or others. A	(1) Sexual revictimisation. (2) PTSD.	The average of age of first abuse was 8.8 years. Most (90%) experienced penetrative vaginal or

		history of childhood sexual abuse. All men reported having sex with men.		trial with 12-month follow-up.	modified and expanded versions of the Traumatic Experiences Questionnaire (TEQ) assessed exposure to traumatic events, including sexual abuse during childhood, and adulthood.		anal sexual abuse as a child or adolescent; 87% experienced sexual revictimization, with more than half of those revictimized as children or adolescents. Only 10% of participants reported a single episode of abuse. On average, CSA lasted 4 years and participants had 2 abusers (only 39% of participants reported 1 abuser). 40% of the sample met diagnostic criteria for posttraumatic stress disorder (PTSD).
(7) Allers (1999).	52 (52/0).	United States. 52 HIV-positive individuals. Of the 45 male and 7 females, 36 were White and 16 were Black.	Not stated.	Qualitative survey design.	A semi-structured interview conducted by male HIV counselors. This interview tapped into variables such as: history of childhood abuse, pre-HIV histories of abusive or revictimising relationships or both, depression, sexual compulsivity and alcohol or other drug abuse.	(1) History of alcohol or drug abuse. (2) Chronic depressive symptomatology. (3) Revictimisation. (4) Sexually compulsive behaviours.	A total of 65% (n = 34) reported a history of childhood sexual or physical abuse or both. 35.3% (n = 12) reported physical abuse only, and 64.7% (n = 22) reported sexual abuse. All 22 participants reporting sexual abuse also reported some additional form of childhood physical abuse. Of these participants, 88% (n = 30) reported a history of alcohol or other drug abuse, 82% (n = 28)

							reported revictimising relationships, 68% (n = 23) reported chronic depressive symptomatology, and 50% (n = 17) reported engaging in sexually compulsive behaviours.
(⁸) Brennan (2007).	936 (936/0).	United States. 936 gay and bisexual men. The majority (95.3%) were gay and white (88.8%) men.	28-41.	Quantitative cross-sectional survey design: retrospective data.	A self-administered survey investigating: HIV/STI infection status, self-defined current use of sex-related drugs, other HIV risk behaviors and history of childhood sexual abuse.	(1) Current drug abuse. (2) Transactional sex practices.	15.5% (n = 134) of survey respondents reported a history of childhood sexual abuse. Those who reported experiencing abuse regularly were more likely to be HIV positive, exchanged sex for payment, and be a current user of sex-related drugs.
(⁹) Clum (2009).	40 (40/0).	United States. 40 young HIV-positive women recruited from HIV clinics.	18-24.	Mixed method design (qualitative and quantitative surveys).	A modified version of the Life Story Interview was used to cover abuse experiences, cognitive and emotional consequences of abuse, coping strategies, and sexual behavior and relationships. PTSD symptoms were assessed with an interviewer-administered Posttraumatic Diagnostic Scale (PDS).	(1) PTSD symptomatology ranging from mild to severe. (2) Reported difficulties in sexual, family, & friend relationships, general life satisfaction, and leisure time activities.	75% of the women reported sexual abuse, 80% reported physical abuse, and 55% reported both types of abuse. The average PTSD score was 20.75, reflecting moderate to severe levels of PTSD symptoms. 15% of the sample reported mild PTSD symptoms (<10), 37.5% reported moderate symptoms (10 to 20), 30% reported moderate to severe

						(3) Substance abuse.	symptoms (21 to 35), and 15% reported severe symptoms (>35). PTSD symptoms had the strongest effects on sexual relationships (67.5%), general satisfaction with life (57.5%), family relationships (52.5%), friend relationships (50%), and fun and leisure activities (45%). Avoidance and substance use were frequently utilized as coping strategies. Sexual and relationship concerns, included avoidance of sex, sexual dysfunction, sex as a trigger for abuse memories, and difficulty establishing intimacy and trust.
(10) Cohen (2000).	1645 (1288/357).	United States. 1288 HIV-positive women and 357 HIV-negative women. The majority (64%) were African American.	35 years in HIV positive women and 34 years in HIV negative women.	Quantitative cross-sectional survey design: retrospective data.	A survey investigating three areas of violence: any domestic violence, recent domestic violence and childhood sexual abuse. Lifetime substance abuse and injection drug use in the past 6 months was assessed. Finally, HIV risk behaviours were	(1) Drug use. (2) HIV-risk behaviours. (3) Revictimisation.	31% of HIV-positive women reported a history of childhood sexual abuse. Women reporting past domestic violence or childhood sexual abuse were more likely than women without such histories to have used drugs at some point in their lives; to have had a

					assessed.		male or female partner who was at risk for HIV infection; to have had more than 10 lifetime male partners; to have traded sex for money, drugs, or shelter; and to have been forced to have sex with a person known to be HIV positive. Women who reported childhood sexual abuse were more likely to report a lifetime history of domestic violence and to have experienced domestic violence in the past year.
(11) Cohen (2004).	1165 (1165/0).	United States. 1165 HIV-positive women. 635 participants were using HAART, 254 participants not using HAART although it had been and 276 participants not on HAART which had not been indicated..	Median age in HAART group: 36.3 and 35.6 in non-HAART group.	Quantitative survey design.	A standardized interview-based survey assessed demographics, medical and psychosocial history, history of cigarette smoking, alcohol use, illicit drug use and drug treatment programs, sexual history and history of medication use, and reasons for non adherence at each 6-month visit. The Center for Epidemiological Studies Depression Scale (CES-D)	(1) Poor treatment adherence. (2). Drug abuse. (3) High levels of depression in all groups.	72% of women using HAART reported a history of physical or sexual abuse. For women who were not using HAART, 80% reported a history of physical or sexual abuse. A lower percentage of women with a history of past and current use of crack, cocaine, or heroin were using HAART. A lower percentage of women with a history of physical or sexual abuse reported using HAART. Current

					measured depressive symptoms. Women were also asked questions about physical, sexual, or emotional coercion.		crack, cocaine, or heroin use, being non-White, and experiencing any physical or sexual abuse increased the likelihood of no HAART use. Women who used crack, cocaine, or heroin in the past year were more than twice as likely to report lack of HAART use, even when indicated. Similarly, women with a history of any physical/sexual abuse were more than 1.5 times more likely to lack HAART when clinically eligible. Women in the groups did not differ significantly in having high levels of depressive symptoms.
(12) Gielen (2001).	287 (287/0).	United States. 287 HIV-positive women. Ninety four percent of the women were African American..	33.1.	Quantitative cross-sectional survey design.	Health status and quality of life were evaluated with a modified version of the Medical Outcomes Study HIV Health Survey. HIV-related characteristics, social support and health promoting behaviours were assessed. Adult violence history & whether they	(1) Drug abuse. (2) Poor mental health, physical functioning, and quality of life. (3) Social networks and health promoting behaviours improved mental	55% had a history of injection drug use and 63% reported having been physically or sexually assaulted at least once as an adult. Women with a history of child sexual abuse reported significantly lower scores on measures of mental health, physical functioning, and quality

					had ever been sexually abused or raped as a child was assessed using a dichotomous response variable (yes/no).	health.	of life. A history of childhood sexual abuse, reported by 41% of the sample, was significantly related to mental health after controlling for socio-demographic and HIV-related characteristics. Women with larger social networks and who practiced more health promoting behaviors reported higher levels of mental health, while those who had been sexually abused as children reported significantly worse mental health.
(13) Henny (2007).	644 (644/0).	United States. HIV-seropositive homeless or unstably housed adults (n = 644). The sample included 15 male-to-female transgender people.	19-63.	Quantitative cross-sectional survey design.	Dichotomous variables (Yes/No) assessed adult & childhood abuse, and current & lifetime illicit drug use. The CAGE questionnaire investigated alcohol use. Depressive symptoms were measured by the CES-D. Self-perception of stress was measured using the Perceived Stress Scale (PSS).	(1) Alcohol abuse. (2) Depressive symptomatology. (3) Transactional sex.	80.3% of the sample reported a history of any physical or sexual abuse. 53% reported childhood physical abuse and 38.7% reported childhood sexual abuse. Victims of childhood physical abuse were more likely to be nonblack race, more likely to never have had stable employment, and more likely to have abused alcohol. Persons

							experiencing childhood physical abuse also were twice as likely to report symptoms indicating depression and to have ever exchanged sex for money, drugs, or shelter. Victims of CSA were nearly three times as likely to be female.
(14) Kalichman (2002).	357 (357/0).	United States. 357 men and women living with HIV/AIDS. Study participants were 242 (68%) men, 110 (31%) women, and 5 (1%) transgender persons. The majority of the sample was African American (76%).	22-69.	Quantitative cross-sectional survey design.	A dichotomous variable (Yes/No) assessed sexual abuse history and substance abuse history. Trauma indicators were adapted from diagnostic symptoms of posttraumatic stress disorder. Symptoms of depression were assessed with the CES-D. The Trait-Anxiety Scale assessed anxiety. A 6-item scale to assess pessimism was developed. Symptoms of obsessiveness–compulsiveness were assessed using six items from the Obsessive–Compulsive Scale of the schedule for nonadaptive personality (SNAP). Similarly, six items from the	(1) Substance abuse. (2) Anxiety symptoms. (3) Depression symptoms. (4) Borderline personality symptoms. (5) Current PTSD symptoms. (6) Trauma symptoms correlated with the number of sexual assaults reported.	Results showed that 68% of women and 35% of men living with HIV/AIDS reported a history of sexual assault since age 15. History of sexual assault was related to history of substance use and mental health treatment. Sexual assault survivors reported greater anxiety, depression, and symptoms of borderline personality than persons who had not been sexually assaulted. Persons who reported having been sexually assaulted reported current trauma symptoms. Specifically, 24% stated that they think of the experience on a regular basis, 20%

