

**PULMONARY TUBERCULOSIS AS A COMORBID CONDITION
IN HIV POSITIVE ADULTS AND ITS EFFECTS ON
NEUROCOGNITIVE FUNCTION IN ZAMBIA**

By

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**A dissertation submitted in partial fulfilment of the requirement for
the award of the degree of Master of Science in Clinical
Neuropsychology**

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Declaration

I, Jonathan Chinyama do hereby declare that this is my own work and it has never been published by any one before. All the materials and published work has been acknowledged.

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Certificate of Approval

Approved as partial fulfilment of the requirements of the award of MSc in Clinical Neuropsychology by the University of Zambia.

Examiners' Signature

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Abstract.

Objective: The objective of the study was to explore the effects of PTB as a co-morbid condition in HIV+ adults on neurocognitive functions

Rationale

The study will help in understanding the impact and effects of pulmonary tuberculosis (PTB) on the HIV+ Zambian adults and how far it affects the neurocognitive functions. The study will also help in determining implications for treatment, adherence and use of CNS penetrating antiretroviral, anti-TB regimens, rehabilitation programmes, Human resource replacements at work and care. It will help clinicians determining as when to start treatment to protect the CNS from damage and promote continued quality of life/productivity over the lifespan.

Methods: The study was conducted in Lusaka urban clinics: Kalingalinga, Matero Main, Matero Referral Centre, Kabwata, Chipata and Chilenje clinics respectively. This was a cross-sectional study, which was both retrospective and prospective case-control that reviewed medical files of clients. 324 medical patients were enrolled. PTB+/HIV+ and PTB-/HIV+ groups were statistically compared in terms of cognitive profiles, biomarkers (current CD4 count and viral load) and current WHO HIV disease staging.

Results: Out of 324, only 243 were studied. Results indicated significant neurocognitive impairment in PTB+/HIV+ group than PTB-/HIV+ , $p < .001$, by using $GDS \geq 0.50$, 56% of PTB+ were globally impaired compared to 32% non PTB. The mean CD4 count for PTB+ was 325 cells/ μ l compared to 512 cells/ μ l for non PTB. The PTB+/HIV+ CD4 count was in the range 201-499 cells/ μ l, whereas the non PTB had above 500 cells/ μ l. 95% of PTB+ were stages 3 and 4, whereas 95% of non PTB were stage 1. 69% of PTB+ had viral-load detected whereas the non PTB had 15%. Linear regression model ($p < .01$), PTB status was predictive of global deficit score even while accounting for demographic and medical variables that have previously been associated with neurocognitive impairments. Specifically, a linear regression model identified PTB status ($F=6.26$, $p < .02$) as a significant predictor of Global Deficit Score (GDS). Current CD4 count ($F = 3.21$, $p < .08$), viral load

detection ($F = 0.54$), current WHO stage ($F = 1.41$), were not significant independent predictors of GDS (all p s $> .10$).

Conclusion: This could be one of the first studies to highlight the fact that there is an association between PTB and neurocognitive impairment in HIV+ adult individuals. Findings of the present study show the presence of neuropsychological impairments in all the domains except motor in the PTB+/HIV+ adults in Zambia. Results indicate that there are lower biomarkers, WHO HIV stage and more global impairments in the PTB+/HIV+ than the PTB-/HIV+.

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LIST OF ACRONYMS

| | |
|--------------|---------------------------------------|
| AIDS | Acquired Immunodeficiency Syndrome |
| ART | Anti-retroviral therapy |
| CNS | Central nervous system |
| DDS | Domain Deficit Scores |
| HAART | Highly Active Anti-retroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| MT | Mycobacterium Tuberculosis |
| PTB | Pulmonary Tuberculosis |
| TB | Tuberculosis |
| TBM | Tuberculosis meningitis |
| TMT | Trail Making Test |
| WHO | World Health Organisation |

CHAPTER ONE

1.0 INTRODUCTION

Immunodeficiency virus (HIV) infection and Pulmonary Tuberculosis (PTB) are so closely connected that their relationship is often described as a co-epidemic and they are far more destructive and lethal together than either disease alone; each speeding the other's progress with PTB killing up to half of all AIDS patients (International Federation of Red Cross and Red Crescent societies, 2013). The human immunodeficiency virus (HIV) that causes AIDS weakens the immune system; and so does mycobacterium tuberculosis the causative agent of PTB (WHO, 2002). As a result, 5-10% of people with TB (but who are not infected with HIV) become ill or infectious at some time during their life (WHO, 2002). HIV-positive individuals who are infected with M tuberculosis bacilli are more likely to develop PTB than HIV-negative individuals infected with M tuberculosis. PTB is a leading cause of death among people who are HIV-positive (WHO, 2002). In Africa, HIV is the single most important factor contributing to the increase in the incidence of PTB since 1990(Corbett et al., 2006). According to Dye and colleagues (2002), the increase in TB deaths in high HIV prevalence populations in sub-Saharan Africa may change the popular perception of tuberculosis as a curable disease and threaten the reputation of national tuberculosis programmes (NTPs). This may have an adverse influence on the willingness of tuberculosis suspects to come forward for diagnosis and on the ability of the NTPs to ensure that tuberculosis patients complete treatment. As a consequence, NTPs face the challenge of not only ensuring the effective diagnosis and treatment of increasing numbers of tuberculosis patients, but also of trying to identify and implement methods of decreasing tuberculosis deaths (Mukadi et al.,2001). The annual global toll of deaths among tuberculosis patients in sub-Sahara Africa is approximately 2 million at present (Mukadi et al., 2001).

HIV enters the central nervous system (CNS) early in the course of infection (Scaravilli, 1993). Primary complications of HIV infection include neurocognitive complications as well as neurobiological complications such as HIV meningitis and neuropathy (Grant et al., 1999). Most of the literature addressing cognition in HIV is

from Europe and the United States where the predominant virus strain is clade B (Osmanov et al., 2002). In Zambia, the virus strain is predominantly clade C (Siddappa et al., 2004), although there are a few anecdotal reports of recombinant strains. Epidemiological trends show that HIV infection due to clade C is increasing in Asia and Africa (Siddapa et al., Ibid). Subtype C is predominant in Southern and East Africa, India and Nepal. It has caused the world's worst HIV epidemics and is responsible for more than half of all infections (Chalmet K, et. al, 2010). Almost 60 % HIV- positive individuals (more than 22 million people) are infected with HIV clade C (Lordanskiy, Waltke, Feng and Wood, 2010).

Mycobacterium tuberculosis is a frequent opportunistic pathogen associated with the acquired immunodeficiency syndrome (AIDS). Its relative virulence and potential for person-to-person transmission distinguishes PTB. Persons infected with HIV are particularly susceptible to PTB, either by the reactivation of latent infection or by a primary infection with rapid progression to active disease (Centre for Disease Control, 1991; Centre for Disease Control, 1988). Latent tuberculosis means that a person is infected with *mycobacterium tuberculosis*, but the patient does not have active tuberculosis disease and is not infectious (the tubercle bacilli is inactive and contained in the body). In addition, disseminated infections with PTB complex are increasingly common in advanced HIV disease and cause substantial morbidity (Horsburgh, 1991). Bacteraemia involving PTB complex produces a wide array of clinical signs and symptoms, including wasting, fever, and night sweats, and is associated with decreased survival (Jacobson et al., 1991)

One third of the world's population is currently infected with TB and about 2 million people die every year from TB (WHO, 2007). Yet only 5-10% of immunocompetent individuals that infected with *mycobacterium tuberculosis* (MT) develop TB during their lifetime, indicating the presence of effective host immunity (Russel, 2001). In Africa, HIV is the single most important factor determining the increased incidence of PTB, in the past years, underlining the synergy between the progress of HIV and PTB (Corbett, 2003). The higher risk of HIV patients developing PTB could be related to the fact that macrophages that are not activated by CD4+ T cells are unable to restrict the growth of PTB (Lawn, Butera & Shinnic, 2002). This makes PTB and HIV/AIDS mankind's major infectious diseases (Rosas et al., 2006). Comorbidity

with HIV and PTB has been highlighted recently and it is well known that PTB and HIV infection are closely associated. HIV infection is thought to contribute to PTB epidemics, especially in Sub-Saharan Africa (Cantwell & Bikin, 1996). It was also reported that treatment of latent PTB infection could also prevent PTB development in PTB/HIV cases (Quigley et al., 2001). The World Health Organization stressed that HIV prevention should be a priority for strategies aimed at controlling PTB and that all PTB patients should be offered HIV counselling and testing (WHO, 2002). HIV contributes to the progression from a recently acquired or latent PTB infection to the active form of the disease and also increases the risk of recurrence of PTB (Fitzgerald et al., 2000). In addition, the relationship between HIV and drug-resistant PTB, including extensively drug resistant (XDR) PTB, is cause for concern. Conversely, it has been reported that PTB may also promote infection with HIV and progression to AIDS. According to the WHO (2006) the number of PTB cases among HIV-infected people was 0.7 million in 2006, which is significant because HIV is thought to contribute to PTB epidemics especially in Sub-Sahara Africa.

PTB infections have a disproportionate effect on the lives of people living with HIV. PTB is the most common opportunistic infection and cause of death (WHO, 2007). According to WHO (2007) of the 9.27 million new cases of PTB in 2007, an estimated 1.37 million (14%) were HIV-positive. 79% of the HIV-positive cases were in the African Region and 11% were in the South-East Asia Region. Although there have been vast improvements in the number of people living with human immunodeficiency virus (PLHIV+) who have access to Anti-retroviral (ARV) treatment, PTB and co-infection with HIV continue to be a real problem. The WHO (2007) stated that more than 450,000 of the people who died from PTB in 2007 were infected with HIV; more than double the estimated global total of 200,000 in 2006.

According to Alliance (2008) data from the recent WHO annual Tuberculosis (TB) report, HIV positive people are about 20 times more likely to develop PTB in countries with a generalized HIV epidemic than HIV-negative people (compared with a previous estimate of six), and between 26 and 37 times more likely to develop PTB in countries where HIV prevalence is lower (compared with a previous estimate of 30).

Neuropsychological assessments are arguably the most important tools for diagnosing and categorizing HIV effects on the CNS, especially in resource-limited settings, where sophisticated neuroimaging technology often is unavailable. Characterization of neurocognitive functioning through neuropsychological assessments is crucial to successful diagnosis and treatment. When assessments are reliable and valid, and appropriate normative standards exist, they are quite sensitive to even milder forms of CNS compromise and may provide valuable estimates of functional impairment. This study presents a review of the current status of neurocognitive assessment of HIV, as well as the potential and challenges to conducting neuropsychological assessments in resource-limited settings, with a focus on co-infection of PTB+/HIV+ infected populations in Zambia.

The International Neurobehavioural test battery, which is sensitive to HIV-associated neurocognitive disorders (HAND) (Cysique et al, 2011), was used to measure performance on neuropsychological tests with Zambian Norms. The Zambian normative data had a sample size of 324 with the following demographic characteristics; age range 20-65 years , levels of education of 5 years and above, rural and urban, HIV negative and clinically health individuals (Heaton et al.,2011 unpublished).The Neuropsychological test battery comprised 14 tests split into 7 neuropsychological domains as shown in table 1.

Table 1. Neuropsychological test battery

| Category | Test | Source |
|----------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------|
| Verbal fluency | Animal fluency | Benton, Hamsher, & Sivan (1994); |
| | Letter fluency | Heaton et al (2004). |
| Attention/working memory | PASAT-50 | Diehr, Heaton, & Miller (1998); |
| | WAIS–III L–N Sequencing | Gronwall (1997). |
| Speed of information processing | WAIS–III Symbol Search | Heaton, Taylor, & Manly (2003); |
| | Trail Making Test A | Psychological Corporation (1997). |
| Executive functioning | WCST-64 | Army Individual Test Battery (1944) |
| | Trail Making Test B | Kongs, Thompson, Iverson, & Heaton (2000). |
| Learning/memory | Verbal (Hopkins Verbal Learning Test–Revised) Total Learning & Delayed | Brandt & Benedict (2001). |
| | Visual (Brief Visuospatial Memory Test–Revised) Total Learning & Delayed Recall | |
| Motor | Grooved Pegboard dominant & non dominant hand. | Heaton et al. (2004); Klove (1963). |

Note. NP: neuropsychological; PASAT: Paced Auditory Serial Addition Test; WAIS–III: Wechsler Adult Intelligence Scale–Third Edition; L–N: Letter–Number; WCST-64: Wisconsin Card Sorting Test.

CHAPTER TWO

2.0 LITERATURE REVIEW

The chapter is a review of literature on the co-infection of PTB/HIV prevalence globally according to regions, with a focus on Africa and Zambia in particular. The chapter also summarizes the published literature on neurocognitive effects of HIV, PTB and the recommended way of measuring neurocognitive functions

2.1 Global Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) Prevalence

Among factors that influence neuropsychological test performance are health conditions such as TB and HIV infections. Both have the capacity to cause brain damage (Beaglehole, Bonita & Kjellstorm, 1993). TB is a contagious disease, and like the common cold, it spreads through the air. Only people who are sick with TB in their lungs are infectious (Beaglehole et al., 1993), and the present study focused only on pulmonary tuberculosis (PTB). When infectious people cough, sneeze, and talk or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to be infected. Left untreated, each person with active PTB disease will infect on average between 10 and 15 people every year (WHO, 2003). Allen (1987) asserts that people infected with TB bacilli will not necessarily become sick with the disease. The immune system "walls off" the TB bacilli which, protected by a thick waxy coat, can lie dormant for years. When someone's immune system is weakened, the chances of becoming ill are greater.

People with HIV and do not have TB infection are much more likely to develop it. In 2008, the estimated per capita TB incidence was stable or falling in all six WHO regions. However, the slow decline in incidence rates per capita is offset by population growth. Consequently, the number of new cases arising each year is still increasing globally in the WHO regions of Africa, the Eastern Mediterranean and South-East Asia (WHO, Ibid). Tuberculosis globally has led to high mortality in both HIV+ as well as the HIV negative populations. For example in 2009, the table below shows the estimated TB incidence, prevalence and mortality according to

different regions. Uncertainty bounds for the table below are available in the Global tuberculosis control 2010 WHO (2010).

Table 2. Summary of tuberculosis estimates for 2009 by WHO region

| WHO region | Incidence ¹ | | | Prevalence ² | | Mortality (excl. HIV) | |
|-----------------------|------------------------|-------------------|-----------------------------------|-------------------------|-----------------------------------|-----------------------|-----------------------------------|
| | No. in thousands | % of global total | Rate per 100 000 pop ³ | No. in thousands | Rate per 100 000 pop ³ | No. in thousands | Rate per 100 000 pop ³ |
| Africa | 2 800 | 30% | 340 | 3 900 | 450 | 430 | 50 |
| The Americas | 270 | 2.9% | 29 | 350 | 37 | 20 | 2.1 |
| Eastern Mediterranean | 660 | 7.1% | 110 | 1 000 | 180 | 99 | 18 |
| Europe | 420 | 4.5% | 47 | 560 | 63 | 62 | 7 |
| South-East Asia | 3 300 | 35% | 180 | 4 900 | 280 | 480 | 27 |
| Western Pacific | 1 900 | 21% | 110 | 2 900 | 160 | 240 | 13 |
| Global total | 9 400 | 100% | 140 | 14 000 | 164 | 1 300 | 19 |

1. *Incidence being the number of new cases arising during a defined period.*
2. *Prevalence being the number of cases (new and previously occurring) that exists at a given point in time or over a named period.*
3. *Pop being abbreviation for population.*

2.2 Tuberculosis (TB) and Human Immune Virus (HIV) infections prevalence in Africa

In Africa, HIV infection is the single most important factor contributing to the increase in the incidence of TB infections since 1990 (Corbett et al., 2006). The world faces the challenge of reducing tuberculosis deaths by half by 2015, as part of achieving the United Nations Millennium Development Goals (MDGs) (Mukadi et al., 2001). Achieving this global target through progress mainly in low and medium HIV prevalence countries would be a hollow victory without progress also in high HIV prevalence countries especially in Africa, which carry a disproportionate share of tuberculosis deaths. Van den Broek (1998) asserts that among patients with tuberculosis (all forms), studies have generally shown a higher case fatality rate (CFR) in HIV-positive than in HIV-negative individuals, e.g. 27% vs. 9% in West Burkina Faso (Malkin et al., 1997), 16% vs. 8% in Mwanza, Tanzania (Van den Broek, 1998), 31% vs. 4% in Kinshasa, Zaire (Parries et al., 1991) and 35% vs. 9% in

Lusaka, Zambia (Elliot et al.,1995) Tuberculosis CFR was 2.5 times higher in HIV positive than in HIV-negative patients in Zomba, Malawi (Harries et al.,1998). It is noteworthy that the tuberculosis CFR among HIV-negative patients is generally higher in populations with high HIV prevalence (e.g. Malawi, Zambia) than with low HIV prevalence (e.g. Mali, Comoros) (Dye et al., 1999).

WHO (2010) estimates that the largest number of new TB cases in 2008 occurred in the South-East Asia Region, which accounted for 35% of incident cases globally. However, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the South-East Asia Region with over 350 cases per 100 000 population. An estimated 1.7 million people died from TB in 2009. The highest number of deaths was in the Africa Region (WHO, 2010).Africa bears the brunt of the burden of HIV-related tuberculosis: of the 2.4 million new cases in the region, 463 000 were attributable to HIV (28% of adult cases); and of 538 000 deaths from tuberculosis, 188 000 (35%) were attributable to HIV. Of the global total of 1.75 million deaths from tuberculosis, 227 000 (13%) were attributable to HIV (WHO, 2005). Table 3 below summarises Tuberculosis cases by regions.

Table 3. Summary of tuberculosis estimates for 2003 by WHO region

| WHO region | Eastern | | South- | Western | Global | | |
|----------------------------------------------|--------------|----------|-----------|---------|--------|-------|-------|
| | Africa | Americas | East Asia | Pacific | | | |
| New cases of TB, all forms | 687 | 868 | 518 | 879 | 1,615 | 1 732 | 6 299 |
| Number of cases (thousands) | 2,372 | 370 | 634 | 439 | 3,062 | 1 933 | 8 810 |
| Incidence rate (per 100 000) | 345 | 43 | 122 | 50 | 190 | 112 | 140 |
| Prevalence of HIV in new adult cases (%) | 33 | 5.8 | 2.3 | 4.3 | 3.6 | 1.3 | 12 |
| Attributable to HIV (thousands) | 463 | 12 | 8.3 | 11.3 | 61 | 13 | 617 |
| Attributable to HIV (% of adult cases) | 28 | 5.2 | 2.1 | 3.9 | 2.9 | 1.2 | 11 |
| New smear-positive cases of TB | | | | | | | |
| Number of cases (thousands) | 1,013 | 165 | 285 | 196 | 1,370 | 868 | 3 897 |
| Prevalence rate SS+ TB (per 100 000) | 220 | 25 | 100 | 31 | 155 | 106 | 109 |
| % of prevalent SS+ cases HIV+ (%) | 6.4 | 1.1 | 0.3 | 0.8 | 0.5 | 0.1 | 1.7 |
| Deaths from TB | | | | | | | |
| Deaths from TB (thousands) | 538 | 54 | 144 | 67 | 617 | 327 | 1,747 |
| Deaths from TB (per 100 000) | 78 | 6.2 | 28 | 7.6 | 38 | 19 | 28 |
| Deaths from TB in HIV+ve adults (thousands) | 187 | 3.8 | 4.3 | 3.3 | 25 | 4.9 | 229 |
| Adult (15–49 years) AIDS deaths due to TB(%) | 11 | 4.1 | 14 | 9 | 7.8 | 7 | 10 |
| TB deaths attributable to HIV (%) | 35 | 7.1 | 3.0 | 4.9 | 4.1 | 1.5 | 13 |

Data in table 3 is derived from estimates provided by WHO. The WHO African Region comprises sub-Saharan Africa and Algeria. TB = tuberculosis; SS+ = sputum smear-positive.

