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Auditory brainstem response and rate study in normal hearing adults with the Human Immunodeficiency Virus

by

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List of abbreviations

ABR – Auditory Brainstem Response

AIDS – Acquired Immunodeficiency Syndrome

AMLR – Auditory Middle Latency Response

APA – American Psychological Association

ARV – Antiretroviral

AUC – Area Under The Curve

BAEP – Brainstem Auditory Evoked Potentials

CMV - Cytomegalovirus

CNS – Central Nervous System

CTL – Cytotoxic Lymphocytes

daPa - DecaPascals

dB - Decibels

dB HL – Decibel Hearing Level

dBnHL – Decibel Normal Hearing Level

dBpeSPL – Decibel Peak Equivalent Sound Pressure Level

dB SPL – Decibel Sound Pressure Level

DIN – Digits In Noise

DNA – Deoxyribonucleic Acid

DP – Distortion Product

DPOAE – Distortion Product Oto-acoustic emission

ENT – Ear- Nose and Throat specialist

EFV - Efavirenz

FTC - Emtricitabine

Hz - Hertz

HIV – Human Immunodeficiency Virus

kOhms – KiloOhms

ml – Millilitre

mRNA – Messenger Ribonucleic Acid

ms – Milliseconds

MS - Multiple Sclerosis

NF – Noise floor

NRTI – Nucleoside Reverse Transcriptase Inhibitor

NNRTI – Non-Nucleoside Reverse Transcriptase Inhibitor

nV - NanoVolts

PTA – Pure Tone Average

RNA – Ribonucleic Acid

ROC – Receiver Operator Characteristics

SD – Standard Deviation

SE – Standard Error

SNR – Signal to Noise Ratio

SOC – Superior Olivary Complex

SRT – Speech Reception Threshold

TDH – Tshwane District Hospital

TDF - Tenofovir

TB – Tuberculosis

WHO – World Health Organization

Formatting

APA referencing style was throughout this dissertation.

Abstract

The human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have become more prevalent throughout the world. The widespread availability of antiretrovirals (ARV's) has now shifted the mindset from mortality to morbidity. Hearing health care professionals now have a wide client base consisting of adults with HIV who have a diminished quality of life due to hearing loss accompanying the virus. The auditory brainstem response (ABR) can be useful in research studies regarding HIV/AIDS as the virus has an affinity to the host's nervous system. The current study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

Forty participants enrolled in the current study (27 female). All participants were using first-line ARV's consisting of Tenofovir, Emtricitabine and Efavirenz. A total of 80 ears were analysed in the data analysis process. The mean age of the participants was 26.30 standard deviation (SD 3.68) range 19 to 31. The mean CD4+ count was 559.40 cells/µL (SD 220.250) range 208 to 1200. The mean duration on ARV's was 6.68 years (SD 5.098) range 1 to 25.

The Shapiro-Wilk test for normality of distribution was statistically significant ($p<0.05$) indicating that the data was not normally distributed. The non-parametric Friedman's test of analysis of variance was used to determine whether there was a statistically significant difference between the latencies of wave V at the different stimulus repetition rates. The diagnostic performance of the rate study was further evaluated using receiver operating characteristic (ROC) curve analysis. Accuracy was measured by the area under the ROC curve (AUC).

No difference between the median absolute latencies and interwave latencies were found within this study sample when compared to recognised normative data. The current study showed a high statistically significant difference ($p<0.001$), between Wave V at the three stimulus repetition rates although the median was still within the

norm. The current study also showed that the diagnostic accuracy of the ABR and the ABR rate study increased with a decrease in CD4+ counts.

Therefore, the current study advocates for the inclusion of the ABR and the ABR rate study in the HIV positive population for early identification of subtle neural disorders. A time-efficient protocol consisting of a neurological ABR at 27.7 Hz followed by a rate study at 61.1 Hz may be recommended.

Keywords

Human immunodeficiency virus (HIV), demyelination, CD4+ count, Auditory Brainstem Response (ABR), ABR rate study, auditory neural function.

Chapter 1: The influence of HIV/AIDS on the immune system and auditory neural functioning

1.1 Introduction

The human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have become more prevalent throughout the world. In 2017, 36.9 million people were living with HIV/AIDS, 1.2 million people were newly infected with the virus, and 1.1 million people died due to the virus (WHO, 2018). It is estimated that in sub-Saharan Africa 25.7 million people are living with HIV/AIDS (WHO, 2018). In South Africa, HIV/AIDS occurs alongside unemployment and poverty and is one of the main challenges South African infectious disease health services face (Khoza-Shangase, 2010).

HIV remains one of the biggest causes of mortality and morbidity worldwide (Fokouo et al., 2015). The HIV pandemic has been known to create more challenges to medicine and science worldwide than any other disease as there is still no cure for this virus (Posel, Kahn, & Walker, 2007; Wang & Cannon, 2016).

1.2 The Auditory Brainstem Response (ABR) and its clinical value in HIV studies

One of the challenges the HIV pandemic creates is the effect the HIV virus has on the auditory pathway in HIV positive individuals. The auditory structure can be examined in HIV positive individuals by making use of the auditory brainstem response (ABR). The ABR test was first described by Jewett and Williston in 1971. The ABR is used to assess the integrity and synchronicity of the central auditory pathway (Carhart & Jerger, 1959; Matas, Silva, Marcon, & Goncalves, 2010; Reyes-Contreras et al., 2002). It is an objective, non-invasive assessment tool that can be used in conjunction with other audiological assessments in order to diagnose hearing related disorders (Hall, 1992). The ABR is elicited by the presentation of a high intensity click stimulus

and consists of five to seven waves (Hall, 1992). Multiple anatomical sites are thought to contribute to the formation of a single wave (Hall, 1992). Wave I is generated by the distal portion of the eight cranial nerve – the afferent nerve fibres exiting the cochlea towards the internal auditory canal (Hall, 1992). Wave II is generated by the proximal part of the eight cranial nerve as it enters the brainstem (Hall, 1992). Wave III is generated by the superior olivary complex (SOC) and the cochlear nucleus (Hall, 1992).

Wave IV is generated by the medial nucleus of the SOC and multiple midline fibres beyond the cochlear nucleus (Hall, 1992). Wave V is generated by the lateral lemniscus and the contralateral inferior colliculus (Hall, 1992). Wave VI and VII are generated by the medial geniculate body (Hall, 1992).

Studies have shown that brainstem auditory evoked potentials (BAEP), specifically the ABR, is affected by the HIV virus (Bankaitis et al., 1998; Matas, Santos Filha, Juan, Pinto, & Gonçalves, 2010; Matas, Silva, et al., 2010). Changes in ABR waves are reported even before the onset of any other clinical or neurological manifestations (Harris et al., 2012; Specter, Bendinelli, & Friedman, 1993). The ABR can, therefore, be used as an audiological monitoring tool in the HIV population.

The inclusion of a rate study within the ABR protocol for individuals with HIV/AIDS can identify subtle neural disorders that emerge when there is minimal neural recovery time delaying a already pathologically stressed auditory nervous system (Ackley, Herzberger-Kimball, Burns, & Balew, 2006).

1.3 HIV/AIDS and the immune system

HIV/AIDS compromises the functioning of the human immune system (Bankaitis, 1998). The human immune system comprises of three levels of immune defence (Sompayrac, 2012). The physical barrier, the innate immune system and the adaptive immune system (Sompayrac, 2012). The adaptive immune system has the ability to

adapt the immune system of the host in order to protect against a variety of viruses (Sompayrac, 2012).

The HIV virus targets a specific immune T cell, the CD4+ helper T cell (Ellis & Hulme, 2017). The CD4+ helper T cell is required in order to initiate an effective immune response. The CD4+ helper T cells secrete cytokines, signalling an immune response and activates cytotoxic lymphocytes (CTL), these cells contest infections in the human body (Kumamoto, Mattei, Sellers, Payne, & Iwasaki, 2011; Luckheeram, Zhou, Verma, & Xia, 2012; Sompayrac, 2012).

HIV is known as a retrovirus (Nisole & Saib, 2004). A retrovirus does not contain the common virus acid, deoxyribonucleic acid (DNA), it contains ribonucleic acid (RNA). A retrovirus has the unique ability to use an enzyme in the nucleus of the cell to transcribe the viral RNA into DNA (Nisole & Saib, 2004). The HIV virus infects the CD4+ T cells during cell replication (Ellis & Hulme, 2017; Welkoborsky & Lowitzsch, 1992). The infection is achieved in the following way: the HIV virus attaches to the helper T cell by binding to the CD4+ receptor on the membrane of the cell; the genetic information of the HIV virus, which is in RNA form, enters the helper T cell and a viral enzyme, copies the RNA into a single strand of helper T cell DNA using the host cell nucleotides (Sompayrac, 2012). Reverse transcriptase, the enzyme responsible for transcribing viral RNA to DNA, is notorious for making random errors in the copying process (Sompayrac, 2012). This single strand DNA is again reverse transcribed into a double strand of DNA which contains the random errors made by the reverse transcriptase.

An enzyme, viral integrase, carries this newly double-stranded erroneous DNA into the nucleus of the host's cell. Viral integrase makes an incision in the host cell DNA, and the HIV virus is inserted into the host chromosome DNA. This process of transcribing and inserting itself into the host's chromosomes is what establishes lifelong HIV infection (Sompayrac, 2012). The helper T cell now continues to produce HIV infected cells instead of cells that were supposed to contest a virus (Sompayrac, 2012).

The successfulness of the HIV virus in compromising immune functioning is attributed to the intricate process of the replication phase (Sompayrac, 2012). The HIV virus infects the immune cells responsible for the signalling of an immune response. A latent infection is established undetected by the CTL's. The rate at which the virus mutates is so rapid causing the virus to continuously stay ahead of the activation of an immune response (Sompayrac, 2012).

The pathological sequelae of the HIV infection are attributed to virus's goal of slowly destroying the immune system of the host which leads to a profound state of immunosuppression. A host in a profound state of immunosuppression is even more susceptible to a variety of other opportunistic infections (Cohen, Durstenfeld, & Roehm, 2014; Harris, Peer, & Fagan, 2012; Sompayrac, 2012). The HIV-virus creates a three-fold challenge for medicine and science: a latent infection, high mutation rate and the immune system itself facilitating the spread of the virus through the host's body (Sompayrac, 2012).

The level of immune suppression, the progression of the disease and the likelihood of developing systematic diseases is indicated by the individual's CD4+ count (Maartens, 2005). The average HIV-negative adult has a CD4+ count of between 547 to 1327 cells/mm^3 (Aina et al., 2005). Research in Africa found that 38% of adults with HIV/AIDS with a CD4+ count of less than 200 cells/mm^3 developed a hearing loss, 28% of participants with a CD4+ count of 200 – 500 cells/mm^3 developed a hearing loss, and 22% with a CD4+ count of more than 500 cells/mm^3 developed a hearing loss (Ongulo & Oburra, 2010). The research indicates that as the CD4+ count decreases individuals are more susceptible to hearing loss (Ongulo & Oburra, 2010).

1.4 The effect of HIV/AIDS on the auditory system

Difficulty hearing, vertigo and otalgia are amongst the first ontological and audiological symptoms of an HIV infection (Bakhshaee, Sarvghad, Khazaeni, Movahed, & Hoseinpour, 2014; Khoza & Ross, 2000; Prasad, Singh, & Lakshmi, 2006). These

symptoms are reported more often in the HIV-positive population than in the HIV-negative population (Fokouo et al., 2015). Three out of four HIV positive patients will experience some of these symptoms throughout their life. These symptoms often worsen, and increases as the disease progress (Iacovou, Vlastarakos, Papacharalampous, Kampessis, & Nikolopoulos, 2012; van der Westhuizen, Swanepoel, Heinze, & Hofmeyr, 2013).

Individuals with HIV/AIDS have an increased risk of 21 to 49% of developing hearing loss, which is most often sensory neural of origin affecting mainly the high frequencies (Harris et al., 2012). Patient reports in South Africa stated that as many as 27.5% of patients with HIV/AIDS present with hearing loss (van der Westhuizen et al., 2013). Research on the peripheral auditory functioning of the HIV/AIDS population indicated that 16.6% of patients who presented with normal pure tone audiometric results had reduced distortion product otoacoustic emission (DPOAE) amplitudes (Ranjan & Bhat, 2008; van der Westhuizen et al., 2013). These findings suggest that there is auditory damage in clinically asymptomatic HIV positive individuals (Ranjan & Bhat, 2008; van der Westhuizen et al., 2013).

At the moment, there is still no clear, consistent pattern of hearing damage in patients with HIV/AIDS (Maro et al., 2015). The hearing loss can be the direct or indirect cause of the virus (Bankaitis & Schountz, 1998). The HIV virus itself can affect auditory function due to its neurotropism, its affinity to the host's nervous system (Harris et al., 2012; Specter, Bendinelli, & Friedman, 1993). The demyelination of subcortical areas of the brain, containing auditory structures, results in neuropathological changes in the central nervous system (CNS) leading to sensorineural hearing loss evident by the high incidence of BAEP abnormalities (Iacovou et al., 2012). The authors concluded that the hearing loss could be directly attributed to damage to the vestibulocochlear nerve, inner ear structures and or the brain caused by the HIV virus (Khoza & Ross, 2000; Modongo et al., 2014; van der Westhuizen et al., 2013).

