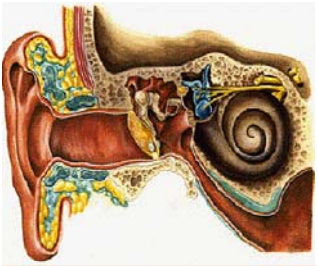

AN INVESTIGATION AND MONITORING OF THE AUDITORY STATUS IN A GROUP OF ADULTS WITH AIDS RECEIVING ANTI-RETROVIRAL AND OTHER THERAPIES ATTENDING A PROVINCIAL HOSPITAL HIV/AIDS CLINIC IN JOHANNESBURG, SOUTH AFRICA

KATIJAH KHOZA

A research thesis submitted for the degree of Doctor of Philosophy in Audiology in the Faculty of Humanities, The University of the Witwatersrand

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To my beautiful precious family, Mandla and Owethu Shangase, and my constant inspiration in life - Kayem. Three fingers to the moon …always… and back again. Shuku!

DECLARATION

I, Katijah Khoza, hereby declare that this submission is my own original work and that the assistance which I have received is detailed in the Acknowledgements of this report. To the best of my knowledge and belief, it contains no material which has been accepted for the award of any other degree or diploma at any other university or other institute of higher learning, except where due acknowledgement has been made in the text. I am responsible for the study and conclusions reached.

_____ _____

KATIJAH KHOZA Date

SCIENTIFIC CONFERENCES AND PUBLICATIONS WHICH EMANATED FROM THIS STUDY

Parts of this thesis have already been presented at scientific conferences and published in the scientific literature as:

Khoza, K. & Mlangeni, N.P. (2008). Ototoxicity in South Africa: Are we there yet? ***Article submitted to The International Journal of Tuberculosis and Lung Disease*** (awaiting reviews)

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ARC	AIDS-related conditions or complex
ART	Antiretroviral Therapy
ARVs	Antiretroviral drugs
ASSA	Actuarial Society of South Africa
AZT	Azidothymidine
CAM	Complimentary/alternative medicine
CD4+	"Cluster Designation 4" T-helper cells
CHL	Conductive hearing loss
CIOMS	Council for International Organizations of Medical Sciences
CMV	Cytomegalovirus
CNS	Central nervous system
CTL	cytotoxic T lymphocytes
dB SPL	decibel sound pressure level
DOH	Department of Health
DPL/R	Distortion product left/right ear
CDC	Centres for Disease Control
ddC	zalcitabine
ddI	didanosine
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DP	Distortion Product
DPOAEs	Distortion Product Otoacoustic Emissions
EBV	Epstein-Barr virus
ELAS	Extended Lymphadenopathy Syndrome
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GLNS	Gay Lymph Node Syndrome
GPL	Generalised Persistent Lymphadenopathy syndrome
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNT	Head and neck tumours
HPV	Human papilloma virus
HR	Human resource
HSRC	Human Sciences Research Council
ICD	International Classification of Diseases
ILS	Idiopathic Lymphadenopathy Syndrome
JCSMF	Joint Civil Society Monitoring Forum
kHz	kilohertz
KSHV	Kaposi's sarcoma-associated herpes virus
L	left
LTNP	Long term non-progressors
MAC	Mycobacterium avium complex
MANOVA	Multivariate Analysis of Variance

MHL	Mixed hearing loss
MOD	Moderate
MRC	Medical Research Council
NACOSA	National AIDS Coordinating Committee of South Africa
NF	Noise floor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NSP	National Strategic Plan
UNAIDS	United Nations AIDS program
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
OAEs	Otoacoustic Emissions
OIs	Opportunistic Infections
OTC	Over the counter
PCP	Pneumocystis carinii Pneumonia
PEP	Post-exposure prophylaxis
PGL	Persistent Generalised Lymphadenopathy
PI	Protease Inhibitor
PML	Progressive multifocal leukoencephalopathy
PMTCT	Prevention of Mother to Child Transmission
PROF	Profound
PTA	Pure tone audiometry
PTL/R	Pure tone left/right ear
R	right
RNA	Ribonucleic acid
RT	Reverse transcriptase
SD	Standard deviation
SEV	Severe
SFOAEs	Stimulus Frequency Otoacoustic emissions
SIL	Squamous Intraepithelial Lesion
S/N	signal to noise ratio
SNHL	Sensorineural Hearing Loss
SOAEs	Spontaneous Otoacoustic emissions
STI	Sexually Transmitted Infection
TAC	Treatment Action Campaign
TB	Tuberculosis
TEOAEs	Transient Evoked Otoacoustic emissions
TM	Tympanic membrane
UHF	Ultrahigh frequency
USPHS/IDSA	U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA)
VCT	Voluntary Counselling and HIV Testing
WHO	World Health Organisation
ZVD	Zidovudine

LIST OF APPENDICES

Appendix A: Letter requesting permission to conduct the study at Johannesburg Hospital

Appendix B: Letter of permission from Johannesburg Hospital Superintendent

Appendix C: Letter of permission from Johannesburg Hospital HIV/AIDS Clinic

Appendix D: Letter of permission from Johannesburg Hospital Audiology Clinic

Appendix E: Medical Ethics Committee Clearance Certificate

Appendix F: Letter of full candidature for the degree of Doctor Philosophy in Audiology

Appendix G: Information and Consent form

Appendix H: Case History Form on Hearing and HIV/AIDS

Appendix I: Monitoring Data collection form

Appendix J: Summary of all results per participant

DEFINITION OF TERMS: GLOSSARY

Acquired: not inherited in the genes from one's parents, but from the environment.

Acute HIV syndrome: short, flue-like illness at the time of seroconversion, when antibodies develop.

AIDS: AIDS is the acronym for 'Acquired Immunodeficiency Syndrome' and was a term coined early on in the history of the disease. It is an epidemic disease caused by an infection by human immunodeficiency virus (HIV), a retrovirus that causes immune system failure and debilitation. Because the body loses the ability to fight against infections because the immune system is weakened by HIV, this disease is often accompanied by infections such as tuberculosis. AIDS is, by definition, the end-stage disease manifestation of the infection with HIV. AIDS is caused by HIV – it is not congenital or inherited but acquired.

Antiretroviral drugs: drugs that fight retroviruses such as HIV/AIDS.

Antiretroviral therapy: use of antiretroviral drugs for the treatment of infection by retroviruses, primarily HIV. Different classes of antiretroviral drugs act at different stages of the HIV life cycle. Combination of several (typically three or four) antiretroviral drugs is known as *Highly Active Anti-Retroviral Therapy* (*HAART)*

Asymptomatic: infected by a disease agent but with no symptoms of disease, subclinical.

Clinical: Pertaining to or founded on actual observation and treatment of patients, as distinguished from theoretical or basis sciences. In the current study, clinical referred to observable and measurable audiological changes – hearing changes observable on audiogram.

Control group: a group of subjects participating in the same experiment as another group of subjects, but which is not exposed to the variable under investigation. In the current study, that variable was the antiretroviral therapy.

Epidemic: an unusual marked increase in cases in a fairly short period of time.

Experimental group: a group of subjects exposed to the variable of an experiment, as opposed to the control group. In the current study, these are the participants that were taking antiretroviral drugs.

HIV: Human immunodeficiency virus is a retrovirus that causes AIDS by primarily infecting vital components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It also directly and indirectly destroys CD4+ T cells. As CD4+ T cells are required for the proper functioning of the immune system, when enough CD4+ T cells have been destroyed by HIV, the immune system functions poorly, leading to the syndrome known as AIDS. HIV belongs to a subgroup of retroviruses called *lentiviruses* (meaning *slow viruses* since they often cause disease extremely slowly) (Hung, Ross & Luis, 2000). Two strains have been identified:

Type 1: the retrovirus recognized as the agent that induces AIDS; and

Type 2: a virus closely related to HIV-1 that also leads to immune suppression. HIV-2 is not as virulent as HIV-1 and is endemic only in West Africa.

Incidence: new cases of infection in a population within a fixed period (usually a year) or the rate, range or amount of occurrence or influence.

Ototoxicity: may be defined as a tendency for certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner

ear and especially of the end organs and neurons of the cochlea and vestibular divisions of the eighth cranial nerve.

Opportunistic infection: an illness caused by an organism that usually does not cause disease in a person with a normal immune system. People with advanced HIV infection suffer opportunistic infections of the lungs, brain, eyes, and other organs.

Pandemic: a global or very widespread epidemic.

Prevalence: the level of existing infection in a population at one point in time, regardless of when the infection occurred or the proportion of individuals in a population having a disease. In the current study, the disease refers to auditory symptoms.

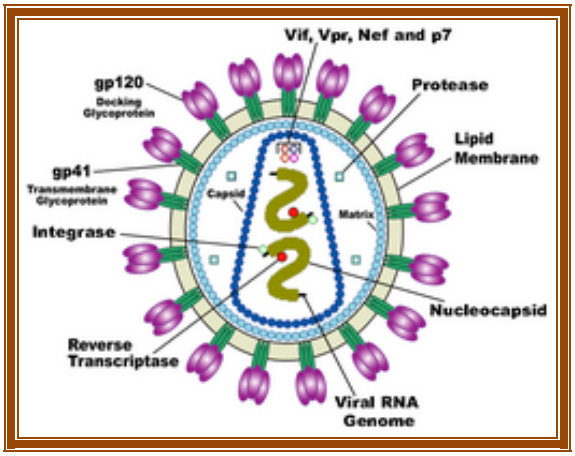
Session 1 of testing: audiological testing before ART (baseline)

Session 2 of testing: audiological testing at 3 months into ART

Session 3 of testing: audiological testing at 6 months into ART

Subclinical: Without clinical manifestations, said of the early stage of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests or of a very mild form of an infection or other disease or abnormality. In the current study, subclinical referred to microcochlea pathology which has not manifested clinically by observable and measurable audiological symptoms on audiogram, asymptomatic.

Diagram of HIV: Retrieved from http://en.wikipedia.org/wiki/HIV. Accessed May 05, 2008



ABSTRACT

Purpose: The main objective of the current study was to investigate and monitor the auditory status in a group of adult patients with AIDS receiving antiretroviral therapy (ART) and other therapies in a hospital outpatient clinic in Gauteng, South Africa. Specific objectives included estimating the prevalence of hearing loss and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth); assessing the type, degree and configuration of the hearing loss; exploring the type of hearing symptom onset; documenting case history data such as signs and symptoms of each participant and identifying any associations between obtained signs and symptoms and hearing loss; documenting the names of all medications used and their possible impact on hearing function (specifically ototoxicity monitoring of ART); and comparing the results of the experimental group to those of a control group.

Participants: A total of 150 participants (104 in the experimental group, and 46 in the control group), including both males and females, comprised the research sample at baseline testing (before ART). Because of the repeated measures design nature of the study and the nature of the disease, some participants did not attend all 3 sessions of testing for various reasons. Furthermore, the variance in the ARV regimen that the participants were taking led to a further reduction in the experimental group's sample size for the monitoring phase of the study where only participants on regimen 1 were included. All participants' data were analysed for the descriptive analysis phase of the study, however not all participants' data were included in the (inferential statistics) monitoring phase of analysis. This had an influence on the total number of participants at each stage of the analysis. Hence, a total sample of 54 participants in the

experimental group and 16 participants in the control group was analysed statistically for the repeated measures analysis phase of the study.