2.3 Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infections prevalence in Zambia

Tuberculosis continues to be a major health threat in Zambia and is ranked among the 10 top causes of morbidity and mortality (Sinkala et al., 2009). According to WHO (2010), Zambia has one of the highest incidence rates of TB per capita in the world. The sputum-smear positive (SS+) case notification rate in Zambia is 193 cases per 100,000 population, more than three times the global average of 61 cases per 100,000 population (WHO, Ibid). It also has the 10th highest incidence rate in the world. With strong government commitment and an assured supply of anti-TB drugs through the Global TB Drug Facility, Zambia has achieved 100 percent DOTS (the internationally recommended strategy for TB control) coverage and about 74 percent case detection for all forms of TB (CSO&CBOH, 2002). The treatment success rate has also continued to rise since 2003 and is at the World Health Organization (WHO) target of 85 percent (Mwaba et al., 2003). Unfortunately, the TB-HIV/AIDS co-infection rate is high in the country, and HIV is a major contributor to increasing numbers of TB cases. The DOTS case detection of SS+ TB was only 58 percent in 2007, still below WHO's target of 70 percent (WHO, 2010). Zambia's National TB Strategic Plan for 2006–2010 identified the treatment of TB as a specific objective for the reduction of the socioeconomic impact of HIV/AIDS in the country. Seventy percent of all new TB patients in Zambia are co-infected with HIV, and Zambia has the seventh highest rate for prevalence of co-infection rate in the world (ZNTP, 2006-2010). The estimated HIV prevalence rate of 14.3 percent in the adult population has made TB treatment difficult and has strained already limited financial and human resources (ZNTP, 2010). Literature on Tuberculosis indicated that Zambia's TB Burden (2006 estimates) Incidence was 563/100,000 per year, the trend in incidence rate -6.1(WHO, 2008). WHO(2009) indicated that prevalence was 568/100,000 per year, mortality 102 deaths/100,000

per year, percentage of new TB cases that were HIV+ 37% and percentage of new TB cases with MDR-TB 1.8%.

Zambia is one of the countries in the world most affected by the dual TB and HIV epidemics. In 2006 Zambia reported over 60,000 cases of tuberculosis, of whom at least 40% are estimated to be HIV positive (WHO, 2010). Zambia experienced a dramatic increase in the numbers of patients reported with tuberculosis over the 1990s and early 2000s due to the increasing HIV epidemic, but now appears to have reached a steady state with an estimated incidence of approximately 550/100,000 population per year (WHO,2010).

2.4 Neurocognitive effects of HIV

HIV enters the CNS early during the course of infection (Andersen et al.1999; Davis et al., 1992) and frequently results in neurological disease marked by a set of cognitive, motor, and behavioural symptoms (Chiodi et al., 1992; Navia et al., 1986). The significant loss of neurons and neuronal processes (e.g. dendritic complexity) in people dying of AIDS clearly correlates with ante-mortem neurocognitive impairment (Masliah et al., 1992). Cells primarily infected by HIV within the CNS are blood-derived macrophages, resident microglia, and perhaps astrocytes, but most studies suggest that neurons are not directly infected (Epstein & Gendelman, 1993).The neuronal damage that occurs is likely caused by shed viral proteins such as gp120 (Dreyer et al., 1990; Lannuzel et al.1995) or indirectly through the elevated production of neurotoxic molecules released by activated astrocytes (Levi et al.199; Mollace et al.1993). HIV infection in the brain has widespread and variable effects but appears to preferentially cause damage to the basal ganglia and deep white matter (Navia et al.1986). However, damage to cortical and subcortical neurons (hippocampus and putamen) (Archibald et al, 2004), particularly dendritic pathology (Masliah et al.1997) also are likely to play a role in CNS disease manifestations.

Based on the fact that the study from two tertiary referral hospitals in Ho Chi Minh City, Vietnam, was looking at similar biomarkers and effects of Tuberculosis meningitis in HIV+ as we did in our study, we were interested in comparing our findings to their results. In their study, 528 adults were treated consecutively for Tuberculosis meningitis (TBM) (96 with HIV infection, 432 without) (Bang, Du

&Thwaites, 2005). At presentation, adults with HIV-associated TBM were significantly ($p < 0.05$) more likely to be younger, lighter, and male; to have extrapulmonary/meningeal TB and lower Glasgow coma scores; and to have a lower haematocrit, peripheral blood leucocyte counts (with fewer neutrophils), and plasma sodium. Concentrations of aspartate transaminase and alanine aminotransferase were significantly higher in the HIV-infected patients, and a greater proportion had hepatitis B surface antigenaemia (Bang, Dung &Thwaites, 2005). These findings relate partly to the epidemiology of HIV infection within the study population (young, male, intravenous drug users with a high prevalence of viral hepatitis) and partly to the effects of systemic immunosuppression (low weight, low haematocrit, and a high prevalence of extrapulmonary/meningeal TB). As reported by other studies, the neurological manifestations of TBM were not altered by HIV infection. In contrast to our study, all our patients were on anti-retroviral drugs as recommended by WHO as opposed to the Vietnam study; anti-retroviral drugs were not available during their study. In settings without prevalent treatment with HAART, it may be more likely to observe an effect of PTB in HIV.

A study done by Gupta et al. (2007) in India showed that the HIV+ had more cognitive impairment compared to the HIV negative. The research sample studied consisted of 119 HIV-1-seropositive adults (men, $N=52$; women, $N=67$) ranging in age from 20 to 44 years (mean=29.9, SD=5.6). The participants had from 0 to 15 years of education (mean=7.6, SD=4.8).The predominant mode of transmission of HIV was through heterosexual contact. Mean CD4 count of the sample was 396.8 cells/mm³ (SD=212.5). The healthy, HIV seronegative group consisted of 126 adults (64 men, 62 women) with mean age of 31.9 years (SD=9.9) and mean number of years of education of 7.75 years (SD=6.6).There was no statistical difference in demographic characteristics of gender, age and level of education between the HIV+ and HIV negative. Subjects were considered to have mild impairment if they had deficits on more than one test variable but less than 25% of test variables, i.e., 2 to 3 of 12 test variables impaired. A deficit between 25% and 50% of test variables (i.e., 4 to 6 test variables impaired) was designated as mild to moderate impairment. Moderate to severe impairment was defined as deficits between 50% and 75% of test variables (i.e., 7 to 9 test variables impaired), and severe impairment was defined as deficits on greater than 75% of test variables, (i.e., >10 test variables impaired).When

compared with gender, age, and education matched normative data, mild cognitive impairment was present in 35.3%, mild-moderate impairment was present in 21.9%, and moderate-severe impairment was present in 3.3% of the sample. None of the subjects had severe cognitive impairment. Combining the different categories of severity 60.5% of subjects had cognitive deficits on at least 2 variables.

Cognitive deficits have been known to vary in different levels of immune suppression (Heaton et al, 1995). Data was analyzed to look at the difference in cognitive performance across groups differing on immune suppression as defined by CD4 count and plasma viral load. Differences in sociodemographic characteristics across the immune suppression groups in terms of age, gender, and years of education were analyzed using analysis of variance (ANOVA) or chi square. Analysis revealed significant age and gender differences across the groups based on CD4 count. Subjects in the <200 cells/mm³ CD4 count group were significantly older (mean=34.3years, SD=5.9). There were also a significantly greater number of males in this group ($\chi^2 = 8.19$, $df=2$, $P = .017$). Cognitive performance based on raw test scores was compared across the immune suppression groups using ANCOVA to control for the influence of sociodemographic covariates of age and gender. Differences in cognitive performance across plasma viral load groups were analyzed using ANOVA. Findings revealed test performance did not differ across levels of immune suppression for majority of the test variables. However, visual working memory was significantly poorer in groups with advanced immune suppression, i.e., when there were, low CD4 counts or high plasma viral loads. This suggests greater deficits are seen in working memory when CD4 counts fall below 200 cells/mm³ or plasma viral load is >1,000,001 copies.

The percentage of patients with deficits on each test variable in the HIV-seropositive group was analyzed to identify any emergent pattern of cognitive deficits. Results show the sample of HIV-1 seropositive adults have cognitive deficits occurring across various domains. As depicted in the results, the percentage of subjects with deficits on each test variable varied from 2.5% (total number problems solved with minimum moves on TOL) to 33.6% (AVLT Trials I–V Total). The largest proportion of subjects with deficits was found in verbal learning (33.6% sample with deficits) and manipulation of verbal information in working memory (30% sample with deficits). A comparison of deficits between the HIV seropositive group and the

matched cohort of healthy seronegative individuals who had also undergone complete neuropsychological assessment was done using chi-square analysis. A significantly greater number of subjects in the HIV seropositive group had deficits in fluency (PF $\chi^2 = 6.4$, $df=1$, $P = .01$), learning and memory (AVLT Trials I–V Total $\chi^2 = 11.4$, $df=1$, $P = .00$; AVLT IR $\chi^2 = 7.3$, $df=1$, $P = 0.00$; AVLT DR $\chi^2 = 6.9$, $df=1$, $P = .00$), and verbal working memory (VM2 $\chi^2 = 9.1$, $P = .00$). These findings suggest significant differences in cognitive profiles between HIV seropositive adults and healthy seronegative individuals

2.5 HIV Gender differences in Neurocognitive function

Hestad et al. (2012) conducted a pilot study in Zambia, and the results showed that greater cognitive deficits were seen in female relative to the male seropositive participants. In fact, there were actually no signs of neuropsychological deficits among the Zambian seropositive men, either in relation to the “at risk” clinic controls or the larger Zambian neuropsychological standardization sample. Although their gender-by-sero-status groups were relatively small, the interaction effect on neurocognitive outcome was highly significant. In earlier studies in Western countries, some authors have suggested that women have poorer neurological outcomes than men (Morlat et al., 1992; Robertson et al., 1996), whereas others have found no such sex difference (Bouwman et al., 1998; Marder et al., 1995 in Hestad et al 2012).

Robertson et al. (2004) designed a prospective study to follow a US cohort to look for sex differences in neuropsychological functions over time in HIV-infected subjects. They found no evidence of differential declines regarding neuropsychological functioning in women and men. Similar inconsistent findings have been reported concerning sex differences in clinical symptoms not involving the central nervous system (Farzadegan et al., 1998; Moore et al., 2003; Napravnik et al., 2002; Robertson et al., 2004). Overall, therefore, available data regarding sex differences in HIV effects remain inconclusive, even though most studies that have seen a sex effect have reported poorer disease-related outcomes in women.

According to Hestad et al (2012), informal observations of Zambian healthcare providers also suggest that women in that country may be at more at risk of

developing HIV-related cognitive deficits than their male counterparts. In the national capital, Lusaka, more women than men are seen with HIV-related mental difficulties at the psychiatric clinic at the University Teaching Hospitals (personal communication/anecdotal information from Drs. Paul and Banda, psychiatrists at The University Teaching Hospital)(Hestad et al 2012). In the last 2 years, Psychiatrists had 12 cases of HIV-related mental disturbances, and all of them were women. Typically, these women are referred to the clinic with low CD4 count, confusion, agitation, marked self-neglect, and poor prognosis as the article cites. The situation related to gender can also be seen in the proportion of women relative to men who are HIV-positive in the Sub-Saharan countries, which appears to have greatly increased during the last 3 decades (Erb-Leoncavallo et al., 2004). Bah (2005) suggests that sex inequality, the subordination of women, and what she calls “predatory behaviour” (by men) are major contributors of the epidemic. Results indicated a larger number of women compared with men with HIV and AIDS and, also, that women contract the virus at a younger age than men. The research therefore tried to find out if PTB/HIV+ co-infection had gender differences in neurocognitive function

2.6 Neurocognitive effects of Tuberculosis (TB).

Central nervous system TB results from the haematogenous dissemination of M.Tuberculosis to the brain with the formation of small subpial or subependymal foci. These are called Rich foci, after the author of the original pathological studies describing the sequence of events that lead to Tuberculosis Meningitis (TBM) (Andersen et al., 2002). The development of TBM requires rupture of a Rich focus with release of M.Tuberculosis into the subarachnoid space. These herald the onset of meningitis, which, if left untreated, will result in death in most cases (Caws et al., 2006). TBM, can also lead to neurocognitive impairments.

Bishburg et al. (1986) assert that three processes produce the subsequent neurological pathology in TB: granulomatous meningeal inflammation with exudate and adhesion formation, an obliterative vasculitis, and an encephalitis or myelitis. Granulomas can coalesce to form tuberculomas, predominantly meningeal in origin, which can cause diverse clinical consequences dependent upon their anatomical location (Fernando et al., 2007). Adhesions result from dense basal meningeal

exudate that contains lymphocytes, plasma cells, and macrophages, with increasing quantities of fibrin. Adhesions can block the basal subarachnoid cisterns, obstruct the flow of cerebral spinal fluid (CSF), and cause hydrocephalus and can also compromise cranial nerves, particularly II, III, IV, VI, and VII (Reed et al., 2004). An obliterative vasculitis of both large and small vessels can cause infarctions, which commonly occur in the territories of the proximal middle cerebral artery and the perforating vessels to the basal ganglia. The intensity of the basal inflammatory process extends into the parenchyma, resulting in encephalitis. Oedema, occurring as a consequence, can be marked throughout both hemispheres and contributes to rising intracranial pressure and the global clinical neurological deficit (Abdelmalek et al., 2006).

According to Paton et al. (1999) their study results in which they investigated the effects of TB in HIV positive adults, indicated that the TB/HIV+ nutritional status of participants was significantly worse than the HIV+ without TB. It also found that the TB/HIV+ patients were severely malnourished and this contributed to the decreased survival. In the study, hyper metabolism was found to play a role in the wasting process of patients who had co-infection of TB/HIV+. TB is known to be characterized by a marked cytokine- induced inflammatory state and might therefore be expected to demonstrate archetypal features of a hypermetabolic pattern of wasting. Whalen et al. (1995) also found that HIV infected patients with TB even after controlling for differences in baseline parameters including CD4 count and antiretroviral therapy had severe malnutrition attributed to the TB infection in HIV+ and decreased survival. WHO (2009) indicates that HIV infection alters the immune response to TB leading to atypical clinical presentation of TB resulting into misdiagnosis and an extremely rapid progression to death

2.7 Measuring Neurocognitive functions

The recommended way to assess for neurocognitive performance, to ascertain whether an individual has neurocognitive impairment or not, is by the use of a neuropsychological test battery. This is done by the administration of a complete and comprehensive standardized neuropsychological assessment instrument. The assessment's purpose is to aid in the proper and accurate diagnosis of patient's illness or the aetiology of symptoms which has obvious implication for medical care

and patients (Burke, 2009). The study used the International Neurobehavioural Battery with Zambian norms (Zambian normative data was based on 324 HIV-negative healthy Zambian adults, formulated by Heaton et al (2012) (Unpublished at the time of our study).

Neuropsychological assessment provides not only the aetiology but quantifies the severity of impairment and provides objective measures of aspects of cognition, emotions, personality and behaviour. It therefore implies that this is a method through which a clinical neuropsychologist can acquire data about a subject's cognitive, motor, behavioural, language and executive functions. It also provides many details about the strengths and weakness of the patient that in turn can help the patient as well as the family to learn how to cope with problems (Burke, Ibid). These instruments aid in identifying an individual's cognitive and behavioural strengths and weaknesses, classifying impairment into correct diagnostic categories (brain injured and non-brain injured persons), measuring cognitive change and also predicting everyday functioning (Burke,2009). It also makes possible the grading of neurocognitive impairment such as mild, mild to moderate and moderate to severe cognitive deficits. "When based on a thorough description of abilities and deficits, neuropsychological assessment leads to recommendation for rehabilitation and treatment" (Zillmer, 2009). However, one of its major limitations is that it is administered in English language.

2.8 Rationale

The study will help in understanding the impact and effects of pulmonary tuberculosis (PTB) on the HIV+ Zambian adults and how far it affects the neurocognitive functions. It also heightened any significance differences in gender on neuropsychological performance. The study will also help in determining implications for treatment, adherence and use of CNS penetrating antiretroviral, anti-TB regimens, rehabilitation programmes, Human resource replacements at work and care. It will help clinicians determining when to start treatment to protect the CNS from damage and promote continued quality of life/productivity over the lifespan.

2.8.1 Overall Objective

- I. To explore the effects of PTB as a co-morbid condition in HIV+ adults on neurocognitive functions.

2.8.2 Specific Objectives.

- i. To identify neurocognitive deficits associated with PTB+ in HIV+ adults.
- ii. To identify PTB disease characteristics (CD4 cell count, viral load and WHO staging) in HIV+ adults.
- iii. To determine whether there are gender differences related to neurocognitive deficits in PTB+/HIV+ adults.

2.8.3 Research questions.

- i. What type of immunological effects does PTB have on HIV positive adults?
- ii. Does PTB exacerbate HIV-associated neurocognitive deficits?
- iii. Is there a difference in neurocognitive performance between males and females in the study groups?
- iv. What disease characteristics exist (i.e.; CD4 count, viral load, and WHO HIV staging) in PTB+/ HIV+ adult patients?

2.8.4 Hypotheses

- i. Adults that are PTB+/HIV+ will perform worse than the HIV+ without PTB in all the seven domains on the Neuropsychological test battery.
- ii. Adults that are PTB+/HIV+ will have worse disease characteristics; CD4 count, viral load, and WHO HIV staging than the HIV+ without PTB.
- iii. Females that are PTB+/HIV+ will perform worse than males who are PTB+/HIV+ on the neuropsychological test battery.
- iv. Adults that are PTB+/HIV+ will have more neurocognitive impairment compared to the HIV+ without PTB group.

2.9 Operational definitions

WHO Disease Staging System

Given the fact that the research was conducted in the African Region- Zambia, the World Health Organization's (WHO) clinical staging and case definition of HIV in resource constrained settings was used. WHO clinical stages were categorized as **Stage 1** through **Stage 4**, and reflected progression from primary HIV infection to advanced HIV/AIDS. Each stage was defined by specific clinical conditions or symptoms: In **Stage 1**, HIV disease was asymptomatic and not categorized as AIDS. In **Stage 2**: minor mucocutaneous manifestations and recurrent upper respiratory tract infections were included. In **Stage 3**, unexplained chronic diarrhoea (longer than a month), and severe bacterial infections and pulmonary tuberculosis were included. In **Stage 4**, diseases used as indicators of AIDS (brain toxoplasmosis, candidiasis of the oesophagus, trachea, bronchi or lungs, and Kaposi's sarcoma) were included.

Active Pulmonary Tuberculosis(PTB):was defined as compatible illness of the lungs, plus positive smear or growth of *M. tuberculosis* from one or more sputum specimens, or positive smear or growth of *M. tuberculosis* from one specimen with suggestive radiological abnormalities and response to PTB treatment; or smear negative but suggestive radiological abnormalities and good prognosis to PTB treatment.

Pulmonary TB patient: A patient with PTB of the lungs with one or more sputum smear examination positive for acid fast bacilli (AFB) or negative sputum smear but suggestive radiological abnormalities of PTB with good prognosis to PTB treatment

Adult: an adult was defined as a person between the ages 20-65 years. This is based on the International Neurobehavioural Test Battery Zambian norms.

Case definition: HIV positive adults' on Highly Active Antiretroviral Therapy (HAART) with active pulmonary Tuberculosis infection and on anti-Tuberculosis treatment (Fixed dose combination therapy either in intensive or continuation phase)

for the last six months and not yet discharged from treatment, 20- 65 years old and educational level of 5 years and above and without any history or form of Tuberculosis.

2.10 Identification of variables

Independent: Pulmonary Tuberculosis. Screened for TB (ie.Sputum, CXR and ESR) and HIV. HIV test was done using Determine and confirmatory test of Abbott and Unigold.

Dependent: Neurocognitive function (Performance on the subtests of neuropsychological test battery; Domain Deficit Scores (DDS) for the seven domains and Global Deficit Scores(GDS) were used; measured by using the International Neurobehavioural test battery with Zambian norms (unpublished as of submission time, 2014).

CHAPTER THREE

3.0 METHODOLOGY

The chapter is an outline of the methods used in the research's data collection. The data collected was part of a larger study, with the present study focusing only on the co-infection of PTB+/HIV+ adults in Zambia. The study commenced after clearance from The University of Zambia Biomedical Research Ethics Committee (UNZABREC) and Ministry of Health. (Appendix A).