The suppression of the immune system, caused by the HIV infection, results in increased susceptibility to opportunistic diseases (Cohen et al., 2014). Opportunistic infections can indirectly cause hearing loss by compromising the structures of the

auditory system. These infections include, and are not limited to, otosyphyllis, meningitis, toxoplasmosis, cytomegalovirus (CMV), herpes zoster virus and otitis media which can cause sensorineural or conductive hearing losses (Chandrasekhar et al., 2000; Prasad et al., 2006; Shaw, 2012).

Tuberculosis (TB) is one of the most common opportunistic infections accompanying HIV. The treatment for TB is highly ototoxic and can cause hearing damage in the individual (Modongo et al., 2014; Sinxadi & Blockman, 2009). The combined TB and ARV treatment regime are highly vestibular- and cochleartotoxic (Harris et al., 2012).

ARV's is the current treatment option available for people living with HIV/AIDS (Khoza-Shangase, 2010). ARV's contains a minimum of three drugs and requires monitoring of plasma concentrations (Matas, Silva, et al., 2010). The most common ingredients in ARV's are Tenofovir, a nucleoside reverse transcriptase inhibitor (NRTI), Emtricitabine, an NRTI and Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Regensberg, Maartens, Mientjies, & Mendelson, 2013). Studies have reported that there is an association between hearing loss and the use of an NRTI (McNaghten, Wan, & Dworkin, 2001; Monte, Fenwick, & Monteiro, 1997; Powderly, Klebert, & Clifford, 1990). When studying the ototoxic effects of ARV's, electrophysiological procedures (ABR, Auditory middle latency response- AMLR and P300) indicated that 19,6% individuals using ARV's, with normal hearing, presented with results indicative of lower- and higher brainstem pathology as well as central impairments (Matas, Silva, et al., 2010). However, it is not clear from the study what audiometric thresholds were considered normal hearing. The ototoxic results described can be attributed to either the reduction in mitochondrial DNA induced by the NRTI's, mitochondrial mutations caused by the HIV-infection or mutations caused by the ageing individual (Simdon, Watters, Bartlett, & Connick, 2001). Hearing loss can occur early in the disease, even before the provision of ARV's or the lowering of CD4+ counts (Cohen et al., 2014). When a hearing loss does develop, it is typically progressive and also deteriorates with a decreasing CD4+ count (Cohen et al., 2014).

Electrophysiological abnormalities such as increased absolute latencies and interpeak latencies of the ABR waves are often reported in individuals with HIV (Matas, Santos

Filha, et al., 2010). (Matas, Santos Filha, et al., 2010) reported that 28,6% of adults with HIV presented with lower brainstem involvement, 7,1% presented with higher brainstem involvement and 21,4% presented with both lower and higher brainstem involvement. However, 40% of the sample size presented with pure tone audiometric results of greater than 25 decibel (dB), which could give rise to the altered brainstem response results. Rosenhall, Hakansson, Lowhagen, Hanner and Johnsson-Ehk (1989) reported that 38% of individuals with HIV/AIDS presented with abnormal latencies of ABR waves when compared to HIV negative individuals.

The life expectancy of people living with HIV/AIDS has increased due to the widespread availability of ARV's (Jolles, Kinlich de Loes, Johnson, & Janossy, 1996). The increase in life expectancy shifts the focus of clinicians from the effects of the virus to the quality of life of people living with HIV/AIDS (Marin, Thiébaut, Bucher, Rondeau, Costagliola, Dorrucci, Hamouda, et al., 2009; Peters et al., 2013). Hearing loss can decrease the quality of life as people are not able to function independently or contribute to the daily living society in the way the used to (Chia et al., 2007; Gopinath et al., 2012; Mick, Kawachi, & Lin, 2014).

1.5 Study rationale

There is a need for intensified research on the auditory function in patients with HIV/AIDS in sub-Saharan Africa, as most research is conducted in developed countries (Khoza-Shangase, 2010). The course and management of the disease may be different in developed countries than in developing countries attributed to contextual differences. South- Africa has one of the highest rates of multi-drug restistand TB, morever statistics shows that 50% of individuals with TB are HIV positive (Tashneem Harris & Heinze, 2013). More specifically, the prevalence of people living with HIV/AIDS in South Africa is higher than in any other country (Khoza-Shangase, 2010). The burden South Africa's hearing health care professions face is doubled by the effect of aminoglycoside induced hearing loss as a result of individuals presenting with both TB and HIV/AIDS. There is an urgency to require relevant data

to not only assist South African hearing healthcare professionals who treat and habilitate HIV/AIDS patients but also to provide better insight into the pathophysiology of HIV and the effect on the auditory system. This is required to guide the management of the ever increasing number of people with HIV/AIDS.

Research regarding HIV/AIDS and the auditory system have been conducted (Bankaitis, 1998; Harris et al., 2012; Khoza-Shangase, 2010; Malessa et al., 1989; Matas, Samelli, Angrisani, Magliaro, & Segurado, 2015; Matas, Silva, et al., 2010; Rosenhall et al., 1989). From these studies, it is evident that the auditory structures are affected in people who are HIV positive even in the absence of clinical manifestations. These studies, however, did not control for age-related hearing loss, noise exposure, ototoxic medications and opportunistic infections all of which can influence ABR recordings.

ABR abnormalities such as increased absolute latencies of wave III and V and I-III and I-V interpeak, are observed in adults with HIV who presents with normal hearing sensitivity (Matas et al., 2010). Matas et al., (2010) suggests that there is evidence of dysfunction in synchrony in the generation and transmission of neural impulses along the auditory pathway in the brainstem of patients who are HIV positive. Reyes-Contreras et al., (2002) described histopathological studies showing local demyelination in areas of the brainstem where auditory structures are found. The study suggests that there will be abnormal auditory neurophysiological results due to the demyelination. The study identified the need to assess the integrity of the pontine and midbrain auditory pathways (Reyes-Contreras et al., 2002). The neurological ABR is useful in early identifications of HIV related neurodegeneration of the auditory system in clinically asymptomatic individuals (Castello, Baroni, & Pallestrini, 1998; Jalali, Banan, & Vahedipour, 2014; Koralnik et al., 1990; Reyes-Contreras et al., 2002).

The ABR is specifically useful in detecting subtle neural disorders or neural degeneration caused by the HIV virus, especially when using a faster stimulus rate (Bankaitis, 1995). Bankaitis (1995) investigated the effect of a varying ABR stimulus rate on adults with HIV/AIDS who presented with normal pure tone results. A comparison of the latency of Wave V with the faster click rate (61.1 Hz) showed

exaggerated prolongations in patients who are HIV positive. (Santos, Munhoz, Peixoto, & Silva, 2004) reported that rate studies, in demyelinating diseases such as multiple sclerosis (MS), significantly improved the detection of abnormal responses that are dependant on rate increases. The study included individuals with multiple sclerosis (MS) who presented with normal hearing sensitivity and reported a higher incidence of abnormal responses with an increase in stimulus repetition rate.

The shift in mindset from mortality to morbidity makes the goal of the hearing healthcare professional clear. To easily and early identify hearing disorders in clinically asymptomatic individuals to initiate habilitation strategies to preserve the quality of life (Marin, Thiébaut, Bucher, Rondeau, Costagliola, Dorrucci, & Chêne, 2009; Peters et al., 2013). Therefore this study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

Chapter 2: Methodology

2.1 Research aim

To investigate the clinical usefulness of the auditory brainstem response (ABR) and the ABR rate study in normal hearing adults with the human immunodeficiency virus (HIV).

2.2 Research design

This study made use of an cross-sectional and exploratory research design yielding quantitative data to investigate the clinical usefulness of the ABR and the ABR rate study in normal hearing adults with HIV (De Vos, Strydom, Fouche, & Delport, 2011; Maxwell & Satake, 2006). An exploratory research design describes research conducted to gain insight into a community, individual, situation or phenomenon where there is little to none previous research to gain insight into further research (De Vos et al., 2011; Maxwell & Satake, 2006). This study was exploratory as it aimed to describe the clinical usefulness of the ABR and the ABR rate study in normal hearing adults with HIV. The results of the ABR recordings and rate study were compared to normative data for healthy adults. This study data was quantitative in nature, as measurable variables predicted outcomes (Leedy & Ormrod, 2005)

2.3 Ethical considerations

2.3.1 Permission

Before data collection commenced, permission to conduct research at the anti-retroviral (ARV) clinic of Tshwane District Hospital (TDH) was granted (Appendix A). Research ethical clearance was obtained from the Faculty of Health Sciences (Appendix B) and the Faculty of Humanities (Appendix C).

2.3.2 Confidentiality

The participant's HIV status was treated with a high level of secrecy. Each participant was assigned a random code during the data collection procedure (i.g. 001A) and the process of statistical analysis. No identifying information was used in any part of the data collection procedure or the reporting of results to ensure the anonymity of the participants and the confidentiality of their results. This was explained thoroughly in the informed consent letter (Appendix D) and reiterated verbally to each participant before testing commenced.

2.3.3 Protection from harm

Participants were informed of what the procedures entail in the informed consent letter as well as verbally before the testing commenced (Appendix D). Participants fully understood what participation entailed and that there was no medical risk or discomfort involved. Participants were informed that they could withdraw from the study at any time with no negative consequences and that participation or the decision to not participate does not affect the treatment they receive at the clinic.

2.3.4 Voluntary and informed consent

Participants were informed about the nature of the study and what was expected of them prior to testing (Leedy & Ormrod, 2014). The informed consent letter gave an extensive explanation of the study and explained that the treatment they are using, their CD4+ count and last viral load would be documented. Participants were informed that they could withdraw from the study at any time with no negative consequences and that participation or the decision to not participate would not affect the treatment they receive at the clinic. Permission from the TDH was granted to document the specific information from the participant's hospital file (Appendix A).

2.3.5 Plagiarism

The research study, dissertation and scientific article is the original work of the researcher. When secondary information was used, it was acknowledged and referenced using the American Psychological Association (APA) 6th edition

referencing guidelines. The plagiarism policy of the University of Pretoria can be viewed in Appendix E.

2.3.6 Data storage

The University of Pretoria policy states that data obtained from the research project must be securely stored for a minimum of 15 years (Appendix F). Data of the research study was stored electronically on a CD and in hard copy at the Department of Speech-Language Pathology and Audiology, University of Pretoria. Data files do not include identifying information of participants.

2.3.7 Referrals

If a participant was identified with a hearing loss or a condition necessitating otologic management (e.g. otitis media) participants were given a referral letter (Appendix G). Participants were also provided with the contact information of their local audiologist or Ear-, Nose- and Throat Specialist (ENT) for the management of the condition.

2.4 Research participants

Non-probability purposive sampling was used in the current study. A purposive sampling technique is used when participants are selected for a specific purpose as they have specific features (Leedy & Ormrod, 2014). Non-probability purposive sampling can be described as a method where the researcher intentionally selects participants with certain attributes (Maxwell & Satake, 2006). Data collection took place over the course of three months. All tests were conducted by the researcher, the primary author of the current study. Testing was done in a quiet room provided by the ARV clinic of the TDH, Pretoria. The room was situated away from patient waiting areas and Distortion Product Otoacoustic emission noise floors were within normal limits.

Forty consenting participants were recruited from the registered patients at the ARV clinic. Nurses in the clinic performing screenings of the vitals informed participants,

matching the specific inclusion criteria, about the research being conducted. If participants were willing to partake in the study, they were sent to the researcher where the purpose of the study was explained and the informed consent form (Appendix D) was given. The research group consisted of 27 female and 13 male participants. Once consent had been obtained from the participants, relevant information from the file was documented. All participants were using first-line ARVs consisting of Tenofovir, Emtricitabine and Efavirenz. All participants had a lower than detectable viral load at the time of testing. No participants were included that had a history of Tuberculosis (TB). A total of 80 ears were analysed in the data analysis process. The mean age of the participants was 26.30 standard deviation (SD 3.68 range 19 to 31). The mean CD4+ count was 559.40 cells/mm^3 (SD 220.25 range 208 to 1200). The mean duration on ARV's was 6.68 years (SD 5.10 range 1 to 25).

Upon completion of the test procedure, a report documenting the findings (Appendix H) was handed to the participant including information regarding the tests conducted and the results thereof.

2.6 Participant inclusion criteria

Table 1 displays the participation selection criteria:

Table 1: Participant selection criteria

Selection Criteria	Required Result Criteria	Equipment Used
The participants were 20 to 30 years of age on the day of testing.	This age range was selected as an increase in ABR latencies and decreased amplitudes are often reported in individuals older than 51 years (Gupta & Gupta, 2017). Hood (1998) furthermore indicated that individuals older than 30 years present with increased latencies.	

Selection Criteria	Required Result Criteria	Equipment Used
The tympanic membrane and ear canal should show no evidence of pathology or occluding cerumen or any other pathology of the external ear canal.	Any conductive pathology can alter ABR latencies (Langdon & Saenz, 2016). Cerumen can obstruct the distortion product otoacoustic emissions (DPOAE's) probe, and a false refer result can be obtained (Hall, 1992). External or middle ear pathology could lead to an erroneous interpretation of a retrocochlear pathology (Hall, 1992).	Welch Allyn Pocketscope™ with reusable specula.
Participants had to present with normal middle ear functioning.	The participant must have had a Jerger Type A tympanogram, characterised by a middle ear pressure of -50 decapascals (daPa) to +50 daPa and compliance of 0.3 millilitre (ml) to 1.75 ml (Jerger, 1970), with present ipsilateral stapedial reflexes at 1000 hertz (Hz) at 75 – 90 decibel hearing level (dB HL). Type A tympanograms and present ipsilateral stapedius reflexes suggest the absence of middle ear pathology (Katz, Medwetsky, Burkard, & Hood, 2009). This is required as external or middle ear pathology can lead to an erroneous interpretation of retrocochlear pathology (Hall, 1992) and can impact ABR latencies.	GSI 39 Auto Tymp Pure tone and tympanometry screener, calibrated prior to data collection SANS 10154-1/2 10182.