Design: The design used was a prospective quasi-experimental repeated measures design with a control group where participants in the experimental group were assessed at baseline (i.e. before initiation of ART), three months into the treatment, and again at six months into the treatment. The same protocol design was followed for the control group; however these participants were not taking ART.

Methods and Materials: Participants underwent case history interviews and medical record reviews, otoscopy and tympanometry, as well as conventional pure tone audiometry and distortion product otoacoustic emission testing.

Data analysis: both descriptive and inferential statistics were used to analyze data from the study. Inferential statistics in the form of repeated measures ANOVA, MANOVA, and Tukey-Kramer post-test were used to establish statistical significance levels, and to determine when the statistically significant changes occurred within the longitudinal design of the study. Furthermore, clinical significance of the findings was also analyzed.

Results: Hearing loss with tinnitus and dizziness in various combinations was established in both the treatment (experimental) and non-treatment (control) group - with a prevalence rate that increased from 10% to 28% after 6 months of monitoring, and this rate was significantly higher than that of the general South African population (which is 20%). A significantly higher percentage of sensorineural hearing loss (SNHL) (90% of clinical hearing loss) was found in both the control and experimental groups with the degree of hearing loss tending to be more severe in the control group when compared to that in the experimental group. A tendency for sloping/high frequency configuration was observed in the experimental group with the control

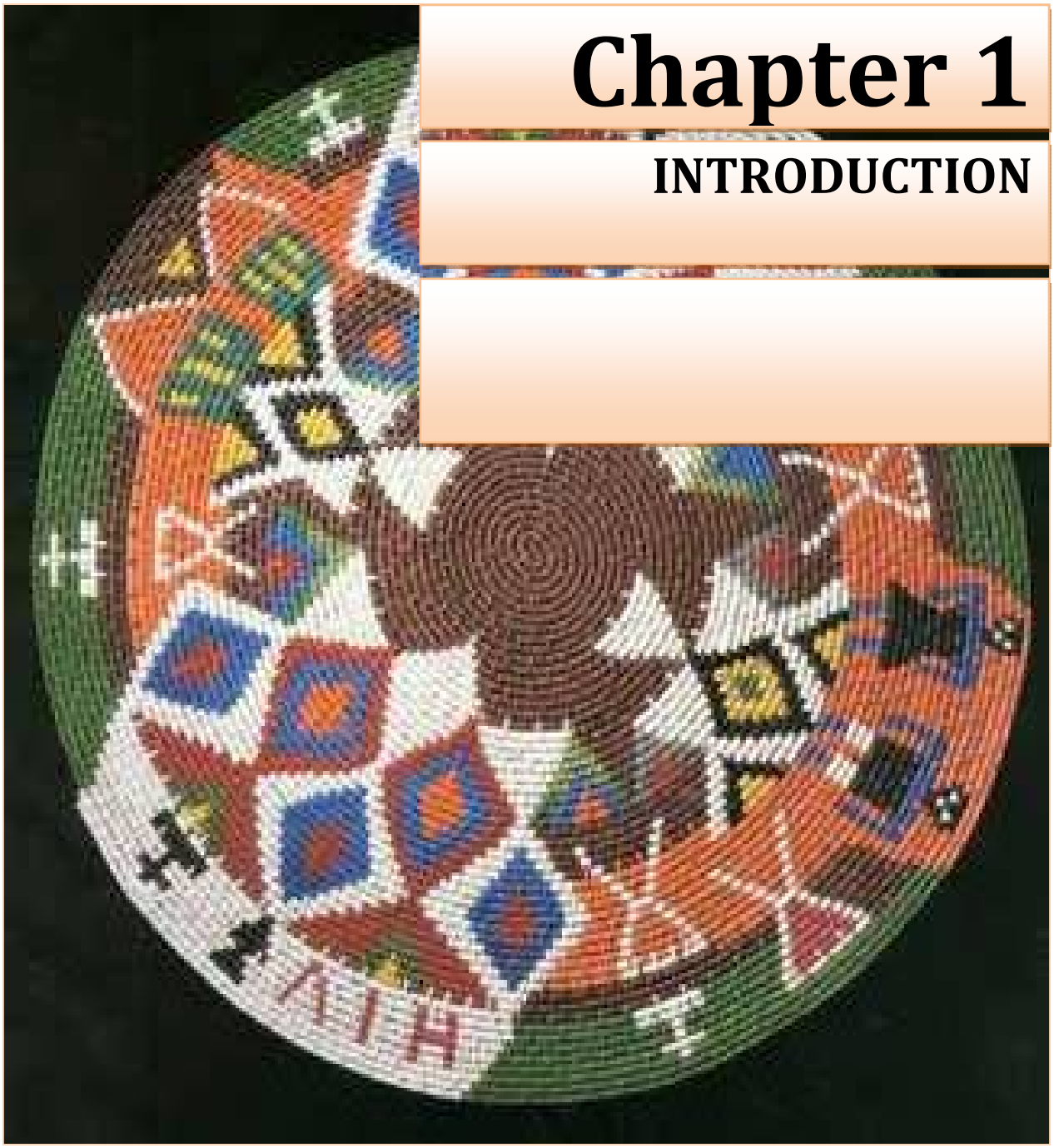
group exhibiting no distinctive pattern of the audiogram configuration. Eighty percent of clinical hearing loss in the control group had a flat/irregular configuration, while 47% of clinical hearing loss in experimental group had a distinctive sloping/high frequency configuration. The sensorineural and high frequency nature of the hearing loss in the experimental group seemed to be consistent with features typical of ototoxic hearing loss. The symmetry of hearing loss was mainly bilateral in both groups with more than 60% of participants with clinical hearing loss presenting with bilateral hearing loss. The type of onset of hearing loss was gradual/progressive for all participants in both the control and experimental groups. The possible causes of hearing loss seemed to be similar in the experimental and control groups with opportunistic infections (meningitis, otosyphilis, otitis media) contributing significantly, even in the experimental group where ARVs were being used. However, another significant possible cause of hearing loss in the experimental group was that of ARVs (in the form of 3TC, D4T and Stocrin) (41% of participants with clinical hearing loss) – although this could not be confirmed because of unidentified interactions with other treatments, and/or other factors. However, the fact that the control group was also exposed to similar interactions raises an index of suspicion about the possible effects of ARVs on hearing function. ARVs used in the current study appeared to have an ototoxic potential that was possibly exacerbated to clinical hearing loss by the presence of risk factors that were thought to contribute to the changes depicted on audiograms. These risk factors included previous use of ototoxic medications such as history of previous TB treatment (31% of participants), previous use of ARVs (6% of participants), and noise exposure at the same time as ARV use.

On audiological monitoring, statistically significant changes were established only in the experimental group for pure tone audiometry – with clinically significant changes in the high frequencies. Moreover, statistically significant changes with clinically significant changes were obtained for DPOAEs in the experimental group, particularly at the high frequencies – implying possible sub-clinical hearing function changes (cochlea function changes detected before the hearing loss is seen on an audiogram), while lack of statistically significant changes with no clinically significant changes were found in the control group. This possibility of subclinical hearing changes in the experimental group was also evident in findings of the subclinical hearing loss group who, although had normal pure tone function after 6 months of follow up, presented with clinical changes on DPOAEs at 6 and 8kHz.

Conclusion: Auditory manifestations in AIDS are complex and are influenced by a variety of factors that audiologists need to be aware of. Results of the current study highlight the crucial need for audiologists to be involved not only in the assessment and management of patients with HIV/AIDS, but perhaps also in the drug development and monitoring process. This involvement can only be appropriate if it is evidence-based, highlighting the need for more intensive research in this field.

Key words: Otoacoustic emissions, HIV/AIDS, antiretroviral drugs, distortion products, ototoxicity, ubhejane, monitoring, adults, South Africa

PART I – PROLOGUE



Chapter 1

INTRODUCTION

The renowned 20th century clinician Sir William Osler (1950, cited in Zapor, Cozza, Wynn, Wortmann & Scott, 2004) once remarked, "*Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you*" The same aphorism might aptly be applied today to HIV/AIDS infection.

CHAPTER ONE

INTRODUCTION

In its third decade, the acquired immune deficiency syndrome (AIDS) pandemic and the Human Immunodeficiency Virus (HIV) that causes it, continues to be one of the biggest challenges faced by South Africa today (Posel, Kahn & Walker, 2007). This is alongside poverty, joblessness and other social ills that the Departments of Health (DOH) and Social Development are trying hard to eradicate (Posel, Kahn & Walker, 2007). In view of the fact that HIV/AIDS spread so rapidly and so extensively in South Africa, it is no longer termed an epidemic, but rather a pandemic (Posel et al., 2007). This pandemic seems to have arguably created more challenges to science and medicine than any other single disease. The virus has taken an enormous toll in human suffering and has had a staggering socioeconomic impact on health care in this country and throughout the world, with possibly more significant challenges in third world countries than in developed countries. Swanepoel (2006) asserts that the virus has also created an overwhelming burden and a unique challenge to audiological service delivery in South Africa.

In this country, the first few cases of HIV and AIDS were identified in the late 1980s (Department Of Health South Africa – DOH, 2006a; Van Dyk, 2001) – considerably later than in the United States. Significant progress has been made in the past two decades in learning about the onset and development of the HIV/AIDS disease process, in public awareness campaigns regarding the disease, and in dispelling the concerns of the general public with regard to the virus. Expenditure on HIV and AIDS activities has increased substantially over the past few years when one compares the budget allocated to these activities on a yearly basis. The

availability and provision of antiretroviral therapy in accredited public health facilities commenced in the first quarter of 2004 as part of the Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (DOH, 2006a). However, much still needs to be done to dispel the many myths surrounding HIV/AIDS, as well as in terms of the provision and administration of antiretroviral drugs to slow down the course of HIV/AIDS in the majority of the South African infected population (Posel, Kahn & Walker, 2007).

This chapter provides an introduction to HIV/AIDS with reference to the effects of the disease and its treatment on the human body as well as specifically on the auditory system, while establishing a rationale for the current study within the South African context. Furthermore, this chapter introduces the reader to the aims of the current study, the methodology adopted, the limitations and the anticipated significance of the research findings. Lastly, this chapter provides the reader with an orientation to the organization of the thesis.

BACKGROUND AND RATIONALE FOR THE STUDY

1.1. HIV/AIDS Defined

Human immunodeficiency virus is a retrovirus that causes AIDS by primarily infecting vital components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It also directly and indirectly destroys CD4+ T cells. As CD4+ T cells are required for the proper functioning of the immune system, when enough CD4+ T cells have been destroyed by HIV, the immune system functions poorly, leading to the syndrome known as AIDS. HIV belongs to a subgroup of retroviruses called *lentiviruses* (meaning *slow viruses* since they often cause disease extremely slowly) (Hung, Ross & Luis, 2000). Two strains have been identified:

Type 1: the retrovirus recognized as the agent that induces AIDS; and

Type 2: a virus closely related to HIV-1 that also leads to immune suppression. HIV-2 is not as virulent as HIV-1 and is endemic only in West Africa.

The current study only focuses on the Type 1 strain of the virus.