3.1 Study Design

This was both a **retrospective and prospective case-control study**. Data collected from the PTB patient's files was retrospective while the physical examination and administration of the Neuropsychological test battery was prospective. This involved the administration of the International Neurobehavioural test battery to assess different brain and central nervous system functions with Zambian norms. The study depended on collection of both prospective and retrospective data from research participants' medical files at their local clinics as well as Neuropsychological performance on the Neurocognitive test battery. The Neuropsychological test battery involved assessing seven domains, namely; learning and memory, speed of information processing, executive functioning, attention/working memory, verbal fluency and motor dexterity. The study had two arms of research participants; PTB+/HIV+ and TB-/HIV+.

3.2 Sample site, size and frame

3.2.1 Sample site.

The sample sites were 6 Lusaka based urban clinics namely: Kalingalinga, Matero Main, Matero Referral Centre, Kabwata, Chipata and Chilenje clinics respectively. The clinics were chosen due to their high numbers of HIV+ and TB patients on HAART and anti-TB therapy respectively. Each respective clinic conducts HIV and TB clinic activities on different specific days. Each clinic is under a Sister-In charge trained either in TB or HIV management and care. All the 6 Sister-In charges were enrolled in the study as research assistants in their respective clinics. The Sister-In charges (research assistants) duties were to identify potential research participants during either ART or TB clinics on specific days when clinics are conducted.

After the research assistants identified potential research subjects by using the inclusion and exclusion criteria, an identification number was issued to the research participants.

3.3 Study Sample

The study included 324 research participants; the number was based on the large sample criteria. There were 10 researchers: Master of Science in Clinical Neuropsychology (from the 2011-2012 NOMA projects) each researcher assigned to collect similar data from 38 research subjects. The research participants were recruited from selected clinics in Lusaka which included: Kalingalinga, Matero Main, Matero Referral Centre, Kabwata, Chipata and Chilenje clinics respectively. Researchers were divided in three groups and had specific days to collect data from all the clinics by rotating with the other groups. The rotation of the groups followed the clinics' specific days for either ART or TB clinics.

Each researcher had to collect data from 38 research participants who were later compiled into one data set. However, the present study collected data from 39 research participants who had PTB. This was done on Tuesdays and Fridays when there were TB clinics in the study sites. The TB Sister-In charge identified potential PTB subjects who were HIV+ during reviews or adherence counselling and screened them for possible enrolment in the study group. The 39 subjects in the study group were statistically compared with their 205 non TB cohort in terms of age, gender, level of education and WHO- HIV staging on neurocognitive function. The data from 205 participants were collected by our 9 other researchers from the same study sites. The two research arms were statistically compared in terms of their neurocognitive profiles, WHO HIV disease staging and bio-makers (CD4 count and viral- load).

3.4 Sampling frame

Research participants were classified according to age, gender, levels of education, PTB+/HIV+, PTB-/HIV+ and WHO staging of HIV disease. The research participants in the cases arm were statistically compared with the non TB using a priori criteria (38 participants as per group dynamic) where each of the 10 researchers had the same sample size for their specific variable related to their research.

3.5 Study procedure

3.5.1 Inclusion-exclusion criteria

Inclusion

- HIV+ adults currently on highly active antiretroviral therapy (HAART)
- Educational level of 5 years and above, per Demographic Questionnaire
- Age 20-65 years (because the battery's Zambian norms are based on this age range).
- Ability to speak and understand English, determined by using the Wide Range Achievement Test (WRAT). Individuals with scores over five words were included in the study.
- Willingness to provide informed consent.
- *For pulmonary TB arm:* Adults with Active pulmonary tuberculosis, who are undergoing current treatment for PTB, determined by the National Tuberculosis and leprosy identity card , Patient Tuberculosis case number, patient TB treatment ID card, Clinic TB register, Clinic TB suspect register and the District Health Office Tuberculosis Treatment Card.
- *For TB-negative arm:* Adults who tested negative for any type of TB.

Exclusion

- History of neurological problems (e.g., Epilepsy, closed head injury, coma etc), assessed using Neurobehavioural Medical Screen (assess past medical and neurological histories)
- History of drug abuse, per substance use history questionnaire (which captured the units of alcohol consumed). Moderate alcohol consumption for males =21 units of alcohol per week and 4 units per day. While moderate alcohol consumption in females is measured as being =14 units of alcohol per week and 3 units per day. (WHO 2004).The history of drug use excluded potential research participants
- HIV negative
- HIV positive, not on HAART.
- HIV+ with a cough for more than three weeks.

- History of Psychiatric illness (Any history of Psychiatry illness excluded individuals) -Use of the Composite International Diagnostic International Interview (CIDI). It is a structured questionnaire using the DSM –IV and ICD-10 diagnosis, it captures major Depression, dysthymia and substance related disorders. Depressive symptoms were quantified by means of means of Beck Depressive Inventory.
- Not able to provide informed consent.
- HIV+ with history of previously treated TB.
- Unable to read and understand the English language, per WRAT (scores below 5 words were not considered sufficient to complete testing)
- Extra-pulmonary Tuberculosis, was determined by patient’s treatment card, Clinic TB register, TB suspect register , the district tuberculosis treatment card and evidence of Chest-X-ray abnormalities

Screening of potential research participants was completed by the study Nurse (PTB+/HIV+ Sister In-Charge) during the HAART and TB clinics at the respective centres on specific allocated days. In some cases, appointments were made with the potential research participants at other times. The screening process depended heavily on the retrospective data from patients’ medical files: All the research participants’ medical files were reviewed by a physician to make sure that they met the inclusion criteria.

Enrolment was done by the researcher after providing information concerning the study (information sheet appendix B). Participants were then asked whether they would like to volunteer their participation in the study.

Research participants who volunteered to participate were asked to sign a written informed consent and completed a demographic questionnaire (appendices C and D, respectively).

After signing the informed consent, the following screening instruments were administered:

- Substance Use (CH13A)- screened for alcohol and drug abuse
- Use of Academic Skills Questionnaire (CN18)- Screened academic skills use
- Neurobehavioural Medical Screen (CH42)-Screened for any history of neurological disease (e.g. epilepsy)

- Zambia Achievement Test (ZAT) - Screened educational attainment and assessed for fluency in the English language (appendix E).

After completing self-report and ZAT measures listed above, the neurocognitive battery was administered to the participant by the researcher. This took between two to two and half hours to complete.

After the administration of the neurocognitive test battery, blood was drawn from the upper arm in order to analyze HIV bio-markers. Laboratory results were given to the researcher for analysis.

Research participants who met study inclusion criteria were enrolled in the study. Those with active PTB (on anti-PTB treatment) and HIV+ (on HAART), were enrolled in the cases arm, while individuals who were negative for all types of TB but were HIV+ (on HAART) were enrolled in the other arm. Following their enrolment in the study, a physician went through the medical records to collect the following information: 1) date of first HIV diagnosis, 2) date when HAART was commenced, 3) date PTB was first diagnosed, 4) date first anti-PTB drugs were commenced, 5) type of PTB: smear positive or negative, 6) current CD4 and total lymphocyte cell count, 7) type of treatment regimen, 8) current WHO HIV/AIDS disease stage, 9) Hb, 10) type of HAART regimen, and 11 condition diagnosed first (between PTB and HIV)

Data collection involved the following laboratory investigations, CD4 lymphocyte count, full blood Count (FBC) Hb and viral load, medical files, sociodemographic questionnaire and the administration of the neurobehavioural test battery.

Data collection was done by 10 researchers of the 2011-2012 students of the University of Zambia (UNZA) Master of Science in Clinical Neuropsychology programme. Two of the researchers, due to the differences of their research design, had collected data from 10 research participants each and 8 researchers had 38 research participants each, making a total of 324 research participants. The present study however, focused on 39 PTB+/HIV+ in the cases arm that was handled by the researcher of the current study. The 205 non TB research participants were from the other 9 researchers. 81 were excluded because 47 had missing neuropsychological data of Wisconsin card sorting Test and Halstead Category test (two major tests of

Executive Function). 34 were excluded because they had extra-pulmonary tuberculosis (EPTB).

3.6 Instruments

Data collection and instruments included four sections: A sociodemographic survey, medical history, laboratory tests and functional status survey, subjective neurological symptoms questionnaire, and a neuropsychological test battery.

3.6.1 Demographic Information

Demographic information was obtained by questionnaire. It included information on age, education, residence, socio-economic status and number of languages spoken (Appendix D) The International Neurobehavioural Test Battery was used (Appendix F). This battery assessed seven cognitive domains. The battery's effort, reading, screening, the seven domains and individual tests included:

3.6.2 International Neurobehavioural Screening Tests

3.6.2.1 Hiscock Memory Digit Test: The test has been designed to clinically identify an individual thought to be giving poor effort or actually faking memory impairment (Prigatano & Amin, 1993). The 18-item HDMT which is a part of the International Neurobehavioural Test Battery is a multiple choice visual memory task on which participants view (and are asked to remember) successive series of 5-digit numbers for 5 seconds each, which are presented singly on a 7.6 X 12.7 cm note cards attached to an easel.

3.6.2.2 Reading Ability

The Wide Range Achievement Test Version Three (WRAT-3). Blue Word Reading List apart from measuring reading ability also served as screening for literacy and proficiency in the English language. The WRAT is one of the widely used measures of academic achievement among neuropsychologists, used for both children and adults, and ranked as one of the most used reading tests (Steven and Price, 1999). Participants were required to read words which are in order of increasing difficulty (in the USA). A minimum of five correctly pronounced words was required to indicate adequate knowledge of the English language.

3.6.2.3 Psychiatric and Drug Abuse assessment

The Psychiatric and Drug Abuse Assessment involves the Composite International Diagnostic Interview (CIDI). The CIDI provides results in terms of presence or absence of DSM/ICD10 diagnosis of present or past depression and substance disorder.

3.6.2.4 Beck Depression Inventory-II (CH3)

Depression symptoms were assessed using the Beck Depression Inventory (II) which is a 21-item self report scale. On each item there are 4 response options of perceived severity within the last two weeks. Administration of the BDI took about 10-15 minutes and participants asked to complete this on their own.

3.6.2.5 Alcohol and Drug abuse was assessed using a Substance Use questionnaire. The questionnaire contained a list of drugs and alcohol and the participant was required to state which ones they used and how much they had used in the last three months. It further required the participant to state details of the frequency of use and the quantities for each drug or alcohol stated to have been used.

3.6.3 International Neurobehavioural Assessment Domains (tests):

The neurocognitive assessment consisted of tests of the following ability domains: verbal fluency, abstraction/executive functions, attention/working memory, and speed of information processing, learning, delayed recall, and motor function. Specific tests are listed below. These are well known NP instruments and have been widely used in neurobehavioral studies of HIV/AIDS (Carey, et al., 2004; Woods, et al., 2004). To explore the real world effects of PTB in HIV+ and associated neurocognitive impairments in Zambia, the international Neurobehavioural test Battery was administered. Below is a brief description of the assessed domains.

3.6.3.1 Speed of information processing

This domain included Digit Symbol & Symbol Search both from the third edition of the Wechsler- Adult Intelligence Scale (WAIS-III). The two tests make up the Processing Speed Index of the WAIS-III. In the Digit symbol, the participant was asked to match a symbol with a specific digit. The participant was asked to complete the task within 120 seconds without stopping or changing the answers. In symbol

Search, the participant was asked to look at two symbols on the left and state whether either of them was on the right by answering “YES” or “NO” on the spaces provided. The Stroop Task being used for the current study was revised by Golden and Freshwater 2002. The colour card (C) in particular measured processing speed. The sheet consisted of a series of ‘X’s printed in green, red and blue. The participant was asked to name the colour as quickly as possible while maintaining accuracy and the subject was given 45 seconds to complete the task. Trail Making Test Part A consisted of encircled numbers from 1 to 25 randomly spread across a sheet of paper. The objective of the test was for the subject to connect the numbers in order, beginning with 1 and ending with 25, in as little time as possible.

The Colour Trails Test Part 1 is designed to minimize the influence of language so that it can be used in cross-cultural settings. The test has all odd-numbers circled in pink and all even-numbers circled in yellow; numbers from 1 to 25 alternate between pink and yellow circles (Strauss, Sherman & Spreen, 2006). The participant was required to move from a pink one to a yellow two, to a pink three and so on until they reach 25. The amount of time taken to complete the task was recorded.

3.6.3.2 Verbal Episodic Memory

It included the Hopkins Verbal Learning Test – Revised (HVLTR) which is a test of learning ability and delayed recall for verbal information. There are three learning trials. It also measures an individual’s capacity to retain, reproduce and recognize information after delay (Strauss, Sherman and Spreen, 2006). The HVLTR used in the current study comprised 12 nouns with four words drawn from three semantic categories: four words each from four legged animals, precious stones, and human dwellings. Some changes were made to adapt the words and make the test suit Zambian situation. For instance the original items such as Emerald, Sapphire, Jade and Pearl were replaced with Copper, Iron, Lead and Zinc, respectively, because these are more familiar to Zambians (Cherner et al 2007).

3.6.3.3 Visual Episodic Memory

The Brief Visuospatial Memory Test – Revised (BVMTR) measures visual learning and delayed recall in a manner similar to the HVLTR (Strauss, Sherman and Spreen, 2006). When administering the test, the participant was presented with an 8

x 11 – inch card containing six simple geometric visual designs in a 2 x 3 matrix, for 10 seconds and after that, the participant was required to reproduce as many of the designs as possible on a blank sheet of paper in the same location as they appeared on the display. These are the three learning trials and delayed recall

3.6.3.4 Abstraction/executive functioning

Consisted of the Wisconsin Card Sorting Test – 64 Items. This was designed as a test of “abstract behaviour and shift of set”. All cards are different and there are no two identical cards. In the test the test taker is supposed to match one of the cards at the bottom to those that are shown among the four (Lezak, 2004). There are three principles in the way the cards are matched and these may be the colour, the shape or the number of items on the card (1-4). The feedback given for each response is either “right” or “wrong”, indicating whether the card has been matched correctly.

The Halstead Category test (Standard Category Test) was developed by Ward Halsted (1947) to assess conceptual reasoning. Reitan in 1948 reduced the subtests to 7 with 208 items. Each subtest has a different principle which may be odd stimulus, number of objects, spatial position, a combination of different principles etc. To complete the test, the participant relied on feedback based on correct or incorrect guesses to show what the principle in that subtest was.

The Stroop Word- Colour task CW which measures inhibition of prepotent responses consisted of names of colours printed in an incongruent ink colour. The client was given 45 seconds to name the colour while suppressing the automatic response to read the word.

Colour Trails II which provided information about mental flexibility, abstraction and executive function was used. The client was instructed to connect numbered circles between 1-25 in sequence as fast as possible, but alternating between pink and yellow colours. The examiner used a stop watch to record the length of time to complete the trial along with qualitative features of performance indicative of brain dysfunction, such as near-misses, prompts, number sequence errors, and colour sequence errors on the record form.

3.6.3.5 Verbal Fluency

This was assessed using the Controlled Oral Word Association Test - (COWAT–FAS) whose purpose was to evaluate the spontaneous production of words within a limited amount of time (Strauss, Sherman, Spreen, 2006). The participant was asked orally to produce as many words as possible, beginning with a given letter (F, A or S). Examinees were allowed 60 seconds for each trial and were not allowed to generate nouns such as name of a person, place also administered were the Category Fluency Test (Animals) where the test taker was asked to mention as many names of animals as they could think of in 45 seconds, and the action Fluency Test where the participant was asked to quickly mention as many things as possible that human beings do.

3.6.3.6 Attention/working memory

This domain included the Paced Auditory Serial Addition Test (PASAT) as cited in (Strauss, Sherman & Spreen, 2006), the PASAT was devised by Gronwall et al. (Gronwall, 1977; Gronwall & Sampson, 1974; Gronwall & Writson, 1974 and measures attention, working memory, mental calculation, and mental tracking. The participants were given a number every 3 seconds and are asked to add the number they just heard with the number they heard before.

The Spatial Span Test is from Wechsler's Memory Scale third edition (WMS-III). The participant was required to follow a sequence of tapping the blocks both forwards and backwards

3.6.3.7 Motor Dexterity

This was assessed with the Grooved Pegboard Test (Dominant & Non-Dominant Hand trials. The "Grooved Pegboard (GP) task measures eye-hand coordination and motor speed" (Strauss et al., 2006). This procedure measured performance speed in a fine motor task and by examining both sides of the body, it allows for inferences to be drawn regarding possible lateral brain damage (Swiercinsky, 2001).

The GP consisted of a metal board with a matrix of 25 holes with randomly positioned slots. Pegs have a ridge along one side and must be rotated to match the hole before they can be inserted in the board. The participants' task was to insert the pegs in the holes as fast as they could in sequence without skipping any slot.

3.7 Data analysis

The collected data was analyzed with Statistical Package for Social Sciences version 16.0 (SPSS). The analysis was made by maintaining the stratification based on cases arm compared to the non TB arm in terms of their neurocognitive profiles. The Global Deficit Score (GDS) was used as an overall measure of cognitive impairments between groups and also within the PTB+/HIV+ groups, and domain deficit scores (DDS) were used to summarize cognitive impairments within each of the seven domains. To examine group differences in neurocognitive status, we used Wilcoxon ranked sum tests to compare the performance between groups on neuropsychological test battery. This nonparametric Wilcoxon test was used instead of ANOVA in order to minimize the potential impacts (i.e., heterogeneity of variance) of testing groups of different sizes. The Wilcoxon rank-sum test is a nonparametric alternative to the two sample t-test which is based solely on the order in which the observations from the two samples fall.

The differences in the means were further analyzed by multiple regressions to determine the independent contributions of independent variables (PTB status, viral-load detection and current WHO HIV disease staging) on the dependent variable (neuropsychological test performance, as determined by global deficit score or domain deficit score). Regression was analyzed by the formula $Y = \beta_1X_1 + \beta_2X_2 + \beta_nX_n + \dots A$; where Y represented the seven neuropsychological domains (dependent variables), X_1 , X_2 are the independent variables used to predict it. β_1 , β_2 are the coefficients or multipliers that describe the size of the effect the independent variables are having on the dependent variable, Y and A is the value Y is predicted to have when all the independent variables are equal to zero. Comprehensive interpretation of neuropsychological test results was done using the Global Deficit Score (GDS), derived from demographically corrected test scores. The GDS has been reported to have a sensitivity of 91.4% and specificity of 87.66% for differentiating brain damaged from adult controls (Heaton, et.al, 2004). The scores of each different domains (specific) battery test were kept separate in order to ascertain which ones were affected most, in cases arm compared to the non TB arm and across gender.

CHAPTER FOUR

4.0 RESULTS

4.1 Participant's demographic characteristics

All the patients in the study were black African Zambians from Lusaka urban clinics: Kalingalinga, Matero Main, Matero Referral Centre, Kabwata, Chipata and Chilenje clinics respectively. In total, 324 participants were enrolled and only 244 HIV+ were studied. Men; 95 (38.93%), Women; 149 (61.06%). The men: women ratio was 95:149. The age range was 21-65 years with a median of 41 years. Out of 244, 205 were non Tuberculosis participants. Of the 205, men 70 (34.15%) and women 134(65.37%) one participant missing. Out of 244 participants, 39 had PTB+, men 25(64.10%) and women 14 (35.89%).21 (53.85%) had smear positive sputum PTB and 18(46.15%) smear negative sputum PTB. Within the study group (39), 22 (56.41%) PTB was diagnosed first and 17 (43.59%) PTB was diagnosed second (after HIV infection). Levels of education range were 5- 20 years of schooling with a mean of 10 years. 34 were excluded because they had extrapulmonary tuberculosis (EPTB). 47 were also excluded because they had missing raw scores for Wisconsin Card Sorting and Halstead Category Tests .See tables 4 and 5 for summaries

Table 4: PTB status

| PTB status | Female | male | SS+ | SS- | PTB first | PTB second | Total number |
|----------------------|--------|------|-----|-----|-----------|------------|--------------|
| PTB+ | 14 | 25 | 21 | 18 | 22 | 17 | 39 |
| PTB- | 149 | 70 | 0 | 0 | 0 | 0 | 205 |
| Total studied | | | | | | | 244 |

Note: SS+ = Sputum smear positive, SS= Sputum smear negative, PTB first = PTB was diagnosed before HIV infection, PTB second = PTB was diagnosed second to HIV infection.