Selection Criteria	Required Result Criteria	Equipment Used
The participants must have presented with normal behavioural pure tone thresholds and normal speech reception thresholds (SRT) in noise.	Normal behavioural pure tone thresholds were considered as a pure tone average (PTA) of ≤ 25 dB HL in both the left and the right ears (Stach, 2010). The South African English Digits-In-Noise (DIN) test, was used to evaluate the SRT and a score of ≤ – 7, 50 dB signal to noise ratio (SNR) had to be obtained (Potgieter, Swanepoel, Myburgh, & Smits, 2017). A sensorineural hearing loss in the high frequencies can result in the inability to obtain ABR waves and can affect the latencies despite an absence of a retrocochlear pathology (Hood, 1998).	• GSI 39 Auto Tymp Pure tone and tympanometry screener, calibrated prior to data collection SANS 10154-1/2 10182. • DIN testing (HearZA smartphone Application) on an Android-compatible Samsung Galaxy S6 device with calibrated supra-aural headphones.
The participant had to present with normal cochlear outer hair cell functioning.	DPOAEs were performed to assess the integrity and functioning of the cochlear outer hair cells. DPOAE measurements were conducted at the following F2 frequencies (F1/F2 ratio of 1.22): 7000, 5000, 3000, 2000, and 1000 Hz. The intensity parameters were set to 65 dB (L1) and 55 dB (L2). DPOAE measurements were considered normal when three or more of the five frequencies distortion product minus the noise floor (DP-NF) difference were > 10 dB. DPOAE	Vivosonic™ Integrity™ V500 calibrated prior to data collection by the ISO 389-6 protocol. VivoLink™ automatically retrieved the OAE probe calibration and performed a system self-test prior to testing, stimulus levels were adjusted according to the patient's occluded ear canal volume, and OAE measurements were conducted.

Selection Criteria	Required Result Criteria	Equipment Used
	measurements were considered abnormal when three or more of the five frequencies are either reduced; DP-NF difference was 6 to 10 dB, or absent, the DP-NF difference was < 6 dB (van der Westhuizen et al., 2013).	
CD4+ count of more than 200 cells/mm^3. Participants had to be using first-line ARVs: • Tenofovir (TDF) • Emtricitabine (FTC) • Efavirenz (EFV)	Participants were only included if they had a CD4+ count of more than 200 cells/mm^3. A CD4+ count lower than 200 cells/mm^3 increased the individuals susceptibility to opportunistic diseases that can influence ABR results (Harris et al., 2012).	The hospital file indicated the CD4+ count and the first-line ARV's.
Not on TB treatment.	TB medication is highly ototoxic and could influence the results (Harris et al., 2012)	The hospital file indicated if the patient was using medication for TB.

(ABR: auditory brainstem response; daPa: decapascals; dBHL: decibel hearing level; DIN: digits-in-noise; DP: distortion product; DPOAE: distortion product otoacoustic emission; EFV: Efavirenz; FTC: Emtricitabine; Hz: hertz; ml: millilitre; NF: noise floor; PTA: pure tone average; SNR: signal-to-noise ratio; SRT: speech reception threshold; TDF: Tenofovir; TB: tuberculosis)

Table 2 summarizes the equipment used for participant selection.

Table 2: Summary of equipment for participant selection in the sequence of test's conducted

Equipment	Description
Welch Allyn Pocketscope™ with reusable specula	The Welch Allyn Pocketscope™ with reusable specula was used to visually inspect the external ear canal and the tympanic membrane.

Equipment	Description
GSI 39 Auto Tymp Pure tone and tympanometry screener *(calibrated prior to data collection SANS 10154-1/2 10182.)*	Acoustic immittance measurements were used to examine middle ear functioning. Acoustic immittance was measured by middle ear pressure, compliance and ear canal volume through the insertion of a probe in the ear canal (Stach, 2010). Acoustic reflexes were measured after the probe was placed in the ear canal. Acoustic reflexes were measured ipsilaterally at 1000 Hz. Air conduction audiometry was used to determine the hearing threshold using the modified Hughson-Westlake method (Jerger, 1970). Thresholds were determined by presenting various intensities at octave intervals including half-octaves of 3000 and 6000 Hz. Thresholds were defined as the lowest intensity the participant responded to 50% of the time (Stach, 2010).
HearZA smartphone Application on an Android-compatible Samsung Galaxy S6 device with calibrated supra-aural headphones.	The South African English DIN test was used to evaluate SRT abilities. Three random digits were presented simultaneously in both ears, with a gradual increase in SNR. A pop-up keyboard appeared after the three random digits were presented, the participant was then required to enter the three digits they heard.
Vivosonic ™ Integrity™ V500 (*calibrated immediately prior to data collection according to the ISO 389-6 protocol.)*	DPOAE were used to determine the functioning and integrity of the outer hair cells in the cochlea (Stach, 2010). DPOAE's were elicited by the simultaneous presentation of two primary frequency tones through a probe inserted into the ear canal. DPOAE's were measured at the F2 frequencies (F1/F2 ratio: 1.22). The two intensities at which tones were presented was set to 65 dB SPL (L1) and 55 dB SPL (L2). Each frequency recorded an amplitude at the 2F1-F2 DP frequency which is the response of the cochlea at F2 frequency (Stach, 2010).

(dB: decibel; DIN: digits-in-noise; DP: distortion product; DPOAE: distortion product otoacoustic emission; Hz: hertz; SNR: signal-to-noise ratio; SRT: speech reception threshold)

2.7 Procedure for participant selection

2.7.1 Informed consent

All participants received an informed consent form before the research procedure was conducted (Appendix D). The rationale of the study and the procedures that would be performed was explained extensively. The informed consent form explained that no identifying information is used during any stage of the research procedure and this was reiterated verbally. Once the participant understood what participation entailed,

and the procedures that would be conducted, the informed consent form (Appendix D) was signed.

2.4.2.2 HIV classification with reference to the WHO classification system of immunodeficiency

The hospital file was used to document the most recent CD4+ count and the viral load of the participant. Individuals were classified according to their CD4+ count in the levels of immunodeficiency categories according to the World health organization classification system (WHO, 2007). The CD4+ count was documented on the data collection sheet (Appendix I).

Table 3 displays the classification system of the levels of immunodeficiency according to the WHO (WHO, 2007).

Table 3: World health organisation classification system of levels of immunodeficiency (WHO, 2007)

HIV-associated immunodeficiency	Age-related CD4 value
	>5 years (absolute number per mm^3)
Not significant (0)	>500
Mild (1)	350-499
Advanced (2)	200-349
Severe (3)	<200

(HIV: human immunodeficiency virus)

2.4.2.3 First line ARV's

The participants recruited from the ARV clinic of TDH were all using first-line ARV's consisting of TDF, FTC and EFV.

2.4.2.4 Otoscopy

Otoscopy, the visual inspection of the external ear canal and tympanic membrane with an otoscope, was conducted to exclude the possibility external or middle ear pathology which can alter ABR's (Hall, 1992; Langdon & Saenz, 2016). Participants with signs

of pathology were not tested and referred to ENT. The result was documented on the data collection sheet (Appendix I).

2.4.2.5 Acoustic immittance

Acoustic immittance measures consisting of tympanometry and acoustic reflexes were conducted. Tympanometry entailed a pressure change in the ear canal via the insertion of a probe and the measurement of the movement of the tympanic membrane (Katz et al., 2009). The participant was required to have a Jerger type A tympanogram (Table 4), characterised by a middle ear pressure of -50 (decapascals) daPa to +50 daPa and compliance of 0.3 (millilitre) ml to 1.75 ml (Jerger, 1970). Acoustic ipsilateral reflexes entailed the presentation of a sound in the ear via a probe and the measurement of the stapedial muscle response. A stapedial reflex at 1000 Hz at 75 - 90 dB HL was considered normal. Jerger type A tympanograms and present stapedius reflexes suggested no middle ear pathology (Stach, 2010). Participants with a tympanogram other than type A or absent reflexes were not included as participants and referred to the ENT. The immittance results were documented on the data collection sheet (Appendix I).

Table 4 displays the Type A tympanogram parameters.

Table 4: Jerger type A tympanogram norms

Variables	Measurements
Pressure	-50 daPa - + 50 daPa
Volume	0.8 – 2.0 ml
Compliance	0.3 – 1.75 ml

(daPa: decapascals; ml: millilitre)

2.4.2.6 Pure tone audiometry

Pure tone audiometry was conducted by presenting pure tones via supra-aural headphones. The participant was required to raise their hand every time they heard the tone. The modified Hughston-Westlake method was used. Testing commenced at

a 30 dB HL intensity and was lowered in 10 dB HL increments every time the participant raised his/her hand indicating to the researcher the tone was heard. If the participant did not respond, the intensity would be raised by 5 dB HL increments. A correct response to 50% of the presented stimulus was recorded as the threshold. The left and the right ear was tested separately. Frequencies included 125- 8000 Hz, and a PTA (the sum of the thresholds of 500-, 1000- and 2000Hz divided by 3) of ≤ 25 dB HL constituted normal hearing (Stach, 2010). Participants with a PTA greater than 25 dB HL were not included in the study and were referred to the audiologist. The audiometric results were documented on the data collection sheet (Appendix I).

2.4.2.7 South-African English DIN smartphone application

This test was used to confirm SRT were within normal limits. The participant code, gender, and date of birth were entered in the application before testing commenced. The participant was asked to adjust the intensity of the narrowband noise level on the application to a level they felt was comfortable. The participant was then required to press the "Start Test" button to begin the procedure. Three random digits were presented simultaneously in both ears with a gradual increase in SNR. The participant was required to enter the three digits heard on the smartphone keyboard.

When the participant inserted the triplet-digit correctly, the next triplet was presented at a 2 dB lower SNR. When a participant entered the triplet presented incorrectly, the next triplet was presented at a 2 dB higher SNR. The SRT was calculated using the average SNR of the triplets presented to the participant.

Results were recorded in dB SNR after the test was initiated. A score of ≤ -7.50 dB SNR was considered normal. Participants with a dB SNR greater than -7.50 dB SNR were not included as participants in the study and was referred to an audiologist. The results were documented on the data collection sheet (Appendix I).

2.4.2.8 Diagnostic DPOAE’s

Diagnostic DPOAE’s were performed to assess the functionality and integrity of the cochlear outer hair cells. DPOAE measured were included in the test battery as early signs of hearing loss are evident in DPOAE when not yet evident on an individual’s

audiogram. The participant was required to sit quietly while a probe was placed in the ear canal. DPOAE measurements were conducted at the following F2 frequencies (F1/F2 ratio of 1.22): 1000, 2000, 3000, 5000 and 7000 Hz. The intensity parameters were set to 65 dB (L1) and 55 dB (L2). DPOAE measurements were considered normal when the DP-NF difference at three or more of the five frequencies was > 10 dB (van der Westhuizen et al., 2013). DPOAE measurements were considered abnormal when three or more of the five frequencies were either reduced (the DP-NF difference was 6 to 10 dB) or absent (the DP-NF difference was < 6 dB) (van der Westhuizen et al., 2013). If a participant did not pass the screening DPOAE test, they were not included as participants in the study and referred to an audiologist. The DPOAE results were documented on the data collection sheet (Appendix I).

2.5 Equipment for data collection

Table 5 displays the equipment used in the process of data collection after participants were selected according to the participant selection criteria.

Table 5: Equipment for data collection

Equipment	Description
Vivosonic™ Integrity™ V500 calibrated prior to data collection ISO 389-6 *(Calibration was done by using an oscilloscope and measured in dB pe SPL (peak equivalent Sound Pressure Level). Clicks were corrected by 35.5 dB, stimuli reported in dB nHL.)*	This equipment was used to assess the auditory nerve functioning, neural synchrony, absolute latencies, interpeak latencies and amplitudes.

(dB: decibel; dBnHL: decibel normal hearing level; dB peSPL: decibel peak equivalent sound pressure level)

2.6 Procedure for data collection

2.6.1 Neurological ABR

Once consent had been given, and participants had been selected based on the selection criteria, a neurological ABR was conducted. The neurological ABR assessed

the neural synchrony of the auditory nerve objectively and did not require active cooperation from the participant. The participant was requested to sit in a reclined position with their eyes closed, to minimise interference. The skin was cleaned prior to the placement of three pre-gelled snap-electrodes with NuPrep prepping gel. Snap electrodes were placed on the forehead (Fz) and both mastoid bones (M_1, M_2). ER-2A insert- earphones with disposable eartips were placed in both ear canals. The order in which the right and left ears were tested were randomized.

A neurological click-evoked ABR was conducted with one trace rarefaction and one trace condensation at 85 decibel normal hearing level (dBnHL) at a rate of 27.7 Hz. Stimuli were filtered 30-3000 Hz, artefact rejection level of 45 nanoVolts (nV) analysis time 15 milliseconds (ms) and sweeps 2000. Impedance values were monitored and kept below five kilo-ohms (kOhms).