					Borderline Personality Scale of the SNAP were used to assess borderline personality characteristics.		have nightmares about the experience, 60% reported that the experience affects them today, and 47% stated that the experience interferes with their relationships. Number of trauma symptoms correlated with the number of sexual assault experiences reported. There were no significant gender effects for these variables.
(15) Kalichman (2004 ^a).	272 (6/19),	South Africa. 272 women living with sexual assault histories. Nearly all (99%) of the women were African.	25-35.	Quantitative cross-sectional survey design.	Self-administered anonymous surveys assessing sexual assault history, substance use, history of HIV risk factors, and sexual behaviour.	(1) Alcohol and drug use. (2) Transactional sex.	6 women (11%) were HIV-positive and 19 (33%) were HIV-negative. The majority of women (56%) did not know their HIV status. 40% (N = /119) of women reported a history of sexual assault. 26 (21%) of the women had experienced sexual assault before the age of 20. Results showed that women who had been sexually assaulted were significantly more likely to have shared injection drug equipment, exchanged sex to meet survival needs, and used

							alcohol compared to women who had not been sexually assaulted.
(16) Kalichman (2004 ^b).	647 (498/142).	United States. 647 men with childhood sexual abuse histories. The majority were Caucasian (70%).	34.8.	Quantitative cross-sectional survey design.	Self-administered surveys were used to assess demographics, sexual abuse history, substance use and sexual risk behaviours.	(1) Symptoms of borderline personality disorder. (2) Alcohol and drug abuse. (3) Having undergone treatment for substance abuse.	93 (15%) of the men reported being forced to have sex when they were 16 years or younger by a man at least 5 years older. Of these 93 men, the average age of first abuse was 9.3 years. Sexually abused men were more likely to report childhood physical abuse relative to non-abused men (41% vs. 12%). Men who were sexually abuse were more likely to have tested HIV-positive (40%) relative to non-abused men (19%). 77% of the men were HIV-negative and 22% were HIV-positive. Abused men endorsed more symptoms of borderline personality disorder. Contrary to expectations, abuse men did not differ in dissociation symptoms or trauma-related anxiety when compared to non-abuse counterparts. Abused men were more

							likely to report alcohol & drug abuse in the past 6 months and having undergone treatment (28%) compared to non-abused men (9%).
(17) Kang (2008).	220 (220/0).	United States. All participants were HIV-positive heroin and/or crack cocaine using African-Americans or Hispanics. There were 146 males and 74 females.	43.7.	Baseline survey for an intervention study.	Childhood abuse experience: Childhood trauma questionnaire (CTQ). Depression: CES-D. Health status items included: general health rating and HIV related symptoms. Lifetime medical conditions were also examined.	(1) Alcohol and drug abuse. (2) High depression levels. (3) Poor treatment adherence.	Women were more likely to report childhood sexual abuse (51% versus 39%) and childhood physical abuse (64% versus 54%). Men were more likely to use alcohol to intoxication and currently inject drugs, and females were more likely to use crack. Both men and women had high depression levels. 81% of women and 76% of men had a score of 16 or higher on the CES-D. For both men and women, use of HIV medications was negatively associated with childhood sexual abuse experience.
(18) Kimerling (1999 ^a).	67 (67/0).	United States. Sample included 67 African-American HIV-infected women beyond the initial	18-45.	Longitudinal design: 12-14 months apart, with an average time of 13.4 months apart.	Life Stressor Checklist: identify life stressors with greater prevalence for women. Impact of Events Scale-Revised: the presence and intensity of PTSD	(1) PTSD (both symptom clusters and full criteria).	62% of the sample reported experiencing at least one traumatic event. 30% of the sample experienced completed rape and 33% experienced physical

		stages of HIV infection.			symptoms.		assault. These both included rape and assault as a child. The time frame for completed rape ranged from occurring in the last year to 20 years ago, with a mean time since occurrence of 10.6 years. The time frame for physical assault ranged from currently occurring to 28 years ago, with a mean time since occurrence of 9.4 years. The majority who met the stressor criterion also met criteria for at least one other symptom cluster for PTSD, while 35% of the sample met full criteria. 88% of the sample met criteria for the re-experiencing symptom cluster, 74% for the avoidance/numbing symptom cluster and 70% for the hyper arousal symptom cluster.
(19) Kimerling (1999 ^b).	236 (88/148).	United States. 88 African-American HIV-infected women and 148	31.6.	Quantitative cross-sectional survey design: retrospective data.	The Life Stressor Checklist: history of victimization. The Brief Symptom Inventory (BSI): level of general or global distress. The	(1) High levels of global psychological distress. (2) Depression.	A history of completed rape contributed the greatest risk for HIV infection. Women who reported completed rape identified the worst

		uninfected women.			Hamilton Clinician's Rating Scale for Depression (HRSD): depression & to serve as a more objective measure of psychological distress.	(3) Greater physical distress and AIDS-defining conditions.	experience to have occurred at 18.27 years old. This variable included rape as a child. HIV-infected victims reported higher levels of global psychological distress, and greater severity of clinician-rated symptoms of depression. HIV-infected victims also reported significantly greater distress with physical symptoms and higher rates of AIDS-defining conditions than did non-victims.
(20) Martinez (2002).	41 (41/0).	United States. 41 HIV-positive women. The majority of the sample (51%) was African-American.	41.8.	Quantitative cross-sectional survey design: retrospective data.	The Life Stressor Checklist-Revised was completed in order to examine the frequency and types of traumatic life events. The PTSD Checklist-Civilian Version (PCL-C) 29 was used to assess current PTSD symptoms.	(1) Partial and full PTSD. (2) Level of PTSD significantly related to number of life events experienced and perceived social support.	The majority of women (61%) had experienced growing up with violence in the home. 59% were emotionally abused or neglected. 32% had been abused or physically attacked by a known person before the age of 16. Similarly, 32% were sexually touched or made to touch someone before age 16 and 31% were forced to have some type of sex before age 16. 42% of the HIV-positive women were likely to

							meet criteria for full current PTSD and an additional 22% for partial PTSD. Women reported having experienced a mean of 12 traumatic life events. The level of PTSD was significantly related to the number of life events experienced and to perceived social support from friends and family.
(21) Martinez (2009).	174 (174/0).	United States. HIV-positive youth enrolled in a young adult HIV clinic between 1998 and 2006. 58 were females and 116 were males. The majority (79%) were African American.	14-24.	Quantitative cross-sectional survey design.	Client Diagnostic Questionnaire (CDQ) was used to screen for mental health disorders and violence. All youth subsequently had diagnostic interviews conducted by psychologists.	(1) Major depressive disorder (MDD). (2) Generalised anxiety disorder (GAD). (3) PTSD. (4) Alcohol & substance abuse disorders.	Violence reported included physical abuse (24% in childhood; 19% in adolescents), sexual abuse (28% in childhood; 15% in adolescents), dating violence (18%), and family violence (44%). Females had higher sexual abuse (p<.001). Psychological disorders included: major depressive disorder (15%), generalized anxiety disorder (17%); posttraumatic stress disorder (28%); alcohol abuse disorder (19%); and substance abuse disorder (31%). Physically abused youth had higher symptoms of

							anxiety and PTSD. Sexually abused youth had higher symptoms of PTSD ($p < 0.05$). Youth with family violence had higher symptoms of Anxiety Disorder ($p < 0.05$) and PTSD ($p < 0.01$). CDQ findings closely correlated with diagnostic assessments of the psychological interview.
(22) McKeown (2003).	20 (20/0).	Canada. 20 HIV-positive women. Eighteen (90%) self-identified as aboriginal.	22-48.	Qualitative research design.	Open ended interviews were conducted to obtain information on childhood and adulthood experiences.	(1) Drug abuse as coping strategy. (2) Transactional sex. (3) Past suicide attempts. (4) Reported diagnoses of MDD, PTSD, Schizophrenia, panic disorder, and multiple personality disorder.	Half of those who experienced childhood sexual abuse reported being afraid to disclose the events to adults at the time due to fear of reprisal and/or shame. The majority reported running away from home to escape violence, with subsequent involvement in the sex trade and drug abuse as economic and emotional survival/coping strategies. A few of the women recounted past attempts of suicide. A number of women, at the time of the interview, reported a diagnosis of mental illness including

							depression, multiple personality disorder, panic attacks, post traumatic stress disorder and schizophrenia. Most participants reported IVDU on a regular basis in the past, with one reporting current use of IV drugs.
(23) Meade (2009).	271 (271/0).	United States. 271 HIV-positive individuals with histories of childhood sexual abuse. 50% Female and 69% African-American. The men were primarily (94%) gay/bisexual.	42.3.	Baseline survey for a coping Intervention trial	A modified version of the Traumatic Experiences Questionnaire was used to verify childhood abuse history. The Beck Depression Inventory (BDI) was used to identify severe depression.	(1) Depressive disorder. (2) Anxiety disorder. (3) Psychotic disorder. (4) Adjustment disorder. (5) Bipolar disorder. (6) Alcohol & drug abuse. (7) Undergone mental health treatment.	Approximately half of the sample (53%) screened positive for one or more psychiatric disorders (30% depressive, 25% anxiety, 11% psychotic, 10% adjustment, 4% bipolar). Approximately one third (37%) used illicit drugs and 10% reported binge drinking in the past 4 months. Many participants also received mental health treatment in the past 4 months, with those screening positive for a psychiatric disorder being more likely than those who did not (59% versus 41%).
(24) Mimiaga (2009).	4295 (258/4037).	United States. 4295 Men who	19- > 40. 40% of the sample was older than	Longitudinal research design. Intervention	The behavioral intervention trial lasted 48 months. HIV infection was the	(1) Depression. (2) Drug use.	Of the 4295 participants enrolled, 39.7% had a history of childhood sexual abuse (CSA).