Table 5: Levels of education and age

| Levels of education | Frequency | Percent. |
|----------------------------|------------------|-----------------|
| 5-7 years | 39 | 16.0 |
| 8-9 years | 71 | 29.2 |
| 10-12 years | 115 | 47.3 |
| 13 years and above | 18 | 7.4 |
| Age | | |
| 20-35 years | 74 | 30.5 |
| 36-45 years | 100 | 41.2 |
| 46-55 years | 53 | 21.8 |
| 56-65 years | 16 | 6.9 |

4.2 Statistical analysis

The GDS was used as an overall measure for cognitive impairment between groups and also within the PTB+/HIV+ group, and domain deficit scores (DDS) were used to summarize cognitive impairments within each of the seven domains. The CD4 count, viral-load detection and WHO HIV disease staging were also compared using Chi-square. The CD4 count represented the levels of immune suppression and was categorised as; < 200 cells/mm³, 201-499 cells/mm³ and > 500 cells/mm³ and viral-load either detected or not. Next, we used multiple regressions to identify any variables that may independently predict neurocognitive status. The advantage of the regression approach is that it accounts for effects of other variables such as viral-load, CD4 count, current WHO HIV disease staging and regression analysis was computed to determine whether these variables had any significant effect on the differences in neuropsychological profiles. SPSS 16.0 and JMP 9.0 were used to complete these analyses. All raw scores for the seven domains were converted T scores to generate domain deficit scores (DDS) and Global deficit Scores (GDS), which were used in the final analyses. P value of 0.05 was considered significant.

4.5 Global Deficit Impairment

Results indicated that neurocognitive impairments were significantly more in the PTB+/HIV+ group than PTB-/HIV+. See figure 1 below.

Figure 1: Global Deficit Score (GDS) by PTB status.

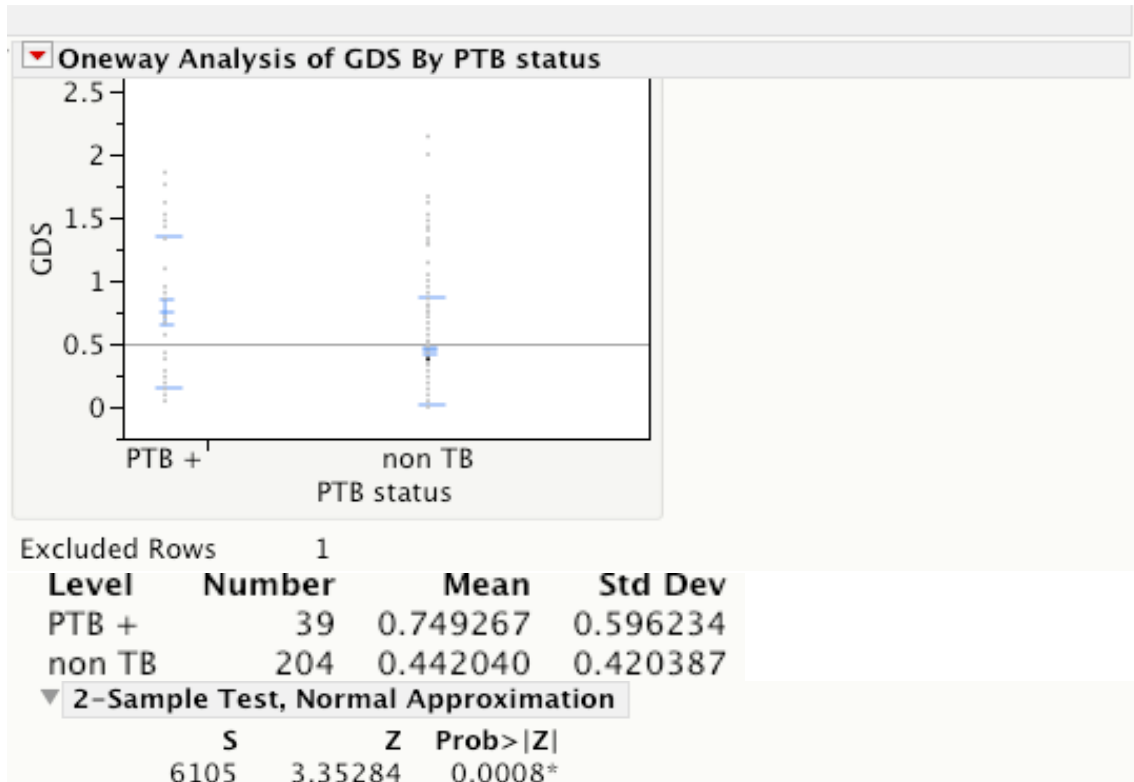
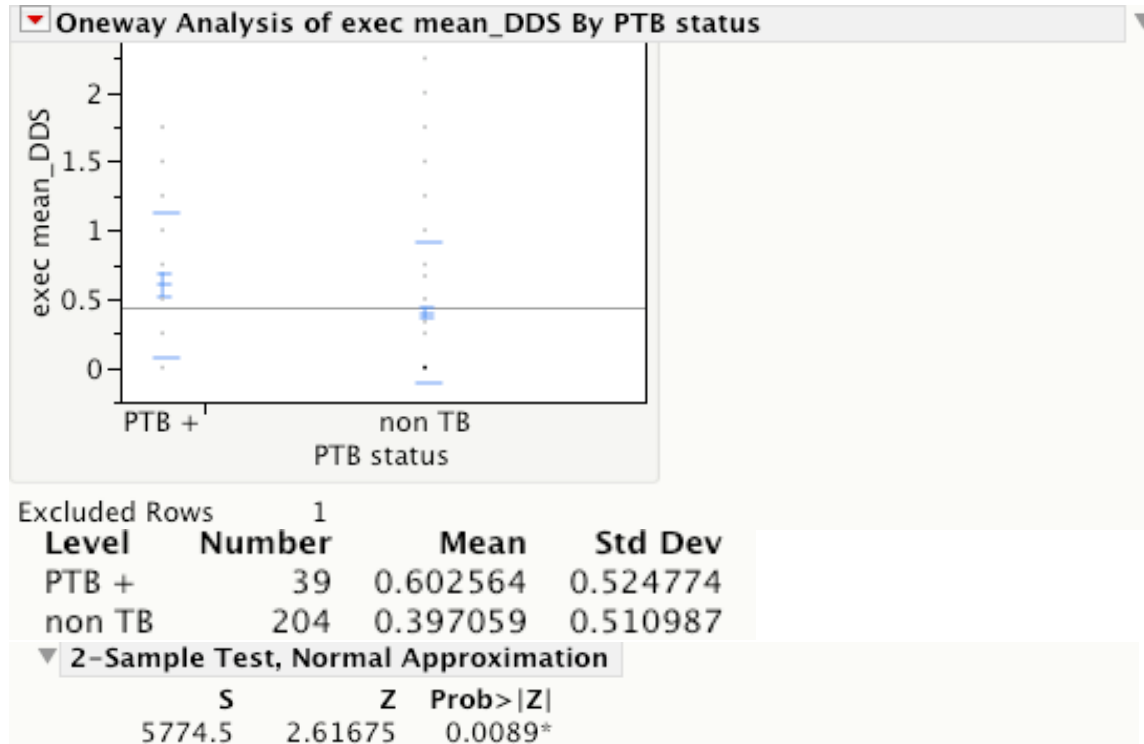


Figure 1 above, shows the levels of neurocognitive deficits using the global deficit score (GDS) between the PTB+/HIV+ and TB-/HIV+ groups. Results show that PTB+/HIV+ group had mean of 0.749 (SD, 0.596), while PTB-/HIV+ group had mean of 0.442 (SD, 0.420). Results indicate that the PTB+/HIV+ group had significantly more neurocognitive deficits compared to the PTB-/HIV+ group and results were statistically significant $z = 2.95558$, $p < .001$. By using $GDS \geq 0.50$, 56% of PTB+ were globally impaired compared to 32% non PTB. This high significant difference in the levels of neurocognitive deficits was further confirmed by Chi-square $\chi^2 = 11.2499$, $df = 1$, $p = 0.0008$. The significant difference in the Global Deficit Score (which predicted neurocognitive impairment) mean that the PTB+/HIV+ group has more neurocognitive deficits compared to the PTB-/HIV+ group. See appendix N for detailed result analysis.

4.3 Overall neuropsychological performance between PTB+/HIV+ and PTB-/HIV+ groups

In order to investigate the differences in performance between the two groups in the seven domains, Wilcoxon ranked sum tests using the global (GDS) and domain deficit scores (DDS) were used. Figures 2, 3, 4,5,6,7 and 8 below summarise the results.

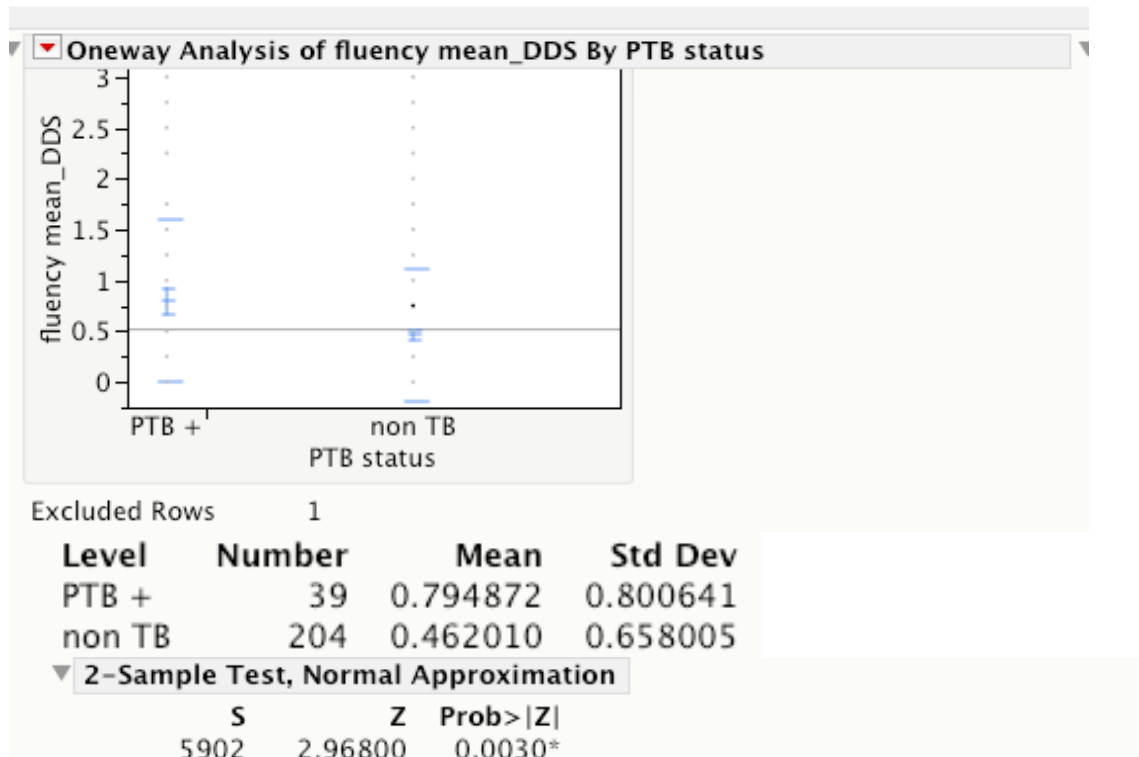
Figure 2: Executive function Domain DDS by PTB status



*= *p* value

Figure 2 above, shows the PTB+/HIV+ group on the left and TB-/HIV+ group on the right with their neurocognitive performance in executive function domain. Neurocognitive performance being measured by Domain deficit Score (DDS). The results show that PTB+/HIV+ group had mean of 0.602 (SD, 0.525), while TB-/HIV+ group had mean 0.397 (SD 0.511). Results indicate that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in executive function domain and results were statistically significant $z = 2.61675$, $p < .001$. Further analysis using chi-square confirmed the results as being statistically significant $\chi^2 = 6.8541$, $df = 1$, $p = 0.0088$. Results mean that the PTB+/HIV+ is more impaired in the executive function domain compared to the PTB-/HIV+ group. See appendix G for detailed results

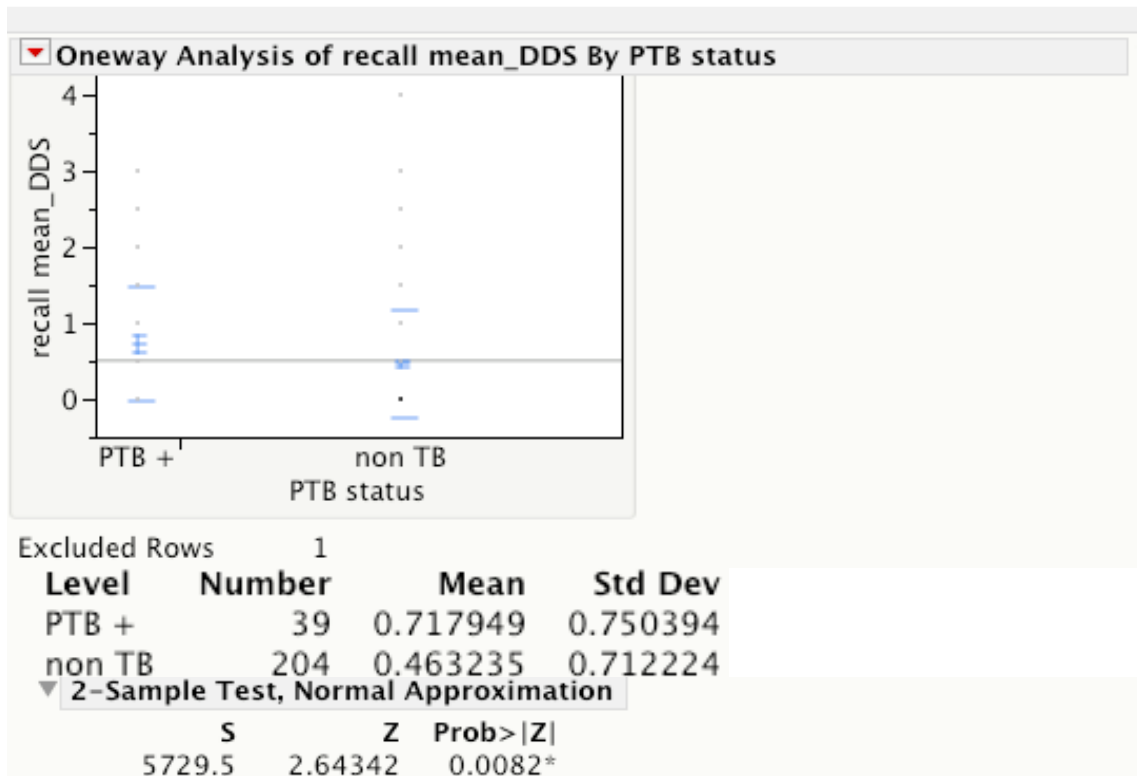
Figure 3: Fluency Domain DDS by PTB status



*= p value

Figure 3 above, shows the PTB+/HIV+ group on the left and the TB-/HIV+ group on the right with their neurocognitive performance in Fluency domain. Neurocognitive performance being measured by Domain Deficit Score (DDS) means. Results show that PTB+/HIV+ group had mean of 0.795 (SD, 0.800), while PTB-/HIV+ group had mean of 0.462 (SD 0.658). Results indicate that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Fluency domain and results were statistically significant $z= 2.96800, p<.001$. Chi-square test also confirmed that neurocognitive performance was statistically significant between groups $\chi^2=8.8168, df=1, p=0.0030$. The statistical difference in performance means that the PTB+/HIV+ is more impaired in Fluency domain than the PTB-/HIV+ group. Appendix H gives a detailed analysis of the results.

Figure 4: Recall Domain DDS by PTB status



*= *p* value

Figure 4 above, analysed the mean values (DDS) of the recall domain using Wilcoxon/Kruskal-Wallis Tests. The results above show that PTB+/HIV+ group had mean of 0.718 (SD, 0.750), while PTB-/HIV+ group had mean of 0.463 (SD, 0.712). Results indicate that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Recall domain and were statistically significant $z = 2.64342$, $p < .001$. It was further confirmed by chi-square to be statistically significant $\chi^2 = 6.9949$, $df = 1$, $p = 0.0082$. The significant difference in performance means that the PTB+/HIV+ group is more impaired in Recall domain compared to the PTB-/HIV+ group. See appendix I for detailed analysis.

Figure 5: Motor Domain DDS- by PTB status

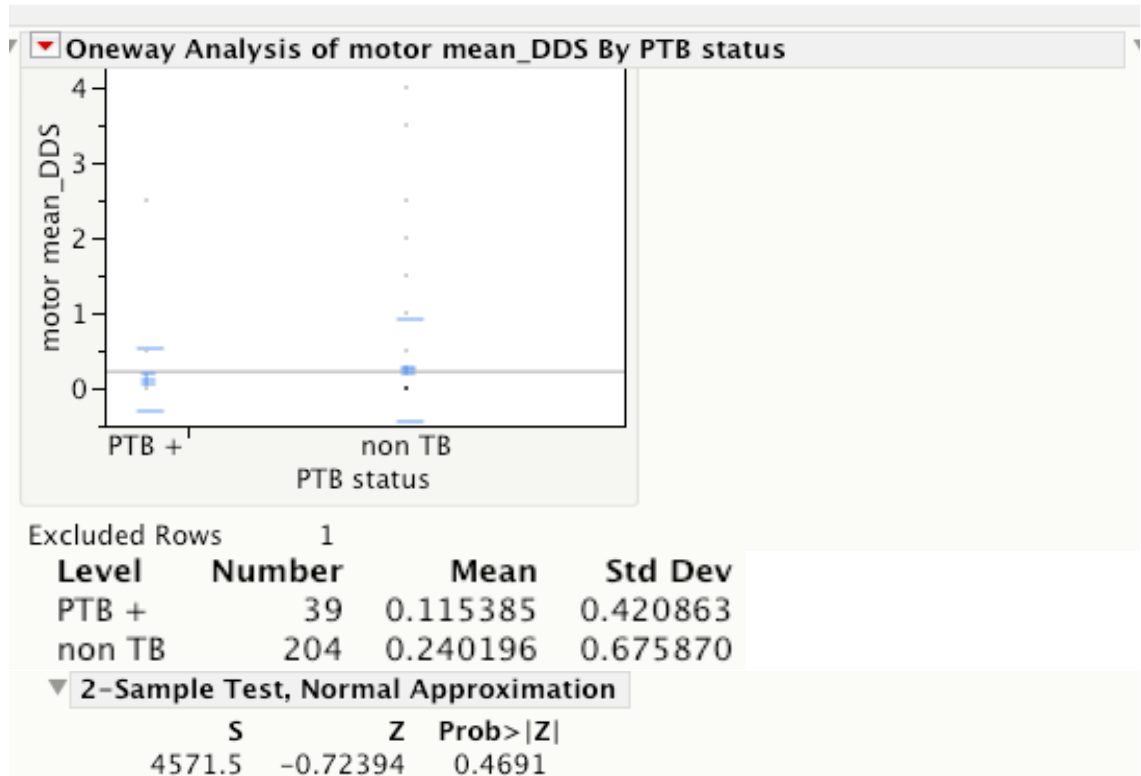
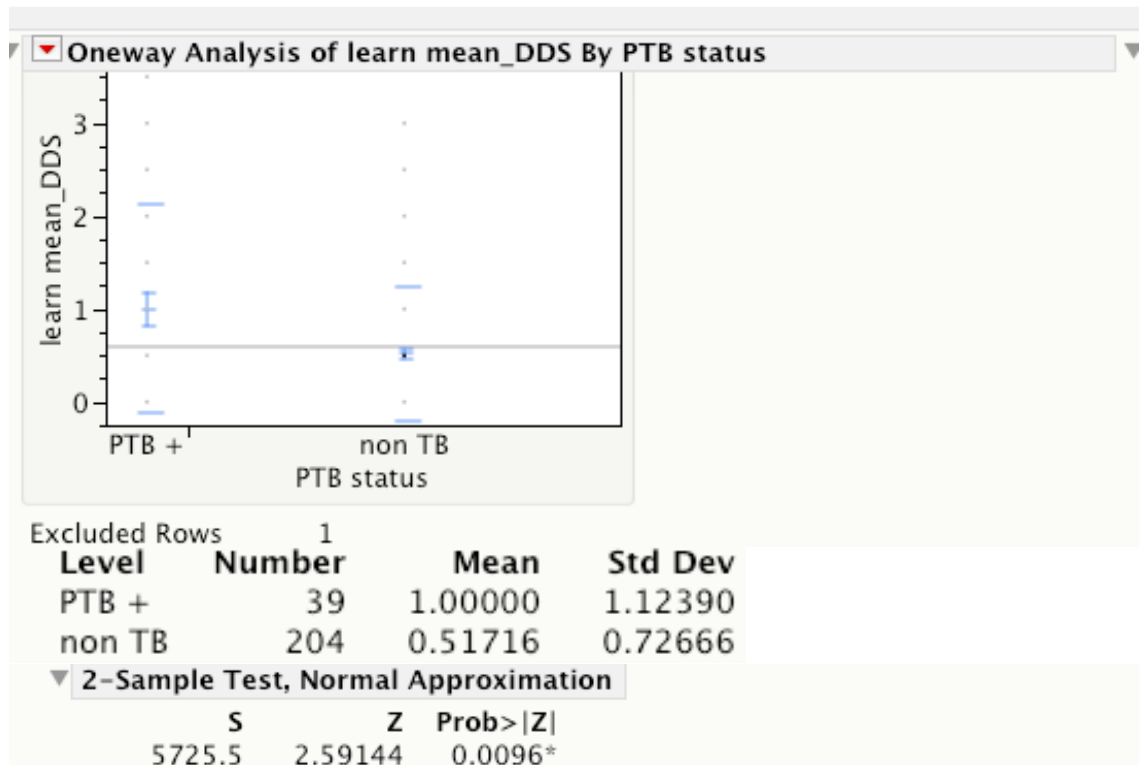


Figure 5 above, shows the PTB+/HIV+ group on the left and the PTB-HIV+ group on the right with their neurocognitive performance in motor domain. The results above show that PTB+/HIV+ group had mean of 0.115 (SD, 0.421), while PTB-/HIV+ group had mean of 0.240 (SD, 0.676). The results indicated no significant difference in performance in motor domain between groups and results were statistically non significant $z = -0.72394$, $p > 0.4691$. The non significant difference was also confirmed by Chi-square test $\chi^2 = .05269$, $df = 1$, $p = 0.4679$. Appendix J gives detailed result analysis.