The results were documented on the data collection sheet (Appendix I). Absolute latencies and amplitudes of wave I, III and V and interwave latencies of wave I-III, III-V and I-V, were marked by two independent, experienced audiologists and compared to recognised normative data (Hall, 1992).

2.6.2 Rate study

Upon completion of the neurological ABR, a rate study was conducted to assess the integrity of the auditory nerve with minimal recovery time. The same electrode placements and intensity (85 dBnHL) were used in the rate study. The rate was increased three times (31.1, 45.1 and 61.1 Hz). Two independent, experienced audiologists marked wave V. The rate study results were documented on the data collection sheet (Appendix I).

Table 6 displays the acquisition parameters for the neurological ABR and the rate study.

Table 6: Acquisition parameters for neurological ABR and rate study

Acquisition parameter	Description
Electrodes	The non-inverting electrode (Fz) was placed on the high forehead. The inverting electrode (Mi) was placed on the ipsilateral mastoid. The ground electrode (Mc) was placed on the contralateral mastoid (Hall, 1992). Electrode impedance was constantly kept below 5kΩ.
Filters (Hall, 1992)	A high pass filter of 30 Hz and a low pass filter of 3000 Hz was applied.
Analysis time (Hall, 1992)	15 ms
Sweeps (Hall, 1992)	2000

(Hz: hertz; ms: milliseconds)

Table 7 displays the stimulus parameters for the neurological ABR and the rate study.

Table 7: Stimulus parameters for neurological ABR and rate study

Stimulus parameter	Description
Type (Hall, 1992)	Click stimulus
Duration (Hall, 1992)	0.1 ms
Polarity (Hall, 1992)	Rarefaction and Condensation
Neurological ABR rate (Hall, 1992)	27.7 Hz
Rate study (Ackley et al., 2006)	31.1, 45.1 and 61.1 Hz
Intensity (Ackley et al., 2006)	85 dBnHL

(dBnHL: decibel normal hearing level; Hz: hertz; ms: milliseconds)

Normative data for healthy individuals who have normal hearing sensitivity was used to compare results (Ackley et al., 2006; Hall, 1992).

All results were documented on the data collection sheet (Appendix I).

3. Data processing procedure and analysis

All statistical analyses were calculated using the Statistical Package for the Social Science (SPSS) version 25 for Windows (Armonk, New York).

Latency and amplitude data were described using descriptive stats including the median, the standard error (SE), mean, SD, 25, 50 and 75th percentile.

The Shapiro-Wilk test for normality of distribution was statistically significant ($p<0.05$) indicating that the data was not normally distributed. The non-parametric Friedman's test of analysis of variance was therefore used to determine whether there was a statistically significant difference between the latencies of wave V at the different stimulus repetition rates value. An alpha level of 0.05 was used to indicate significance.

The diagnostic performance of the ABR and the ABR rate study was further evaluated using receiver operating characteristic (ROC) curve analysis (Metz, 1978; Zweig & Campbell, 1993). ROC curves were calculated with reference to the WHO classification of levels of immunodeficiency in established HIV-infections (WHO, 2007). Diagnostic accuracy was measured by the area under the ROC curve (AUC).

4. Reliability and validity

Reliability is the consistency and accuracy of research measures (Leedy & Ormrod, 2014). Validity is the extent to which one measures what one intends to measure (Leedy & Ormrod, 2014). The following measures ensured reliability and validity:

- The same calibrated equipment was used for all participants. Equipment was calibrated prior to data collection by the ISO 389-6 protocol.
- Participants did not have a history of TB. The inclusion of this infectious disease may have introduced a confounding variable that may influence the ABR data.
- Data was collected in a cross-sectional manner with each participant tested in a single session.
- The order in which the right and left ears were tested were randomized to avoid order-bias.
- Two independent, experienced audiologists marked the ABR waves to ensure objectivity. The simultaneous and independent marking of the ABR waves ensured objectivity and increased reliability.

- Data of the neurological ABR was compared to standardized normative data of Hall (2007).
- Two ABR recordings were obtained in succession from each ear for each stimulus rate to ensure repeatability of waveforms. In addition, waves were averaged together before recording latencies and amplitudes.

Chapter 3: Research article

ABR and rate study in normal hearing adults with HIV

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Abstract

Purpose: The current study aimed to investigate the clinical usefulness of the auditory brainstem response (ABR) and ABR rate study in adults with the human immunodeficiency virus (HIV) who presented with normal hearing sensitivity.

Method: An exploratory research design yielding quantitative data was used. ABR measures were compared to recognised normative data for healthy adults. Forty adults with HIV were enrolled in the study (57,5% female; mean age of 26.3 years SD 3.68).

Data analysis procedures included the Friedman's test of analysis of variance which was used to determine whether there was a statistically significant difference between the latencies of wave V at the different stimulus repetition rates. The diagnostic performance of the rate study was further evaluated using receiver operating characteristic (ROC) curve analysis. Accuracy was measured by the area under the ROC curve (AUC). Analysis was also completed with participants categorised into levels of immunodeficiency as defined by CD4+ counts.

Results: No difference between the normative data of healthy adults and the median absolute latencies and interwave latencies were found within this study sample. The current study showed a highly statistically significant difference between Wave V at the three stimulus repetition rates ($p<0.001$), although the median latency of wave V at each stimulus repetition rates fell within the normal limits. A fair to good diagnostic accuracy of the ABR and the ABR rate study was reported for adults who were in advanced stages of immunodeficiency (AUC = 0.700 - 0.812). For the mild and non-significant stages of immunodeficiency diagnostic accuracy was poor (AUC = 0.313 - 0.674).

Conclusions: This study suggests that the ABR rate study is of clinical value in the identification of auditory neural pathology in neurologically asymptomatic HIV positive individuals. The current study advocates for the inclusion of the ABR rate study in the audiometric test battery for adults with HIV.

Background

The human immunodeficiency virus (HIV) can cause demyelination of subcortical areas in the brain, containing auditory structures, resulting in neuropathological changes in the central nervous system (CNS) (Iacovou, Vlastarakos, Papacharalampous, Kampessis, & Nikolopoulos, 2012; Li, Li, Gao, Yuan, & Zhao, 2014). The auditory brainstem response (ABR) test is specifically useful in detecting subtle neural disorders caused by the HIV virus (Matas, Silva, et al., 2010; Santos et al., 2004; Serafini, Stagni, Chiarella, Brizi, & Simoncelli, 1998).

It is estimated that in sub-Saharan Africa 25.8 million people are living with HIV (UNAIDS, 2015). In South Africa, HIV occurs alongside joblessness and poverty and is one of the main challenges South African infectious disease health services face (Khoza-Shangase, 2010).

As many as 27.5% of patients with HIV in South Africa present with a hearing loss (van der Westhuizen et al., 2013). The hearing loss can be the direct or indirect cause of the virus (Bankaitis & Schountz, 1998). The HIV virus can affect auditory function due to its neurotropism and the suppression of the immune system. The suppression of the immune system, caused by the HIV infection, results in increased susceptibility to opportunistic diseases, and their treatments, that can cause hearing loss (Cohen et al., 2014).

Reyes-Contreras et al., (2002) described histopathological studies showing local demyelination in areas of the brainstem where auditory structures are found. The study suggests that abnormal auditory neurophysiological results are due to the demyelination in HIV positive patients even in the absence of any clinical neurological manifestations. The study identified the need to assess the integrity of the pontine and midbrain auditory pathways in HIV positive individuals (Reyes-Contreras et al., 2002). Matas et al. (2010) suggest that there is evidence of dysfunction in the synchrony of the generation and transmission of neural impulses along the auditory pathway in the brainstem of patients who are HIV positive. Even in HIV positive adults with normal behavioural hearing thresholds, 57% ABR abnormalities such as prolonged absolute latencies of wave III and V, and I-III and I-V interpeak latencies were reported (Matas, Santos Filha, et al., 2010). The abnormal findings suggest that adults with HIV are more likely to present with lower brainstem pathology, then with both lower and upper brainstem pathology, followed by upper brainstem pathology (Matas et al., 2010).

The neurological ABR is, therefore, a useful tool in the early identification of HIV related neurodegeneration of the auditory system in clinically asymptomatic individuals (Castello et al., 1998; Jalali et al., 2014; Koralnik et al., 1990; Reyes-Contreras et al., 2002). The ABR is specifically useful when using a faster stimulus repetition rate (Bankaitis, 1995). Bankaitis (1995) investigated the effect of a varying ABR stimulus rate on adults with HIV/AIDS who presented with normal pure tone results in a pilot study. A comparison of the latency of Wave V with the faster click rate (61.1 Hz) showed exaggerated prolongations in patients who were HIV positive.

The ABR rate study has also been found to be particularly sensitive to the identification of disorders resulting in demyelination (Santos et al., 2004). A study comprising of normal hearing Multiple Sclerosis (MS) participants suggested using a faster stimulus repetition rate, as part of a standard auditory test battery, significantly improved the detection of abnormal responses that are dependant on the rate increase (Jacobson, Murray, & Deppe, 1987; Santos et al., 2004). However, there is no standard auditory neural test battery for individuals with HIV in South Africa. Previous research using increased ABR stimulus repetition rate in normal hearing HIV positive individuals have been conducted by Lima and Fukuda (1999). The study made use of a very strict inclusion criteria by the Centers for Disease Control and Prevention (1986), the study only included individuals who have never shown signs of previous infections or had lower than normal immunological tests. The study concluded that using a rate of 61.1 Hz is not an efficient method of detecting subtle neurological involvement (Lima & Fukuda, 1999). However, it is not clear how this conclusion was drawn as there is no way to calculate the true percentage of prevalence of pathology in this population.

The shift in mindset from mortality to morbidity makes the goal of the healthcare professional clear. To easily and early identify hearing disorders in clinically asymptomatic individuals in order to initiate habilitation strategies to preserve the quality of life (Marin, Thiébaut, Bucher, Rondeau, Costagliola, Dorrucci, & Chêne, 2009; Peters et al., 2013). Therefore this study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

Materials and methods

The research consisted of an exploratory study yielding quantitative data conducted by the Department of Speech-Language Pathology and Audiology of the University of Pretoria.

The study was approved by the Health Science Ethics Committee under protocol number 41/2018 as well as by the Department of Humanities and departmental ethics committees. All participants provided written informed consent. Data collection took place at the Anti-retroviral (ARV) clinic of Tshwane District Hospital, a community-based hospital in Gauteng, South Africa.

Participants

A sample of 40 normal hearing HIV positive adults participated in the study (27 females). A non-probability purposive sampling technique was used in the current study. All participants were using first-line ARV's consisting of Tenofovir, Emtricitabine and Efavirenz. All participants had a lower than detectable viral load during the time of testing and a CD4+ count of more than 200 cells/µL. No participant had a history of Tuberculosis (TB) treatment. A total of 80 ears were analysed in the data analysis process. The mean age of the participants was 26.30 years standard deviation (SD 3.68, range 19 - 31). The mean CD4+ count was 559.40 cells/µL (SD 220.250, range 208 - 1200). The mean duration on ARV's was 6.68 years (SD 5.098, range 1 - 25).

Participant selection

Otoscopy was performed using a Welch Allyn otoscope to ensure no obstructions were present which could influence electrophysiological tests (Hall, 1992; Langdon & Saenz, 2016).

Pure tone audiometry and acoustic immittance measures were conducted with a GSI 29 Auto Tymp, with supra-aural headphones and a 226 Hz probe tone. Participants were required to present with Jerger Type A tympanograms (middle-ear pressure: -100 to 50 daPa; acoustic compliance: 0.3 to 1.7 ml; ear canal volume: 0.9 to 2 ml) and present ipsilateral acoustic reflex at 80 to 95 dB at 1000 Hz (Jerger, 1970; Stach, 2010).

Pure tone audiometry was conducted from 125 - 8000 Hz. A 3-tone pure tone average (PTA) (500, 1000 and 2000 Hz) was calculated. A normal PTA was classified as ≤

25dB HL (Stach, 2010). The mean PTA was 17.65 dB HL (SD 8.83). Individuals with a PTA of ≥ 25 dB HL were excluded from the study.

To further ensure normal hearing sensitivity speech reception thresholds (SRT) were recorded using the South African English Digits-in-Noise (DIN) test smartphone application was conducted on a Samsung Galaxy S6 device with calibrated earphones. (Potgieter et al., 2016). A normal SNR of ≤ -7.50 dB was required to participate in the study. The mean SNR was -9.88 dB (SD 1.27 dB).

Screening distortion product otoacoustic emissions (DPOAE) measures were conducted to eliminate the possibility of a cochlear hearing loss influencing the ABR results. DPOAE were conducted at the following F2 frequencies (F1/F2 ratio of 1.22): 1000, 2000, 3000, 5000 and 7000 Hz. The intensity parameters were 65 dB SPL (L1) and 55 dB SPL (L2). DPOAE screening was considered normal when three of the five intensities had an SNR of ≥ 10dB SPL, NF < 3 dB SPL and a DP > 3 dB SPL (van der Westhuizen et al., 2013).