		have sex with men (MSM). The men were enrolled in the EXPLORE Study.	40.	lasted 48 months with assessments every 6 months.	primary efficacy outcome. Behavioral assessments were done every 6 months. Abuse histories, drug and alcohol use and other psychosocial factors were assessed. A shortened version of the CES-D assessed depression.		Participants with a history of CSA were at increased risk for HIV infection over study follow-up. Among participants reporting CSA, the EXPLORE intervention had no effect in reducing HIV infection rates. Participants reporting CSA were significantly more likely to have symptoms of depression and use nonprescription drugs.
(25) Pence (2007).	611 (611/0).	United States. 611 HIV-infected individuals. Sixty four percent of participants were African-American and 31% were female.	20-71.	Quantitative cross-sectional survey design.	Patients completed the Brief Symptoms Inventory (BSI), an assessment of current psychological symptoms. Substance use was measured with the Addiction Severity Index (ASI). PTSD symptoms were assessed with the PTSD Checklist.	(1) PTSD. (2) More than half had a probable psychiatric disorder on the BSI. (3) High levels of depression. (4) High levels of anxiety. (5) Substance abuse.	Most respondents (91%) reported experiencing at least one traumatic event in their lifetime. 30.4% experienced childhood sexual abuse and 20.6% severe physical abuse as a child. 16% of the sample met criteria for PTSD, 53.9% of the sample had a probable psychiatric disorder on the BSI. 34.7% of the sample had depressive symptoms above the 90 th percentile and 29.5% had anxiety symptoms above the 90 th percentile. 22.3% of the sample was

							engaging in any non-marijuana substance abuse and 20% were using multiple substances.
(26) Sikkema (2004).	28 (28/0).	United States. Twenty-eight HIV-positive participants (7 men and 21 women).	47.43 (men) and 41.81 (women).	Baseline survey for a coping Intervention trial.	Trauma Symptom Checklist: childhood and adult traumatic experiences. Personality Assessment Inventory: self-administered objective inventory of adult personality. Trauma Symptom Inventory: acute and chronic posttraumatic symptomatology.	(1) Mood disorders. (2) Anxiety disorders, including PTSD. (3) Substance abuse. (4) Personality disorder. (5) Revictimisation.	All men reported experiencing unwanted touching or fondling in childhood (age 12 or younger). Prior to age 12, 71.4% reported oral sexual abuse and 85.7% reported penetrative anal sexual abuse. During adolescence (13–17 years), 57.1% of the men experienced some form of sexual abuse. 76.2% of women reported unwanted touching or fondling, 25% reported oral sexual abuse, and 57.1% reported penetrative anal or vaginal sexual abuse during childhood (age 12 or younger). During adolescence, 85.7% unwanted touching or fondling, 57.1% oral sexual abuse, and 81.0% penetrative anal or vaginal sexual abuse. 85% of the participants received an indicator of

							an Axis I diagnosis: the most frequent diagnostic categories were mood disorders (46.4%), anxiety disorders, including PTSD (32%), and substance abuse (25%). On Axis II, 28.5% received at least one diagnostic indicator of a personality disorder.
⁽²⁷⁾ Sikkema (2007).	198 (198/0).	United States. 107 women and 91 men with childhood sexual abuse. All men reported having sex with men.	43.18 (women) and 41.75 (men).	Baseline survey for a coping Intervention trial.	Depressive symptomatology: BDI. The Impact of Events Scale: PTSD symptoms.	(1) PTSD.	89% of participants experienced penetrative anal or vaginal abuse during childhood (age 12 and under) or adolescence (age 13–17). Fifty-five percent of participants reported sexual abuse during both childhood and adolescence. 40% of study participants met DSM-IV diagnostic criteria for posttraumatic stress disorder (PTSD).
⁽²⁸⁾ Sikkema (2009).	256 (256/0).	United States. 256 HIV-positive adults with CSA histories. There were 132 women and 124 men who have sex with men. The majority	42.2.	Quantitative cross-sectional survey design.	A modified version of the Traumatic Experiences Questionnaire (TEQ) assessed abuse history. Depression and suicidal ideation: BDI. Trauma Symptom Inventory (TSI): PTSD. Substance	(1) Sexual revictimisation. (2) Mood and anxiety symptoms. (3) PTSD symptoms.	All participants reported abuse histories. 90% had experienced penetrative vaginal or anal sexual abuse as a child or adolescent. Additionally, 87% experienced sexual revictimization at some point in their lives and,

		(67.3%) was African-American.			abuse and sexual behaviour were also assessed using self-developed screening tools.	(4) Alcohol and drug use.	on average; participants were abused by two different perpetrators. The mean score for mood and anxiety symptoms was 29.8 in women and 28.2 in men. Mean score for trauma-related symptoms was 40.4 in women and 28.9 in men. Alcohol use in the past 4 months was 31.8% in women and 53.2% in men. Marijuana use in the past 4 months was 18.2% in women and 36.3% in men. Cocaine and/or Crack use in the past 4 months was 18.9% in women and 33.1% in men.
(29) Simoni (2002).	230 (230/0).	United States. Sample consisted of 230 HIV-positive women. The majority (46%) described themselves as African-American.	25-61.	Quantitative cross-sectional survey design.	Demographics, trauma, coping strategies and current depressive symptomatology were assessed. Respondents completed the CES-D. Self-reported trauma histories were documented.	(1) High scores of depressive symptoms. (2) Positive correlation between childhood abuse and current adaptive and avoidant coping strategies. (3) Avoidant coping was	Results revealed a high prevalence of abuse in childhood (50%) and adulthood (68%); 7% reported physical assault or rape in the last 90 days. Childhood abuse was significantly correlated with both adult and recent trauma, and each type of trauma correlated with CES-D scores. The mean CES-D score was 22.49; 66%

						strongly associated with CES-D scores.	had a sum score of 16 or above, indicative of possible clinical depression. Childhood abuse also positively correlated with the frequency of current adaptive and avoidant coping strategies, although avoidant coping had a stronger association with CES-D scores. The association between childhood abuse and CES-D scores persisted even after controlling for relevant demographic variables, more recent trauma and coping strategies.
(30) Tarakeshwar (2005).	28 (28/0).	United States. 28 HIV-positive women with childhood sexual abuse histories. The majority were African American (67.9%).	27-57.	Qualitative research design.	A clinical psychologist and a social worker conducted in-depth qualitative interviews. The interview was developed on the basis of the published literature and the goal of developing a coping-focused intervention for women with CSA history and HIV. The interview protocol used a semi structured interview format that	(1) Reported cumulative trauma-related distress. (2) Current use of psychiatric medications for: depression, anxiety (agoraphobia, panic disorder), PTSD. (3) Frequent hospital visits for	78.6% of the sample revealed unwanted touching or fondling, 57.1% reported sexual intercourse, and 57.1% were asked to engage in sexual acts under verbal and emotional pressure (before 13). During adolescence (13–17 years), their reports of unwanted sexual abuse experiences increased: 82.1% for intercourse, 64.3% for oral sex,

					<p>addressed the impact of sexual abuse and HIV on their life and the ways they coped with these traumas.</p>	<p>physical complaints.</p> <p>(4) Substance abuse.</p> <p>(5) Revictimisation.</p>	<p>71.4% for forced or threatened sexual acts, 75.0% for verbal and emotional pressure, and 35.7% for unwanted sexual acts that occurred when they had passed out or were drunk or asleep. Many (40%) of the women were abused by family members, and most (75%) reported sexual revictimization. All women were reportedly abused by men. Most of the women reported having encountered multiple traumatic experiences and reported cumulative distress as a result of these experiences. Many were using psychiatric medications for symptoms of depression, anxiety (e.g., agoraphobia, panic disorder), and posttraumatic stress (PTSD) disorder. Symptoms of PTSD such as flashbacks and hyper vigilance around places and occasions that reminded them of their</p>
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							sexual abuse were common. A few women stated that their distress led to frequent visits to the hospital for physical complaints as they psychologically struggled to comprehend their sexually abusive experiences since childhood. Using illicit substances (e.g. drugs) helped all the women numb their emotional distress and feelings of anger and betrayal generated by their CSA.
(31) Tarakeshwar (2006).	266 (266/0).	United States. 266 HIV-positive participants. There were 133 males, 129 females, and 4 transgender. The majority (71.5%) was African-American.	43.14 (women) and 41.19 (men).	Quantitative cross-sectional survey design.	Participants were screened for abuse histories in childhood, adolescence, and adulthood. The BDI was used to assess depressive symptomatology. Perspectives on addressing trauma symptoms, HIV-related stress, and Resiliency were also assessed using self-developed screening tools and modified scales.	(1) Substance use treatment in the past four months. (2) Lower resiliency and greater HIV-related stress was related to negative feelings about addressing trauma. (3) Revictimisation.	91% of the participants had been sexually abused as children, 77% had been abused during adolescence, and 56% had been sexually revictimized as adults. 71.5% of men and 66.7% of women reported unwanted vaginal or anal sex in childhood. 54% of men and 52% of women had at least one visit to a mental health provider in past 4 months. 39.5% of men and 38% of women were on psychiatric medications. Substance