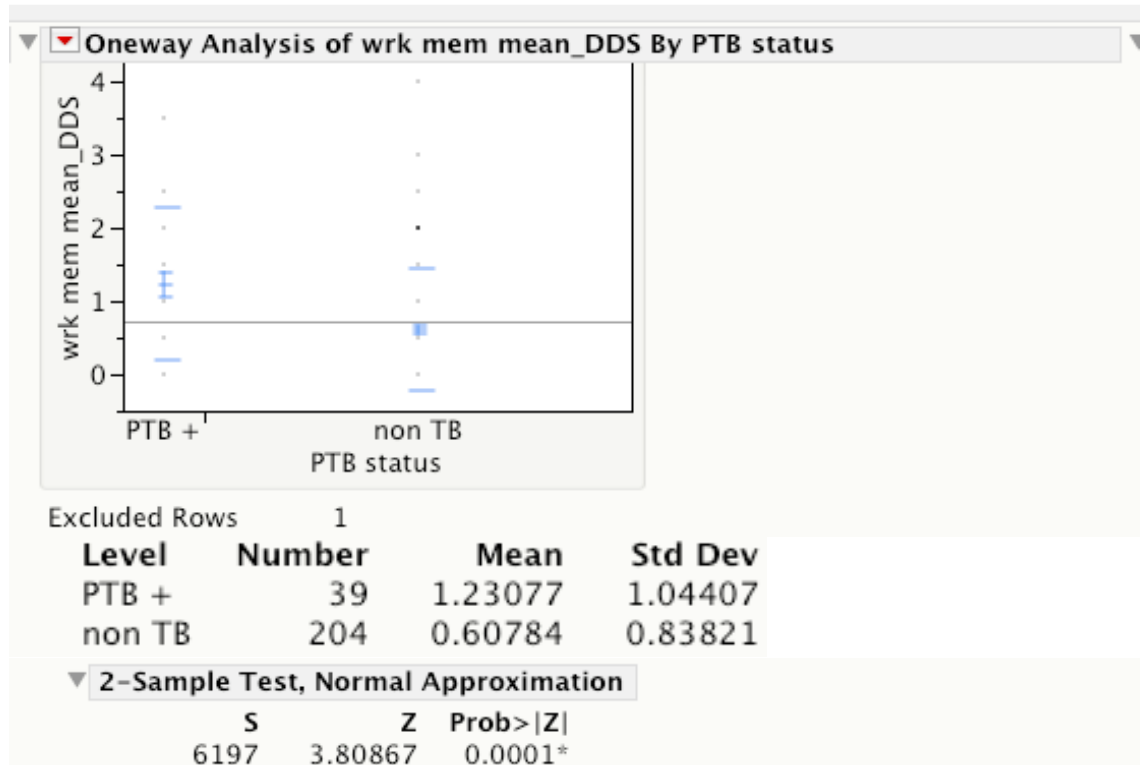
Figure 6: Learning/Memory Domain -DDS by PTB status



*= p value.

Figure 6 above, shows the PTB+/HIV+ group on the left and the PTB-/HIV+ group on the right with their neurocognitive performance in Learning / Memory domain. The results show that PTB+/HIV+ group had mean of 1.000 (SD, 1.124), while PTB-/HIV+ group had mean of 0.517 (SD, 0.727). Results indicate that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in Learning/memory domain and results were statistically significant $z= 2.59144$, $p<.001$. This was further confirmed by Chi-square test $\chi^2=6.7225$, $df=1$, $p=0.0095$. This significant difference in neurocognitive performance means that the PTB+/HIV+ is more impaired in learning/memory domain compared to the PTB-/HIV+ group. See appendix K for detailed analysis of results.

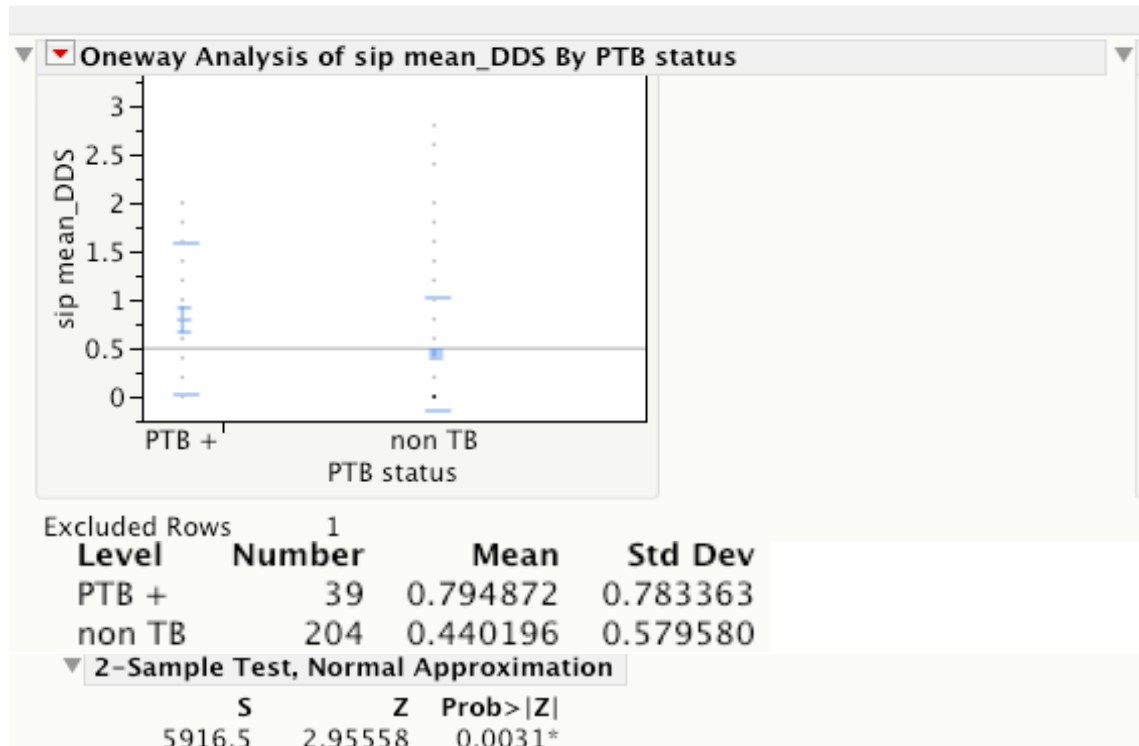
Figure 7: Working memory Domain- DDS by PTB status



*= p value.

Figure 7 above measured neurocognitive performance using domain deficit scores (means) with the PTB+/HIV+ group on the left and PTB-/HIV+ on the right. The results above show that PTB+/HIV+ group had mean of 1.231 (SD, 1.044), while PTB-/HIV+ group had mean of 0.608 (SD, 0.838). Results indicate that the PTB+/HIV+ group's performance was worse than the PTB-/HIV+ group in working memory domain and results were statistically significant $z = 3.80867$, $p < .001$. Chi-square also confirmed the statistical difference in neurocognitive performance $\chi^2 = 14.5160$, $df = 1$, $p = 0.0001$. The high significant difference in performance means that the PTB+/HIV+ is more impaired in working memory domain compared to the PTB-/HIV+ group. See appendix L for detailed analysis.

Figure 8: Speed of information processing Domain DDS by PTB status



*= p value.

Figure 8 shows the PTB+/HIV+ on the left and PTB-/HIV+ on the right with their neurocognitive performance in speed of information processing domain. The deficit domain score (DDS) means for the two groups were statistically compared. Results show that the PTB+/HIV+ group had mean of 0.795 (SD, 0.783), while PTB-/HIV+ group had mean of 0.440 (SD, 0.596). Results indicate that the PTB+/HIV+ group performed worse than the PTB-/HIV+ group in speed of information processing domain and results were statistically significant $z = 2.95558, p < .001$. The Significant difference in neurocognitive performance was further confirmed by Chi-square test $\chi^2 = 8.7430, df = 1, p = 0.0031$. The high significant difference in performance means that the PTB+/HIV+ is more impaired in speed of information processing domain compared to the PTB-/HIV+ group. Appendix M describes the results in details.

4.4 Multiple Regression analysis

Regressions were run using Global Deficit Scores (GDS) and domain deficit scores (DDS) as the dependent variables, with PTB status in the model. The independent variables included were; current CD4 count, viral load and current WHO HIV disease staging. Table 6 below summarises the results which show that PTB predicts Neurocognitive impairments in HIV+ adults.

Table 6: Multiple Regressions Predicting Global and Domain Neurocognitive Performance

| | <i>F</i> | <i>β</i> | Adj. <i>R</i> ² | <i>p</i> |
|----------------------|----------|----------|----------------------------|----------|
| GDS | 3.930 | | 0.47 | .004 |
| PTB status | | -.327 | | .015* |
| Current CD4 count | | -.037 | | .586 |
| Viral load det/undet | | .036 | | .638 |
| Current WHO stage | | -.130 | | .346 |
| Exe | 1.550 | | .009 | .189 |
| PTB status | | -.253 | | .054* |
| Current CD4 count | | -.039 | | .578 |
| Viral load det/undet | | -.006 | | .936 |
| Current WHO stage | | -.141 | | .317 |
| Fluency | 2.208 | | 0.020 | .069 |
| PTB status | | -.170 | | .210 |
| Current CD4 count | | -.070 | | .286 |
| Viral load det/undet | | .004 | | .956 |
| Current WHO stage | | -.019 | | .892 |
| Wrk/memory | 5.238 | | .067 | .000 |
| PTB status | | -.490 | | .000* |
| Current CD4 count | | .061 | | .370 |
| Viral load det/undet | | .011 | | .884 |
| Current WHO stage | | -.256 | | .062 |

| | | | | |
|----------------------|-------|-------|-------|-------|
| Learning/mem | 2.987 | | .032 | .020 |
| PTB status | | -.241 | | .053* |
| Current CD4 count | | -.032 | | .648 |
| Viral load det/undet | | .015 | | .845 |
| Current WHO stage | | -.046 | | .740 |
| Recall | 2.626 | | .027 | .035 |
| PTB status | | .102 | | .447 |
| Current CD4 count | | -.063 | | .364 |
| Viral load det/undet | | .084 | | .281 |
| Current WHO stage | | .201 | | .151 |
| Motor | 0.720 | | -.005 | .579 |
| PTB status | | -.059 | | .664 |
| Current CD4 count | | .010 | | .885 |
| Viral load det/undet | | .043 | | .587 |
| Current WHO stage | | -.173 | | .225 |
| SIP | 2.900 | | .031 | .023 |
| PTB status | | -.312 | | .021* |
| Current CD4 count | | -.023 | | .745 |
| Viral load det/undet | | .037 | | .632 |
| Current WHO stage | | -.150 | | .283 |

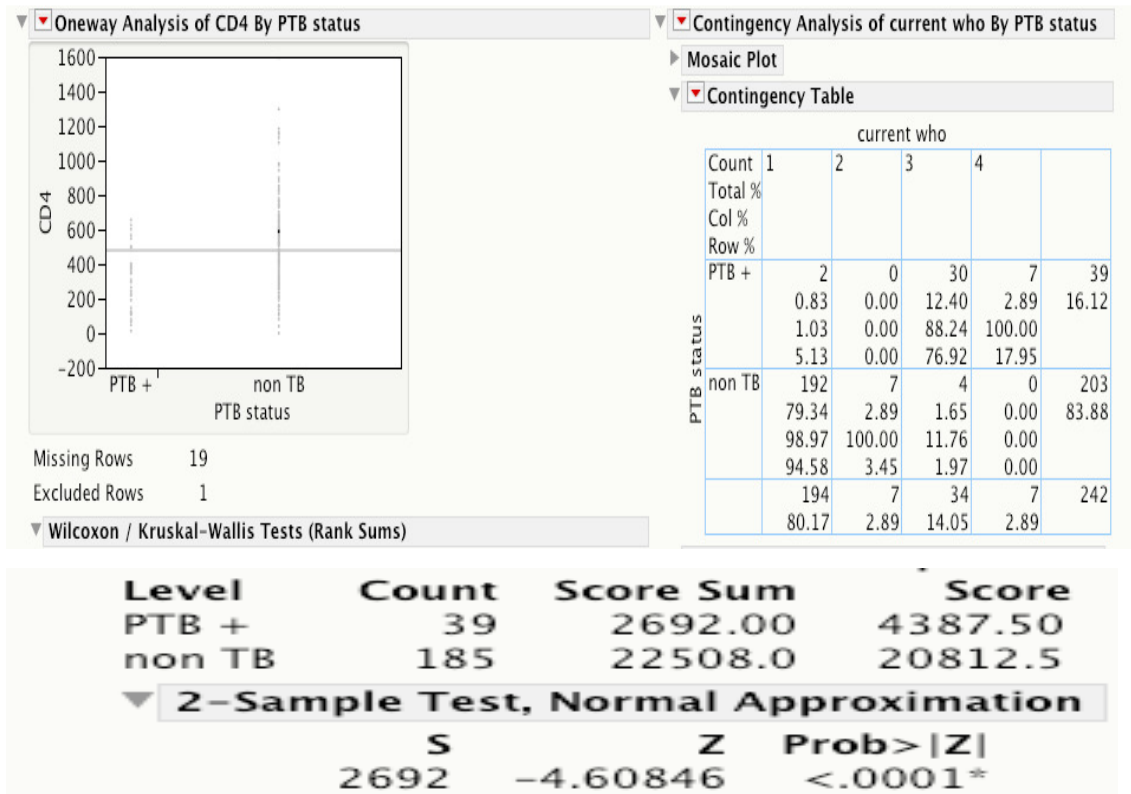
Note: GDS= global deficit scores, exe= executive functioning, fluency= fluency domain, wrk/mem= working memory, recall= recall memory, SIP= speed information process domain, viral load det= viral load detected, viral load undet= viral load undetected, current WHO stage=current WHO HIV staging; stages 1, 2, 3 and 4. Where * significant at 10%, ** significant at 5%, and *** significant at 1%

4.6 Global Deficit Impairment across gender

The results indicated that the difference in overall performance was not statistically significant between males and females within the PTB+/HIV+ group ($p > .311$). This lack of statistical significance was also observed in neuropsychological test performance in all cognitive domains ($ps > .10$). The results mean that gender has no effect on neuropsychological performance and neurocognitive deficits in adults with PTB+/HIV+.

4.7 Medical characteristics (biomarkers and WHO HIV staging)

Figure 9: WHO stage and CD4 cell count by PTB status



*=p value.

Clinical characteristics analysed in the study were WHO HIV disease staging, and the biomarkers under analysis were CD4 count and viral load. WHO HIV disease staging; 95% of PTB+ were stages 3 and 4, whereas 95% of PTB negative were stage 1. Viral load detection; 69% of PTB+ had viral load detected compared to 15% of non PTB. The PTB+/HIV+ had lower mean CD4 count compared to PTB-/HIV+.

$p < .01$. The PTB+/HIV+, CD4 count mean was 325 cells/ μ l compared to 512 cells/ μ l for PTB-/HIV+. The PTB+/HIV+, CD4 count was in the range 201-499 cells/ μ l, whereas the non PTB was above 500 cells/ μ l. Cognitive deficits have been known to vary in different levels of immune suppression (Heaton et al, 1995). Data was analyzed to look at the difference in cognitive performance across groups differing on immune suppression as defined by CD4 count, viral load detection and WHO HIV disease staging. See figure 9 above for summarised results. Appendix O gives a detailed analysis.

CHAPTER FIVE

5.0 Discussion

The dual epidemic of Pulmonary Tuberculosis and HIV is probably the greatest clinical challenge facing health workers in sub-Saharan Africa. Zambia is one of the countries in the world most affected by the dual PTB and HIV epidemics. In 2006 Zambia reported over 60,000 cases of tuberculosis, of whom at least 40% are estimated to be HIV positive (WHO, 2010). The estimated HIV prevalence rate of 14.3 percent in the adult population has made PTB treatment difficult and has strained already limited financial and human resources (ZNTF, 2010).

The first hypothesis of the study stated that adults that are PTB+/HIV+ will perform worse than the PTB-/HIV+ in all the seven domains on the Neuropsychological test battery. The hypothesis was supported by the results obtained. The PTB+/HIV+ group performance was significantly worse compared to the PTB-/HIV+ group in all domains except the Motor Domain. In order to investigate the differences in performance between the two groups in the seven domains, Wilcoxon ranked sum tests using the global (GDS) and domain deficit scores (DDS) were used. The study hypothesized a priori that PTB+/HIV+ group would have a lower performance on the neuropsychological tests compared to PTB-/HIV+. Results indicated significant differences in performance. Overall, the PTB+/HIV+ GDS performance was lower than PTB-/HIV+ group in Executive function, fluency, recall, Learning memory, Working Memory and Speed of information process domains (all $p < .001$). The results indicated that there was significant neurocognitive impairment in PTB+/HIV+ group compared to the PTB-/HIV+ group in the Global deficit score, $p < .001$. This may mean that PTB in HIV affects the neurocognitive function.

Study results may mean that adult Zambians with the dual infection of PTB/HIV are most likely going to have problems in decision making, planning, evaluation and monitoring due to impairments in the executive function. Since the Fluency domain is affected, this may lead to patients having problems with generating new information in their day to day life. The implication of the results may indicate that patients with the co-infection of PTB+/HIV+ may have problems in recalling and retrieving stored information from the brain, making them prone to forgetting. The

results also may mean that PTB as co-morbid condition in HIV+ adult individuals leads to individuals having problems with learning memory (difficulties with learning and storing of new information). This will make patients have difficulties in learning and keeping new information due to impairment in the learning memory domain. Another important fact is that the duo infection of PTB and HIV will slow down the rate at which individuals process information in the brain due to the impairment in the Speed of information processing domain. The implications of the study results are that, adult Zambians with the duo infection of PTB+/HIV+, may require human resource placement and care at work depending on the kind of work involved, some may require rehabilitation and clinicians will have to be vigilant as to when to start treatment for both PTB and HIV infections so as to protect the CNS from further damage in order to promote continued quality of life/productivity over the lifespan.