HIV is reported to cause a total breakdown of the body's natural immune system by reducing the immune cell count (Bankaitis, 1998; Larsen, 1998). This reduction in immune cell count leads to the development of various diseases; however this development does not seem to occur similarly in all patients infected with the virus. Bankaitis (1998) reports that many of the patients infected with the virus remain asymptomatic and maintain normal immune cell counts for long periods of time. These are the patients that are reported to fall outside the documented clinical definition of Acquired Immunodeficiency Syndrome (AIDS).

AIDS is the acronym for 'Acquired Immunodeficiency Syndrome' and was a term coined at an early stage in the history of the disease. As stated previously, AIDS is a disease caused by an infection by HIV, a retrovirus that causes immune system failure and debilitation (which means that the body loses the ability to fight against infections because the immune system is weakened by HIV) and is often accompanied by infections such as tuberculosis (Hung et al., 2000).

Hence AIDS is, by definition, the end-stage disease manifestation of the infection with HIV. The Center for Disease Control and Prevention (CDC), which is the Atlanta based epidemiological agency governed by the U.S. Public Health Service of the U.S. Department of

Health and Human Services, classifies HIV/AIDS clinical stages for adults based on the CD4+. CDC developed official criteria for the definition of AIDS, and this definition of AIDS includes all HIV-infected people who have fewer than 200 CD4+ T cells per cubic millimeter of blood (CDC, 1993). In addition, the CDC definition includes clinical conditions that affect people with advanced HIV disease – conditions, most of which are opportunistic infections that generally do not affect healthy people. In people with AIDS, these infections are often severe and sometimes fatal because the immune system is so ravaged by HIV that the body cannot fight off certain bacteria, viruses, fungi, parasites, and other microbes (CDC, 1993). Therefore, for patients to be diagnosed with AIDS, this clinical definition states that they must either have extremely low T-helper lymphocyte counts or CD4+ counts (below 200 cells/mm^3 of blood) or present with at least one AIDS-defining condition (CDC, 1993). Lastly, the definition of AIDS clearly states that AIDS is caused by HIV – it is not congenital or inherited but acquired.

T-helper lymphocyte cells are white blood cells derived from the thymus gland that participate in a variety of cell-mediated immune reactions (Van Dyk, 2001). They, along with the other T cells (killer, and suppressor cells) are responsible for fighting infected or cancerous cells. CD4+ cells are a type of T cell involved in protecting against viral, fungal, and protozoal infections. These cells normally orchestrate the immune response, signalling other cells in the immune system to perform their special functions (also known as T helper cells) (Van Dyk, 2001). HIV's preferred targets are cells that have a docking molecule called "cluster designation 4" (CD4) on their surfaces. Cells with this molecule are known as CD4-positive cells. Destruction of CD4+ lymphocytes is the major cause of the immunodeficiency observed in

AIDS and decreasing CD4+ lymphocyte levels appear to be the best indicator for developing opportunistic infections (Larsen, 1998).

1.2. The general effects of HIV/AIDS on the human body

As a consequence of the inevitable deterioration of the immune system, the infected individual suffers from immunologic dysregulation. The end result is vulnerability to a diverse array of opportunistic infections and neoplasms as well as an increased incidence of immune-mediated diseases (Larsen, 1998). These disease manifestations may occur at any point following acute infection and prior to significant CD4+ lymphocyte depletion. They are thought to occur as a result of disordered B-cell regulation since B lymphocytes are highly dependent on immunocompetent inducer T-lymphocytes for their proper function (Walker et al., 2004). Improperly activated B-cells synthesize and release large quantities of non-functional immunoglobulins with a resultant increase in immunologic sequelae (Walker et al., 2004). However, the majority of problems related to HIV infection occur as a direct result of the loss of cell-mediated immunity that accompanies the destruction of CD4+ helper T-lymphocytes (Larsen, 1998), hence leading to generalized body effects.

The general effects of HIV/AIDS on the human body can be divided into direct (primary) effects and indirect (secondary) effects (Larsen, 1998). According to Larsen (1998), examples of direct effects of HIV on the body include conditions such as AIDS dementia, cytomegalovirus (CMV) encephalitis, cryptococcal meningitis, and vacuolar myelopathy. The indirect effects are in the form of opportunistic infections (such as fungal, viral and bacterial infections), neoplasms, and HIV-associated systemic disorders. Examples of indirect effects in the form of opportunistic

infections include tuberculosis, neurosyphilis, CMV, and toxoplasmosis. Those in the form of neoplasms include Kaposi's sarcoma, Non-Hodgkin's lymphoma, and primary central nervous system (CNS) lymphoma; and those in the form of HIV-associated systemic disorders include cerebrovascular disorders, metabolic, and nutritional diseases (Larsen, 1998).

There is a strong correlation between the absolute or percentage CD4+ lymphocyte counts and the risk of various infections (CDC, 1993). For example, non-specific symptoms such as lymphadenopathy, fever, night sweats, and intermittent diarrhoea often occur when the CD4+ count declines below normal levels (~ < 500 cells/mm^3) (Walker et al., 2004). Oral candidiasis, bacterial pneumonias, tuberculosis, and non-Hodgkin's lymphomas are first clinically recognized with increasing frequency at CD4+ counts of 200–350 cells/mm^3. *Pneumocystis* pneumonia (PCP), caused by *Pneumocystis jiroveci (f*ormerly *Pneumocystis carinii)* is most commonly seen with CD4+ counts below 150–200 cells/mm^3. Fungal esophagitis, cryptococcal meningitis, and disseminated endemic fungal diseases usually occur at counts below 100 cells/mm^3, while disseminated mycobacterial and cytomegalovirus infection usually do not become clinically apparent until CD4+ counts fall to less than 50 cells/mm^3 (CDC, 1993). In general, the more profound the degree of immunosuppression, the more susceptible a given individual becomes to different infectious or neoplastic diseases. Unless treatment is initiated prior to this development, the infected host will usually succumb to one or more of these pathologic processes (Louie & Markowitz, 2002).

Furthermore, the rate of clinical disease progression and presentation of HIV/AIDS effects on the human body varies widely between individuals and has been shown to be affected by

many factors such as host susceptibility, health care, and co-infections (CDC, 1993). Also, the specific opportunistic infections that patients with AIDS develop depend, in part, on the prevalence of these infections in the geographic area in which the patient lives (Louie & Markowitz, 2002). The following are some of the major effects of HIV/AIDS on the body:

The major pulmonary illnesses

- ***Pneumocystis jiroveci* pneumonia**: originally known as *Pneumocystis carinii* pneumonia (PCP) is relatively rare in normal, immunocompetent people but common among HIV-infected individuals. Before the advent of effective treatment and diagnosis in developed countries, PCP was a common immediate cause of death (Larsen, 1998). In developing countries, it is still one of the first indications of AIDS in untested individuals, although it does not generally occur unless the CD4 count is less than 200 cells/mm^3 (Larsen, 1998; Walker et al., 2004).
- **Tuberculosis**: Among infections associated with HIV, tuberculosis (TB) is unique in that it may be transmitted to immunocompetent persons via the respiratory route, is easily treatable once identified, may occur in early-stage HIV disease, and is preventable with drug therapy (Hung et al., 2000). However, multi-drug resistance is a potentially serious problem. Even though its incidence has declined because of the use of directly observed therapy and other improved practices in industrialized countries, this is not the case in developing countries where HIV is most prevalent (Benatar, 2004; Hung et al., 2000; Wilson et al., 2004). In early-stage HIV infection (CD4 count >300 cells/mm^3), TB typically presents as a pulmonary disease. In advanced HIV infection, TB may present atypically and extrapulmonary (e.g. TB infecting bone marrow, bone, urinary and

gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system (Van Dyk, 2001; Walker et al., 2004).

The major gastro-intestinal illnesses

- **Esophagitis**: Esophagitis is an inflammation of the lining of the lower end of the esophagus. In HIV infected individuals, this could be due to a fungus (candidiasis) or virus (herpes simplex-1 or cytomegalovirus) (Wilson et al., 2005). In rare cases, it could be due to mycobacteria (DOH, 2006).
- **Unexplained chronic diarrhoea**: In HIV infection, there are many possible causes of diarrhoea, including common bacterial (*Salmonella*, *Shigella*, *Listeria*, *Campylobacter*, or *Escherichia coli*) and parasitic infections (DOH, 2006). Uncommon opportunistic infections such as cryptosporidiosis, microsporidiosis, *Mycobacterium avium* complex (MAC) and cytomegalovirus (CMV) colitis have also been implicated in diarrhoea in HIV (DOH, 2006; Opie, 2005). Diarrhoea may follow a course of antibiotics (common for *Clostridium difficile*). It may also be a side effect of several drugs used to treat HIV, or it may simply accompany HIV infection, particularly during primary HIV infection (Larsen, 1998). In the later stages of HIV infection, diarrhoea is thought to be a reflection of changes in the way the intestinal tract absorbs nutrients, and may be an important component of HIV-related wasting (DOH, 2006).

The major neurological illnesses

- **Toxoplasmosis**: Toxoplasmosis is a disease caused by the single-celled parasite called *Toxoplasma gondii*. *T. gondii* which usually infects the brain causing toxoplasma encephalitis (Jackson, 2002). It can also infect and cause disease in the eyes and lungs (Jackson, 2002).
- **Progressive multifocal leukoencephalopathy (PML)**: is a demyelinating disease, in which the myelin sheath covering the axons of nerve cells is gradually destroyed, impairing the transmission of nerve impulses (Larsen, 1998). It is caused by a virus called JC virus which occurs in 70% of the population in latent form, causing disease only when the immune system has been severely weakened, as is the case for AIDS patients (Hung, Ross, & Luis, 2000). It progresses rapidly, usually causing death within months of diagnosis (Wilson et al., 2005).
- **HIV-associated dementia**: HIV-1 associated dementia is a metabolic encephalopathy induced by HIV infection and fueled by immune activation of brain macrophages and microglia (Hung, Ross, & Luis, 2000). These cells are actively infected with HIV and secrete neurotoxins of both host and viral origin. Specific neurologic impairments are manifested by cognitive, behavioral, and motor abnormalities that occur after years of HIV infection and are associated with low CD4+ T cell levels and high plasma viral loads (Wilson et al., 2005).
- **Cryptococcal meningitis** This infection of the meninges (the membrane covering the brain and spinal cord) by the fungus *Cryptococcus neoformans* can cause fevers, headache, fatigue, nausea, and vomiting (Lalwani & Sooy, 1992). Patients may also

develop seizures and confusion (Larsen, 1998). If untreated, it can be lethal (Wilson et al., 2005).

The major HIV-associated malignancies

Patients with HIV infection have substantially increased incidence of several malignancies (Larsen, 1998). Several of these, Kaposi's sarcoma, high-grade lymphoma, and cervical cancer confer a diagnosis of AIDS when they occur in an HIV-infected person (CDC, 1993).

- **Kaposi's sarcoma:** Kaposi's sarcoma is the most common tumor in HIV-infected patients (Abemayor & Calcaterra, 1983; Grant & De Cock; 2001; Wilson et al., 2005). It is caused by a gammaherpesvirus called Kaposi's sarcoma-associated herpes virus (KSHV). It often appears as purplish nodules on the skin, but other organs, especially the mouth, gastrointestinal tract, and lungs can be affected (Hung, Ross, & Luis, 2000).
- **High-grade lymphoma:** Several high-grade B cell lymphomas have substantially increased incidence in HIV-infected patients and often signify a poor prognosis (Saltzman et al., 2005). The most common AIDS-defining lymphomas are Burkitt's lymphoma, Burkitt's-like lymphoma, and diffuse large B-cell lymphoma (DLBCL), including primary central nervous system lymphoma with primary effusion lymphoma being less common (Saltzman et al., 2005). Many of these lymphomas are caused by either Epstein-Barr virus (EBV) or KSHV (Fryback & Reinert, 1997; Grant & De Cock; 2001).
- **Cervical cancer:** Cervical cancer in HIV-infected women is also considered AIDS-defining (Piketty et al., 2003). It is caused by human papillomavirus (HPV) (Feingold et al., 1990; Palefsky, 1991).