							use treatment in the past 4 months was reported in 38.8% of men and 29.5% of women. Structural equation modeling analyses indicated that lower resiliency and greater HIV-related stress was related to negative feelings about addressing trauma, whereas greater resiliency and higher perceived impact of sexual trauma were associated with positive feelings about addressing trauma.
⁽³²⁾ Welles (2009).	593 (593/0).	United States. 593 HIV+ men who have sex with men (MSM).	77% were 36 years or older.	Baseline survey for a risk reduction Intervention trial.	Participants reported the frequency of childhood sexual abuse (CSA). Brief Symptom Checklist was used to assess depression and anxiety.	(1) High levels of depression. (2) High levels of anxiety. (3) Reported current and lifetime alcohol and drug problems.	Of participants, 47% reported CSA, with 32% reporting CSA occurring often or sometimes. While most (154 or 58%) reported the gender of the perpetrator as male, 38 (14%) reported CSA by a female, and 75 (28%) by both. HIV+ reporting history of CSA had significantly higher levels of depression and anxiety, with 39% reporting the highest quartile scores for the depression and anxiety

							inventory, compared with 24% of men reporting no CSA. Men reporting CSA were more likely to believe that they have or had problems with drugs or alcohol.
(33) Williams (2008).	137 (137/0).	United States. 137 HIV-positive gay and non-gay identifying African American and Latino men with histories of childhood sexual abuse.	43.5.	Randomized clinical trial compared the effects of two 6-session interventions.	A randomized clinical trial, compared the effects of two 6-session interventions aimed at decreasing high-risk sexual behaviors, number of sexual partners, and depressive symptoms. The CES-D assessed depression.	(1) High levels of depression at baseline. (2) Significant decrease in depression from 3 to 6 months follow-up.	There were high levels of depression at baseline, M = 23. The clinical cutoff score for the CES-D is 16 for mild depressive symptoms and 21 for moderate to severe symptoms. There was a significant decrease in depressive symptoms from the 3 month to the 6 month follow-up assessment for the sample as a whole (M = 22.42, for 3 months depression and M = 20.66 for 6 months depression).
(34) Wyatt (2005).	75 (75/0).	United States. 75 HIV-positive women with histories of childhood sexual abuse.	40.0.	Baseline survey for an Intervention trial.	Women were administered the revised Wyatt Sex History Questionnaire (WSHQ-R). Five measures were used to assess patterns of substance abuse.	(1) Substance abuse. (2) Lifetime alcohol or drug treatment.	All women in the sample had a history of childhood sexual abuse. 83% of the sample reported having used at least 1 of 13 substances regularly at some point in their lives. 28% of the sample reported engaging in regular

							injection drug use. 54% of the women reported having taken part in an alcohol or drug treatment program at some point in their lifetime.
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Results

All databases searched yielded abstracts, and there were duplicates between the databases. All the studies had published results in peer-reviewed journals. Two hundred and five abstracts were identified and reviewed. Of the 205 abstracts identified, 153 articles were of no relevance to the present review. Of the relevant studies reviewed, 35 articles met inclusion criteria. The reviewed articles are summarised in table 1. There was heterogeneity in sample characteristics, study methodologies and outcome measures among all studies reviewed in this article. Moreover, some studies included an HIV comparison group while others did not, further limiting comparability. For these reasons, it was decided that a meta-analysis of these data was not feasible.

Variability in measurement of mental health impairment was noted. Psychiatric symptoms and disorders were assessed according to standard diagnostic criteria, using a structured clinician administered interview⁽¹⁻⁶⁾ and/or through self-report⁽⁷⁻³⁴⁾. While some studies differentiated symptoms and diagnoses, others reported more global levels of psychological distress. For example, two articles sourced reported on global psychological distress and mental health in general, without delineating whether symptoms were depressive in nature or anxiety-related, for example (Gielen, McDonnell, Wu, O'Campo, & Faden, 2001; Kimerling, Armistead, & Forehand, 1999). Furthermore, some studies simply stated the percentage of HIV-positive maltreatment victims reporting symptoms of anxiety. While these studies reported global anxiety levels, they failed to differentiate by diagnosis (Kalichman, Sikkema, DiFonzo, Luke, & Austin, 2002; Meade, Hansen, Kochman, & Sikkema, 2009; Pence et al., 2007; Welles et al., 2009). A history of childhood maltreatment was also assessed in different ways, but all studies relied on self reported history of childhood maltreatment, and most assessments were retrospective in nature. In some studies, childhood maltreatment included various forms/types such as physical abuse and neglect, emotional

abuse and neglect, and sexual abuse (Kang, Goldstein, & Deren, 2008; Roy, 2003). Other studies only examined childhood sexual abuse (Brennan, Hellerstedt, Ross, & Welles, 2007; Cohen et al., 2000; Gielen et al., 2001) or combined sexual and physical abuse into one category of child abuse (Allers & Benjack, 1991; Clum et al., 2009; Cohen et al., 2004). Some studies utilised validated self-report measures sensitive in tapping into various forms of childhood abuse and neglect (Kang et al., 2008; Roy, 2003). A widely used example of such a measure is the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). However, many studies established a history of childhood abuse by simply asking a single question such as “have you ever experienced a sexual assault or rape as a child or teenager, that is, when you were 18 years of age or younger?” and using a dichotomous response option (Yes/No) (Gielen et al., 2001; Henny, Kidder, Stall, & Wolitski, 2007; Kalichman et al., 2002).

In reviewing the articles, early maltreatment exposure was associated with a wide range of mental health symptoms and disorders. The most commonly reported psychiatric symptomatology among HIV-positive individuals with a history of childhood maltreatment included (reference no. in table 1): drug and/or alcohol abuse/dependence, ^(1, 4, 5, 7-17, 21-26, 28, 30-32, 34) depression, ^(5, 7, 11, 13, 17, 18, 21-26, 28-30, 32, 33) and posttraumatic stress ^(2-4, 6, 9, 18, 20, 21, 23, 25, 27, 28, 30). Other mental health outcomes reported included (reference no. in table 1): anxiety, ^(14, 23, 25, 26, 28, 30, 32) generalized anxiety disorder, ⁽²¹⁾ borderline personality, ^(14, 16) panic disorder, ^(22, 30) agoraphobia, ⁽³⁰⁾ schizophrenia, ⁽²²⁾ psychotic disorder, ⁽²³⁾ adjustment disorder, ⁽²³⁾ bipolar disorder, ⁽²³⁾ suicidality, ^(5, 22) neuroticism, ⁽⁵⁾ personality disorder, ⁽²⁶⁾ and multiple personality disorder ⁽²²⁾. Moreover, when examining mental health outcomes such as drug abuse and depressive symptomatology, two articles also reported an association between childhood maltreatment and poor treatment adherence to antiretroviral regimens ^(11, 17). Physical complaints/distress and reduced quality of life was also a finding in the studies reviewed ^(12, 18, 30). Findings from several studies indicated that participants had at some time in their lives

undergone mental health treatment^(16, 23, 30, 31, 34). Many studies found participants commonly reporting engagement in high-risk behaviours such as transactional sex or compulsive sexual behaviours^(4, 7, 8, 10, 13, 15, 22) and adult revictimisation was common^(6, 7, 10, 26, 28, 30, 31).

Discussion

We performed a comprehensive systematic review of the literature to assess mental health outcomes in HIV positive individuals with histories of childhood maltreatment. To our knowledge, this is the first review of its kind; no published systematic reviews assessing this association have been conducted to date.

The reported mental health outcomes in dually affected individuals (HIV positive individuals with histories of childhood maltreatment) are in keeping with studies that have investigated these variables separately (Evans et al., 2002; Johnson, 2004; Kaplow & Widom, 2007; Lipsitz et al., 1994; Myer et al., 2008; Olley et al., 2003; Olley et al., 2004; Olley et al., 2005; Olley et al., 2006; The WHO World Mental Health Survey Consortium, 2004), supporting at least common outcomes, although assessment of the additive effects of HIV and childhood trauma is difficult in this retrospective review.

The most commonly reported mental illnesses in dually affected individuals included mood, anxiety, and substance abuse disorders. Very few studies examined Axis II disorders. It has been suggested that an HIV diagnosis alone may constitute a significant stressor and thus increase the likelihood of mental illnesses among HIV-positive individuals (Nott, Vedhara, & Spickett, 1995). Apart from depression or anxiety being a secondary diagnosis to HIV/AIDS, anxiety and depressive symptoms measured over time were also associated with faster progression of the disease after five years. This finding may suggest a reinforcing relationship between HIV and mental illnesses such as depression or anxiety (Leserman et al., 1999). However, the majority of studies reviewed were cross-sectional in nature, therefore limiting

their ability to make causal conclusions around the onset of mental illness in HIV. This highlights the importance of longer-term assessment in order to better delineate the nature, severity, and temporal nature of mental health outcomes. Importantly, mental disorders such as depression or anxiety can further impact immune system functioning in HIV, and in turn, influence quality of life and health status (Cruess et al., 2003).

Substance abuse was the most predominant mental health outcome reported in reviewed articles. For the most part, drugs and/or alcohol are used to numb emotional distress and feelings of anger and betrayal resulting from the experience of childhood maltreatment (Tarakeshwar et al., 2005). Not only does substance abuse have direct implications for the progression of the disease in infected individuals (Lucas, Gebo, Chaisson, & Moore, 2002), it also has direct and indirect implications for the transmission of HIV. Antiretroviral regimens are known to have strong positive effects on quality of life and in improving health status in infected individuals (Miller, Ketlhapile, Rybasack-Smith, & Rosen, 2010). Few articles have reported an association between childhood maltreatment and poor treatment adherence to antiretroviral regimens or HIV medications (Cohen et al., 2004; Kang et al., 2008).

Some studies that investigated both early life trauma and adult trauma found an association between childhood trauma and later life trauma (Cohen et al., 2000; Kalichman et al., 2002; Myers et al., 2006; Simoni & Ng, 2002). For example, the study by Simoni and Ng (2002) found that childhood abuse was correlated with both adult and recent trauma. Moreover, each type of trauma was also correlated with depression scores. Several studies have also found that adult revictimisation was very common in survivors of childhood maltreatment (Allers & Benjack, 1991; Cohen et al., 2000; Sikkema et al., 2004; Sikkema et al., 2008; Tarakeshwar et al., 2005; Tarakeshwar, Kochman, Fox, & Sikkema, 2006). Further investigation of this relationship and the implications for prevention and intervention is warranted.