Data collection

ABR measures were conducted with Vivosonic™ Integrity™ V500 system. Calibration was done by using an oscilloscope and measured in dB pe SPL (peak equivalent Sound Pressure Level). Clicks were corrected by 35.5 dB and reported in dB nHL. The skin was cleaned prior to electrode placement, and pre-gelled snap electrodes were placed on both mastoids and the high forehead (Mi-Fz single channel electrode). ER-3A insert earphones with disposable foam tips were used. Participants were reclined in a chair and asked to close their eyes to minimise interference.

A neurological click-evoked ABR was conducted with one trace rarefaction and one trace condensation at 85 dB nHL at a rate of 27.7 Hz. Stimuli were filtered using 30 to 3000 Hz, artefact rejection set at a level of 45 dB SPL, with a 15 milliseconds analysis time and a minimum of 2000 sweeps were collected per trace. Impedance values were monitored and kept below five kOhms.

Absolute latencies and interpeak latencies were measured and marked using roman numerals.

The rate study followed the neurological ABR and was measured with click-evoked rarefaction stimuli presented at 31.1; 45.1 and 61.1 Hz. Wave V latency was marked in each trace of the rate study.

Waves were marked independently by two experienced audiologists to ensure consensus and objectivity. The left and right ears were tested in a randomized order to minimise bias.

Statistical methods

Latency and amplitude data were described using descriptive statistics including the median, mean, standard deviation and the standard error (SE).

The Shapiro-Wilk test for normality of distribution was statistically significant ($p<0.05$) indicating that the data was not normally distributed. The non-parametric Friedman's test of analysis of variance was therefore used to determine whether there was a statistically significant difference between the latencies of wave V at the different stimulus repetition rate values within the participant group. An alpha level of 0.05 was used to indicate significance.

The diagnostic performance of the rate study was further evaluated using receiver operating characteristic (ROC) curve analysis (Metz, 1978; Zweig & Campbell, 1993). ROC curves were calculated with reference to the World Health Organization (WHO) classification of levels of immunodeficiency in established HIV-infections (Table 1) (WHO, 2007). The WHO classifies CD4+ counts into levels of immunodeficiency namely: Non-significant (stage 0) a CD4+ count above 500, mild (stage 1) a CD4+ count between 350 – 499, advanced (stage 2) a CD4+ count between 200 – 249 and severe (stage 3) a CD4+ count below 200. No participants were included that were in the severe stages of immunosuppression (stage 3) to eliminate the possibility of the presence of opportunistic infections interfering with ABR results. Accuracy was measured by the area under the ROC curve (AUC).

Table 1: WHO immunological classification for established HIV-infection

HIV-associated immunodeficiency	Age-related CD4 value
	>5 years (absolute number per mm^3)
Not significant (0)	>500
Mild (1)	350-499
Advanced (2)	200-349
Severe (3)	<200

All statistical analyses were calculated using the Statistical Package for the Social Science (SPSS) version 25 for Windows (Armonk, New York).

Results

Neurological ABR

Table 2 displays the median, mean, 25, 50, 75th percentile, SD and SE values of waves I, III and V. Absolute latencies were found at a median of 1.52, 3.70 and 5.59 ms for waves I, III and V respectively. Equivalent SE was found in absolute latencies (SE 0.02). The largest amplitude was found in wave V. Mean absolute latencies were of 1.53, 3.0 and 5.53 ms were found for waves I, III and V respectively. SD were found between 0.13 to 0.18.

Table 2: Median, mean, 25, 50 and 75th percentile absolute latencies (ms) and amplitude (μV) of neurological ABR.

	Latency (ms)			**Amplitude (μV)**		
	I	III	V	I	III	V
Median	1.52 (SE 0.02)	3.70 (SE 0.02)	5.59 (SE 0.02)	0.28 (SE 0.02)	0.23 (SE 0.03)	0.43 (SE 0.02)
Mean	1.53 (SD 0.13)	3.70 (SD 0.16)	5.53 (SD 0.18)	0.29 (SD 0.17)	0.26 (SD 0.23)	0.45 (SD 0.19)
25 percentile	1.46	3.60	5.37	0.16	0.15	0.32
50 percentile	1.52	3.60	5.51	0.28	0.23	0.43
75 percentile	1.58	3.81	5.59	0.39	0.33	0.59

(ms = milliseconds; SD = standard deviation; SE = standard error)

Table 3 displays the median, mean, 25, 50, 75th percentile SD and SE values of the neurological ABR. The median I-V interwave latency was measured at 4.01 ms and presented with the largest standard error (SE 0.03). The mean I-V interwave latency was measured at 4.00 ms (SD 0.20).

Table 3: Median, mean, SD, SE, 25, 50, 75th percentile interwave latencies (ms) of neurological ABR (n=80 ears).

	I-III	III-V	I-V
Median latency	2.16 (SE 0.02)	1.82 (SE 0.02)	4.01 (SE 0.03)
Mean	2.16 (SD 0.15)	1.83 (SD 0.20)	4.00 (SD 0.20)
25 percentile	2.08	1.71	3.86
50 percentile	2.14	1.80	3.96
75 percentile	2.24	1.98	4.10

(ms = milliseconds; SD = standard deviation; SE = standard error)

Table 4 displays the median, mean, 25, 50, 75th percentile SD and SE values of the neurological ABR with reference to the WHO classification of levels of immunodeficiency. The latest absolute latencies were measured at wave III and V in the advance (2) stage of immunodeficiency, along with the longest interpeak latencies of wave I-III and I-V. Interpeak latencies for wave III-V were similar for all stages of immunodeficiency.

Table 4: Median, mean, SD, SE, 25, 50 and 75th absolute and interwave latencies (ms) with reference to the WHO classification of levels of immunodeficiency.

Stage		I	III	V	I-III	III-V	I-V
0	**Median**	1.52 (SE 0.02)	3.60 (SE 0.02)	5.48 (SE 0.03)	2.14 (SE 0.02)	1.82 (SE 0.03)	3.96 (SE 0.03)
	Mean	1.53 (SD 0.13)	3.69 (SD 0.16)	5.53 (SD 0.18)	2.16 (SD 0.15)	1.84 (SD 0.20)	4.00 (SD 0.20)
	25	1.46	3.60	5.37	2.08	1.71	3.86
	50	1.52	3.60	5.51	2.14	1.80	3.96
	75	1.58	3.81	5.59	2.24	1.98	4.10
1	**Median**	1.57 (SE 0.03)	3.73 (SE 0.03)	5.58 (SE 0.03)	2.14 (SE 0.03)	1.83 (SE 0.03)	4.01 (SE 0.04)
	Mean	1.57 (SD 0.16)	3.73 (SD 0.16)	5.61 (SD 0.19)	2.16 (SD 0.17)	1.89 (SD 0.19)	4.04 (SD 0.22)
	25	1.46	3.60	5.47	2.02	1.77	3.85
	50	1.57	3.70	5.58	2.14	1.85	4.02
	75	1.69	3.82	5.79	2.31	1.99	4.18
2	**Median**	1.49 (SE 0.06)	3.92 (SE 0.10)	5.89 (SE 0.10)	2.38 (SE 0.09)	1.80 (SE 0.13)	4.25 (SE 0.13)
	Mean	1.52 (SD 0.16)	3.93 (SD 0.29)	5.78 (SD 0.29)	2.41 (SD 0.26)	1.84 (SD 0.13)	4.22 (SD 0.37)
	25	1.41	3.72	5.46	2.21	1.73	3.95
	50	1.49	3.92	5.89	2.38	1.80	4.25
	75	1.56	4.20	6.04	2.65	1.93	4.56

(ms = milliseconds; SD = standard deviation; SE = standard error)

Rate study

Table 5 displays the median, mean, 25, 50, 75th percentile, SD and SE latency of wave V at each of the different stimulus rates. Wave V increased with increased stimulus

rate. Wave V (45.1 Hz) shifted 0.09 ms from wave V (27.7 Hz), with the largest shift, namely 0.25 ms from the wave V (27.7 Hz), measured at a rate of 61.1 Hz. The shift in latency from 31.1 to 45.1 Hz was 0.1 ms, and 45.1 to 61.1 Hz was 0.16 ms.

Table 5: Median, mean, SD, SE, 25, 50 and 75th percentile latencies (ms) of wave V 31.1 Hz, 45.1 Hz and 61.1 Hz.

	V(31.1 Hz)	V(45.1 Hz)	V(61.1 Hz)
Median latency	5.58 (SE 0.03)	5.68 (SE 0.03)	5.84 (SE 0.03)
Mean	5.60 (SD 0.22)	5.71 (SD 0.24)	5.85 (SD 0.23)
25 percentile	5.45	5.53	5.61
50 percentile	5.58	5.68	5.84
75 percentile	5.71	5.89	6.10

(ms = milliseconds; SD = standard deviation; SE = standard error)

Table 6 shows the median, mean, 25, 50, 75th percentile SD and SE values of wave V at each of the different stimulus rates with reference to the WHO classification of levels of immunodeficiency. The latest absolute latencies were measured in the advanced stage of immunodeficiency while the median absolute latencies of wave V stayed the same for stage 0 and 1 of immunodeficiency. The median was measured at 6.28 ms (SE 0.14). The shift from the baseline wave V at 27.7 Hz was 0.39 ms.

Table 6: Median, mean, SE, SE, 25, 50 and 75th percentile latencies (ms) of wave V 31.1 Hz, 45.1 Hz and 61.1 Hz with reference to the WHO classification of levels of immunodeficiency.

Stage		V(31.1 Hz)	V(45.1 Hz)	V(61.1 Hz)
0	**Median**	5.58 (SE 0.04)	5.68 (SE 0.04)	5.84 (SE 0.04)
	Mean	5.60 (SD 0.22)	5.71 (SD 0.24)	5.85 (SD 0.27)
	25	5.45	5.53	5.62
	50	5.58	5.68	5.84
	75	5.71	5.89	6.10
1	**Median**	5.58 (SE 0.35)	5.68 (SE 0.04)	5.84 (SE 0.04)
	Mean	5.65 (SD 0.20)	5.74 (SD 0.25)	5.86 (SD 0.24)
	25	5.52	5.58	5.67
	50	5.58	5.68	5.82
	75	5.80	5.84	6.00
2	**Median**	6.05 (SE 0.13)	6.10 (SE 0.14)	6.28 (SE 0.14)
	Mean	5.89 (SD 0.36)	5.95 (SD 0.39)	6.11 (SD 0.39)
	25	5.56	5.56	5.72
	50	6.05	6.10	6.28
	75	6.13	6.20	6.44

(ms = milliseconds; SD = standard deviation; SE = standard error)

Friedman's two-way analysis of variance by rank yielded a highly significant difference between the wave V latencies at the three stimulus repetition rates (p<0.001). Post hoc pairwise comparisons with a Bonferroni correction for multiple comparisons was consequently performed. This indicated a highly significant difference between each of the pairwise comparisons, namely between the wave V latency 31.3 and 45.1 Hz, 31.1 and 61.1 Hz and 45.1 to 61. 1 Hz.

ROC curves

ROC curves were calculated to investigate the diagnostic accuracy of the neurodiagnostic ABR and ABR rate study. ROC's were calculated using the WHO classification system of stages of immunodeficiency.

The AUC values for discrimination of stage of immunodeficiency were poor for identification of a mild and non-significant state of immunodeficiency for all presentation rates but was fair for the advanced stage of immunodeficiency for waves III, V, I-III and I-V at 27.7 and wave V at 31.1 Hz and 61.1 Hz.

Figure 1 displays the ROC curves for absolute latencies of wave III (Figure 1a) and V (Figure 1b) at 27.7 Hz with reference to the identification of the advanced stage of

immunodeficiency. The AUC (AUC = 0.739) and *p* = 0.027 indicates that the ABR is fair for determining prolonged wave III latencies between the three stages of immunodeficiency. The AUC (AUC = 0.720) and *p*= 0.042 indicates that the ABR is fair for determining prolonged wave V latencies between the three stages of immunodeficiency.

Figure 1: Receiver operator characteristics for the neurological auditory brainstem response absolute latencies of wave III (a) and V (b) at 27.7 Hz with reference to the identification of advanced stage of immunodeficiency (n=8 ears).

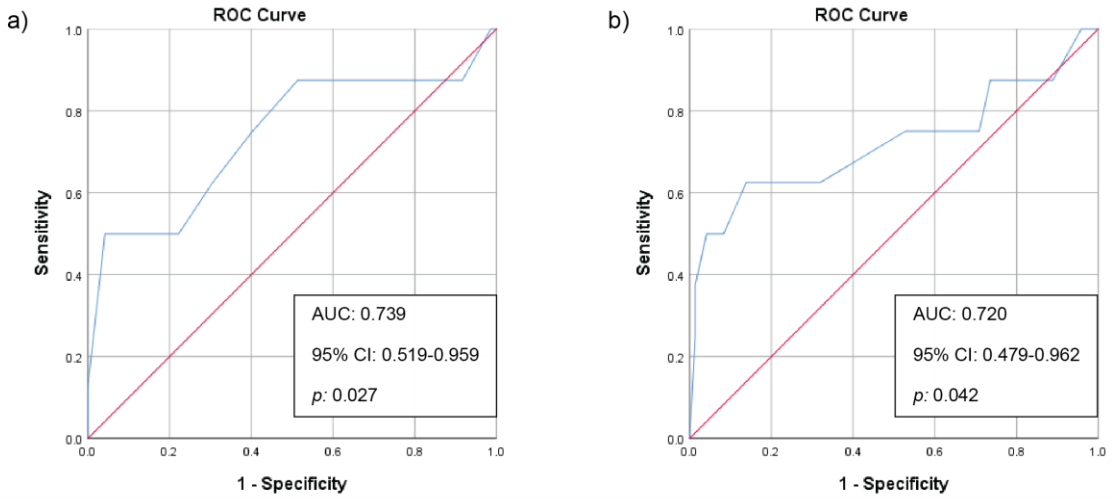


Figure 2 displays the ROC curves for interwave latencies of wave I-III (Figure 2c) and I-V (Figure 2d) at 27.7 Hz with reference to the identification of advanced stage of immunodeficiency. The AUC (AUC = 0.812) and *p* = 0.004 indicates that the ABR has good diagnostic accuracy for determining prolonged wave I-III between the three stages of immunodeficiency. The AUC (AUC = 0.701) indicates the ABR has fair diagnostic accuracy for identifying delayed wave I-V between the three stages stage of immunodeficiency.