- **Other tumors:** In addition to the AIDS-defining tumors discussed above, HIV-infected patients are also at increased risk of certain other tumors, such as Hodgkin's disease and anal and rectal carcinomas (Saltzman et al., 2005). However, the incidence of many common tumors, such as breast cancer or colon cancer, is not increased in HIV-infected patients (Grant & De Cock; 2001; Saltzman et al., 2005). Most AIDS-associated malignancies are caused by co-infection of patients with an oncogenic DNA virus, especially Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), and human papillomavirus (HPV). In areas where HAART is extensively used to treat AIDS, the incidence of many AIDS-related malignancies has decreased (Hung, Ross, & Luis, 2000; Wilson et al., 2005), but at the same time malignancies overall have become the most common cause of death of HIV-infected patients (Saltzman et al., 2005).

Other opportunistic infections

Patients with AIDS and severe immunosuppression often develop opportunistic infections that present with non-specific symptoms especially low grade fevers and weight loss (Mindel. & Tenant-Flowers, 2001) – with fever seen in over 75% of patients (Vanhems & Dassa, 1999). These opportunistic infections include infection with *Mycobacterium avium-intracellulare* and CMV (Mindel. & Tenant-Flowers, 2001). CMV can also cause colitis, as described above, and CMV retinitis can cause blindness (Mindel & Tenant-Flowers, 2001; Wilson et al., 2005).

The most efficient way of discussing the aforementioned effects of HIV/AIDS on the body can be summarised following the CDC classification of HIV/AIDS which divides the HIV

infected patients into three distinct general groups (A, B, and C) according to their CD4+ blood count and their symptomatology (CDC, 1993) – with the earliest stage of HIV infection given a CDC classification of A, while the most severe HIV infection classified as C. Table 1 provides a list of general effects as reported by CDC (1993).

Table 1: Summary of HIV/AIDS signs and symptoms as reported by CDC (1993, pp. 1-13)

Category CDC-A
Asymptomatic HIV infection
Persistent Generalized Lymphadenopathy (PGL)
Acute (primary) HIV infection with accompanying illness or history of acute infection
Category CDC-B
Bacillary angiomatosis
Candidiasis, oropharyngeal (thrush)
Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
Cervical dysplasia (moderate or severe)/cervical carcinoma-in-situ
Constitutional symptoms, such as fever (38.5^{o} C) or diarrhoea lasting longer than 1 month
Hairy leukoplakia, oral
Herpes zoster (shingles involving at least 2 distinct episodes or more than one dermatome)
Idiopathic thrombocytopenic purpura
Listeriosis
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
Peripheral neuropathy
Category CDC-C
Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Coccidiomycosis, disseminated, or extrapulmonary
Cryptococcus, extrapulmonary
Cryptosporidiosis lasting longer than one month
Cytomegalovirus (CMV) disease (other than liver/spleen/nodes)
CMV retinitis
HIV encephalopathy
Herpes simplex, chronic ulcers (lasting longer than one 1 month)
Herpes simplex, bronchitis/pneumonitis/oesophagitis
Histoplasmosis, disseminated, or extrapulmonary
Isosporiasis lasting longer than one month
Kaposi's sarcoma
Lymphoma
Mycobacterium avium complex
Mycobacterium tuberculosis
Pneumocystis carinii pneumonia
Progressive multifocal encephalopathy
Salmonella sepsis
Toxoplasmosis (cerebral)
Recurrent pneumonia (greater that two episodes)
Invasive cervical carcinoma
Wasting syndrome – loss of weight (greater than 20% of body weight)

Scrutiny of the aforementioned effects of HIV/AIDS on the human body clearly indicates the extensively widespread effects on the body involving nearly every system and every organ.

Further categorization of these effects is provided by Larsen (1998) who distinguishes dermatological effects (e.g. ulcerations, nodules); ocular effects (e.g. decreased visual acuity, periocular skin lesions, dry eyes); oral effects (e.g. candidiasis, hairy leukoplakia, periodontal disease); gastrointestinal effects (e.g. diarrhoea, dysphagia, liver infection, jaundice); musculoskeletal effects (e.g. arthritis, Reiter's syndrome); neurological effects (e.g. seizures); cognitive dysfunction (e.g. inattention, reduced concentration); and behavioural manifestation (e.g. apathy, depression). All these signs and symptoms may present differently from one individual to the next, and may also affect individuals differently. However, from reviewing these signs and symptoms, it is clear that HIV/AIDS affects every system in the body, including sensory systems, although very little is known about the effects of HIV/AIDS on the auditory system.

1.3. HIV/AIDS and Auditory Manifestations

The known effects of HIV/AIDS on the auditory system have been reported in the literature based mainly on cross-sectional studies and case reports conducted internationally in industrialised countries, with very limited information coming from third world countries where the presentation of the virus and its treatment may be different. An extensive review of the literature on the topic revealed that although it has been suggested that there are direct and indirect effects of HIV/AIDS on the auditory system, the distinction between these effects is neither clear nor consistent.

The process of clearly delineating between the direct and indirect causes of auditory manifestations of HIV/AIDS is a complex one. The fact that opportunistic infections are deemed indirect causes by some researchers even though they may be a direct consequence of a compromised immune system from HIV has created much debate. By the same token, the fact that sensorineural hearing loss, for an example, has been attributed to direct effects of HIV since the effects are neural by some authors (Larsen, 1998) – regardless of the fact that the vestibulocochlear nerve could have been affected by an opportunistic infection such as CMV adds to this debate of whether a clear distinction between direct and indirect effects exists or not. In the current discussion, as a backdrop to the objectives of the study, the discussion will take the form of discussing prevalence and incidence data on auditory manifestations in this population; type of auditory manifestations and type of hearing loss most prevalent; the degree, configuration, and symmetry of the hearing loss; the type of onset of hearing loss; and the proposed direct and indirect causes of auditory manifestations in HIV/AIDS. Possible effects of treatment of HIV/AIDS on the auditory system, as an indirect cause of hearing loss, are also discussed later.

There are indications that hearing changes may be one of the presentations at any stage of the disease (Birchall, Wight, French, Cockbain & Smith, 1992; Campanini, Marani, Mastroianni, Cancellieri, & Vicini, 2005; Noffsinger & Friedman, 1996). The reported prevalence and incidence rates of hearing loss in HIV/AIDS varies widely but this inconsistency may be attributed to the vastly different samples, varying research methodologies, as well as participant inclusion criteria used in the different documented studies. Generally, the incidence of otologic

manifestations of HIV/AIDS has been reported to be relatively small (Abemayor & Calcaterra, 1983; Chandrasekhar et al., 2000; Gold & Tami, 1998; Khoza & Ross, 2002; Kohan, Rothstein & Cohen, 1988; Lalwani & Sooy, 1992). However, Flower in 1991 reported on the high prevalence of hearing impairment in patients with HIV/AIDS when he stated that 75% of adults with AIDS and 50% of persons with AIDS Related Complex manifest clinical auditory system abnormalities. Other authors such as Sooy (1987) suggested that hearing loss occurs in up to 50% of cases of patients with AIDS. More recently, Khoza and Ross (2002) found hearing loss to be present in 23% of their study sample of persons with HIV/AIDS. The different reports from these studies could very well be due to methodological differences as opposed to actual incidence differences. The most obvious difference in these studies is the fact that while some focused on general HIV/AIDS (with samples that were more encompassing – including patients from all stages of the disease), others were more specific in their sampling.

Consistent with the reports that claim minor auditory manifestations of HIV/AIDS, are claims that this small incidence rate is specific to adults, but is very different in children. These studies have concluded that there is an extremely low incidence or no incidence of otologic disease in adults, with a much higher incidence in paediatric patients. The high incidence of conductive hearing loss in paediatric patients is attributed in part to the high incidence of serous otitis media which may occur in up to 80% of cases (Smith & Canalis, 1989). Rosenberg, Schneider and Cohen (1985) reviewed medical records of 102 adult patients with AIDS and found that although 71% of the patients had symptoms localised in the head and neck, none had otologic signs and symptoms. Similar results were reported by Marcusen and Sooy (1985) who also could not find any otologic findings in 165 AIDS infected patients they evaluated. Lalwani

and Sooy (1992) argue that otologic manifestations associated with HIV/AIDS do occur but are less prevalent than other head and neck complaints.

With regard to comparing the occurrence of auditory manifestations to other head and neck effects of HIV/AIDS, there is considerable variation in reports. For example, Rosenberg et al. (1985) reported a total absence of otologic symptoms in patients who presented with head and neck signs and symptoms, while Booth (1997) noted an increase in the number of people living with HIV/AIDS who presented with otologic symptoms from AIDS. Lalwani and Sooy (1992) insist that ear related manifestations of HIV/AIDS occur to a lesser degree when compared to other head and neck complaints. None of these studies employed an audiological test battery approach to be able to categorically make conclusions about auditory symptoms. Chandrasekhar et al. (2000) believe that as many as one third of patients with HIV infection may have significant otologic complaints or difficulties, and maintain that this is a significant percentage which may actually be higher than figures reported in the otolaryngologic and infectious diseases literature. Studies that have included audiological assessments such as Sooy's (1987) research described abnormal audiologic findings greater than 25dB HL on pure tone testing in 49% of the total sample tested while Birchall, Wight, French, Cockbain, & Smith (1992) noted a common presence of hearing loss on pure tone testing in 39% of a small sample of patients who were HIV-positive and syphilis-negative with no neurological symptoms.

A review of the literature on auditory findings suggests heterogeneity as far as type, severity, and configuration of hearing losses diagnosed in patients with HIV/AIDS. The reported hearing loss may be conductive, sensory/neural, or central; the degree of the loss may range from mild to

severe; the onset of the loss may be sudden or gradual; and the hearing loss may be stable or may fluctuate (Bankaitis; 1996; Chandrasekhar et al., 2000; Friedman & Noffsinger, 1998; Khoza & Ross, 2002; Lalwani & Sooy, 1992; Timon & Walsh, 1989). Khoza and Ross (2002) argue that the hearing loss may also be profound in nature.

Friedmann and Noffsinger, (1993); Gold and Tami (1998); and Lalwani and Sooy (1992) have reported that the most common otologic problems documented in this population are serous otitis media and recurrent acute otitis media, which are predominantly due to Eustachian tube dysfunction – implying that one would expect the conductive type of hearing loss to be common. However, this finding is not confirmed in the literature. The rate of occurrence of SNHL is reported by Gold and Tami (1998) to range between 20% and 50% based on reviews of studies by Bankaitis and Keith (1995); Lalwani and Sooy (1992); and Tami and Lee (1994). These reports are also echoed in earlier findings by Khoza and Ross (2002) of higher prevalence of SNHL in HIV/AIDS. A high prevalence of SNHL was reported by Khoza and Ross (2002) where a definite increase in the number of occurrences of SNHL from stage 1 (asymptomatic) to stage 3 (full-blown AIDS) was also established.