HIV-infected men and women may face many current and past negative life events (Lipsitz et al., 1994) and this may lead to significant adult psychopathology and poor adherence to antiretroviral medications (Mugavero et al., 2006; Cohen et al., 2004; Pence, 2009). In light of this, it is evident that HIV-positive individuals, women in particular, are vulnerable to risk factors associated with abuse, and abuse-related changes in behavioural functioning. These risk factors and behavioural changes may in turn complicate HIV infection.

There are several limitations that warrant mention. First, no search strategy can guarantee the identification of all relevant research, and omission of important studies remains a possibility and may contribute to bias in inferences drawn. Second, the heterogeneity across studies presents a problem as it impedes statistical pooling of studies. Third, it is important to note the controversy that abounds in the classification of search terms. There is no standard definition for the experience of abuse as a child. This construct is one that is classified and assessed in a variety of ways. Some studies use broader terms such as childhood adversity or maltreatment, while others use more specific terms such as child abuse. For example, in some studies reviewed, childhood maltreatment included diverse types of trauma such as physical abuse and neglect, emotional abuse and neglect, and sexual abuse. Other studies have used more restricted definitions and have only examined childhood sexual abuse or resorted to combining sexual and physical abuse into one category of child abuse. Childhood maltreatment in the present review included emotional, physical, and sexual abuse and neglect. The lack of a standard definition is a further source of bias. It should also be noted that there is a bias towards publishing studies with positive findings. However, despite these limitations, this review adds substantially to available evidence for both clinical and research decision making.

These findings highlight the need to screen for childhood maltreatment, psychopathology, treatment adherence and associated functioning in HIV positive individuals and to address these issues in management. Increased focus on the identification and support for children and youth who have experienced childhood maltreatment is necessary. HIV prevention interventions such as education in high-risk behaviours are also a necessity.

Implications for future studies

From the present review, it is clear that very few prospective studies have been executed in this domain (Kimerling et al., 1999; Williams et al., 2008). The majority of research has been cross-sectional and has included retrospective assessment of childhood maltreatment in HIV-infected individuals. This may be partly due to reasons associated with feasibility and logistics. As cross-sectional study designs preclude follow-up observations and longer-term assessment of outcomes, future research should be prospective in nature and should better delineate the nature, severity, and temporal relationship of childhood maltreatment to mental health outcomes and treatment utilisation, as well as the mediators and moderators of these outcomes. These studies will allow both clinicians and researchers to better understand the etiology of common mental disorders in HIV-infected samples and reduce bias when making causal inferences. Thus, longitudinal investigation of mental health outcomes in HIV infected individuals with childhood maltreatment will be key to explaining these causal relationships.

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DISCUSSION

6.1 *Introduction*

The principal aim of the present study was to explore neurocognitive differences, both separately and in combination, among HIV-positive women (with and without histories of childhood abuse) and HIV-negative women (with and without histories of childhood abuse).

6.2 *The effects of HIV on neurocognitive functioning*

6.2.1 *Learning and delayed memory (HVLTR)*

The ANCOVA revealed that HIV status had a significant effect on the HVLTR learning and delay trials, $p < .01$. HIV-positive women scored lower on all three trials of the HVLTR immediate learning trial ($M = 23.18$) compared to HIV-negative women ($M = 25.40$).

Similarly, HIV-positive women scored lower on the delay trial of the HVLTR ($M = 8.11$) compared to HIV-negative women ($M = 9.37$). In a multivariate analysis, HIV status significantly predicted HVLTR learning and delay trials, $p < .01$. In the best subsets regression analysis, 22% of the variance in the HVLTR learning trial could be explained by the model. In looking at the delay trial, 26% of the variance could be explained by the model. The HVLTR tests one's ability to learn and immediately recall verbal information, as well as the ability to retain, reproduce, and recognise this information after a delay. The finding that HIV influences memory is not unexpected and is in keeping with previous studies. According to Grant (2008), memory disturbances in particular tend to be most prominent, with individuals displaying impairments in learning and retrieval of information. HIV-related deficits in memory have been consistently reported in the both the developed world (Grant et al., 1987; Heaton et al., 1995; Heaton et al., 2011; Maki et al., 2009; Mason et al., 1998; Saykin et al., 1991; Tozzi et al., 2005) and the developing world (Cysique et al., 2007; Gupta

et al., 2007; Kanmogne et al., 2010; Lawler et al., 2010; Robertson et al., 2007; Sacktor et al., 2006; Wong et al., 2004; Yephthomi et al., 2006).

Although impairments in learning and retrieval of information have been widely reported, women have been under-represented in neurocognitive studies of HIV. The majority of all-female studies have been conducted in areas where clade B predominates. In South Africa, clade C predominates and whether the neurocognitive profile differs among the different strains of HIV is still largely under investigation. Moreover, antiretroviral (ARV) naïve samples have also been rare. Of all the studies mentioned above, only two were all female case-control studies like the present study (Maki et al., 2009; Mason et al., 1998). Three studies consisted of all male samples (Grant et al., 1987; Heaton et al., 1995; Saykin et al., 1991) and others consisted of more males than females (Cysique et al., 2007; Heaton et al., 2011; Tozzi et al., 2005; Yephthomi et al., 2006). A recent review suggests that only 6 all-female case control cross-sectional studies have been conducted and although memory deficits have been reported, collectively, impairment was most evident in psychomotor tasks (Maki & Martin-Thormeyer, 2009). Consistent with the findings of the present study, deficits in memory were reported among HIV-positive women compared to HIV-negative women in the studies conducted by Maki et al. (2009) and Mason et al. (1998). However, sample sizes were smaller in these studies than in the present study, consisting of 43 (Mason et al., 1998) and 63 (Maki et al., 2009), respectively. Contrary to the present study, the women in these studies met criteria for current/past illicit drug use and came from areas where HIV clade B predominates. Instrumentation used was similar to that of the present study. As in the present study, Maki et al. (2009) assessed verbal memory using the Hopkins Verbal Learning Test (HVLT). Moreover, similarities in demographic characteristics are evident. The age and education levels among women in the present study were similar to those in the studies of

Maki et al. (2009) and Mason et al. (1998). Refer to Table 1 for details on the above mentioned all-female studies.

Although the studies conducted by Grant et al. (1987) and Saykin et al. (1991) reported impairments in memory among HIV-infected men, these studies differed from the present study. The studies consisted of prospective (Saykin et al., 1991) and cross-sectional (Grant, 1987) assessments of neurocognitive functioning in homosexual men. Heaton et al. (1995) assessed neurocognitive performance in 389 males infected with HIV and reported increased rates of impairments at each successive stage of HIV infection. Tozzi et al. (2005) assessed 432 men and women from 1996 to 2002. However, the majority of the sample consisted of males (70%). Education levels were similar to those of the sample in the present study. However, the instrumentation used to assess memory was different to that used in the present study. A follow-up study aimed to screen and assess large groups of HIV-positive and HIV-negative participants from the pre-cART era (1988-1995) and the cART era (2000-2007). A total of 857 participants from the pre-cART era and 937 from the cART era were included (Heaton et al., 2011). Contrary to the present study, the majority of participants were male. The instrumentation used to assess memory differed to the present study. Although memory impairments were evident, these were more evident in those individuals on antiretroviral therapy, unlike the present study where 90% of women were ARV naïve. All of the abovementioned studies were conducted in areas which differ in HIV clade to South Africa.

The samples used in studies by Cysique et al., 2007; Gupta et al., 2007; Kanmogne et al., 2010; Lawler et al., 2010; Robertson et al., 2007; Sacktor et al., 2006; Wong et al., 2004; and Yepthomi et al., 2006 were similar to the sample utilised in the present study. Although they were conducted in countries where clade A, B, C, and D predominate, all the abovementioned

studies were carried out in the developing world. All of the abovementioned studies consisted of mixed male and female samples and the education levels of women in the present study were similar to many of the abovementioned studies.

Cysique et al. (2007) conducted a pilot study comparing NP effects of HIV infection in Anhui China and the U.S. 28 HIV-positive individuals and 23 matched controls were assessed. There were more males than females in the sample. The predominant HIV clade in both China and the U.S. is clade B and differs from that of South Africa. However, the education levels reported in Cysique et al. (2007) are similar to those evident in the present study.

Instrumentation used was similar to the present study and the HVLT was also used to measure verbal memory. HIV-infected individuals performed worse than control subjects on all NP measures, including verbal memory, as in the present study (Cysique et al., 2007).

The clinical characteristics of the samples used in Gupta et al. (2007) and Yepthomi et al. (2006) were similar to those in the present study. Both of these studies assessed neurocognitive function in ARV naïve patients infected with clade C. Moreover, education levels evident in the present study were similar to these studies. More females were included in the study conducted by Gupta et al. (2007) whereas more males were represented in the study by Yepthomi et al. (2006). As in the present study, Gupta et al. (2007) utilised the HVLT-R as a measure of learning. Moreover, impairments in memory were also evident in both the aforementioned studies.

Unlike the present study, participants who took part in the study conducted by Kanmogne et al. (2010) were tested in their mother tongue, French. The sample was mixed but consisted of more women than men. Instrumentation used was similar to the present study and the HVLT

was also used to measure verbal memory. As with the present study, HIV-infected individuals performed worse than control subjects on verbal memory. Unlike the present study, 34% of the sample in this study was on antiretroviral therapy. Several HIV strains and recombinant forms are in circulation in Cameroon, unlike in the present study where the majority of women were infected with clade C HIV. Similarities in demographic characteristics are evident, with similar education levels evident among the women included in the present study.