In the second hypothesis, it was hypothesised that adults that are PTB+/HIV+ will have worse disease characteristics; CD4 count, viral load, and WHO HIV staging than the PTB-/HIV+. The hypothesis was confirmed with the results indicating patients, who had the dual infection of Pulmonary Tuberculosis and HIV, having worse clinical (WHO HIV staging) and biomarker characteristics (CD4 cell count and viral load). The results were statistically significant at WHO staging $f(959.221)$, $P < .01$ and Viral load detection $f(30.983)$, $p < .01$. In the study, we found that the PTB+/HIV+ group had lower CD4 count with a mean of 325 cells/ μ l compared to 512 cells/ μ l for the PTB-/HIV+ group. The PTB+/HIV+ CD4 count was in the range 201-499 cells/ μ l, whereas the PTB-/HIV+ was above 500 cells/ μ l. Viral load detection; 69% of PTB+ had viral load detected compared to 15% of non PTB. 95% of PTB+ were stages 3 and 4, whereas 95% of non PTB were stage 1. The results may suggest that PTB in HIV lowers the CD4 cell count and contributes to the deterioration of the immune system as evidenced by the results. These effects of PTB may also contribute to the deterioration of the neurocognitive impairment in HIV+ adults. The results are supported by the study done in Vietnam which found that patients who had Tuberculosis Meningitis/HIV+ had lower CD4 count, haematocrit and immunosuppression (Bang, Du&Thwaites, 2005). The results therefore suggest that PTB contributes to HIV disease progression and cognitive deficits in HIV+ adults in Zambia. Cognitive deficits have been known to vary in

different levels of immune suppression (Heaton et al, 1995). The results suggest that there is a strong association between neuropsychological performance and PTB infection in HIV+ adults in Zambia

The third hypothesis was to determine whether there were gender differences related to neurocognitive deficits within the study group. Our results showed that, both the levels of impairments (GDS) and test performance were not statistically significant across gender. The results indicated that the difference in overall performance was not statistically significant between males and females within the PTB+/HIV+ group ($p > .311$). This lack of statistical significance was also observed in neuropsychological test performance in all cognitive domains ($ps > .10$). In earlier studies in Western countries, some authors have suggested that women have poorer neurological outcomes than men (Morlat et al., 1992; Robertson et al., 1996), whereas others have found no such gender difference (Bouwman et al., 1998; Marder et al., 1995 in Hestad et al 2012). The pilot study by Hestad et al., (2010) conducted in Zambia, showed that greater cognitive deficits were seen in female relative to the male seropositive participants. To the contrast, in our study, results indicated no significant gender differences in their cognitive profiles and test performance.

The fourth hypothesis was confirmed by the results. Results indicated that the PTB+/HIV+ group had significant more neurocognitive impairment (GDS) compared to the PTB-/HIV+ group and results were statistically significant $z = 2.95558$, $p < .001$. By using $GDS \geq 0.50$, 56% of PTB+ were globally impaired compared to 32% non PTB. The significant difference in the Global Deficit Score, mean that the PTB+/HIV+ group has more neurocognitive deficits compared to the PTB-/HIV+ group. The results therefore suggest that if an individual adult has the duo infection of PTB/HIV, they are likely going to have more neurocognitive deficits compared to one who is only HIV- positive without PTB.

When multiple regression was run to determine effects that the independent variables (current WHO HIV stage, current CD4 count and viral load detection) had on the dependent variables (neurocognitive domains), we found that all independent variables had no significant effects in all domains. In a significant linear regression

model ($p < .01$), PTB status was predictive of global deficit score even while accounting for demographic and medical variables that have previously been associated with neurocognitive impairments. Specifically, a linear regression model identified PTB status ($F=6.26$, $p < .02$) as a significant predictor of GDS. Current CD4 count ($F = 3.21$, $p < .08$), viral load detection ($F = 0.54$) and current WHO stage ($F=1.41$) were not significant independent predictors of GDS (all $ps > .10$; see Table 6). A similar study conducted in 2007 in south India investigating neuropsychological deficits in HIV+ type 1 clade c adults, reported that cognitive performance on the neuropsychological test battery did not differ according to immune suppression levels, except for visual working memory. In the present study, we also found that CD4 count, viral load detection and WHO HIV disease staging which determined immune suppression levels did not have any significant effect on test performance and global deficit score.

Previous HIV research from the United States, where clade B viral strain predominates, have found that individuals with advanced immune suppression, the severity of cognitive deficits is associated with lower CD4 counts (Ellis et al., 1997). However, when the CD4 counts are high, indicating better immune functioning, cognitive impairment is weakly associated with immune suppression (grant et al., 1999). The Indian study compared HIV+ individuals to healthy seronegative individuals. To the contrast, our study had compared PTB+/HIV+ to PTB-/HIV+. The pre-dominant HIV type in Zambia is clade c. This might explain why all the neuropsychological test performance was affected in all the domains except motor. Literature indicates that HIV disturbs the dopaminergic neuronal function hence motor dysfunction. In our study, the non significance in motor domain may be due to the fact that clade C does not affect the dopamine system.

It appears from the study that Pulmonary Tuberculosis in Zambia occurs largely in people with CD4 counts of ≤ 349 cells/ μ l. In a study from Zambia by Sinkala et al. (2009) found abdominal TB patients in Zambia occurring largely in people with CD4 counts of 49 cells/ μ l as the median. In a study from Brazil, the mean CD4 counts of patients with extrapulmonary TB were 184 cells/ μ l. Jones, Young, Antoniskis, Davidson, Kraner and Barnes (1993) observed that abdominal TB in Zambia occurs largely in people with CD4 counts of ≤ 150 cells/ μ l. But in our study, the CD4 count

mean was 325 cells/ μ l in the PTB+/HIV+ group and 512 cells/ μ l in the PTB-/HIV+ group. This could be a genuine biological difference or could be attributable to the fact that in our study, PTB+ patients were already on anti-tuberculosis treatment by the time of the study and that pulmonary tuberculosis can be detected early as compared to extrapulmonary TB investigated in Brazil and Zambia, hence CD4 count being higher compared to the previous studies whose patients were not on TB treatment. This may reflect that if PTB is early detected and treated effectively, the CD4 count improves. It is therefore very important in our resource limited setting like Zambia with high PTB and HIV co-infection rates, for clinicians to have a high clinical suspicion of PTB so that it can be detected early and treated. Every HIV+ individuals should be screened for PTB and every PTB+ patient should be counselled and tested for HIV.

The cognitive profile in the PTB+/HIV+ group in our study is suggestive that they are more impaired compared to their cohort. The global deficit score indicated that the study group was significantly impaired, $p < .01$. This was also supported by the results obtained in all the domains except motor domain. A study from Uganda which investigated the neurocognitive deficits associated with AIDS Dementia also found no significant difference in fine and motor tests between the HIV+ and HIV- groups. To the contrast however, in our study, all our participants were HIV+ with the study group having dual infection of PTB and HIV.

Having controlled for age, gender and levels of education in the norms, results remained consistent with literature that HIV affects the neurocognitive functions. The cognitive profile and impairment levels differed in PTB+/HIV+ and PTB-/HIV+ groups in all domains except motor. Thus cognitive deficits in these domains can be strongly associated with PTB infection. Previous studies have also reported similar deficits that support the involvement of subcortical and frontal brain processes in clade B infection of HIV. (Alyward et al, 1993; Kiebertz et al., 1996; Stern et al., 1992; York et al., 2001).

Most of the available literature has only studied TB in HIV+ adults in terms of other effects rather than neurocognitive. This is among the first studies to highlight the fact that PTB is associated with neurocognitive impairments in HIV+ adult individuals.

Previous studies have reported a lower prevalence of HIV dementia and other immune suppression in PTB+/HIV+ groups. However, the absence of severe cognitive deficits in the present sample may be due to both individuals being on anti-PTB treatment and Anti-retroviral therapy. The other reason is that the study had stringent exclusion criteria resulting in sample bias. Individuals with any symptoms associated with any form of TB including TB meningitis which could have had severe neuropsychological deficits were excluded.

5.1 Limitations

The Study had some limitations. Due to mostly retrospective nature, gathered information could only reflect the data available from the patient's medical files which were often incomplete and did not necessarily contain the desired level of detail.

5.2 Conclusion

Based on the discussion of the results, several conclusions were arrived at from this study. The results show that adult patients in Zambia who have the co-infection of PTB and HIV can perform worse than the HIV+ without PTB on Neurocognitive test battery in all the seven domains except the motor domain, and this is also supported by other literature. The study has shown that if a patient has the duo infection of PTB and HIV, they will have more Neuropsychological impairments (based on the Global deficit Score) than adult individuals who are HIV positive but without PTB. Our results have also heightened the fact that PTB as a co-morbid condition in HIV lowers one's immune system as evidenced by the WHO HIV disease staging and the biomarkers which determine the levels of immune suppression. Consistent with other studies, the current study has shown that there are no gender differences in neurocognitive performance and impairments between males and females with co-infection of PTB and HIV among the adult Zambian population.

Findings of the present study show the presence of neuropsychological impairments in all the seven domains except motor in the PTB+/HIV+ adults in Zambia. In addition, patients in the study arm did not have any clinically identifiable functional impairment. They were maintaining well and able to carry out routine daily activities .The PTB+/HIV+ had lower immune levels compared to PTB-/HIV+ group as also

evidenced by their CD4 counts, viral load detection and WHO disease staging. It is important therefore to increase awareness of PTB neurocognitive effects in HIV+ individuals amongst general physicians as PTB can occur at any stage of HIV infection in order to reduce its neuropsychological effects. Further research is required to address questions regarding the progression of cognitive deficits in those who are HIV+ and successfully completed the PTB treatment and declared cured. Further research can be conducted to compare the cognitive profiles of PTB+/HIV+, PTB-/HIV and PTB successfully completed treatment and declared cured groups.

Recommendations

1. The instructional booklet especially the Wisconsin card Sorting test (computerised 64 items) and Halstead Category tests needs to be edited to include words that are more familiar to most of the Zambian population as this will allow for easier understanding.
2. Extra instruments or questionnaires should be administered preferably on a separate day from the one being used for testing. This will reduce the amount of time spent on one client thus reducing fatigue experienced by the clients and the researcher.
3. Testing rooms must be set up that are free from distracting noise and activity. During the study, there were no specific conducive testing rooms, sometimes conference rooms were used which attracted a lot of human traffic.
4. The normative data for Zambia should be made available locally. At the time of the current study, there were sent from USA- University of California, San Diego (where data is analysed for NOMA project).

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Appendices

1. **Appendix A.** Clearance letter from University of Zambia Biomedical Ethics committee.
2. **Appendix B.** Information Sheet
3. **Appendix C.** Informed Consent
4. **Appendix D.** Demographic questionnaire
5. **Appendix E.** Zambia Achievement Test
6. **Appendix F.** Zambia Neurobehavioural Battery
7. **Appendix G.** Executive function Domain DDS by PTB status
8. **Appendix H.** Fluency Domain DDS by PTB status
9. **Appendix I.** Recall Domain DDS by PTB status
10. **Appendix J.** Motor Domain DDS- by PTB status
11. **Appendix K.** Learning/Memory Domain -DDS by PTB status
12. **Appendix L.** Working memory Domain- DDS by PTB status
13. **Appendix M.** Speed of information processing Domain DDS by PTB status
14. **Appendix N.** Global Deficit Score (GDS) by PTB status.
15. **Appendix O.** WHO stage and CD4 cell count by PTB status
16. **Appendix P.** Clearance letter from the Ministry of Health

Appendix B

Information sheet

The study is trying to find out about the effects that the disease Pulmonary Tuberculosis (PTB) has on adults who are HIV positive in terms of their brain function (Neurocognitive function). Pulmonary Tuberculosis is a contagious disease like the common cold, it spreads through the air. Only people who are sick with PTB in their lungs are infectious. When infectious people cough, sneeze, talk or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to be infected. Human immunodeficiency virus (HIV) infection is a disease that is caused by a virus and there is no cure currently. The virus attacks the immune system (body's defence mechanism) and can lead to Acquired Immune Deficiency Syndrome (AIDS). HIV and TB infect form a lethal combination, each speeding the other's progress. HIV weakens the immune system. Someone who is HIV-positive and infected with TB bacilli is many times more likely to become sick with TB than someone infected with TB bacilli who is HIV negative. PTB is a leading cause of death among people who are HIV-positive. In Africa, HIV is the single most important factor contributing to the increase in the incidence of PTB.

When one is infected with HIV, the virus causes a lot of problems in the body and some are neurocognitive deficits (causes damage to the central nervous system) thereby affecting the process of thinking, attention, motor movements, memory and the speed in which an individual will be able to carry out day to day life activities. Tuberculosis which is one of the commonest opportunistic infection in people who are HIV positive has the capacity to infect the brain and spinal cord (central nervous system and cause impairment to the brain). The co- infection therefore forms a lethal combination which may complicate the neurocognitive effects. In order to know the extent of brain damage due to the PTB and HIV combination, a comprehensive validated test battery is administered. A test battery has several specific subtests that measure specific cognitive functions in an individual.

The study is trying to explore the effects of pulmonary tuberculosis in HIV positive adults who are on HAART and the extent to which neurocognitive functions are impaired in Zambia. The research is studying the load that PTB has on the HIV positive people in terms of their brain functions. This is done by administering a

neurobehavioural test battery in order to determine the deficits due to the co-infections of PTB and HIV+. For further information contact the addresses below:

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Appendix C– Informed Consent Form

Informed Consent Form

Informed Consent for Participants

University of Zambia

School of Medicine

Department of Psychiatry

PLEASE READ THIS DOCUMENT CAREFULLY. SIGN YOUR NAME BELOW ONLY IF YOU AGREE TO PARTICIPATE AND YOU FULLY UNDERSTAND YOUR RIGHTS. YOUR SIGNATURE OR THUMBPRINT IS REQUIRED FOR PARTICIPATION. FOR THIS PROJECT, YOU MUST BE 20 YEARS OF AGE AND ABOVE TO PARTICIPATE. IF YOU DESIRE A COPY OF THIS CONSENT FORM, YOU MAY REQUEST ONE AND WE WILL PROVIDE IT.

Description of the Study: You are being invited to take part in this study: **Pulmonary Tuberculosis (PTB) as a co morbid condition in HIV positive adults and its effects on neurocognitive function in Zambia.** You will be required to answer questionnaires and take a group of tests of attention, language, motor functions, speed of information processing, executive functions and memory. The tests will involve answering questions and doing certain activities. You will also be required to undergo laboratory investigations where about 10mls of blood will be withdrawn from your upper arm for the purpose of the study.

Time: To complete the entire test will take approximately between two to three hours.

Risks: The following might be the risk involved in the study

- You may experience fatigue due to the length of time required for the testing process. To reduce on this, you are free to ask for a short break whenever you require it.
- You may feel some discomfort and pain from the needle when withdrawing blood.

Benefits

- We cannot guarantee that you will receive any direct benefits from this study though you will have an opportunity to contribute to the study that will help Zambians in general.
- You may benefit with assisted referrals if you have a condition related to study which may require special attention.
- Free viral load, CD4 count and ESR.

Compensation:

Your Time: You will be compensated for your time with K30, 000.

Refreshment: You will be given K20, 000 for your refreshment

Total amount of money: K50, 000

Participation Rights:

- Participation in this study is purely voluntary so that if you decide to withdraw at any point ;the health care or benefits you receive will not be affected by your withdraw from the study.
- All personal identifying information will be kept confidential and the data sheets will be kept in secured lockers in accordance with the standards of the University of Zambia Biomedical Ethics Committee. All results will be grouped and no participant will be identifiable in any reports or publication

Signature

I,.....(names) have read and understood the above information. As the participant in this project, my signature or right thumbprint testifies that I understand the consent process and management of confidentiality as indicated above. I also understand that I can withdraw at any time.

Signature of Research Participant.....Date.....

Right Thumbprint of Research Participant:Date.....

Name and Signature of Witness.....Date.....

Name and Signature of Principle Researcher.....Date.....

Contacts:

If you have any further questions about this research please contact:

The Project Coordinator

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APPENDIX D

THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF PSYCHIATRY

P. O. Box 32379, Lusaka, Zambia

CLINICAL NEUROPSYCHOLOGY
DATA COLLECTION QUESTIONNAIRE

FOR OFFICIAL USE ONLY

Date:.....

Clinic/Centre:.....

Examiner:.....

Subject Study Number:.....

INSTRUCTIONS

- A. Please give/tick [] the appropriate answer to the question.
- B. All the information you will provide will be used for the purpose of this study only, therefore, provide genuine information and ensure that all questions are carefully answered.

AGE AND GENDER

Q1. What is your age?

1.1 20 – 35 []

1.2 36 – 45 []

Q1. What is your age?

- 1.1. 20 – 35 []
- 1.2. 36 – 45 []
- 1.3. 46 – 55 []
- 1.4. 56 – 65 []

Q.2. what is your gender?

- 2.1. Female []
- 2.2. Male []

MARITAL STATUS

Q. 3. What is your marital status?

- 3.1. Single []
- 3.2. Married []
- 3.3. Widowed []
- 3.4. Divorced []
- 3.5. Living with opposite sex []

EDUCATION

Q4. What is your highest attained level of education?

- 4.1. 5 -7 years []
- 4.2. 8 – 9 years []
- 4.3. 10 – 12 years []
- 4.4. 13 years + []

Q5. Has your education been helpful in your execution of daily activities?

- 1.1 Yes []
- 5.2. No []

EMPLOYMENT, INCOME, & RESIDENCE

Q6. What are you currently doing?

- 6.1 Unemployed []
- 6.2 Self-employed []
- 6.3 Employed []
- 6.4 Retired []

Q7. What is your occupation?

- 1.1 Unskilled (e. g maid, farm labourer, etc) []
- 1.2 Semi-skilled (e. g plumber, bus driver, etc) []
- 1.3 Skilled (e. g, accountant, physician, etc) []
- 1.4 Specialist (e. g consultant, economic analysts) []

Q8. What is your income per year?

- 8.1 Less than K30 million []
- 8.2 K30 million to less than K60 million []
- 8.3 K60 million to less than K120 million []
- 8.4 K120 million and above []

Q9. Where do you currently live?

- 9.1 Low cost rural area (e. g village) []
- 9.2 High cost rural area (e. g 'boma') []
- 9.3 Low cost urban area (e. g high density area) []
- 9.4 High cost urban area (e. g low density area) []

LANGUAGE & TECHNOLOGY

Q10. What is your mother tongue?

- 10.1 Bemba []
- 10.2 Tonga []
- 10.3 Lozi []
- 10.4 Kaonde []
- 10.5 Luvale []
- 10.6 Lunda []
- 10.7 Other (please indicate)..... []

Q11. How much do you use your mother tongue in communicating?

- 11.1. Rarely (just know and use one or two words) []
- 11.2. Sometimes (few times at home) []
- 11.3. Often (in home conversations) []
- 11.4. Very often (in almost all my conversations) []
- Q12. How much would you say you use the English language in communicating?
- 12.1. Rarely (just know and use one or two words) []
- 12.2. Sometimes (only in formal situations) []
- 12.3. Often (at least in one conversation in a week) []
- 12.4. Very often (in almost all my conversations) []
- Q13. How often do you use computers?
- 13.1. Not at all []
- 13.2. Sometimes (less than 4 times in a year) []
- 13.3. Often (at least once in a month) []
- 13.4. Very often (at least once in a week) []

DOMESTIC VIOLENCE

Physical/Psychological Abuse

Q14. Now I need to ask some more questions about your relationship with your (last/current) partner. Does your (last/current) partner ever:

- 14.1. Say or do something to humiliate you in front of others?
- 14.1.1. Rarely []
- 14.1.2. Often []
- 14.1.3. Very often []
- 14.1.4. Not at all []
- 14.2. Threaten to hurt or harm you or someone you care about?
- 14.2.1 Rarely []
- 14.2.2. Often []
- 14.2.3. Very often []
- 14.2.4 .Not at all? []
- 14.3. Insult you or make you feel bad about yourself?
- 14.3.1 Rarely []
- 14.3.2. Often []
- 14.3.3. Very often []
- 14.3.4. Not at all? []

14.4 How often did this happen during the last 12 months?

14.4.1 Rarely []

14.4.2. Often []

14.4.3. Very often []

14.4.4. Not at all? []

14.5. How often does it happen in a month?

14.5.1 Rarely []

14.5.2. Often []

14.5.3. Very often []

14.5.4. Not at all? []

14.6. Did your (last/current) partner ever do any of the following things to you?

Attack or threaten you with a knife, gun, or other weapon?