A review of the literature revealed limited information in terms of the specific details regarding degree of hearing loss in patients with HIV/AIDS. As early as 1987, Sooy found abnormal audiologic findings of thresholds worse than 25dB HL, with a sloping configuration on pure tone audiometry of between 30 and 50dBHL at 8000Hz. A third of these patients were reported by Sooy (1987) to have had moderate-severe hearing loss at three or more test frequencies, at least unilaterally. More recently, Chandrasekhar et al. (2000) reported that on all

audiometric data in their study (pure tone, speech discrimination, and otoacoustic emissions) collapsed across CDC group, otologic complaint, and age; there was no statistically significant effect on the ear. However, when right and left ear data were combined in their sample, a statistically significant effect for the high frequencies (4000 and 8000Hz) was found with these frequencies being significantly elevated relative to the others but not from each other. These authors' results are in line with previously reported findings that indicate that the audiometric data trends imply worsening hearing loss in high frequencies. For example, Marcusen and Sooy (1985) discovered that in their sample some of their participants presented with a hearing loss, on pure tone testing, involving 8000 Hz.

Chandrasekhar et al. (2000), Gold and Tami (1998), and Lalwani and Sooy (1992) state that the hearing loss steadily worsens with an increase in frequency, with high frequencies at a moderate degree of severity. Mata, Yebra, Tudor, Villarreal, and Garcia (2000) reported that in their study of 30 patients, the most common findings included high frequency sensorineural hearing loss. However, Khoza and Ross (2002) reported that the configuration of the hearing loss may not be frequency-range-specific, but may rather involve all frequencies either unilaterally or bilaterally – as was the case in their study. Again, these variations in reports are attributed to the samples studied. For example, Chandrasekhar et al. (2000) and Gold and Tami (1998) studied patients that were on ARVs while Khoza and Ross (2002) did not, and this may have direct implications for configuration of the hearing loss as drug-induced hearing loss as a general rule usually presents as a high frequency configuration (especially in the initial stages) as opposed to other causes.

The description of hearing loss varies even when one considers type of onset and symmetry of hearing loss in HIV/AIDS. Several studies have reported on sudden SNHL in patients with HIV/AIDS (Khoza & Ross, 2002; Real, Thomas, & Gerwins, 1987; Solanellas, Soldado & Lozano, 1996; Timon & Walsh, 1989). Smith and Canalis (1989) assert that the otologic symptoms can include unilateral or bilateral SNHL, which can occasionally be of a sudden onset in nature but is commonly rapidly progressive. Khoza and Ross (2002) found the sudden onset of the hearing loss to be more prevalent in participants with more severe SNHL than in conductive or mixed hearing loss. Chandrasekhar et al. (2000) evaluated 50 patients and reported that of the 29% with hearing loss, 3% presented with sudden onset and 21% with gradual onset, with the remainder presenting with intermittent onset. Comparison of these studies suggests a greater tendency towards bilateral gradual onset of hearing loss rather than sudden onset.

There is evidence in the literature that suggests a relationship between audiological manifestations and the progression of the HIV/AIDS disease. As early as 1992, Lalwani and Sooy reported the effects of HIV/AIDS to increase with the progression of the disease. Later, Chandrasekhar et al. (2000) reported that in their study, pure tone audiometric data suggested worsening hearing loss with worsening HIV infection. This finding differed from that of Birchall et al. (1992) who found no correlation between pure tone audiometry averages and progression in the clinical stage of the disease. Khoza and Ross (2002) reported that the degree of hearing loss in their study did not seem to worsen with the progression of the HIV/AIDS disease (i.e. patients in Stage 3 of the disease did not necessarily present with poorer hearing thresholds than patients in Stage 1); however there did seem to be an increase in the occurrence of sensorineural hearing loss (SNHL) with the deterioration of patients' immunological status. The increase in the

occurrence of SNHL with advanced stages of the disease may be attributed to the progressive decline in patients' immunologic status which potentially places the patients at risk for being susceptible to the neurotrophic nature of the disease and to opportunistic infections, which have been found to cause hearing loss (Friedmann & Arnold, 1993; Khoza & Ross, 2002; Real et al., 1987; Schuknecht, 1993; Stephens, 1997). The development of opportunistic infections during HIV disease has been found to not only indicate the degree of immunosuppression; but may also influence disease progression itself and disease presentation (Saravolatz et al., 1996).

Numerous clinical, and mostly medically oriented, studies have demonstrated the occurrence of hearing loss and other auditory manifestations in HIV/AIDS. According to the research literature, auditory abnormalities associated with HIV/AIDS and its treatments have been reported in persons with varying degrees of HIV infection, in both symptomatic and asymptomatic patients, as well as in patients on antiretroviral treatment. Indications exist that the HIV effects on the auditory system can be direct as well as indirect; however this distinction is not always clear and consistent. Early reports in the literature demonstrated that the HIV might directly affect the auditory function due to the fact that the virus is neurotropic and commonly manifests itself neurologically (McArthur, 1987). These direct causes have been reported to possibly give rise to central pathology observed in this population (Bankaitis; 1996; Lalwani & Sooy, 1992). More commonly though, reports in the literature focus significantly on the indirect effects of the virus on the ear. It is believed that indirect causes that result in hearing loss stem from opportunistic infections which require suppressive therapy, thereby leading to ototoxicity (Bankaitis; 1996; Bankaitis & Schountz, 1998; Lalwani & Sooy, 1992).

Larsen's (1998) delineation (discussed earlier) of direct versus indirect effects of HIV/AIDS can be applied to the causes of auditory manifestations as well. Based on this distinction, it would seem that generally, the majority of auditory manifestations can be attributed to indirect effects in the form of opportunistic infections (e.g. SNHL due to CMV, otosyphilis, meningitis, encephalitis, otitis media, and TB of the ear), and neoplasms (e.g. nasopharyngeal masses, Kaposi's sarcoma of the external ear, and Non-Hodgkin's lymphoma of the external ear), with some direct effects including central hearing loss due to primary CNS lymphomas (Friedmann & Arnold, 1993), necrosis of the vestibulocochlear nerve due to herpes simplex and herpes zoster, and SNHL due to cryptococcal and aseptic meningitis, and neurosyphilis. Lastly, side effects of HIV/AIDS treatment can also be viewed as indirect effects (Chandrasekhar et al., 2000; Friedmann & Arnold, 1993; Gold & Tami, 1998; Lalwani & Sooy, 1992; Larsen, 1998; Stern, Lin & Lucente, 1990).

A review of literature with regard to causes of hearing loss in HIV/AIDS confirms the significant role that opportunistic infections play in the development of auditory manifestations. Khoza and Ross (2002) reported that in their study opportunistic infections in the form of intracranial events such as encephalitis, and meningitis; syphilis and herpes contributed to the causes of hearing loss. Furthermore, auditory manifestations in HIV/AIDS could be due to the fact that serous otitis media and associated conductive hearing loss have been found to be more common in patients with HIV/AIDS as one of the opportunistic infections (Gold & Tami, 1998).

Reports in the literature claim that conductive hearing loss in this population is usually due to otitis media, which may be caused by Eustachian tube dysfunction (Gold & Tami, 1998). In

patients with HIV/AIDS, it is reported that decreased cell-mediated immunity; recurrent viral infections; non-malignant lymphoid hyperplasia of the adenoids; nasopharyngeal tumours; sinusitis; or allergic autoimmune reaction to HIV can all lead to poor Eustachian tube function and middle ear effusions (Friedmann & Arnold, 1993; Gold & Tami, 1998; Lalwani & Sooy, 1992). Stern et al. (1990) state that benign nasopharyngeal lymphoid hyperplasia occurs frequently in AIDS and has been documented as a cause of nasal obstruction and otitis media with effusion, while Chandrasekhar et al. (2000) argue that otitis media, which is reportedly extremely uncommon in adults with "normal" health, affects up to 23% of HIV-infected patients.

A significant amount of information exists in the literature regarding causes of sensorineural hearing loss (SNHL) as a manifestation of HIV/AIDS (Friedmann & Arnold, 1993; Real et al., 1987; Smith & Canalis, 1989). Larsen (1998) argues that the exact cause and site of lesion of SNHL in patients with HIV infection is not known and this claim is substantiated by Lalwani and Sooy (1992) who argue that in up to 50% of HIV-infected people with hearing loss, no cause can be identified. Friedmann and Arnold (1993) attribute SNHL in HIV/AIDS to involvement of the CNS and of the sensory end organs, which may be due to neurosyphilis and neoplasms. According to these authors, these conditions may be complicated by opportunistic infections such as cryptococcus and cytomegalovirus (CMV); as well as the side effects of some drugs used to treat the opportunistic infections.

Birchall et al. (1992, p.117) carefully documented the potential causes of SNHL in HIV infection. These were:

- Viruses – cytomegalovirus, hepatitis B, herpes simplex and syphilis, herpes zoster, and toxoplasma as opportunistic conditions
- Intracranial events – encephalitis, meningitis, and haemorrhage
- Cranial neuropathy due to meningitis or lymphoma, and
- Drug treatment of opportunistic infections and neoplasms with ototoxic medications.

These authors however did not differentiate between what they believe to be the direct versus indirect effects of HIV/AIDS.

Birchall et al. (1992) and Khoza and Ross (2002) listed syphilis and meningitis as possible causes of SNHL in the participants they evaluated. Syphilis has been linked to SNHL that can be sudden or gradual/progressive in nature (Cummings, 1993; Stephens, 1997). Booth (1997) states that otosyphilis is more common in late acquired syphilis than in congenital syphilis and may cause sudden hearing loss consistent with a Meniere's syndrome pattern. Darmstadt and Harris (1989) maintain that SNHL may occur in primary, secondary and late acquired syphilis. Acquired syphilis that is in a dormant stage (onset of symptoms after a period of quiescence) following successful therapy may erupt as otosyphilis at any stage of HIV infection (Schuknecht, 1993). Schuknecht reported on two patients, one in Stage 1 and the other in Stage 3 of HIV, who presented with SNHL due to syphilis. A review of the literature on the type of hearing loss that results from otosyphilis revealed that the reported hearing loss is often cochlear in nature (Booth, 1997; Friedmann & Arnold, 1993; Smith & Canalis, 1989).

Cryptococcal meningitis has been reported to be the most common manifestation of AIDS, and is an opportunistic infection that has its primary focus in the lung and spreads mainly

to the meninges (Schuknecht, 1993). This infection causes similar tissue damage both in people with and without HIV infection, with the exception that in people with HIV, because of their immunocompromised status, the damage tends to be more extensive and destructive (Larson, 1998). Booth (1997) reports cryptococcal meningitis as being increasingly associated with sudden SNHL with the incidence as high as 27%.

From the above discussion it is clear that there is great heterogeneity in the reports on auditory manifestations of HIV/AIDS. It is clear that these manifestations do occur, although to what nature and degree is still unclear, and to what they can be attributed to still needs further clarity. Hence more investigations are still required in this population, which underpins the rationale for the current study.