The sample size in the study conducted by Lawler et al. (2010) was similar to that of the present study. However, the sample consisted of both men and women. Unlike the women in the present study, the majority (97.5%) were on ART. However, as in South Africa, clade C is predominant in Botswana where this study was conducted. Instrumentation was not similar to that used in the present study, however, impairments in memory were also evident. Participants differed in age and education levels to those in the present study. Women in the present study were more educated than the participants in the Lawler et al. (2010) study.

The majority of the participants in the study conducted by Robertson et al. (2007) were female. Demographic similarities in education are evident between the aforementioned study and the present study. As with the present study, HIV-positive individuals performed worse on learning/memory tasks than controls. However, the instrumentation used to measure this differed between the two studies. Half of the sample was on antiretroviral treatment. Moreover, unlike in South Africa, clade A and D are prevalent in Uganda where the abovementioned study was conducted.

It is therefore clear that although impairments in learning and retrieval of information have been widely reported in both the developed and developing world, participant characteristics, methodological aspects, and instrumentation have varied widely among studies conducted to date. Women have been under-represented in neurocognitive studies of HIV. Beside the present study, only two all-female studies have been conducted to date and in areas where clade B predominates. Moreover, antiretroviral (ARV) naïve samples have been rare. Taking all these factors into consideration, the present study is one of the first all-female studies to document impairments in learning and retrieval of information among HIV-infected individuals with a history of childhood trauma.

6.2.2 *Executive functions (HCT)*

The ANCOVA revealed that HIV status had a significant effect on the Halstead Category Test, $p < .05$. HIV-positive women had significantly more errors on the Halstead Category Test ($M = 75.97$) compared to HIV-negative women ($M = 65.86$). In a multiple regression analysis, HIV status significantly predicted the HCT, $p < .05$. However, in the best subsets regression analysis, HIV status did not reach statistical significance, $p = .07$. Results revealed that 28% of the variance in the HCT could be explained by the model. The HCT is a test of categorisation and frontal lobe executive functioning. The finding that HIV influences executive functions is not unexpected and is in keeping with previous studies. HIV is highly neurovirulent and is frequently associated with deficits in higher order brain functions. Grant (2008) states that besides the predominance of memory disturbances, disturbances with executive functions are also frequent among HIV patients. HIV-related deficits in executive functioning have been consistently reported in the both the developed world (Grant et al., 1987; Heaton et al., 2011; Richardson et al., 2005) and the developing world (Cysique et al.,

2007; Kanmogne et al., 2010; Robertson et al., 2007; Sacktor et al., 2006; Yepthomi et al., 2006).

The study conducted by Grant et al. (1987) reported impairments in abstracting ability among an HIV-infected all-male sample. This study differed from the present study and focused on a sample of homosexual men. The study utilised Magnetic Resonance Imaging (MRI) and consisted of a cross-sectional assessment of neurocognitive functioning. The sample size was smaller than that of the present study. Participants were a mix of AIDS and non-AIDS patients who were also ARV naïve (Grant, 1987).

A follow-up study assessed large groups of HIV-positive and HIV-negative participants from the pre-cART era (1988-1995) and the cART era (2000-2007). A total of 857 participants from the pre-cART era and 937 from the cART era were included (Heaton et al., 2011). Contrary to the present study, the majority of participants were male. The instrumentation used to assess executive functioning was similar to the present study, with both studies using the Halstead Category Test and the Wisconsin Card Sorting Test. Impairments in executive functioning were more evident in those individuals on antiretroviral therapy, unlike the present study where 90% of women were ARV naïve. Although it has been suggested that risk for a significant brain involvement is highest in the more advanced HIV disease stages, this difference in findings demonstrates that subtle changes are also evident in medically asymptomatic individuals. The abovementioned studies were conducted in the developed world where the HIV strain differs to South Africa and where participants were more educated.

The studies by Richardson et al. (2002) and Richardson et al. (2005) are the only all-female studies to document impairments in abstraction using the Colour Trails Test. The sample size in Richardson et al. (2002) was bigger than that of the present study and consisted of 231 women. Education levels between the two studies were fairly similar but the age of women differed between this study and the present study. The instrumentation used to assess executive functioning/abstraction was similar to the present study, with both studies using the Colour Trails 2 Test. Impairments in abstraction were more evident in HIV-infected individuals. Differences in clinical characteristics such as HIV strain were evident in both studies.

The sample size in Richardson et al. (2005) was bigger than that of the present study and consisted of 220 women. However, contrary to the present study, 70 out of 145 HIV-positive women were co-infected with hepatitis C (HCV). Women co-infected with HCV and HIV demonstrated greater abnormal NP performance than those not infected with either, demonstrating an association of HCV with the risk of neurocognitive impairment in women living with HIV/AIDS and suggesting that co-infection has an additive effect (Richardson et al., 2005). Demographic similarities were evident in age and education among HIV-positive women in the two studies. However, differences in clinical characteristics such as HIV strain were evident in both studies.

Although Cysique et al., 2007; Kanmogne et al., 2010; Robertson et al., 2007; and Yephthomi et al., 2006 were conducted in countries where clade A, B, C, and D predominate, all the abovementioned studies were carried out in the developing world, making them similar to the present study. All of the abovementioned studies consisted of mixed male and female

samples. The education levels of women in the present study were similar to most of the abovementioned studies.

Cysique et al. (2007) conducted a pilot study comparing NP effects of HIV infection in Anhui China and the U.S. 28 HIV-positive individuals and 23 matched controls were assessed. There were more males than females in the sample and the sample size was smaller than that of the present study. Education levels were similar and the age of participants ranged from 18-50, making this study demographically similar to the present study. Unlike the present study, participants were tested in Mandarin. The predominant HIV clade in both China and the U.S. is clade B and differs from that of South Africa, where clade C is common. Instrumentation used was similar to the present study, with both studies using the Wisconsin Card Sorting Test. HIV-infected individuals performed worse than control subjects on all NP measures, including executive functions (Cysique et al., 2007).

The sample size in Kanmogne et al. (2010) was smaller than that of the present study and consisted of more women than men. Participants were tested in their mother tongue, French. Instrumentation used was similar to the present study, with both studies using the Wisconsin Card Sorting Test, the Halstead Category Test, and Colour Trails II. As with the present study, HIV-infected individuals performed worse than control subjects on executive functioning. Thirty four percent of the sample in this study was on antiretroviral therapy, making the samples clinically different. Several HIV strains and recombinant forms are in circulation in Cameroon, unlike in the present study where the majority of women were infected with clade C HIV. Similarities in demographic characteristics are evident, with similar education levels evident among the women included in the present study.

Education levels among HIV-positive women were lower in the study conducted by Robertson et al. (2007), however, similarities in age were evident. The majority of the participants were female and sample sizes were similar in both studies. As with the present study, HIV-positive individuals performed worse on executive functions than controls. Instrumentation used to measure executive functions/abstraction was similar, with both studies using the Colour Trails II Test. Contrary to the present study, half of the sample were on antiretroviral treatment. Moreover, unlike South Africa, clade A and D are prevalent in Uganda, highlighting differences in clinical characteristics.

Impairments in higher order brain functions such as executive functioning/abstraction have been widely reported in both the developed and developing world. However, participant characteristics, methodological aspects, and instrumentation have varied widely among studies conducted to date. Women have been under-represented in neurocognitive studies of HIV. Beside the present study, only two all-female study to date have demonstrated impairment in abstraction using the Colour Trails Tests. However, these studies differed to the present study with regard to demographic and clinical characteristics. The present study is therefore one of the first all-female studies to document impairments in executive functions among HIV-infected individuals with a history of childhood trauma. The present study demonstrated that subtle changes are also evident in medically asymptomatic individuals.

Refer to table 1 on the next page for the summary of the all-female studies reporting learning and executive function impairments.

Table 1. Summary of neuropsychological studies in HIV-positive women

Author (Year)	N (HIV+/-)	Origin and HIV Clade	Mean age (education level)	Neurocognitive Tests	Results
Masson et al. 1998	43 (33/10)	U.S.A. Clade B	HIV negative: 40 (11.85) HIV asymptomatic: 35.8 (12.83) HIV symptomatic: 39.3 (11.46) AIDS: 35.3 (11.60)	WAIS-R vocabulary subtest; Digit Span; Trail Making A & B; WMS-R visual reproduction; CVLT	HIV-negative > AIDS on CVLT (verbal learning and verbal recall)
Richardson et al. 2002	231 (149/82)	U.S.A. Clade B	HIV negative: 34.6 (11.9) HIV-positive: 36.3 (11.3) AIDS: 37.7 (12.1)	Colour Trails 1 & 2; WHO/UCLA AVLT; Grooved Pegboard; Digit Symbol; WMS-R visual reproduction; Mental Alternations Test	HIV - > HIV + Colour Trails 2 (abstraction)
Richardson et al. 2005	220 (145/75)	U.S.A. Clade B	HCV-/HIV-: 33 (12.3) HCV+/HIV-: 37.3 (11.3) HCV-/HIV+: 33.8 (12.3) HCV+/HIV+: 39.6 (10.7)	Colour Trails 1 & 2; WHO/UCLA AVLT; Grooved Pegboard; Digit Symbol; WMS-R visual reproduction; Mental Alternations Test	HIV+ > HIV – abstraction Risk of neuropsychological impairments
Maki et al. 2009	63 (51/12)	U.S.A. Clade B	HIV negative: 43.37 (12.92) HIV positive: 42.92 (11.86)	HVLT; Rey Osterreith Complex Figure Task; Stroop letter number sequence	HIV- > HIV + on HVLT learning and delayed recall
Spies et al. 2011	130 (83/47)	South Africa Clade C	HIV negative: 26.2 (11.1) HIV-positive: 31.6 (10.5)	HVLT-R; BVMT-R; Trail Making A; Colour Trails 1 & 2; Grooved Pegboard; Digit Symbol; Symbol Search; WCST; Halstead Category; Stroop; PASAT; Spatial Span; COWAT; Category fluency	HIV - > HIV + HVLT learning and delay; executive functions