Figure 2: Receiver operator characteristics for the neurological auditory brainstem response interwave latencies of wave I-III (c) and I-V (d) at 27.7 Hz with reference to the identification of advanced stage of immunodeficiency (n=8 ears).

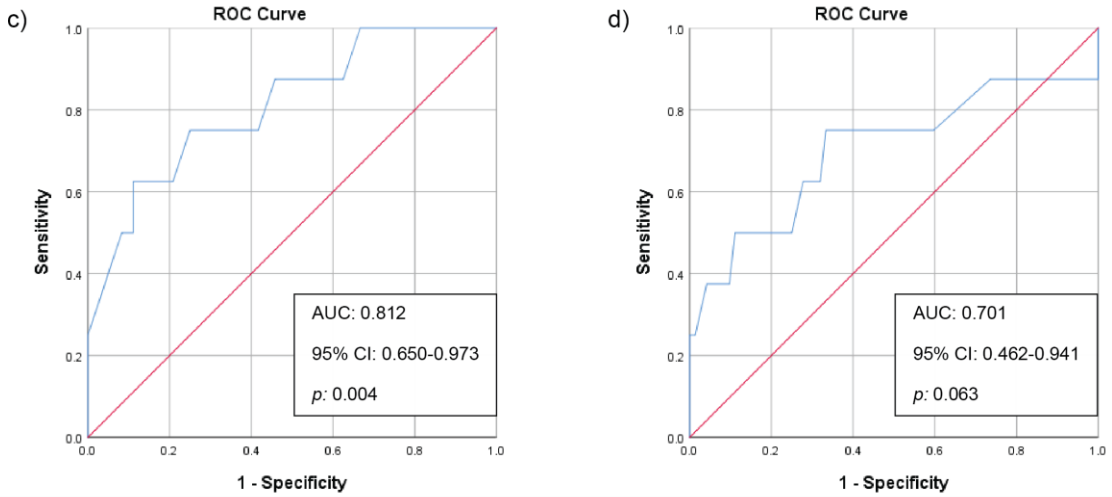
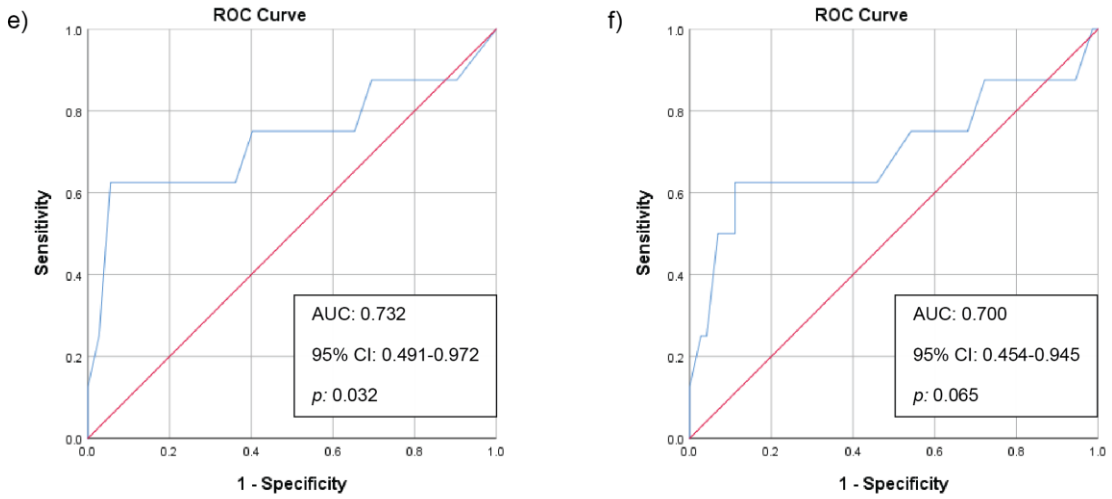


Figure 3 displays the ROC curves for the ABR rate study of Wave V (Figure 3e) at 31.1 Hz and wave V (Figure 3f) 61.1 Hz with reference to the identification of advanced stages of immunodeficiency. The AUC (AUC = 0.732 & p = 0.004; AUC = 0.700) indicates fair diagnostic accuracy for the identification of prolonged wave V latencies between the three stages of immunodeficiency. In the study sample 15% (n=6 participants) within in the advance stage of immunodeficiency showed an abnormal increase in wave V latency (> 6.25 ms) when using the 61.1 Hz stimulus repetition rate (Ackley et al., 2006).

Figure 3: Receiver operator characteristics for the rate study's absolute latencies of wave V at 31.1 Hz (e) and 61.1 Hz (f) with reference to the identification of advanced stage of immunodeficiency (n=8 ears).



Discussion

The ABR can assist in defining the extent of damage to the auditory neural tissue in the brain and monitor the speed of the evolution of the lesion caused by the HIV-virus (Matas, Silva, et al., 2010; Serafini et al., 1998). HIV is a viral demyelinating disease that can cause white matter abnormalities, and the use of ARV's can lead to the development of severe inflammatory demyelination (Love, 2006). The inclusion of faster stimulus repetition rates when using the ABR should be part of routine audiological care in demyelinating diseases, to identify increased latencies that are rate dependent (Jacobson et al., 1987; Santos et al., 2004). Therefore the present study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

The current study showed a high statistically significant difference between Wave V at the three repetition rates, despite the median latency of wave V at the three rates all falling within normal limits (Ackley et al., 2006). The current study also showed that the diagnostic accuracy of the ABR rate study was greater for adults who were at an advanced stage of immunodeficiency compared to mild and non-significant stages of immunodeficiency.

No difference was found between the median absolute latencies of normal hearing adults who are HIV positive when compared to recognised norms (Hall, 1992). The median absolute latencies of wave I (1.52 ms; SE 0.02), III (3.70 ms; SE 0.02) and V (5.59 ms; SE 0.02) were within normal limits when compared to normative data for healthy adults. The current study's results correlated with studies done by Lima & Fukuda. (1999) and Matas, Samelli, Angrisani, Magliaro, & Segurado. (2015) who compared normal hearing HIV positive adults, using ARV's, to adults who do not have HIV and found no significant difference between the two groups. This study is not in agreement with studies who found that an increased wave III and V is a common phenomenon in individuals with HIV (Bankaitis et al., 1998; Castello et al., 1998; Mata Castro, Yebra Bango, Tutor de Ureta, Villarreal Garcia-Lomas, & Garcia Lopez, 2000; Matas, Silva, et al., 2010). These studies, however, used a slower stimulus rate, participants with a hearing loss and individuals older than 30 years of age were included which could delay ABR waves, and results can therefore not be attributed to the HIV virus or the combined effect of HIV and ARV's (Hood, 1998).

Delayed wave V latencies were found in 12.5% of the study sample, indicative of possible involvement of the lateral lemniscus and the contralateral inferior colliculus (Hall, 1992). This shows that there is early neurological involvement even in the absence of clinical symptoms (Koralnik et al., 1990; Malessa et al., 1989). Delayed wave III latencies were present in 8.75% of the study sample indicative of the possible involvement of the cochlear nucleus and the superior olivary complex (Hall, 1992).

No difference between median interwave latencies of normal hearing adults who are HIV positive was found when compared to recognised norms (Hall, 1992). Normal median interwave latencies of wave I-III (2.16 ms SE 0.02), III-V (1.82 ms SE 0.02) and I-V (4.01 ms SE 0.03) were found. This correlates with studies on normal hearing HIV positive adults who reported no significant differences in interwave latencies between individuals who are HIV positive and HIV negative (Lima & Fukuda, 1999; Matas et al., 2015). In contrast to the current study, Bankaitis et al. (1998); Pierelli et al. (1996) and Reyes-Contreras et al. (2002) reported prolonged interwave latencies I-III, I-V in individuals who are HIV positive as compared to HIV negative individuals. The current study differs from this finding possibly due to the low stimulus rate, some participants presenting with a hearing loss and the inclusion of participants older than 30 years of age which could prolong interpeak latencies (Hood, 1998). The results of

these studies can therefore not be attributed to the effect of the HIV virus or the combined effect of HIV and the use of ARV's.

Prolonged wave I-III interpeak latencies were found in 25% of the study sample and 17.5% of participants presented with prolonged interpeak latencies of wave III-V. The prolonged interpeak latencies of wave I-V and III-V is indicative of possible lower brainstem involvement in individuals with HIV (Matas et al., 2015). This is an indication of early neurological involvement even in the absence of clinical symptoms (Koralnik et al., 1990; Malessa et al., 1989).

Median absolute latencies of participants were calculated with reference to the WHO classification of levels of immunodeficiency. No difference in median absolute latencies was found in stage 0 and stage 1. However, in stage 2 of immunodeficiency, the median wave V latency was measured at 5.89 ms (SE 0.10), which does not fall within normal parameters (Hall, 2007). The delayed wave V latency in HIV positive individuals who are in advanced stages of immunodeficiency is indicative of the possible pathology of the lateral lemniscus and the contralateral inferior colliculus (Hall, 1992). Studies investigating individuals with HIV also reported prolonged wave V latencies in individuals who were in advanced stages of immunodeficiency (Koralnik et al., 1990; Mata Castro et al., 2000; Pierelli et al., 1996). This demonstrates early neurological involvement, in advanced stages of immunodeficiency, even in the absence of clinical symptoms (Koralnik et al., 1990; Malessa et al., 1989).

With regard to interwave latencies, no difference was observed for stage 0 and 1 of immunodeficiency. However, in stage 2 the interwave latencies of wave I-III was measured at 2.38 ms (SE 0.09), which falls outside the normative values, as was the median interwave latencies of wave I-V (median 4.25 ms SE 0.13; Hall, 2007). An increased I-III and I-V interwave latency is indicative of possible involvement of the lower brainstem (Matas et al., 2015; Matas, Silva, et al., 2010). This finding is in contrast to that of Castello et al. (1998) who reported upper brainstem pathology in adults with HIV. In their smaller participant group, Castello et al. (1998) included 11 individuals who were severely immunocompromised with CD4+ counts below 200. No participant in the current study had a CD4+ count below 200. The presence of other opportunistic infections may have contributed to the upper brainstem prolongations reported by Castello et al. (1998).

The rate study in the present study showed a statistically significant difference between the three stimulus repetition rates. The median wave V latency of the three stimulus rates were within normal limits when compared to healthy normal hearing individuals (Ackley et al., 2006). However, 15% of the study sample showed an abnormal increase in wave V latency (> 6.25 ms) when using the 61.1 Hz stimulus repetition rate (Ackley et al., 2006). This increase in latency when increasing the stimulus repetition rate is indicative of a compromised eight cranial nerve. The minimal neural recovery time allowed by the faster stimulation rate delayed wave V in asymptomatic HIV positive individuals when the nerve was compromised (Ackley et al., 2006).

A similar percentage of HIV positive individuals in a study by Lima and Fukuda (1999) presented with abnormal latency shifts with increased stimulus repetition rates. As with the selection criteria of the current study, Lima and Fukuda (1999) excluded individuals with a hearing loss. Lima and Fukuda (1999) concluded that 61.1 Hz is not an efficient method to detect early neurological involvement in asymptomatic individuals who have HIV. However, it is not clear how this conclusion was drawn as there is no way to calculate the true percentage of prevalence of pathology in this population. The current study suggests that the rate study has increased diagnostic accuracy with an increased stage of immunodeficiency.

The significant increase in wave V latency at different stimulus repetition rates is in agreement with rate studies done in the multiple sclerosis population, which, like HIV, is a demyelinating disease (Jacobson, Murray, & Deppe, 1987; Robinson & Rudge, 1977). The study concluded that the number of abnormal ABR's (absolute latencies) increases as a function of an increased rate and that faster stimulus repetition rates should be included in the audiometric test battery in patients with demyelinating diseases.

When looking at the diagnostic accuracy of the neurodiagnostic ABR and ABR rate study, the measures were consistently more accurate in the identification of adults with HIV who were in advanced stages of immunodeficiency compared to those that were mildly and non-significantly immunodeficient. This trend was seen in absolute latency of wave III and V and interwave latency of wave I-III and I-V at 27.7 Hz. This indicates possible cochlear nucleus, olivary complex and lower brainstem pathology. This trend was seen in the rate study when looking at wave V at 31.1 and 61.1 Hz. This

demonstrates that the diagnostic value of the ABR and the ABR rate study increases with a decrease in CD4+ count. Although there is no gold standard to determine sensitivity on specific auditory neural functioning, the AUC value for diagnostic accuracy for the rate study increased with increased levels immunodeficiency amongst participants in the current study. This suggests that the rate study is capable of identifying auditory dysfunction at different stages of the disease and as the disease progresses. In addition, the inclusion of a rate study in the audiometric test battery is recommended in demyelinating diseases for the purpose of identifying subtle neural disorders (Jacobson et al., 1987). A time-efficient protocol with neurological ABR using a rate of 27.7 Hz, followed by a rate study at only 61.1 Hz may be recommended for audiological monitoring in the HIV positive population.