1.4. The treatment of HIV/AIDS

When AIDS first surfaced in the United States, there were no medicines to combat the underlying immune deficiency and few treatments existed for the opportunistic diseases that resulted. Over the years, however, researchers have developed drugs to fight both HIV infection and its associated infections and cancers. The US Food and Drug Administration (FDA) has approved a number of drugs for treating HIV infection. These drugs may slow down the spread of HIV in the body and delay the onset of opportunistic infections, although currently available antiretroviral drugs do not cure people of HIV infection or AIDS (DOH, 2006). Nevertheless, they all have side effects that can be severe (Grabar et al., 2002).

The treatment of HIV/AIDS involves effective use of highly active antiretroviral therapy. Researchers have credited highly active antiretroviral therapy, or HAART, as being a major factor in reducing the number of deaths from AIDS (Louie & Markowitz, 2002). HAART is a treatment regimen that uses a combination of reverse transcriptase inhibitors and protease inhibitors to treat patients. While HAART is not a cure for AIDS, it has greatly improved the health of many people with AIDS and is said to reduce the amount of virus circulating in the blood to nearly undetectable levels. However, researchers have shown that HAART cannot eradicate HIV entirely from the body. HIV remains present, lurking in hiding places such as the lymph nodes, the brain, testes, and the retina of the eye, even in patients who have been treated (Louie & Markowitz, 2002).

Management of patients with HIV infection is one of the rapidly changing and dynamic clinical fields in medicine today. With over 20 antiretroviral drugs currently available, one can easily construct a potent 3- to 4-drug treatment regimen that can suppress viral replication, enhance immunity, and delay or prohibit clinical deterioration (Max & Sherer, 2000). Among patients who take their prescribed therapy, successful and sustained treatment responses as high as 90-95% have been reported (Department of Health and Human Services - DHHS, 2003; Murphy, 2000). The biggest challenge for clinicians today is choosing an effective treatment regimen to which an individual patient will adhere, and experience as minimal negative side effects of the treatment as possible (Murphy, 2000).

Evidence of reduced mortality and morbidity due to HIV disease exists in the literature. These data show broader populations with significant mortality reductions and suggest that a

system of care and support that gives access to potent antiretroviral therapy can benefit diverse populations of people with HIV disease (Grabar et al., 2002). Nonetheless, there are numerous reasons for caution regarding antiretroviral therapy (ART). Firstly, not all patients taking ART achieve the goal of maximal virus suppression (Murphy, 2000). The reason for this includes the fact that HAART regimens are often complex. Regimens can include numerous pills with frequent dosing and various, sometimes conflicting, food requirements. Secondly, adverse events are common and may lead to discontinuation of therapy, dose interruption, and significant reductions in quality of life (Max & Sherer, 2000). Thirdly, adherence may be compromised because of adverse events, and adherence is increasingly recognized as an important determinant of successful antiretroviral therapy (DHHS, 2003). Because adverse events are common with all available antiretroviral agents, it is critical to anticipate, detect, recognize, and manage them when providing primary care for HIV-infected patients. With regard to adverse events, patients should be informed of potential side effects of the treatment of HIV/AIDS on the body during consideration of the first regimen, options for subsequent regimens, and possible management strategies in case of adverse events.

1.5. The general effects of the treatment of HIV/AIDS on the body

Combination therapy with at least three antiretroviral agents has been shown to have a significant positive effect upon morbidity and mortality in HIV disease (Grabar et al., 2002). These positive responses are mediated through suppression of HIV replication, preservation of immune function and reconstitution of specific immune responses (Louie & Markowitz, 2002). Treating patients with AIDS with antiretroviral drugs has been shown, internationally where treatment is instituted earlier in the disease, to be effective in prolonging the lives of people who

would have progressed to stage 3 and 4 of AIDS – this benefit still needs to be confirmed in developing countries such as South Africa where treatment is given at the last stage of the disease. However, the drugs do not cure people - they merely arrest the progression of the disease. Moreover, the drugs can be toxic and have adverse side effects that may make patients feel temporarily more ill.

Several general potential adverse effects of the treatment of HIV/AIDS on the human body have been reported and include the following:

- **Skin Rash:** Skin rash occurs most commonly with the non-nucleoside reverse transcriptase inhibitors (NNRTI) class of drugs. The majority of cases are mild to moderate, occurring within the first weeks of therapy (Fagot, Mockenhaupt, & Bouwes-Bavinnck, 2001).
- **Osteonecrosis, Osteopenia, and Osteoporosis:** Avascular necrosis and decreased bone density are now recognized as emerging metabolic complications of HIV infection that might be linked to HAART regimens. Both of these bone abnormalities have been reported among adults and children with HIV infection who are now surviving longer with their disease in part because of HAART (Scribner et al., 2000; Mora et al., 2001).
- **Increased Bleeding Episodes among Patients with Hemophilia:** Increased spontaneous bleeding episodes among patients with hemophilia A and B have been observed with Protease Inhibitors (PI) use (Racoosin & Kessler, 1999).
- **Fat Maldistribution:** Antiretroviral therapy has been associated with unique fat distribution abnormalities. Localized fat accumulations have been reported with nucleoside reverse transcriptase inhibitor (NRTI) monotherapy (Mulligan et al., 2001).

- **Hyperlipidemia:** Antiretroviral therapy is associated with complex metabolic alterations, including dyslipidemia (Coodley, Loveless, & Merill, 1994; Grunfeld & Feingold, 1992).
- **Lactic Acidosis/Hepatic Steatosis:** Chronic compensated hyperlactatemia can occur during treatment with NRTIs (John et al., 2001).
- **Hepatotoxicity:** Hepatotoxicity, which is defined as a 3–5 times increase in serum transaminases with or without clinical hepatitis, has been reported among patients receiving HAART (denBrinker, Wit, Wertheim-van Dillen, 2000; Martinez et al., 2001).
- **Hyperglycemia:** Hyperglycemia, new-onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of preexisting diabetes mellitus have been reported among patients receiving HAART (Dube, 1998; Eastone & Decker, 1997; Mulligan et al., 2000; Visnegarwala, Krause, & Musher, 1997).
- **Other mitochondrial toxicities:** myopathy (zidovudine), neuropathy (stavudine, didanosine) (Carr & Cooper, 2000).
- **Other toxicities:** nausea, headache, dizziness, diarrhoea, mouth ulcers, central nervous stimulation, perioral paraesthesiae, reflux oesophagitis, retinoid effects, hypersensitivity (Carr & Cooper, 2000).

These general side effects on the body highlight the fact that much is known about general treatment effects on the body but little is known about the effects of the treatment of HIV/AIDS on the auditory system.

1.6. The effects of the treatment of HIV/AIDS on the auditory system

Because of all the diseases and infections that the population with HIV/AIDS present with, it is not surprising to find patients with hearing loss due to ototoxicity, as this population goes through a drug regimen that often involves potentially ototoxic medications (Birchall et al., 1992). Bankaitis and Schountz (1998) report that the use of experimental antiretroviral drugs with undocumented or unknown side effects contributes to this hearing loss. In addition, ototoxic drugs that are often used in the treatment of opportunistic infections such as tuberculosis may increase the potential for a drug-induced hearing loss in this population.

In South Africa, treatment of TB is one of the major forms of treatment that the population with HIV/AIDS goes through, and this treatment includes aminoglycosides such as streptomycin. Streptomycin is reported as the best and most effective aminoglycoside drug that is still employed (despite its established cochleotoxic and vestibulotoxic potential) in the treatment of TB when prior treatments have failed to deliver expected outcomes (De Lima, Lessa, Aguiar-Santos & Medeiros, 2006). De Lima et al. (2006) reported on high frequency sensorineural hearing loss in 75% of TB patients they evaluated in their study. These authors assert that when patients discontinue their TB treatment, they are often forced to resume it, using more toxic drugs for even longer periods of time, and this increases the chances of ototoxicity. This is not even when interaction with ART has been taken into consideration. Mata et al. (2000) associated the sensorineural hearing loss found in their study to the administration of antiretroviral drugs. In contrast, Chandrasekhar et al. (2000) report no correlation between sensorineural hearing loss and routine medications used in management of HIV in their sample of 50 participants.

While ototoxic hearing loss has been described in HIV-infected people after beginning nucleoside reverse transcriptase inhibitors (NRTIs) (Kakuda, 2000), there have been extremely limited prospective studies, with one example of a prospective study by Schouten, Lockhart, Rees, Collier and Marra, (2006). Hence there still needs to be extensive investigations to confirm this relationship. The study by Schouten et al. (2006) investigated hearing changes longitudinally in treatment-naïve HIV-infected subjects following initiation of regimens containing NRTIs. The goal of their study was to perform a prospective assessment of the contribution of zidovudine (ZVD) and didanosine (ddI) to hearing loss. Changes in hearing levels at all frequencies and in low and high frequency pure tone averages were measured at baseline, 16, and 32 weeks after initiating antiretroviral therapy.

There are at least three major criticisms that can be levelled against the aforementioned mentioned study. Firstly, Schouten et al.'s (2006) study did not incorporate otoacoustic emissions (OAEs) as part of their monitoring battery, and this could have had a significant impact on their results since OAEs have been shown to be sensitive in ototoxicity monitoring. Secondly, only 33 participants were included in their study, which is a small sample size, and this significantly reduces the strength of the study in terms of the ability to generalize the results. Thirdly, there was no control group, although they did acknowledge that this was a pilot study. To their credit, their pure tone testing included 12 kHz, which is an ultrahigh frequency. Ultrahigh frequencies have been reported to be finely tuned to the effect of damaging environmental factors such as noise and ototoxic drugs. The current study endeavoured to build on previous studies like this one by including distortion product otoacoustic emissions

(DPOAEs) as part of the test battery, conducting a prospective study on a larger sample size with a control group to enhance generalizability of the results.

In Schouten et al.'s (2006) study, treatment with ZVD and ddI did not result in loss of hearing, even after taking into account noise exposure, immune status and age. The results of this prospective pilot study did not support the view that treatment with nucleoside antiretroviral drugs damages hearing. This finding contradicts reports from previous cross-sectional studies and case reports that have indicated that hearing loss may be common among HIV-infected people due to ototoxic drug therapy (Khoza & Ross, 2002; Marra et al., 1997). The results of the prospective study by Schouten et al. (2006) did not corroborate this relationship and are consistent with the report from the Adult/Adolescent Spectrum of HIV Disease Project Group that demonstrated no association between hearing loss and drugs used. Of note, however, the Adult/Adolescent Spectrum of HIV Disease Project Group study was centred on a retrospective chart review for International Classification of Diseases (ICD) -9 coding for hearing loss and not on formal audiometry (McNaghten, Wan & Dworkin, 2001). This represents a significant weakness in the methodology for a study attempting to determine ototoxic effects which can be subclinical in nature, hence requiring sensitive audiological monitoring tools.

Previous cross-sectional studies and case reports have shown an association between hearing loss and NRTI therapy (Marra et al., 1997; McNaghten et al., 2001; Simdon, Watters, Bartlett & Connick, 2001). There have been two case reports of hearing loss in persons receiving ART regimens that included NRTIs and a second class of antiretroviral drugs; one with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Nevirapine) and one with a protease

inhibitor (PI) (lopinavir/ritonavir) each combined with NRTIs, (both these subjects were also receiving stavudine and lamivudine). One case reported sudden hearing loss two weeks subsequent to the person completing one month of post-exposure prophylaxis which resulted in long-term hearing loss (Rey, L'Heritier & Lang, 2002). The other case described hearing loss in a subject with extensive HIV pre-treatment, and suggested a possible relationship with the protease inhibitor, although there were other possible explanations noted in Simdon's reply to this case report (Simdon et al., 2001; Williams, 2001). Simdon reported three subjects who experienced ototoxicity, all of whom were over the age of 45 and received combination ART with 2-3 NRTIs plus a NNRTI or a PI. All three of the subjects had prior hearing problems, prior exposure to occupational noise and all developed significant tinnitus (Simdon et al., 2001). Clearly, the presence of these confounding variables (prior hearing loss, noise exposure history, and older age) needs to be taken into consideration when interpreting findings from these cases. The authors suggested that NRTIs should be used cautiously in patients with pre-existing hearing loss. Again, the ability to generalize these results is limited as they were based on case reports and not on large samples.