6.3 *The effects of trauma on neurocognitive functioning*

6.3.1 *Learning and delayed memory (HVLTR)*

The ANCOVA revealed that trauma status had a significant effect on the HVLTR delay trial, $p < .05$. Women with a history of childhood trauma scored lower on the delay trial of the HVLTR ($M = 8.37$) compared to women without a history of childhood trauma ($M = 9.11$). However, in a multiple regression analysis, the experience of childhood trauma and adult posttraumatic stress disorder symptoms did not reach statistical significance, $p > .05$. In the best subsets regression analysis, results revealed that the cognitive negotiation, minor sexual coercion, and severe injury sub-scales of the CTS-2 (a measure of intimate partner violence; IPV) significantly predicted the HVLTR delay trial, $p = .01$. The results demonstrated that 26% of the variance in the HVLTR delay trial could be explained by the model. The finding that trauma is associated with deficits in memory recall is in keeping with previous studies. Studies assessing stressful life events, acute stress, and/or PTSD have found evidence for memory deficits (Clark et al., 2003; Jelinek et al., 2006; LaGarde, Doyon, & Brunet, 2010; Yasik et al., 2007). Memory deficits in individuals with PTSD have also been shown to be associated with small hippocampal volumes (Bremner et al., 1995; Bremner, 2006; Heim and Nemerhoff, 2009). However, findings have been inconsistent and some studies have not found memory deficits in PTSD patients (Twamley et al., 2004; see reviews by Horner & Hamner, 2002; Isaac et al., 2006).

Similarly, studies assessing early life trauma have also reported deficits in memory (Choi et al., 2009; Majer et al., 2010). Choi et al. (2009) screened healthy young adults for exposure to childhood adversity. The study was a diffusion tensor imaging (DTI) study and demonstrated preliminary evidence for white matter tract abnormalities in 16 young adults exposed to parental verbal abuse. The method of assessing exposure to early life adversities differed from

that of the present study. Participants completed an online assessment providing a vast array of information regarding childhood history. Parental verbal abuse was assessed using the verbal abuse scale (VAS). There were more females than males and the sample size was smaller than that of the present study. Demographic characteristics were not similar as participants were younger than women in the present study. Moreover, parental education levels were only reported. Instrumentation used differed to that of the present study. Results revealed that fractional anisotropy (FA) in the left superior temporal gyrus was correlated with the average parental VAS score and verbal IQ in these youth (Choi et al., 2009).

Majer et al. (2010) assessed the association of childhood trauma with neurocognition in a sample of 47 healthy adults. Majer et al. (2010) assessed the type and severity of childhood trauma with the Childhood Trauma Questionnaire (CTQ), highlighting similarities in instrumentation. However, the method of assessing memory and learning differed to that of the present study. The sample consisted of more females than males. Demographically, participants differed. The healthy adults were older and more educated than those in present study. In both the present study and the study by Majer et al. (2010), the highest mean score was for the emotional neglect subscale. Mean scores on all the CTQ subscales were lower than the scores in the present study, suggesting lower levels of childhood trauma.

Nevertheless, results demonstrated that physical neglect and emotional abuse was associated with memory deficits in this sample of healthy adults.

However, findings have been inconsistent in the early life trauma research. The present study's finding that trauma is associated with deficits in memory recall is contrary to those of Jelacic et al. (2008), who found no deficits in the memory of traumatised versus nontraumatised individuals. Jelacic et al. (2008) examined verbal learning in 54 women with a

history of childhood abuse and 40 women without a trauma history. However, results did not demonstrate evidence for trauma related impairments in learning. As in the present study, the sample consisted of all women. The group sizes were similar among traumatised women but not among controls. There were more control subjects in the study by Jelacic et al. (2008). Instrumentation was similar, with both studies using the CTQ to examine type and severity of trauma. Participants were older but no report of education is given. The authors suggest that the finding may be a result of selection bias. As all participants were recruited via advertisements, it is possible that only resilient trauma survivors volunteered to participate in this study and trauma survivors with memory impairments did not respond.

An interesting observation from the best subsets regression analysis is that the cognitive negotiation, minor sexual coercion, and severe injury sub-scales of the CTS-2 (a measure of intimate partner violence) significantly predicted the learning and memory task. This finding suggests that adult trauma may have influenced learning and memory recall. It is known that in developing countries such as South Africa, women and children are exposed to high rates of gender-based violence (GBV). This includes IPV, rape, and childhood maltreatment (Andersson et al., 2008; Jewkes et al., 2001; Kalichman & Simbayi, 2004). Studies have also found that childhood maltreatment is strongly associated with adult revictimisation (Arriola et al., 2005; Dunkle et al., 2004). The comorbidity of childhood trauma and adult revictimisation in this sample is therefore not surprising. It has been suggested that the experience of stress possibly releases excessive levels of cortisol, damaging brain structures such as the hippocampus, thereby resulting in memory impairments (Bremner, 1999). Fennema-Notestine et al. (2002) examined brain morphometry in female victims of IPV with and without PTSD. Interestingly, although they did not find any significant differences in the hippocampus, they did find smaller mesial temporal lobe gray matter volumes (including the parahippocampal

region) in IPV subjects, regardless of PTSD status. The gray matter abnormalities were associated with executive functioning and auditory working memory tasks. In light of these findings, the experience of IPV may very well impact neurocognitive outcomes in this sample of women. The finding that IPV is associated with poor memory is consistent with that of Stein, Kennedy, & Twamley (2002), who demonstrated that regardless of PTSD status, women who had experienced IPV had poorer performance on tasks of learning/memory.

6.4 *The interaction effects of HIV and trauma on neurocognitive functioning*

6.4.1 *Psychomotor speed*

The ANCOVA revealed a significant interaction effect between HIV status and trauma status on the WAIS-III Symbol Search Task, $p < .05$. However, there was very little difference in the mean scores on the WAIS-III Symbol Search Task between the HIV-positive ($M = 18.75$) and HIV-negative women ($M = 18.88$). It was also evident from the results that women with a history of childhood trauma performed better ($M = 20.21$) than those without a history of childhood trauma ($M = 17.42$). HIV-negative controls with a history of childhood trauma scored the highest on the WAIS-III Symbol Search Task, compared to all other groups. In a multiple regression analysis, HIV status, childhood trauma and adult posttraumatic stress disorder symptoms did not significantly predict the WAIS-III Symbol Search, $p > .05$.

Childhood sexual abuse and adult minor physical assault significantly predicted the WAIS-III Symbol Search, $p < .05$. Results revealed that 35% of the variance in the WAIS-III Symbol Search task could be explained by the model.

Although impairments in psychomotor speed have been reported in the childhood trauma literature (Palmer et al., 1997), studies have also reported the contrary. The results of the present study demonstrated that HIV-negative controls with a history of childhood trauma

scored the highest on the WAIS-III Symbol Search Task. This finding is indeed unexpected and inconsistent with the study hypotheses; however, it is in keeping with a recent study conducted by Majer et al. (2010). In a sample of healthy adults, no significant association between the Childhood Trauma Questionnaire scales and psychomotor speed was found (Majer et al., 2010). One possible explanation for this unexpected finding is that psychomotor speed may not be a sensitive or discriminating test of childhood trauma in healthy adults. Another argument for this unexpected finding is that individuals who experience childhood trauma develop a heightened sensitivity to visual cues (such as facial expressions), and this may translate into a more rapid response on a measure such as the WAIS-III Symbol Search, where the participant must quickly detect incongruent visual stimuli. Research has shown that survivors of childhood maltreatment may be predisposed to biases in emotional processing of cues such as facial expressions. For example, they may over attend to potential threat when interpreting emotional meaning in faces or have broader definitions of what constitutes an angry face. Behavioural and neural differences between maltreated and non-maltreated youth in their processing of angry faces has been reported (Pollak, Cicchetti, Klorman, & Brumaghim, 1997; Pollak, Cicchetti, & Klorman, 1998; Pollak, Cicchetti, Hornung, & Reed, 2000). However, it must be noted that no direct evidence was found to back this argument up.

Although studies have assessed each of these constructs separately, there is a paucity of research assessing the synergistic relationship of HIV and trauma to neurocognitive outcomes. Pukay-Martin et al. (2009) demonstrated that trauma impacted on the executive functions, attention, and processing speed in HIV-positive men. Neurocognitive deficits were only evident in those trauma survivors who were HIV-positive, relative to HIV-negative controls. For HIV-positive subjects, negative life stressors were related to poor performance on measures of executive functions, attention, and processing speed.

Given the brain effects of both HIV and stress, women living with HIV/AIDS, who also have a history of childhood trauma, and/or acute stress or PTSD as an adult, may be especially vulnerable to psychiatric and neurocognitive dysfunction due to the additive or interaction effects of HIV and trauma. Risk for a significant brain involvement is highest in the more advanced HIV disease stages but subtle changes are also evident in medically asymptomatic individuals (Heaton et al., 1995). Moreover, profound neurocognitive impairment has been documented in victims of childhood sexual abuse (Palmer et al., 1997). The majority of the women in this sample were medically asymptomatic and ARV-naïve (83%), which could have affected the ability to detect HIV-related deficits. Moreover, the highest mean score on the CTQ was evident on the emotional neglect sub-scale ($M = 11.7$). The lowest mean score was on the sexual abuse sub-scale ($M = 6.93$). Taking the socio-economic status of the sample into account, everyday living conditions apparent in peri-urban/township areas might be mistaken for or regarded as emotional neglect. This might be one reason for the high scores on the emotional neglect sub-scale. It could be a possibility that this sub-type of childhood trauma may not influence neurocognitive outcomes or that the influence may have been too subtle. Therefore, the type and severity of childhood abuse may play an important role in influencing neurocognitive outcomes and should be carefully considered in future research. Thresholds for trauma experience may be important to consider in future research.