A limitation of the current study was that although at the time of testing all participants had a lower than detectable viral load, the researchers made use of CD4+ counts to determine the stage of immunodeficiency. CD4+ counts vary significantly among individuals, populations, sites and devices (Ying, Granich, Gupta, & Williams, 2016). CD4+ counts can be influenced by gender, time of day, body mass index, smoking and exposure to pathogens in the environment, the use of viral loads instead of CD4+ counts could provide a more clear presentation of the virus in the individual (Ying et al., 2016). Future research should include a larger study sample, control for the use of ARV's, and compare results to age and gender-matched HIV negative control group.

Conclusion

The current study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

The number of abnormal ABR's increased as a function of increased stimulus rate and level of immunodeficiency. Statistically significant differences were found between the stages of immunodeficiency and between the latency of wave V at faster stimulus rates. The diagnostic accuracy of the rate study also increased with an increased stage of immunodeficiency. This study suggests that the rate study is of clinical value in the identification of auditory neural pathology in neurologically asymptomatic adults with HIV. The current study advocates for the inclusion of the neurological ABR and ABR rate study in the audiometric test battery for adults with HIV.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Chapter 4: Discussion and conclusion

4.1 Rationale and aim

The neurological auditory brainstem response (ABR) is useful in early identifications of human immunodeficiency virus (HIV) related neurodegeneration of the auditory system in clinically asymptomatic individuals (Castello et al., 1998; Jalali et al., 2014; Koralnik et al., 1990; Reyes-Contreras et al., 2002). The ABR is specifically useful when using a faster stimulus rate in individuals who are HIV positive (Bankaitis, 1995).

The ABR rate study has been found to be particularly sensitive to the identification of disorders resulting in demyelination (Santos et al., 2004). A study comprising of normal hearing Multiple Sclerosis (MS) participants suggested using a faster stimulus repetition rate in demyelinating diseases, as part of a standard auditory test battery, significantly improved the detection of abnormal responses that are dependant on the rate increase (Jacobson et al., 1987; Santos et al., 2004). However, there is no standard auditory neural test battery for individuals with HIV in South Africa. Previous research using an increased ABR stimulus repetition rate in normal hearing adults with HIV have been conducted by Lima and Fukuda (1999). The study only included individuals who had never shown signs of previous infections or had lower than normal immunological tests. This study concluded that using a rate of 61.1 Hz is not an efficient method of detecting subtle neurological involvement (Lima & Fukuda, 1999). However, it is not clear how this conclusion was drawn as there is no gold standard method of determining the true prevalence of auditory neural pathology in this population.

The shift in mindset from mortality to morbidity makes the goal of the healthcare professional clear. To facilitate early identification of hearing disorders in clinically asymptomatic individuals in order to initiate habilitation strategies to preserve the quality of life (Marin, Thiébaut, Bucher, Rondeau, Costagliola, Dorrucci, & Chêne, 2009; Peters et al., 2013). Individuals with HIV/AIDS should be audiologically monitored for ototoxic effects hereof. Patients should be informed of the possible involvement of the auditory structures when they test positive for HIV. The effect on auditory processing should be examined further and audiologists should provide auditory processing intervention as well as hearing amplification when needed. Therefore this study aimed to investigate the clinical usefulness

of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity.

4.2 Summary of results

No difference was found between the median absolute latencies of waves I, III and V of normal hearing adults who are HIV positive when compared to recognised normative data (Hall, 1992). Delayed wave V latencies were found in 12.5% of the study sample, indicative of possible involvement of the lateral lemniscus and the contralateral inferior colliculus (Hall, 1992). The delayed wave V latency, therefore, indicates that there is early neurological involvement even in the absence of clinical symptoms (Koralnik et al., 1990; Malessa et al., 1989). In addition, delayed wave III latencies were present in 8.75% of the study sample, indicative of the possible involvement of the cochlear nucleus and the superior olivary complex (SOC) (Hall, 1992).

No differences between median interwave latencies of normal hearing adults who are HIV positive was found when compared to recognised normative data (Hall, 1992). Prolonged wave I-III interpeak latencies were however found in 25% of the study sample and 17.5% presented with prolonged interpeak III-V latencies. The prolonged interpeak latencies of waves I-V and III-V is indicative of possible lower brainstem involvement in individuals with HIV (Matas et al., 2015).

Median absolute latencies of participants were calculated with reference to the World Health Organisation (WHO) classification of levels of immunodeficiency based on CD4+ counts. No difference in median absolute latencies was found in stage 0 and stage 1. However, in stage 2 of immunodeficiency, the median wave V latency was measured at 5.89 ms (SE 0.10), which is delayed compared to normative latencies reported by Hall (2007). The delayed wave V latency in HIV positive individuals who are in advanced stages of immunodeficiency is indicative of the possible pathology of the lateral lemniscus and the contralateral inferior colliculus (Hall, 1992). This shows that there is early neurological involvement, in advanced stages of immunodeficiency, even in the absence of clinical symptoms (Koralnik et al., 1990; Malessa et al., 1989).

In the advanced stage of immunodeficiency, pathology of the lower brainstem was observed in the current study. No difference was observed for stages 0 and 1.

However, in stage 2 the interwave latencies of wave I-III fell outside the normative values as did the interwave latencies of wave I-V.

The rate study in the present study showed a statistically significant difference in latency of wave V between the three stimulus repetition rates ($p<0.05$). The median wave V latency of the three stimulus rates was within normal limits when compared to healthy normal hearing individuals (Ackley et al., 2006). However, 15% of the study sample showed an abnormal increase in wave V latency (> 6.25 ms) when using the 61.1 Hz stimulus repetition rate (Ackley et al., 2006). This increase in latency with the increased stimulus repetition rate is indicative of a compromised eighth cranial nerve. The minimal neural recovery time allowed by the faster stimulus presentation rate resulted in delayed wave V latencies in asymptomatic HIV positive individuals when the nerve is compromised (Ackley et al., 2006).

Area under the curve (AUC) values of the receiver operating characteristic curve (ROC) increased with an increase in level of immunodeficiency. Although there is no gold standard to determine sensitivity of identification of pathology of auditory neural functioning, the increased AUC values suggest increased diagnostic accuracy with greater levels immunodeficiency. In addition, abnormal findings for both the neurological ABR (specifically latency of waves III and V, and interwave latencies of I-V and III-V) and the latency of wave V with the fast stimulus rate (viz. 61.1 Hz), were more frequently reported in advanced stages of immunodeficiency. This trend serves to confirm the value of ABR and the ABR rate study in asymptomatic adults with normal hearing who are HIV positive.

This suggests that the rate study is capable of identifying auditory dysfunction at different stages of the disease and as the disease progresses. In addition, the inclusion of a rate study in the audiometric test battery is recommended for adults with HIV, as is done in other demyelinating diseases for the purpose of identifying subtle auditory neural disorders (Jacobson et al., 1987).

4.3 Clinical implication

The neurological ABR and the ABR rate study was found to be capable of identifying subtle changes in auditory neural functioning of adults with HIV. This was evident by the increase in abnormal findings in patients in more advanced stages of immunodeficiency. The diagnostic accuracy of the ABR and the ABR rate study also increased as CD4+ counts decreased. This study, therefore, supported the inclusion of the neurological ABR and an ABR rate study in the HIV positive population even when clinically asymptomatic. An increased in auditory neural pathology was measured in advanced stages of immunodeficiency, this emphasises the importance of regular audiological monitoring of not only symptomatic but asymptomatic HIV positive individuals. The AUC value for the latency of wave V during the neurological ABR and during the faster, 61.1 Hz, stimulus repetition rate was both fair with regards to diagnostic accuracy, while the AUC value for identification of abnormal wave V latency using a rate of 45.1 Hz was poor. This finding suggests that a time efficient protocol with neurological ABR using a rate of 27.7 Hz, followed by a rate study at only 61.1 Hz, may be recommended for audiological monitoring in the HIV positive population. This may possibly improve the early identification of auditory neural involvement, as well as the involvement of the higher brainstem structures involved in auditory processing.

4.4 Critical evaluation

The strengths and limitations of this study design are described below:

4.4.1 Strengths of this study

- All participants had a CD4+ count above 200 cells/mm^3 minimising the possibility of opportunistic infections being present and altering ABR results.
- None of the participants had a history of Tuberculosis (TB) minimising the possibility of the altered ABR results.
- All participants last viral load count was lower than the detectable limit, therefore indicating that the virus replications in the body is not multiplying as such during the time of testing.

- All participants had normal hearing sensitivity and cochlear functioning on the day of testing confirmed by pure tone audiometry and distortion product otoacoustic emissions (DPOAE); only normal hearing participants were included to exclude the possibility of a hearing loss altering results.
- ABR is an objective measure, and two independent audiologists marked the waves to minimise the bias effect.
- All participants were using the same first line anti-retroviral (ARV) medications. Therefore, all participants were exposed to the same therapeutic drugs.

4.4.2 Limitations of this study

- The researchers used a CD4+ classification system to group individuals – CD4+ counts vary greatly within individuals and from time of day and gender (Ying et al., 2016).
- This study used clinically available data to compare HIV ABR results due to the ethical considerations of disclosing an individual's HIV status. Therefore results were not age and gender-matched in this study.
- Participants were included regardless of the time they were using ARV's. The study population was not homogenous.
- The extraneous factors such as age of infection and the progression of the disease could not be controlled in the current study, the age and progression of the disease differ within individuals due to the complexity of the HIV virus (Kumar, 2013).

4.5 Future research

A larger-scale study involving normal hearing adults with HIV is needed to identify early neurological involvement in this ever-growing population. The HIV positive population should be further investigated using late latencies responses to investigate possible central involvement. The ARV clinic will have an amended treatment regime in 2019, the possible implication of the new treatment regime should be explored.

4.6 Conclusion

The current study aimed to investigate the clinical usefulness of the ABR and ABR rate study in adults with HIV who presented with normal hearing sensitivity. Median absolute and interpeak latencies fell within normal limits in the study sample. The diagnostic accuracy as measured by the ROC and AUC values indicates increased diagnostic accuracy with an increased level of immunodeficiency.

This suggests that the rate study is capable of identifying auditory dysfunction at different stages of the disease and as the disease progresses. The inclusion of a rate study in the audiometric test battery is therefore recommended in adults with HIV. This emphasises the need for regular audiological monitoring in HIV adults despite normal audiometric thresholds.

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Appendix A: Permission from the CEO of Tshwane District Hospital

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

Permission to access Records / Files / Data base at the Tshwane District Hospital

To: Clinical Manager
Tshwane District Hospital
Dr S Nkusi

From: Adriana Smit
The Department of Speech-Language Pathology and Audiology

Re: Permission to do research at the Tshwane District Hospital

Professor Bart Vinck, Prof Anton Stoltz, Dr Leigh Biagio de Jager and I are researchers and I am requesting permission on behalf of us all to conduct a study on the patients of the Tshwane District Hospital. I am requesting permission to conduct a study on the Tshwane District Hospital grounds that involves access to patient records.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

The title of the study is: Auditory neural function in normal hearing HIV positive adults.

The researchers request access to the following information:

Access to the clinical files, record book and the data base of HIV positive patients.

We intend to publish the findings of the study in a professional journal and/ or at professional meeting like symposia, congresses, or other meetings of such a nature.
We intend to protect the personal identity of the patients by assigning each patient a random code

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University of Pretoria, Private Bag X20
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Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely,

Adriana Smit
BA Audiology Student (University of Pretoria)

Permission to do the research study at this hospital and to access the information as requested, is hereby approved.

Clinical Manager
Tshwane District Hospital

Dr
Signature of the clinical manager

Hospital Official Stamp

Faculty of Humanities
Department of Speech-Language Pathology and Audiology
Fakulteit Geesteswetenskappe
Departement Spraak-Taalpatologie en Oudiologie
Lefapha la Bomotho
Kgoro ya Phatholotši ya Polelo-Maleme le Go kwa

Appendix B: Ethical clearance from Health Sciences

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

12/02/2018

Approval Certificate
New Application

Ethics Reference No: 41/2018

Title: Auditory neural function of normal hearing HIV positive adults

Dear Miss Adriana Smit

The **New Application** as supported by documents specified in your cover letter dated 16/01/2018 for your research received on the 18/01/2018, was approved by the Faculty of Health Sciences Research Ethics Committee on its chairs meeting of 12/02/2018.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**41/2018**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research

Yours sincerely

Dr R Sommers; MBChB MMed (Int) MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Good Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

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Appendix C: Ethical clearance from the faculty of Humanities

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Ethics Committee

5 March 2018

Dear Ms Smit

Project:	**Auditory neural function in normal hearing HIV positive adults**
Researcher:	**A Smit**
Supervisors:	**Prof B Vinck, Prof A Stoltz and Dr L Biagio de Jager**
Department:	**Speech-Language Pathology and Audiology**
Reference number:	**14036275 (GW20180204IHS)**

Thank you for the application that was submitted for ethical consideration.