One should note that not all of these studies utilized sensitive ototoxicity monitoring protocols such as ultra-high frequency audiometry and/or otoacoustic emissions. Furthermore, some of these studies, for example the study by Chandrasekhar et al. (2000), also did not follow longitudinal research designs that could have allowed the researchers to investigate within-subject changes – but rather followed cross sectional methodology designs. In addition, the reports that other factors such as age, drug interactions, concomitant noise exposure, and so on may have an influence on the ototoxicity of ARVs should be taken into consideration when

reviewing the effects of ARVs on hearing. For example Marra et al. (1997) suggested an association between age and antiretroviral effects on hearing. These authors report that in their study of 99 HIV infected adults, an interaction existed between age and antiretroviral therapy where an association between hearing loss and antiretroviral therapy was significant for subjects aged 35 years or older.

Understanding the effects of HIV/AIDS and the treatment of HIV/AIDS on the auditory system is becoming more important because patients with HIV/AIDS are living longer due to the positive effects of ART. The discovery of antiretroviral drugs for the treatment of HIV/AIDS has changed the face of the HIV/AIDS pandemic internationally, and has also led to changes in the medical field with people who have HIV/AIDS living for longer periods of time experiencing toxic-related morbidity that influences quality of life indicators (Zapor et al., 2004). There is a concern, however, that HIV-associated auditory disorders may be seriously under-reported. Zuninga (1999) makes reference to anecdotal reports suggesting that hearing loss and dizziness which are often the initial symptoms of underlying auditory system disease may not have been reported by patients prior to HAART because many patients focused on the life-threatening complications of HIV disease rather than on quality of life issues. This situation is yet to be fully realized in South Africa as ARVs have only been available since April 2004 – and not even to the entire population infected by the virus. People who will benefit from these drugs may in the near future become more conscious of the quality of life issues and complain about them. Auditory manifestations may be one of the issues that the population will have to deal with, and therefore over and above management of the known side effects of ARVs, research into the identification and monitoring of all other manifestations of the disease is required. With regard to

auditory manifestations, both identification and monitoring of ototoxicity require rigorous research to enhance the patients' quality of life.

Zuninga (1999) reports a major concern about the fact that some physicians' responses to the potential ototoxicity of ARVs may be inappropriate. He states that some physicians believe that the potential risk of hearing loss due to ototoxicity of antiretroviral drugs is so negligible that there is no need to screen for symptoms of hearing loss. Zuninga's (1999) concern is supported by the current researcher, and this sentiment is supported by the following facts:

(1) there do not appear to have been appropriately designed trials to determine the risk of hearing loss and other communication disorders in people with HIV disease;
(2) reports in the literature on auditory function and HIV/AIDS have been largely based on small sample sizes – including case reports, screening methods, and cross sectional designs
(3) the questionable pre-HAART data may not be applicable to those people with HIV disease whose survival has been significantly extended and in whom new symptoms of the disease and side effects of more complex therapies are increasing; and
(4) audiologists hardly ever serve as clinical trial consultants, thus the collection of data on patient responses to symptoms of hearing loss could be biased by not asking the questions according to audiologists' established standards for symptom screening and identification.

The aforementioned factors not only accentuate the importance of conducting studies such as the current one, where the auditory status of patients with HIV/AIDS and the possible ototoxic effects of antiretroviral drugs are investigated, but also highlight the vital need for improved scope of practice for audiologists during the drug development process.

Clinically used drugs and chemical agents may potentially cause adverse effects to the human auditory and vestibular systems (Jackson & Arcieri, 1971). Many of these drugs can play a critical role in the treatment of serious or life-threatening diseases; others offer such important therapeutic effects compared to the ototoxic side effects; that the ototoxicity risk can be considered to be of minor importance – such may be the case with HIV/AIDS (a sentiment echoed by some physicians). The problem of ototoxic side effects is reported to be more critical in developing countries, where highly effective and low-cost drugs are more easily prescribed without adequate monitoring (Arslan, Orzan & Santarelli, 1999). It is possible that such a situation may exist in some parts of South Africa.

Medical awareness of doses, forms of administration, populations at risk, and possible synergism with other factors is necessary in order to develop appropriate care in the prescription of drugs with ototoxic side effects. Furthermore, issues such as risk-benefit analysis, patient-informed consent, and quality-of-life considerations, particularly when life expectancy can be low, are also crucial factors to be considered. Regardless of whether the effects of the drug are negligible or not, these effects still need to be determined so that proper patient adherence counselling can occur. It is fundamental that audiologists establish and become aware of ototoxic effects of medications used to manage chronic conditions such as HIV/AIDS, and medications prescribed to significant numbers of people – such as the 11% of the population afflicted by HIV/AIDS in South Africa (Dorrington, Johnson, Bradshaw & Daniel, 2006). This awareness is critical to ensure that proper patient education occurs as patients may not notice ototoxic hearing loss until a communication problem becomes evident, signifying that hearing loss within the frequency range, which is vital for understanding speech, has already occurred. Likewise, by the

time the patient complains of dizziness, permanent vestibular system damage may have already occurred.

Whilst it is evident that a cure for AIDS does not appear to be imminent, treatment strategies have been improving rapidly and access to antiretroviral treatment seems to also be improving steadily. The drugs that are currently available have significantly improved the prognosis and quality of life for patients living with HIV/AIDS thereby allowing them to continue to be productive members of society (Berns & Kasbekar, 2006). Improved hearing and enhanced communication has the potential of improving the patients' quality of life and hence enhancing their ability to remain productive members of society. Improving communication is also in line with the South African Government's policy on creating a supportive environment so that HIV infected individuals are able to continue working under normal conditions in their current employment for as long as they are medically fit to do so (Government Gazette – no. 21815, 2000/2001; Curlee, 2000).

It is clear that South Africa is currently experiencing Africa's fastest growing HIV/AIDS pandemic. With the growing prevalence rate of HIV/AIDS in the country and the increasing number of people on antiretroviral drugs and anti-tuberculosis (TB) medications, the numbers of people at risk for ototoxic hearing loss may also be growing. As a result there is an increasing need for audiologists to become aware of the audiological sequelae of both HIV/AIDS and its treatment in order to prevent this type of morbidity. The prevention, detection and monitoring of ototoxic hearing loss associated with antiretroviral drugs (ARVs) is essential for the comprehensive and efficacious management of this vulnerable population. Prevention and/or

early detection of ototoxic effects or its progression to a point where aural rehabilitation in the form of amplification is required may need to be a part of the clinical management of the individual with HIV/AIDS.

As early as 1987, Real advocated that with the increase in the number of people infected with HIV/AIDS, it was very important for the audiologists and otolaryngologists to be able to recognize and manage the complications of this disease that involve the ear. In South Africa, as the prevalence of HIV/AIDS continues to rise as a condition that is an infectious terminal disease with no known recovery from infection, all aspects of its varied presentation require characterization (DOH, 1999). Describing and characterizing the audiologic manifestations of HIV/AIDS in the form of ototoxicity monitoring endorses aspects of the ABUJA DECLARATION (2001), which recognizes the need to intensify efforts in all areas of research in order to provide improved care and support, as well as enhanced quality of treatment to populations infected with HIV/AIDS.

An additional concern to the management of HIV/AIDS patients who may be on potentially ototoxic medication is that noise exposure following treatment with ototoxic drugs can act synergistically with the drugs that have not been fully cleared from the inner ear (Fausti et al., 2005). Increased susceptibility to hearing loss can continue for several months after completion of treatment or therapy. Due to this likelihood, it is imperative to implement hearing conservation in the form of advising patients to avoid excessive noise exposure for at least six months. In addition, patients who use amplification in the form of hearing aids may need to be counselled and warned to closely monitor and control the hearing aid maximum output during

this critical time (Edmunds et al., 2006). Given this scenario, it seems more pressing than ever to endeavour to prevent or ameliorate the possible ototoxic hearing loss in this population.

When life-threatening illness necessitates treatment with ototoxic drugs, preserving the quality of the patients' remaining life is customarily a treatment goal. Early detection of ototoxic hearing loss provides physicians with the critical information and opportunity necessary to minimize further impairment and, in some cases, prevent hearing loss from progressing to the point where permanent damage occurs. Although hearing loss is not a life-threatening condition, it does however become a severe threat to essential quality of life indicators unless intervention occurs early during treatment. The adverse effects of a hearing loss on cognitive-linguistic skills and psychosocial behaviour are well documented, as well as the serious vocational, social, and interpersonal consequences for the patient.

While hearing loss related to HIV/AIDS is receiving increasing attention in the international literature, the results are from first world countries and may not necessarily be relevant in the South African context. There continues to be a dearth of information available to the general public concerning this issue in South Africa. This paucity of audiological information which is based on local circumstances and practices goes against one of the four pillars of HIV/AIDS programmes advocated by the United Nations at the early stages of the epidemic (UNAIDS, 2000) which emphasize the importance of expanding the knowledge base to help countries design and manage comprehensive programmes for management of patients with HIV/AIDS. This complex situation is aggravated by the fact that scientific and audiological knowledge about HIV/AIDS is incomplete, often inconclusive and controversial. In view of the

increase in the number of patients who are reported to be infected with this disease who are now receiving antiretroviral therapy (ART), it is anticipated that drug-induced hearing loss might be one of the adverse effects of ART. Audiologists are generally not fully informed about these side effects on hearing, which underscored the need for the current study. As a profession, over and above identifying auditory changes in HIV/AIDS that may be due to opportunistic infections, audiologists also need to ensure the safe and effective use of antiretroviral drugs; the care provided to patients must be of the highest quality; and it must be monitored on a regular basis.

At present, a uniform method of monitoring for all potentially ototoxic therapeutics does not seem practical or affordable. It has been recommended, however, that individual auditory function be noted for a particular drug being employed (Campbell, 2007). Protocols and examinations that are easy, quick, sensitive, reliable, and as objective as possible have been suggested. Benefits of such audiological monitoring include the opportunity to change the patient's treatment course, improvement of patient and family awareness of the impact of hearing impairment, instituting hearing conservation measures where required, and timely as well as suitable prescription of amplification devices (Arslan et al., 1999).