Scores on the childhood trauma questionnaire (CTQ) were relatively low in this cohort of women. It should be taken into account that several factors could influence the reporting of childhood trauma, and thereby may have confounded the results. In using self-report instruments, there is always a risk of social desirability. Despite assurances of confidentiality, respondents may have attempted to create a more favourable impression of themselves or may not have felt comfortable about providing information relating to childhood trauma. The

variation in years and quality of education among the participants may have contributed to response bias. Less literate women may have encountered more difficulty understanding and completing the CTQ despite guidance from the researcher. Respondents may underreport their trauma due to intentional or unintentional memory suppression/denial (MD). Studies investigating childhood trauma report high rates of MD scores (Villano et al., 2004). The study involved the retrospective measurement of childhood trauma, possibly resulting in recall bias.

Similarly, HIV disease stage is also known to play a role (Heaton et al., 1995). It is notable that 10% of the sample as a whole and 15.5% of the HIV-positive sample were on antiretroviral therapy (ART). While there is growing evidence for the neuroprotective effects of ART (Joska, Stein, & Flisher, 2008), neurocognitive disorders persist despite the increased access to and use of ART, resulting in neurodegeneration (Nath et al., 2008). In South Africa, the trend to date has been to treat later in the course of infection (CD4 count of < 200 cells/mm³). Only recently has the threshold at which HIV-positive pregnant women, and those co-infected with tuberculosis (TB) can access ART been raised to a CD4 lymphocyte count of 350 cells/mm³. It can therefore be argued that women on ART in this cohort were presenting with more advanced disease than those women who were ARV-naïve. Risk for a significant brain involvement is highest in the more advanced disease stages but subtle changes are also evident in medically asymptomatic individuals (Heaton et al., 1995). The CHARTER study found that neurocognitive impairment remained most common among people with a history of more severe HIV disease. Moreover, findings highlight that mild NP impairment is common in all stages of infection, despite the use of cART (Heaton et al., 2011). While it has been established that neurocognitive impairment increases with disease progression, the impact that ART has on neurocognitive functioning is still largely under debate. In light of

this, it is plausible that neurocognitive outcomes may have been influenced by the use of ART in this subset of HIV-positive women. The effects of ART on neurocognitive performance needs to be accounted for in future research.

Although the present study did not find evidence for a combined effect of HIV and trauma, it did provide evidence for both HIV and trauma effects separately on neurocognitive outcomes, providing support for one of the present study's hypotheses. The importance of these findings should not be disregarded. Instead, this study should be used to inform future research. The findings of the present study should therefore be explored further. A larger sample size and a prospective study design will be more sensitive to answer these questions presented in this dissertation.

6.5 *Principle study findings*

- (1) HIV-positive women scored lower on all three trials of the HVLT-R immediate and delayed learning trials compared to HIV-negative women, suggesting an HIV related impairment in learning and memory recall.
- (2) HIV-positive women had significantly more errors on the Halstead Category Test compared to HIV-negative women, suggesting an HIV related impairment in abstraction/executive functions.
- (3) Women with a history of childhood trauma scored lower on the delay trial of the HVLT-R compared to women without a history of childhood trauma, suggesting a trauma related impairment in memory recall.
- (4) A significant interaction effect between HIV status and trauma status was evident for psychomotor speed. However, HIV-negative controls with a history of childhood trauma scored the highest on the WAIS-III Symbol Search Task. This finding suggests

that psychomotor speed may not be a sensitive or discriminating test of childhood trauma in healthy adults.

6.6 *Contribution to knowledge gaps*

- (1) Although deficits in learning and executive functions have been widely reported in the developed world, a paucity of research has been carried out in the developing world. Very few studies have been conducted in areas where clade C predominates. Moreover, there are very few all-female studies reporting similar impairments. None have been conducted in South Africa to date. The present study is therefore the first study to report deficits in learning and memory recall and executive functions in an ARV-naïve, all-female sample of women infected with clade C HIV and who have histories of childhood trauma.
- (2) Findings from neurocognitive studies in childhood trauma have been mixed. This is the first study to assess neurocognitive functioning in a sample of South African women with histories of childhood adversities. The study provides evidence for learning deficits in adulthood as a result of early life stress.
- (3) Although no evidence of a combined effect was found, it is still the first study that sought to assess the combined impact of HIV and childhood trauma on neurocognition in women. Similar studies are therefore warranted in order to further investigate this relationship.

6.7 *Limitations*

A few limitations are worth noting. Firstly, given that all study participants were recruited from community health facilities in one South African province, the question of generalisability is raised. However, the characteristics of the sample recruited for the present

study represent the sociodemographic and economic conditions of HIV-infected individuals across South Africa.

Given the cross-sectional nature of the present study, the assessment of childhood trauma was retrospective. Retrospective measurement precludes the drawing of conclusions about causality and increases the chance of recall bias. Moreover, the relatively small sample sizes may have influenced the statistical power of the study to detect HIV/childhood trauma-related impairments. In addition, the risk of making statistical errors (i.e. Type I error) increases with the occurrence of multiple comparisons.

Low levels of education may have had implications for both self-report and neurocognitive assessments. The variation in years and quality of education among the participants may have contributed to response bias. Less literate women may have encountered more difficulty understanding and completing self-report instruments and the neuropsychological battery. Given that the majority of the sample was Xhosa speaking, the administration of all assessments in English may have further contributed to response bias. Difficulty understanding instructions and poor performance on verbal fluency measures may be a possibility if individuals are not tested in their native language. Bilingualism and trilingualism may also affect performance on specific NP measures, such as verbal fluency and executive functions.

Moreover, although efforts were made to match HIV-positive and HIV-negative participants as closely as possible, HIV-positive women were older and less educated than their HIV-negative counterparts. Differences in these sociodemographic characteristics can potentially influence performance on neurocognitive measures. Verbal and non-verbal cognitive tests

have been shown to be significantly influenced by demographic factors, with education and/or illiteracy playing a significant role (Ardila, 1995; Byrd et al., 2005; Cherner et al., 2007; Manly et al., 1999). It has been suggested that performance based tasks specifically decline with advanced age. Although non-verbal tests can also be affected by education, the most education sensitive tasks are those involving vocabulary, information, arithmetic, and comprehension (Grant, 2008). This highlights the importance of sociodemographic characteristics on neuropsychological performance.

Finally, it is worth noting that relatively low CTQ scores (childhood trauma severity) were evident in this cohort of women. Moreover, the HIV cohort was relatively healthy/asymptomatic. It is therefore plausible that both the aforementioned could have affected the detection of HIV/childhood trauma-related impairments.

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CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

7.1 *Conclusion*

In conclusion, the present study demonstrated evidence for HIV and trauma effects in the ability domains of learning and delayed memory and executive functions in an all-female cohort. HIV related impairments were found in memory (both immediate and delayed) and executive functions. This finding is in keeping with research in both the developed and developing world. Similarly, a trauma related impairment was evident in delayed memory. This has also been demonstrated in prior research. However, in looking at the synergistic effects of HIV and trauma, no impairments were evident in the present study. No other studies to date have investigated the additive effects of these two constructs on neurocognitive outcomes. Further investigation is therefore warranted.

7.2 *Directions for future practice and research*

7.2.1 *Recommendations for practice*

The findings of the present study highlight the need to screen for childhood and adult trauma, associated psychopathology and neurocognitive functioning in women and men who are HIV positive and to address these issues in management, in both asymptomatic and symptomatic individuals. HIV prevention activities such as education in HIV risk behaviors and an increased focus on identification and support for children and youth who have experienced childhood traumas is warranted. There is also an urgent need for HIV interventions specifically focusing on gender issues. Interventions dominated by promotion of male condom use and male circumcision provide little help to vulnerable women and children. Increased attention needs to be directed to how trauma may contribute to HIV risk and disease

symptoms. Research to date has demonstrated evidence for successful coping interventions in reducing transmission risk behaviour among HIV and childhood sexual abuse survivors (Puffer, Kochman, Hansen, & Sikkema, 2011; Sikkema et al., 2008). The necessity of early recognition and management of neurocognitive and neuropsychiatric disorders is emphasised. Interventions should aim to improve and maintain quality of life (QoL) and everyday functioning in HIV positive and traumatized individuals. This includes social support interventions which have the potential to improve QoL and cognitive and psychiatric symptom burden.

7.2.2 Recommendations for future research

A pressing research need is the collection of normative data in HIV-positive South Africans. Without age and education appropriate norms, drawing conclusions about the CNS effects of HIV among South Africans becomes complicated. Applying norms from the developing world may result in the over diagnosis of NP impairments due to the differing education and literacy levels throughout the world. The correct diagnosis of HAND in South African men and women relies on appropriate norms for this country. Therefore, this is an important direction for future research.

Moreover, it is clear that the synergistic relationship between HIV and trauma (whether it be early or adult onset) has been grossly under researched. Therefore, an important direction for future HIV studies in women is the stress related neurocognitive and/or neuroimaging outcomes. As cross-sectional study designs preclude follow-up observations and longer-term assessment of mental health and neurocognitive outcomes, future research should be prospective in nature and should better delineate the nature, severity, and temporal relationship of childhood trauma to neurocognitive outcomes, as well as the mediators and

moderators of these outcomes. These studies will allow both clinicians and researchers to better understand these relationships and reduce bias when making causal inferences. Thus, longitudinal investigation of neurocognitive outcomes in large samples of HIV infected individuals with childhood trauma will be key to explaining these causal relationships.

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