I am pleased to inform you that the above application was **approved** by the **Research Ethics Committee** at the meeting held on 1 March 2018. Data collection may therefore commence.

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the proposal. Should the actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely

Prof Maxi Schoeman
Deputy Dean: Postgraduate Studies and Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail:tracey.andrew@up.ac.za

cc: Prof J van der Linder (Acting-HoD)
Dr L Biagio de Jager (Supervisor)
Prof B Vinck (Co-supervisor)
Prof A Stoltz (Co-supervisor)

Appendix D: Informed consent – Tshwane District Hospital: ARV clinic

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech-Language Pathology and Audiology

INFORMATION LEAFLET AND INFORMED CONSENT FOR HIV POSITIVE PARTICPANTS

AUDITORY NEURAL FUNCTION IN NORMAL HEARING HIV POSITIVE ADULTS

January 2018

Dear Participant,

1) INTRODUCTION

You are invited to volunteer for a research study that I am conducting for a Masters degree in Audiology at the Department of Speech-Language Pathology and Audiology, Faculty of Humanities, University of Pretoria. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask me Adriana Smit at 0786604146. You should not agree to take part unless you are completely happy about all the procedures involved.

2) THE NATURE AND PURPOSE OF THE STUDY

The main aim of my study is to describe the auditory neural function in normal hearing HIV positive patients. The results will be compared to recognised norms.

3) EXPLANATION OF PROCEDURES TO BE FOLLOWED

You will undergo a single assessment that will last for one hour at the ARV Clinic of Tshwane District Hospital. I will collect clinical information from your hospital file and the following procedures will be included in the assessment: Auditory tests and electrophysiological tests.

Summary of the tests that will be used in this research study:

Assessment category	Test	Expected from participant
Auditory Tests	Otoscopy	Inspection of the ear canal and eardrum with a otoscope, while you are seated upright.
	Acoustic Immittance Measurements	You will not have to respond in any way, a soft probe will be inserted into the ear canal while you are seated upright.
	Pure tone Audiometry	You will be required to press a button when a beep sound is heard trough earphones.

	DIN -test	You will be required to listen to 4 digits played through earphones and enter the digits on the phone provided
	Oto-accustic emissions	You will not be required to respond in any way. A probe will be inserted into your ear and sounds will be presented.
Electrophysiological tests	Neurological ABR	You will be required to lie down with your eyes closed. 3 Electrodes will be placed on your head (2 on forehead and 1 behind the ear). Probes will be placed in both ears. Clicking noises will be presented to you. You are not required to respond in any way.

4) RISK AND DISCOMFORT INVOLVED

There are no risks involved in participating in the study.

5) POSSIBLE BENEFITS OF THIS STUDY

There will be no direct benefit to the participants. If a hearing problem is identified, you will be referred to the Department of Speech-Language Pathology and Audiology for further investigation.

6) WHAT ARE YOUR RIGHTS AS A PARTICIPANT

Your participation in this research study is voluntary. You can withdraw from the study at any time; data already collected will be excluded from the study. This will not affect your treatment at the ARV Clinic of Tshwane District Hospital.

7) HAS THIS STUDY RECEIVED ETHICAL APPROVAL

This study has received written approval from the Research Ethics Committee of the Faculty of Humanities and the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria. The contact details for the Faculty of Health Sciences at the University of Pretoria: Me Manda Smith: 012 356 3085.

8) INFORMATION AND CONTACT PERSON

The contact person for this study is Ms Adriana Smit. If you have any questions about the study feel free to contact me at 078 660 4146 or at riana.smit.3@gmail.com. Alternatively you can contact my supervisor, Dr Leigh Biagio de Jager at leigh.biagio@up.ac.za or my co-supervisors Prof Bart Vinck at bart.vinck@up.ac.za or Prof Anton Stoltz at anton.stoltz@up.ac.za.

9) COMPENSATION

You will not be paid for participating in the study; no extra costs are expected to be concurred by you.

10) CONFIDENTIALITY AND ANONYMITY

Personal information and the results of the tests from participants will be kept strictly confidential. A numeric code will be allocated to each participant; this code will only be known to the researchers and supervisors. Results will be anonymously used in an article.
All the results will be stored safely for a period of 15 years, as per university policy, this data may be used for future research.

11) CONSENT TO PARTICIPATE IN THIS STUDY

I have read this information document and I understand the above information. I hereby agree to participate in the above mentioned research project. I have read the above information and understand what is required of me in this research study. I acknowledge that my results may be used anonymously for research purposes. I am aware that I participate voluntarily and that I may withdraw from the research study at any time.
I have received a signed copy of this informed consent agreement.

..... Participant name	..... Date
..... Participant signature	..... Date
..... Investigator's name	..... Date
..... Investigator's signature	..... Date
..... Witness name and signature	..... Date

VERBAL INFORMED CONSENT

I, the undersigned, have read and explained fully to the participant the information leaflet, which explains the nature, process, risks, discomforts and benefits of the study, in which I have asked the participant to participate in.

The participant acknowledges that the results may be used anonymously for research purposes. The participant indicates that she/he understand what is expected of them. She/he understands that there is no penalty should she/he wish to withdraw from the study. This withdrawal will have no effect on his/her medical treatment in any way. I hereby certify that the participant has agreed to participate in this study.

Participant's Name _____
(Please print)

Person seeking consent _____
(Please print)

Signature _____ Date _____

Witness's name _____
(Please print)

Signature _____ Date _____

Appendix E: Plagiarism declaration

DECLARATION OF ORIGINALITY UNIVERSITY OF PRETORIA

The Department of Speech-Language Pathology and Audiology places great emphasis upon integrity and ethical conduct in the preparation of all written work submitted for academic evaluation.

While academic staff teach you about referencing techniques and how to avoid plagiarism, you too have a responsibility in this regard. If you are at any stage uncertain as to what is required, you should speak to your lecturer before any written work is submitted.

You are guilty of plagiarism if you copy something from another author's work (e.g. a book, an article or a website) without acknowledging the source and pass it off as your own. In effect, you are stealing something that belongs to someone else. This is not only the case when you copy work word-for-word (verbatim), but also when you submit someone else's work in a slightly altered form (paraphrase) or use a line of argument without acknowledging it. You are not allowed to use work previously produced by another student. You are also not allowed to let anybody copy your work with the intention of passing if off as his/her work.

Students who commit plagiarism will not be given any credit for plagiarised work. The matter may also be referred to the Disciplinary Committee (Students) for a ruling. Plagiarism is regarded as a serious contravention of the University's rules and can lead to expulsion from the University.

The declaration which follows must accompany all written work submitted while you are a student of the Department of Speech-Language Pathology and Audiology. No written work will be accepted unless the declaration has been completed and attached.

Full names of student: Adriana Smit

Student number: 14036275

Topic of work: ABR and rate study in normal hearing adults with HIV.

Declaration

1. I understand what plagiarism is and am aware of the University's policy in this regard. 2. I declare that this thesis (e.g. essay, report, project, assignment, dissertation, thesis, etc.) is my own original work. Where other people's work has been used (either from a printed source, Internet or any other source), this has been properly acknowledged and referenced in accordance with departmental requirements.

3. I have not used work previously produced by another student or any other person to hand in as my own.

4. I have not allowed, and will not allow, anyone, to copy my work with the intention of passing it off as his or her own work.

SIGNATURE

Date: 15/01/2018

Appendix F: Data storage

Principal Investigator's Declaration for the storage of research data and/or documents

I, the Principal Investigator(s), Adriana Smit of the following trial/study titled ABR and rate study in normal hearing adults with HIV will be storing all the research data and/or documents referring to the above-mentioned trial/study at the following non-residential address:

Department of Speech-Language Pathology and Audiology,

University of Pretoria

Pretoria

South Africa

I understand that the storage for the abovementioned data and/or documents must be maintained for a minimum of 15 years from the end of this trial/study.

START DATE OF TRIAL/STUDY: 01/01/2018

END DATE OF TRIAL/STUDY: 01/01/ 2019

SPECIFIC PERIOD OF DATA STORAGE AMOUNTING TO NO LESS THAN 15 YEARS:

02/01/2019 until 02/01/2034

Name: Adriana Smit (14036275)

Signature  **Date** 15/02/2018

Appendix G: Referral letter – Tshwane District Hospital

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech Language Pathology and Audiology

Research Participant Referral Letter

Date: ___/___/___

DOB: ___/___/___

To: _____

_____ participated in a research study titled **Auditory neural function in normal hearing HIV positive adults**, on ___/___/___ at the ARV Clinic at Tshwane District Hospital. The following tests were performed:

- Otoscopy
- Acoustic Immitance
- Behavioural pure tone audiometry
- Digits-in-Noise
- DPOAE's
- Neurological ABR

Results and recommendations:_____

Thank you for your participation in this research project. Should you require any further information please contact Adriana Smit at 0786604146.
Kind regards

_____
Adriana Smit
Researcher

Appendix H: Pass letter – Tshwane District Hospital

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech Language Pathology and Audiology

Research Participant Pass Letter

Date: ___/___/___

DOB: ___/___/___

To: _____

Thank you for participating in the research study titled, **Auditory neural function of normal hearing HIV positive adults** on ___/___/___ at the ARV Clinic at Tshwane District Hospital.

The following tests were conducted:

- Otoscopy
- Acoustic Immitance
- Behavioural pure tone audiometry
- Digits-in-Noise
- DPOAE's
- Neurological ABR

The results indicated that you present with normal peripheral hearing sensitivity. It is recommended that you test your hearing annually.

Thank you for your participation in this research project. Should you require any further information please contact Riana Smit at 0786604146.
Kind regards

_____
Adriana Smit
Researcher

Appendix I: Data collection sheet

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Department of Speech Language Pathology and Audiology

Auditory neural function of normal hearing HIV positive adults

Data collection sheet
Adriana Smit

Date of test: _____ Date of birth: _____

Participation code: _____ Age: _____

Cellphone number: _____ Gender: M F

CD4+ count: _____

HAART: _____ Co-morbid diseases: _____

Acoustic Immittance

Right		Left
	Tympanogram	
	Middle Ear Pressure	
	Static Compliance	
	Ear Canal Volume	

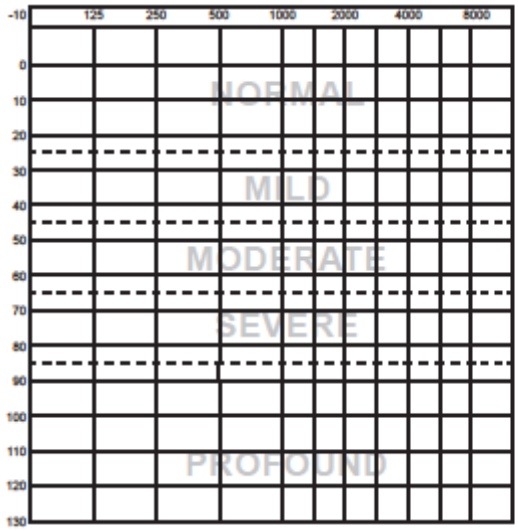
Otoscopic examination	
Right	Left

Acoustic Reflex

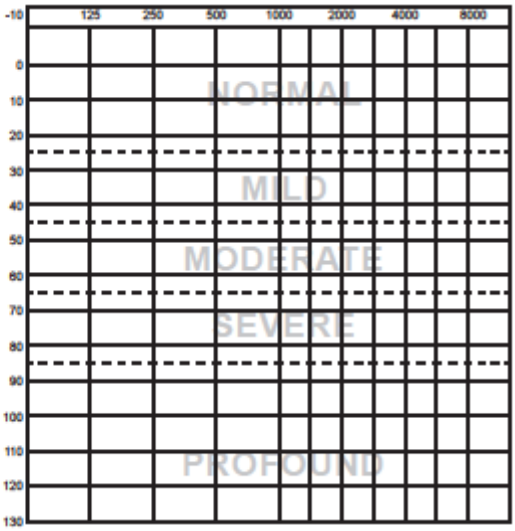
Reflex Threshold		Frequency	Reflex Threshold	
R Contra	R Ipsi		L Contra	L Ipsi
		250 Hz		
		500 Hz		
		1 kHz		
		2 khz		
		4 kHz		

Pure Tone Audiogram

Right Ear



Left Ear



Masking

LG/AC							
BG/BC							

Masking

LG/AC							
BG/BC							

PTA: _____

PTA: _____

Transducer:

Insert earphones
Earphones
Free field

Test reliability:

Good	Average	Poor

Digits in noise: _____

DPOAE

Right Ear

Present ☐
Absent ☐

Left Ear

Present ☐
Absent ☐

Neurological ABR

Right Ear	Normal	Abnormal	Left Ear	Normal	Abnormal
Wave I _____	☐	☐	Wave I _____	☐	☐
Wave III _____	☐	☐	Wave III _____	☐	☐
Wave V _____	☐	☐	Wave V _____	☐	☐

Rate study:

	Right Ear	Left Ear
31,1/sec		
45,1/sec		
61,1/sec		

Appendix J: Proof of submission to journal

The American Journal of Audiology

Home

Author

Review

Submission Confirmation

Print

Thank you for your submission

Submitted to
The American Journal of Audiology

Manuscript ID
AJA--18-0175

Title
ABR and rate study in normal hearing adults with HIV

Authors
Smit, Adriana
Biagio de Jager, Leigh
Stoltz, Anton

Date Submitted
12-Nov-2018

Author Dashboard