14.6.1 Rarely []

14.6.2. Often []

14.6.3. Very often []

14.6.4. Not at all? []

14.7 Try to choke or burn you on purpose?

14.7.1 Rarely []

14.7.2. Often []

14.7.3. Very often []

14.7.4. Not at all []

14.8 Kick you, drag you, or beat you up?

14.8.1 Rarely []

14.8.2 Often []

14.8.3 Very often []

14.8.4 Not at all []

14.9 Punch you with his/her fist or with something that could hurt you?

14.9.1 Rarely []

14.9.2 Often []

14.9.3 Very often []

14.9.4 Not at all? []

14.10 Push you, shake you, or throw something at you?

14.10.1 Rarely []

14.10.2 Often []

- 14.10.3 Very often []
- 14.10.4 Not at all []
- 14.11 Slap you?
- 14.11.1 Rarely []
- 14.11.2 Often []
- 14.11.3 Very often []
- 14.11.4 Not at all []
- 14.12 Twist your arm or pull your hair?
- 14.12.1 Rarely []
- 14.12.2 Often []
- 14.12.3 Very often []
- 14.12.4 Not at all []

14.13. Did the following ever happen as a result of what your (last/current) partner did to you?

14.13.1 You had cuts, bruises, or aches?

14.13.1.1. Yes []

14.13.1.2. No []

14.13.2 You had eye injuries, sprains, dislocations, or burns?

14.13.2.1 Yes []

14.13.2.2 No []

14.13.3. You had deep wounds, broken bones, broken teeth, or any other serious injury?

14.13.3.1 Yes []

14.13.3.2 No []

Sexual Abuse

Q15. Has your partner (husband/wife) or any person of opposite sex ever done any of the following?

15.1 Force you to have sexual intercourse with him/her when you did not want to?

15.1.1 Rarely []

15.1.2 Often []

15.1.3 Very often []

15.1.4 Not at all []

15.2 Physically force you to perform any other sexual acts you did not want to?

15.2.1 Rarely []

- 15.2.2 Often []
- 15.2.3 Very often []
- 15.2.4 Not at all []
- 15.3 Threatens in any way to perform sexual acts you did not want to?
- 15.3.1 Rarely []
- 15.3.2 Often []
- 15.3.3 Very often []
- 15.3.4 Not at all []
- 15.4 How long has this been happening?
- 15.4.1 Less than 6months []
- 15.4.2. 6 – 12 months []
- 15.4.3. 1 – 2 years []
- 15.4.4. 2 – 5 years []
- 15.4.5. More than 5 years []

FAMILY RELATIONSHIPS

Q16. How would you rate your family relationships?

- 16.1 satisfactory []
- 16.2 very satisfactory []
- 16.3 dissatisfactory []
- 16.4 very dissatisfactory []
- 16.5 neither []

Q17. How satisfied are you with the support you get from your family?

- 17.1 very satisfied []
- 17.2 satisfied []
- 17.3 dissatisfied []
- 17.4 very dissatisfied []
- 17.5 neither []

Q18. How satisfied are you with your living conditions?

- 18.1 very satisfied []
- 18.2 Satisfied []
- 18.3 Dissatisfied []
- 18.4 very dissatisfied []
- 18.5 neither []

Q19. I interact the most with

- 19.1 Mother
- 19.1.1 Yes []
- 19.1.2 No []
- 19.2 Father
- 19.2.1 Yes []
- 19.2.2 No []

| | | |
|---------------------------------------------------------------|---|---|
| 19.3. Guardian | | |
| 19.3.1 Yes | [|] |
| 19.3.2 No | [|] |
| 19.4 Wife | | |
| 19.4.1 Yes | [|] |
| 19.4.2 No | [|] |
| 19.5 Children | | |
| 19.5.1 Yes | [|] |
| 19.5.2 No | [|] |
| 19.6 Siblings | | |
| 19.6.1 Yes | [|] |
| 19.6.2 No | [|] |
| 19.7 Friends | | |
| 19.7.1 Yes | [|] |
| 19.7.2 No | [|] |
| Q20. I am involved in making decisions in the family. | | |
| 20.1 Rarely | [|] |
| 20.2 Sometimes | [|] |
| 20.3 Very often | [|] |
| 20.4 Never | | |
| Q21. How far do you travel to access your treatment? | | |
| 21.1 Far | [|] |
| 21.2 Very far | [|] |
| 21.3 Near | [|] |
| 21.4 Very near | [|] |
| Q22. How does this movement affect your family relationships? | | |
| 22.1 Very much | [|] |
| 22.2 Very little | [|] |
| 22.3 No much | [|] |
| 22.4 Not at all | [|] |
| Q23. To what extent do you feel your life is meaningful? | | |
| 23.1 Not at all | [|] |
| 23.2 A little | [|] |
| 23.3 Moderate | [|] |
| 23.4 very much | [|] |
| Q24. How would you rate your quality of life? | | |
| 24.1 Very satisfied | [|] |
| 24.2 Satisfied | [|] |
| 24.3 Dissatisfied | [|] |
| 24.4 very dissatisfied | [|] |
| 24.5 neither | [|] |

NUTRITION

Q25. Have you ever received nutritional advice since testing?

- 25.1 Yes []
25.2 No []

Q26. Are you following the nutritional advice given to you at the health centre?

- 26.1. Yes []
26.2 No []

Q27. If not, what would be the reasons for not following the nutritional advice?

- 27.1 Advice is not necessary to me []
27.2 Lack of money to buy the prescribed foods []
27.3 Lack of time to prepare the food []
27.4 Too many family members []
27.5 Others reasons please indicate..... []

Q28. How many meals do you eat per day?

- 28.1 One meal []
28.2 Two meals []
28.3 Three or more meals []

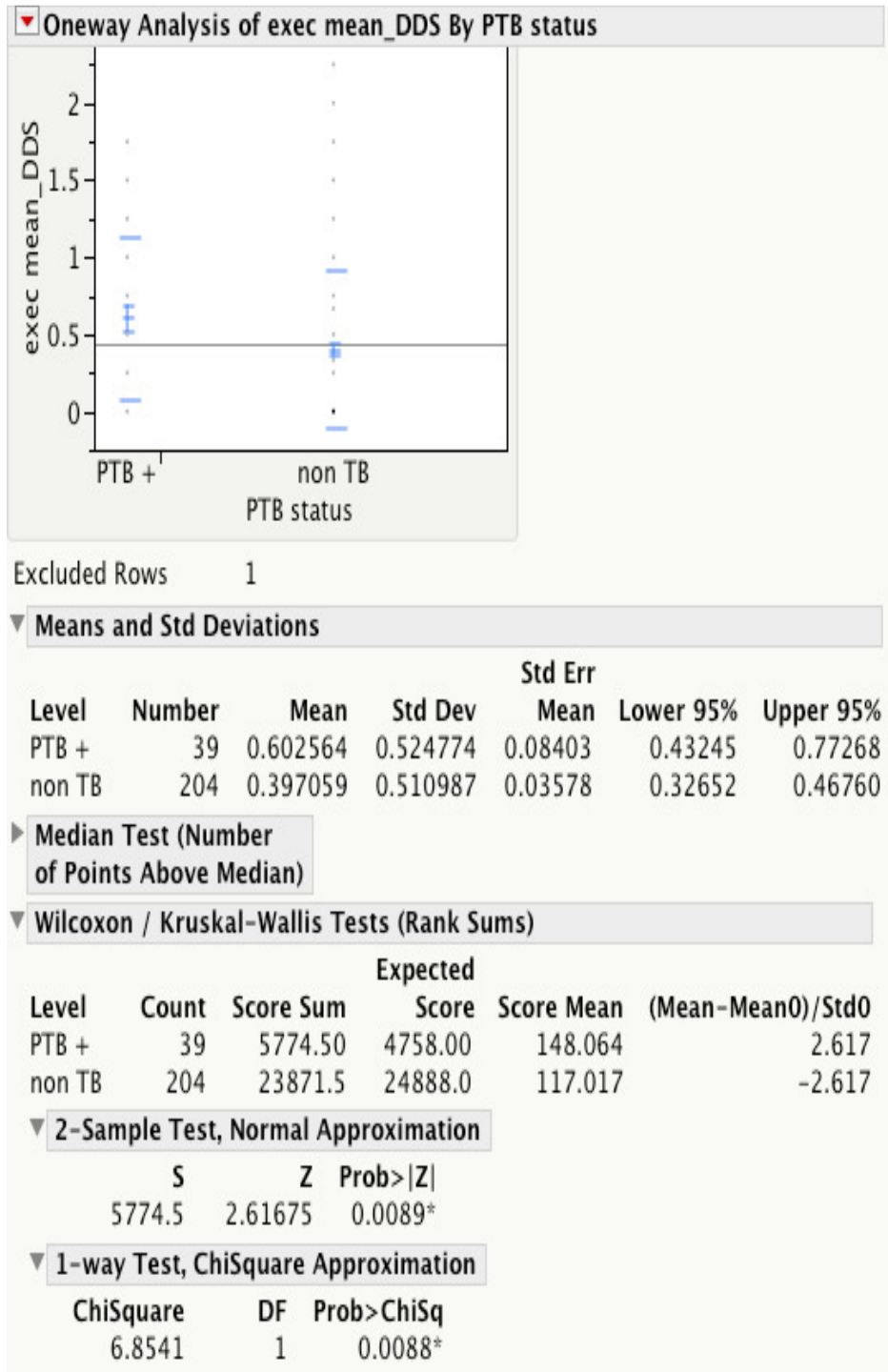
Q29 .How would you describe the quality of food that you usually eat at each meal

- 29.1 Not enough []
29.2 Just enough []
29.3 Plenty []

Q30. How much fluid (water, juice, coffee, tea, milk) do you consume per day?

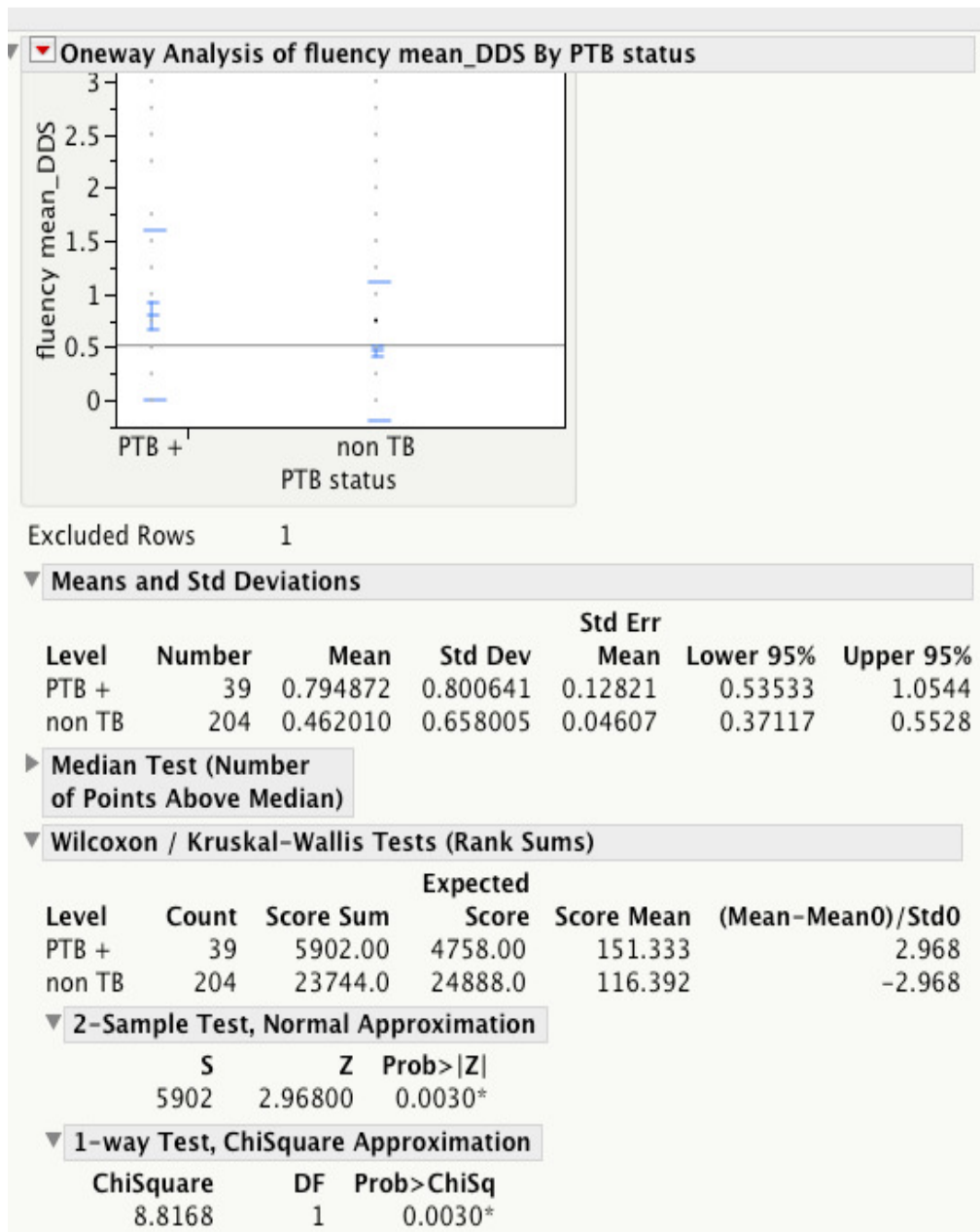
- 30.1 Less than one cup/ glass []
30.2 Three to five cups/glasses []
30.3 More than 5 cups/glasses []

Appendix G. Executive function Domain DDS by PTB status.



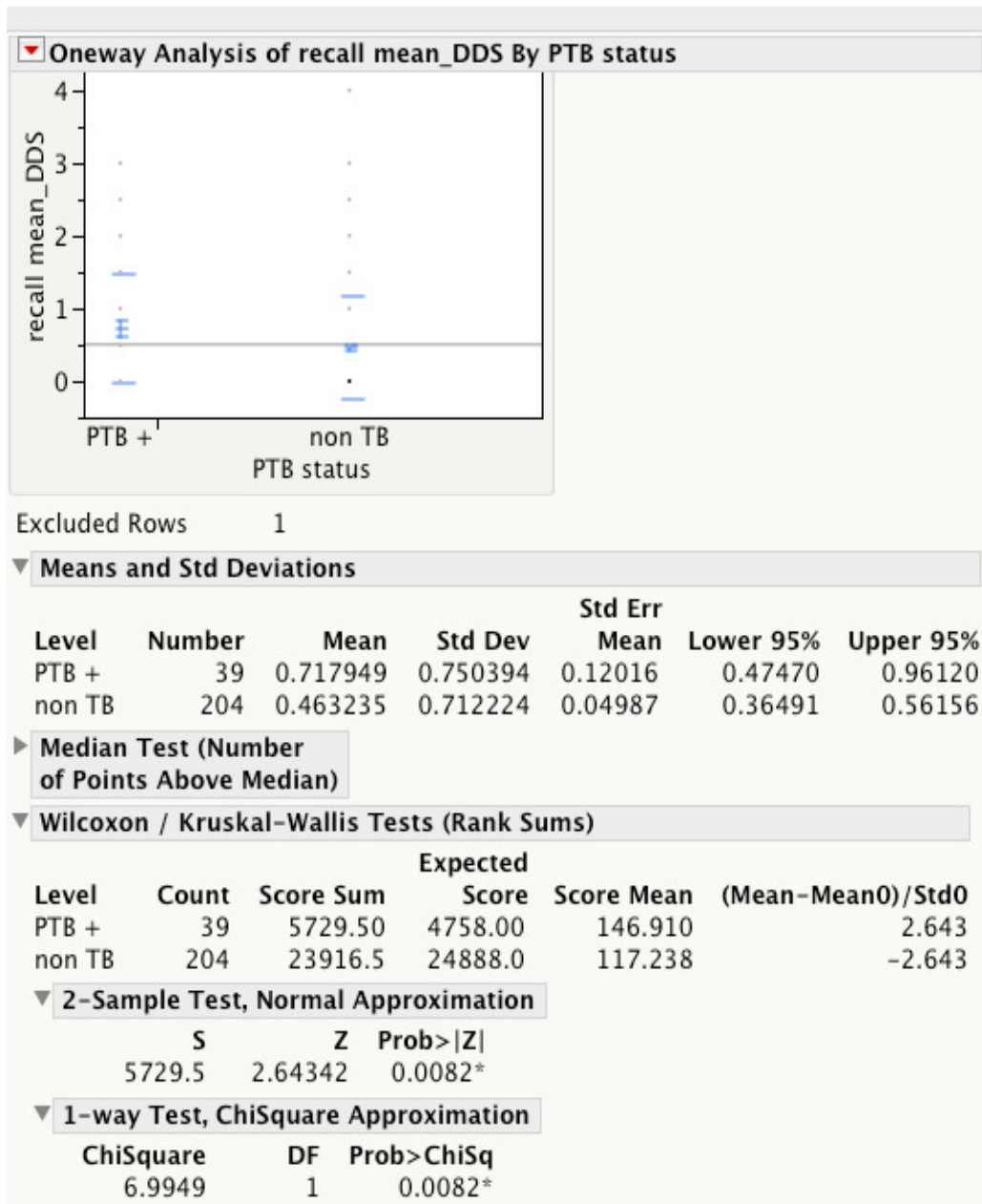
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Appendix H. Fluency Domain DDS by PTB status



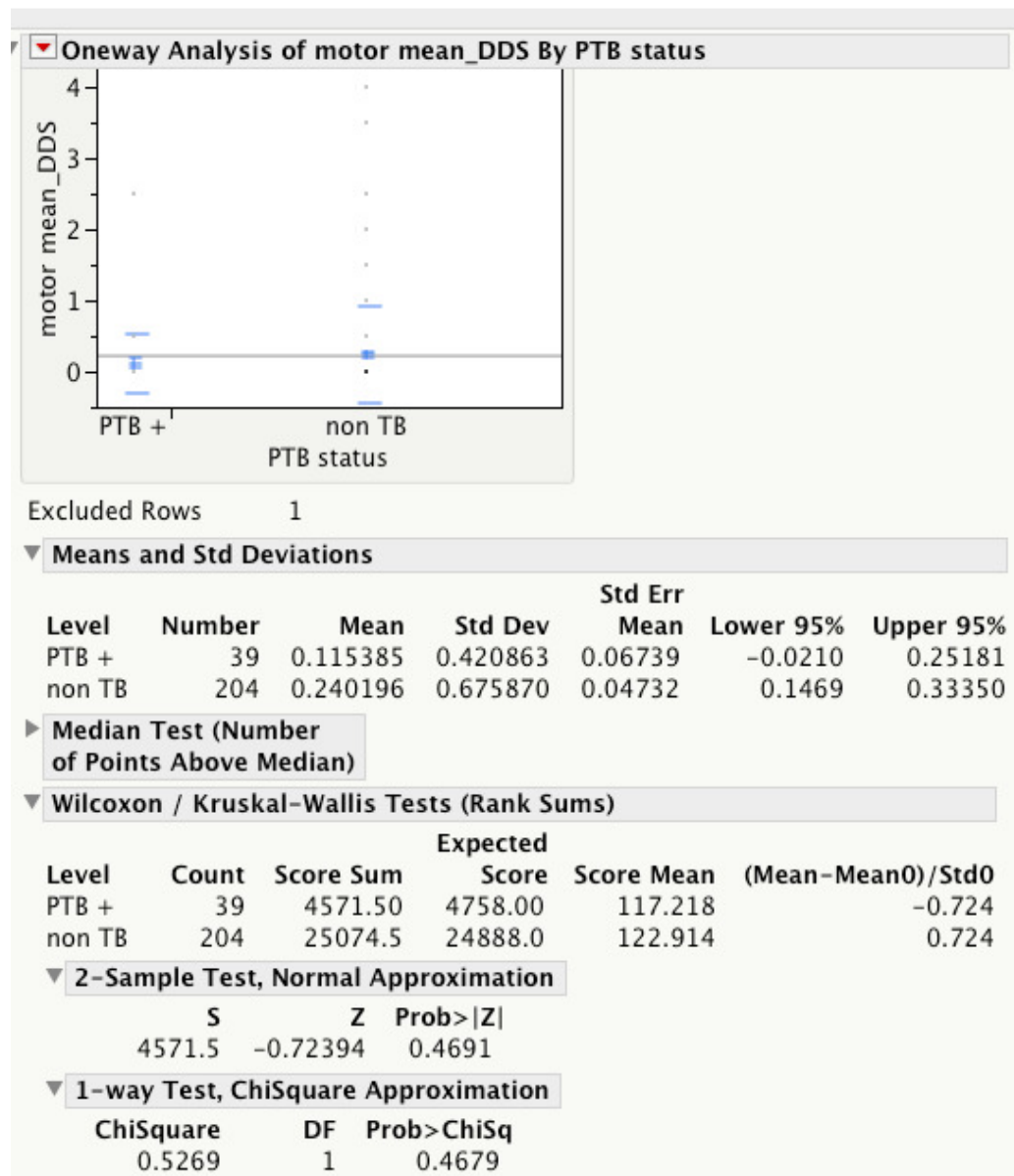
*= p value.

Appendix I. Recall Domain DDS by PTB status



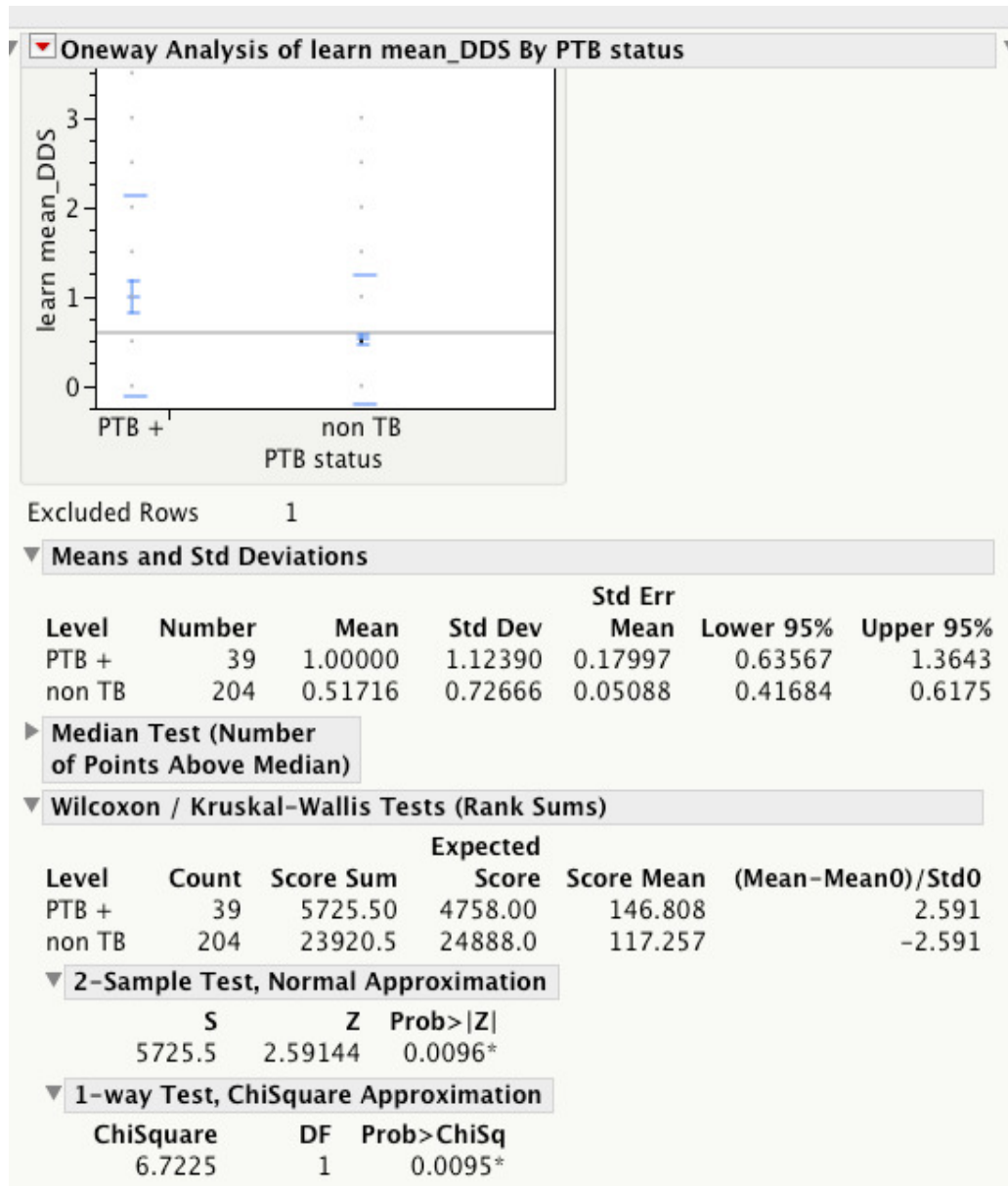
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Appendix J. Motor Domain DDS- by PTB status



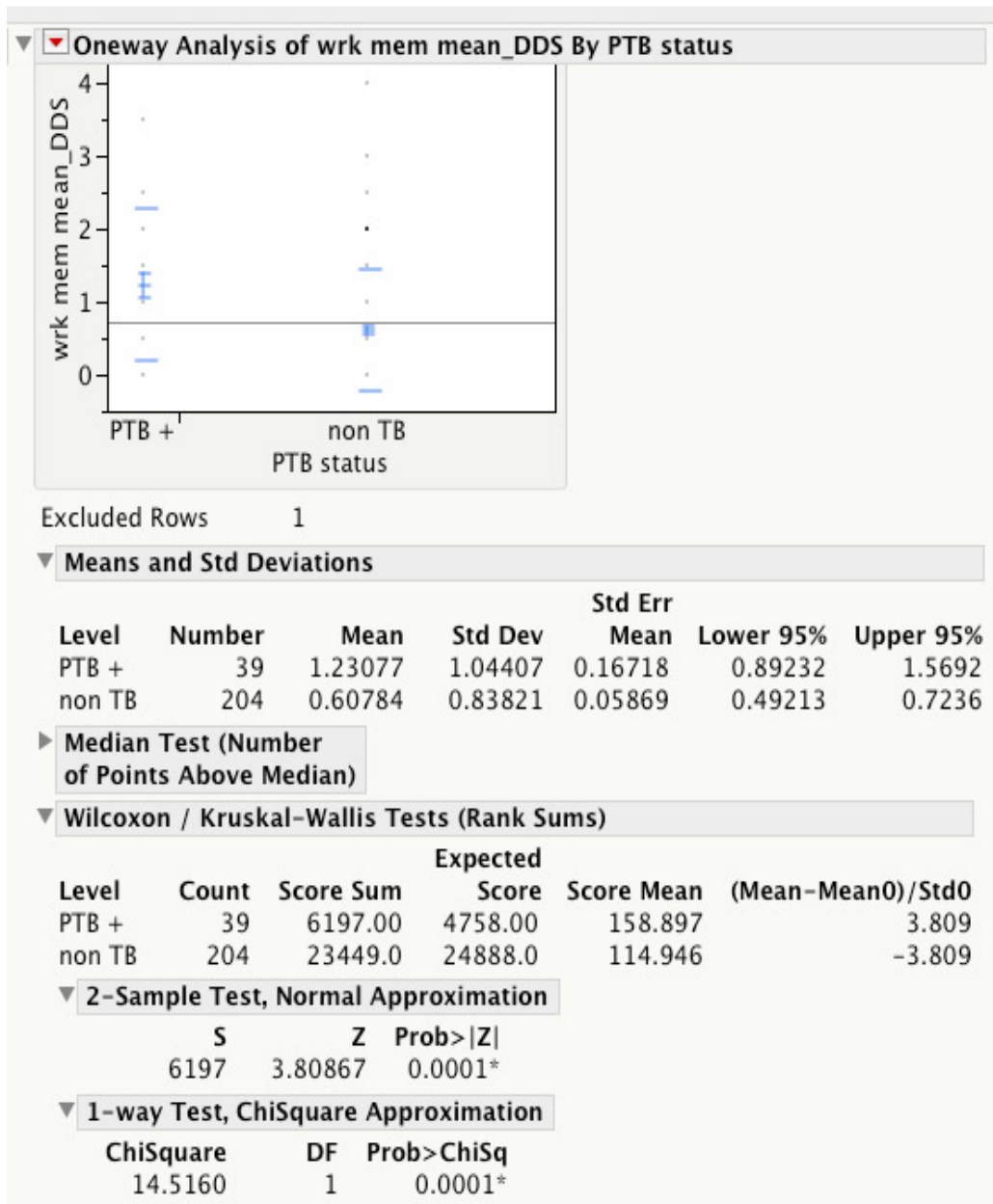
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Appendix K. Learning/Memory Domain -DDS by PTB status



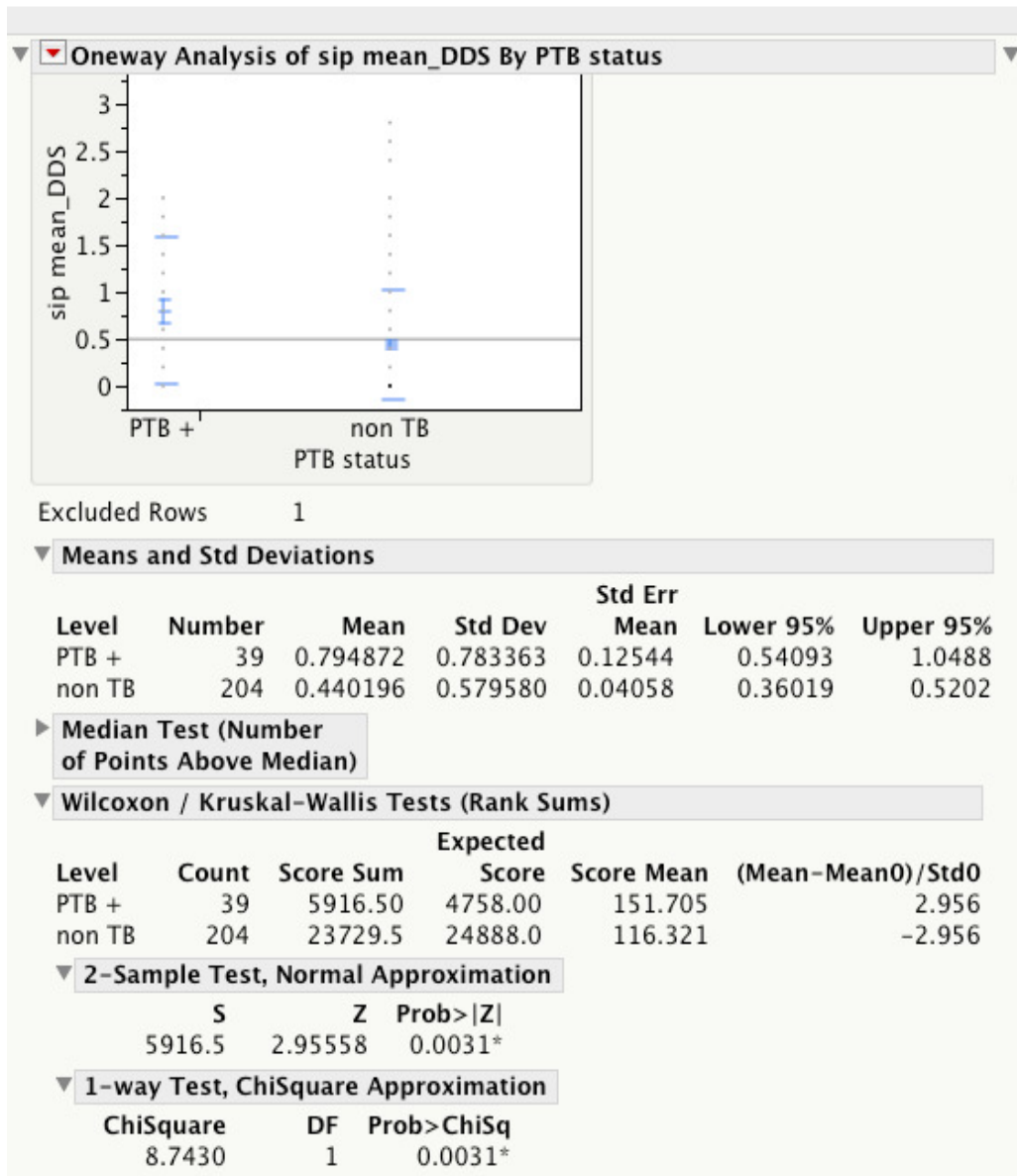
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Appendix L. Working memory Domain- DDS by PTB status



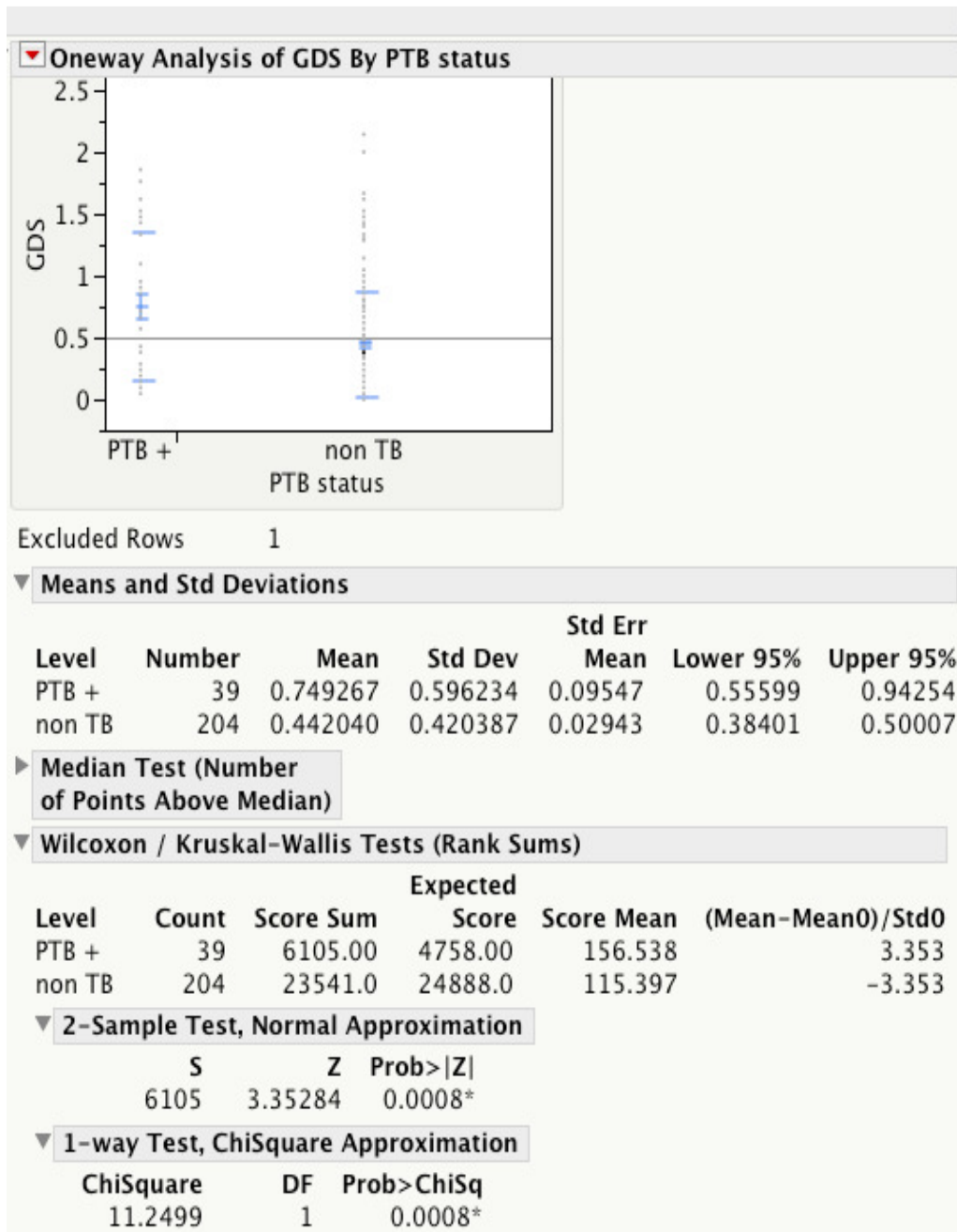
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Appendix M. Speed of information processing Domain DDS by PTB status



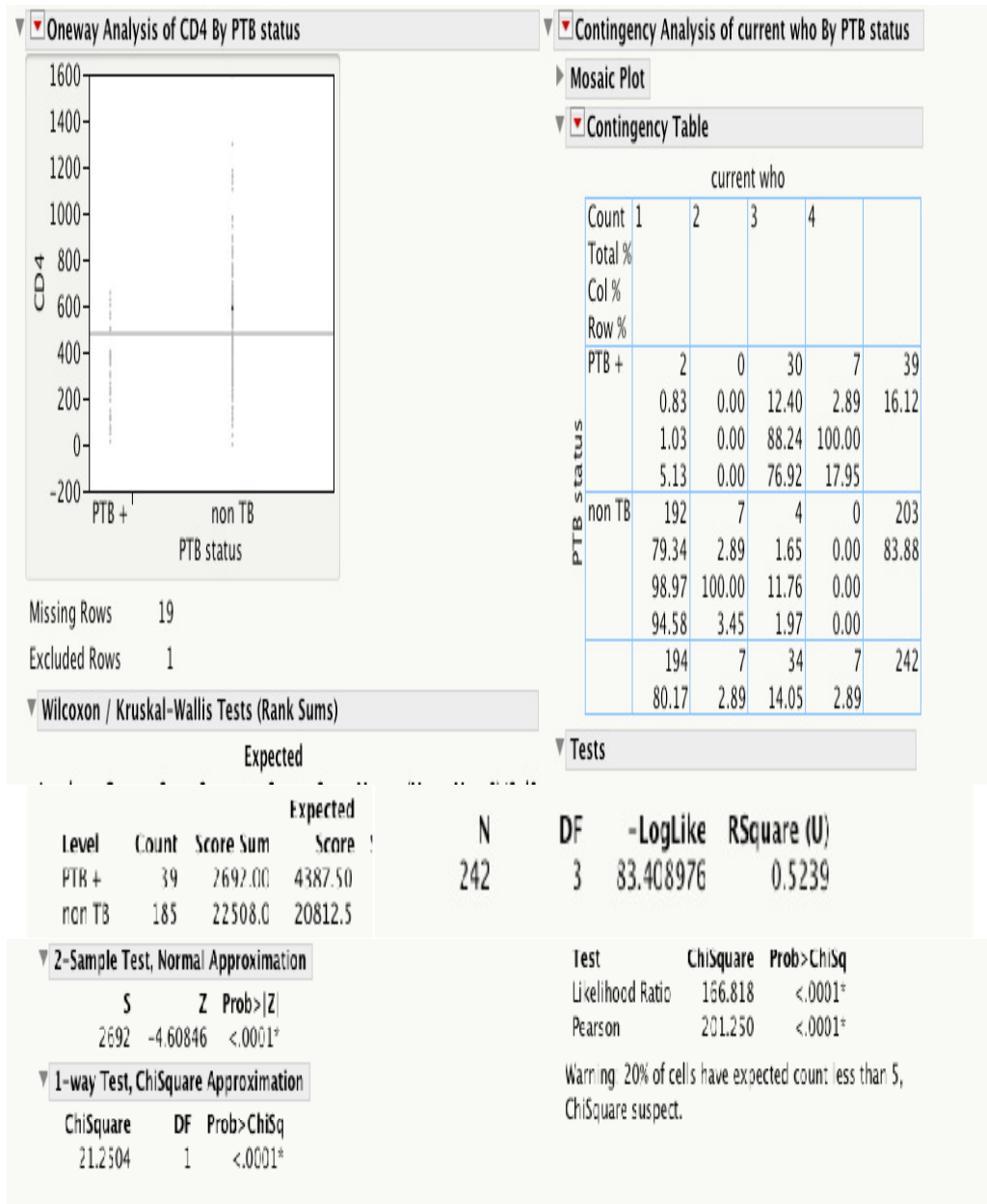
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Appendix N. Global Deficit Score (GDS) by PTB status.



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Appendix O. WHO stage and CD4 cell count by PTB status



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