The professional best placed to understand the effects of HIV/AIDS, and the treatment of HIV/AIDS, on the auditory system is the audiologist. Audiological changes attributable to HIV/AIDS and the medications used to treat the condition and its associated opportunistic infections are likely to increase the demand for audiologists to work with patients with HIV/AIDS. Furthermore, in order for audiologists to provide effective services for this population, it is crucial for them to understand and be able to identify potential ototoxic agents in

the patients' treatment regimen and their effect on auditory function. During the early stages of the pandemic, treatment strategies did not seem to have a positive influence on patients' lives, and therefore hearing loss did not seem to be an important manifestation of HIV/AIDS that required characterisation. However, with the subsequent development of different antiretroviral drugs that extend patients' life spans, hearing loss has become one of a number of sensory disabilities associated with HIV/AIDS that must now compete for attention by the research and medical community. Informing practising doctors, audiologists, and all other health-care professionals is a crucial part of this process. Friedman and Noffsinger in 1998 advocated that as primary professionals in hearing health care, audiologists have a responsibility to inform both themselves and other relevant health-care professionals about this issue.

An extensive field of research has developed in the area of HIV/AIDS focusing on all aspects of the disease including the medical (diagnosis and treatment), social, psychological, as well as the economic impact that this pandemic has had in the country. Under the medical aspect, hearing changes associated with HIV/AIDS have received some attention in the literature; however not in their entirety. As early as 1987, Flower and Sooy (1987) proposed that as new treatments concerned with the slowing down of the course of the disease are discovered, a large number of people with AIDS would have long term disabilities. These disabilities may include communication disorders (Johnston & Ross, 1991). This therefore highlights the vital role that audiologists have to play in the treatment of these patients – research being cornerstone to this role.

1.7. The context of HIV/AIDS research in South Africa

The major issue that has for years caused much debate and contention among the population of HIV/AIDS infected people in South Africa has been the failure of the South African government to provide antiretroviral therapy to the people living with the virus (Posel et al., 2007). This situation changed with the antiretroviral therapy roll-out programme instituted in government hospitals since April 2004. The programme emphasizes the need for pharmacovigilance and encourages research into the possible adverse events associated with this kind of therapy. It was anticipated that hearing loss in the form of ototoxicity could be one of these adverse events associated with the use of antiretroviral drugs, hence the need for the current study. As an attempt to contribute towards the volume of literature on HIV/AIDS, the current study endeavoured to investigate and monitor the auditory status (including ototoxicity monitoring) in adult patients on anti-retroviral drugs and other therapies attending a provincial hospital HIV/AIDS clinic in Johannesburg, Gauteng, South Africa. The researcher was personally motivated to undertake this research study based on her extensive clinical experience of working in adult and paediatric HIV/AIDS clinics in Gauteng.

Research is a critical component of the South African government's plan for Comprehensive Treatment and Care for HIV and AIDS. The objective of the research agenda of the South African government is to conduct studies whose answers may define the most effective provision of HIV and AIDS care and treatment, and guide programme implementation. The role of the audiologist in the conduction of research and implementation of treatment of HIV/AIDS has been limited and significantly restricted. It is the contention of the current researcher that audiological research should form part of this plan as audiologists are members of the health care

team. The scope of the treatment effort being undertaken creates an opportunity to understand the impact of ARVs in a largely treatment-naïve population. The information currently available on the use of ARVs is derived from studies not representative of the South African context, where local factors, including poverty, local host genetics, the impact of co-infections with other pathogens such as tuberculosis, and the co-use of traditional medicine have not been considered.

1.8. The Primary Aim of the Study

The main aim of the current study was therefore to investigate and monitor the auditory status in a group of adult patients with AIDS receiving ART and other therapies in a hospital outpatient clinic in Gauteng, South Africa. This study aimed to bridge the gap that exists in the literature regarding this issue and establish initial baseline information that could be used to develop a protocol that would be appropriate for the South African environment.

1.9. Specific Objectives of the Study

All of the following objectives were examined at baseline (before initiation of ARVs) and with repeated measures (at 3 and 6 months into treatment) for both the control and experimental group. The specific objectives were:

1. To estimate the prevalence of hearing loss and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth)
2. To assess the type, degree and configuration of the hearing loss
3. To explore the type of hearing symptom onset (e.g. sudden or gradual/progressive onset)

4. To document case history data such as signs and symptoms of each participating participant and to identify any associations between obtained signs and symptoms and hearing loss
5. To document the names of all medications used to establish their possible impact on hearing function, specifically ototoxicity monitoring
6. To compare the results of the experimental group with those of a control group.

1.10. Methodology:

Following ethical clearance from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, this study was conducted at an Adult HIV/AIDS clinic at Johannesburg Hospital where participants were recruited utilizing a convenient sampling technique and were asked to volunteer for participation in the study. A total of 150 participants formed the study sample with 104 participants in the experimental group and 46 participants in the control group at baseline testing. This sample size formed the sample for the descriptive analysis phase of the study. However, this sample size decreased to a sample of 54 participants in the experimental group and 16 participants in the control group for the repeated measures analysis phase of the study, which involved all participants who attended all three sessions of testing. For the experimental group, this sample comprised of all participants who were on regimen 1 of ART (3TC, D4T and Stocrin). The design used was a prospective repeated measures design where participants were assessed at baseline (before initiation of ART), three months into the treatment, and at six months into the treatment. The same protocol was followed for the control group; however these participants were not on ART. The audiological test battery that participants underwent included: obtaining case history information, performing otoscopy

and tympanometry, as well as conducting pure tone testing and Distortion Product Otoacoustic emissions testing. Results were analyzed utilizing both descriptive and inferential statistics, and are reported in accordance with the main aim and specific objectives of the study. Interpretation of the results was done taking into account the methodological concerns that were identified in the design and implementation of the protocol of this study.

The main limitations of the study included, firstly, that the nature of the disease and the population being studied precluded complete control over confounding variables that could have had an influence on the results such as interactions of ARVs with other therapies. Secondly, the sample size for the control group was small thereby preventing randomized matching of participants in the control group with those in the experimental group. Moreover, the sample size was further reduced by attrition which had an effect on generalizability of the results of the study. Thirdly, due to lack of equipment, ultra-high frequency audiometry did not form part of the test battery and this may have influenced the type of results found. Lastly, the length of time for which the audiologic monitoring occurred (6 months) may have been too short to allow for clinical hearing loss possibly caused by ART to manifest and therefore be detected on the audiogram.

1.11. Anticipated Significance of the Study

It was envisaged that as more people become diagnosed with HIV/AIDS, audiological manifestation of this disease may be on the rise as well. As more drugs become available to either treat HIV or to prevent or treat opportunistic infections the potential for drug interactions leading to audiological consequences has also become of increasing concern. Not only does

every therapy have potential side effects, but simultaneous ingestion of experimental, government approved, and prophylactic drugs significantly increases the risk of irreversible ototoxicity. Audiologists need to be aware of the auditory effects of the virus and of the potential risk of HIV- related ototoxicity; thereby improving their ability to educate patients, primary-care physicians, and other health-care workers. While antiretroviral drugs are vital and necessary in extending the lives of infected patients, health-care teams need to consider the roles of hearing and balance in maintaining or improving the quality of life of HIV-infected individuals during and following any type of drug therapy (Bankaitis & Schountz, 1998).

Identification and monitoring as well as management of auditory manifestations of HIV/AIDS and ototoxic effects of ART could potentially contribute towards improving the quality of life of individuals with HIV/AIDS. The audiologist's involvement in the clinical management of this population group needs to be highlighted and strengthened, with the scope of involvement also including participation in the initial stages of drug development as well as monitoring the side effects of the drugs. Consistent use of sensitive protocols for audiological monitoring (particularly ototoxicity monitoring), such as ultrahigh frequency pure tone and/or otoacoustic emissions testing needs to be emphasized as these measures are more sensitive to detecting microcochlear pathologies than normal pure tone audiometry. Identification of microcochlear pathology and subclinical hearing loss before it can be seen on an audiogram can enhance ototoxicity preventative measures. The use of such sensitive tools is particularly critical where research is being conducted to determine possible ototoxic effects of a drug.

It was hoped that findings from this study which are detailed within this thesis would evoke discussion and debate among the audiology community regarding the impact that HIV/AIDS might have on auditory function of individuals with this disease, and also alert audiologists to the possible effects of ART and other therapies on the hearing status of this population. Furthermore, it was envisaged that this thesis would enhance the audiologists' scope of practice in as far as the drug development and monitoring process is concerned, allowing for careful and thorough ototoxicity monitoring of new drugs before they are FDA approved. This thorough ototoxicity monitoring would hopefully take into account realistic factors that coexist with use of ART such as co-administration of other medications, nutritional supplements, traditional medicine, and so on. Lastly, it was anticipated that results from the current study outlined in this thesis would spur significant academic debate and encourage more research into areas other than medical aspects of HIV/AIDS, areas such as the area of HIV/AIDS and sensory, motor, cognitive, and communication functions.

1.12. Organization of the thesis

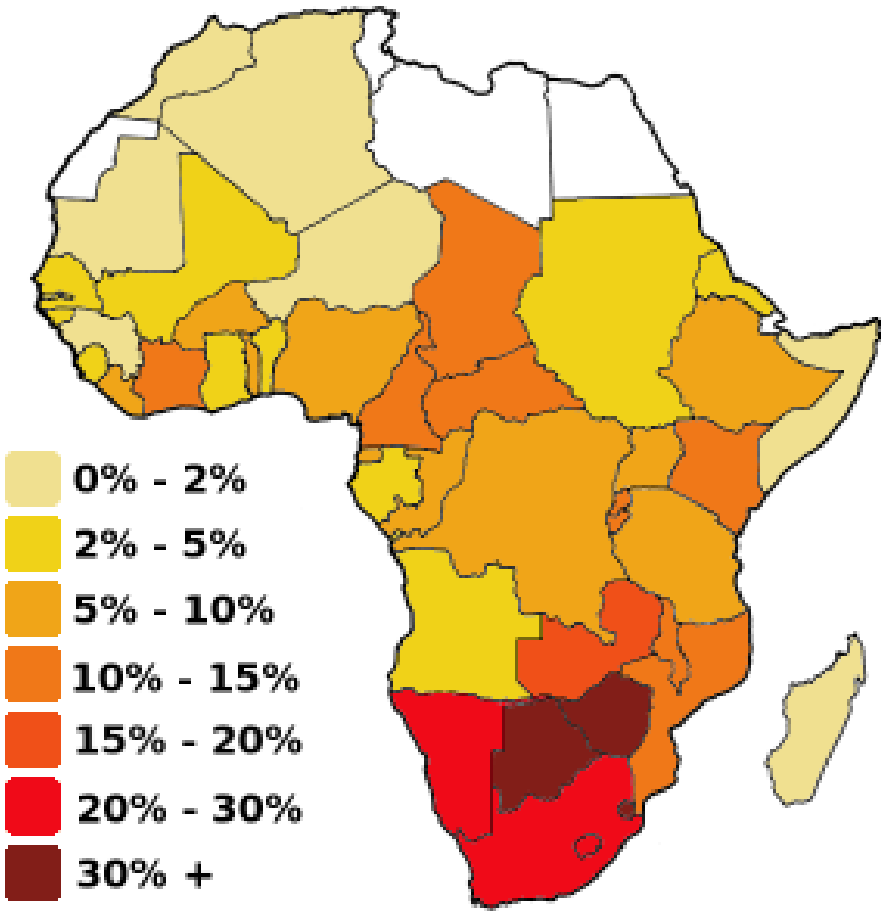
Chapter One provided a broad overview and rationale for the study – with an extensive review of literature on the effects of HIV/AIDS and its treatment on the human body, and specifically on the ear. Chapter Two introduces HIV/AIDS within the global and South African contexts, and attempts to orient the reader to the context within which the HIV/AIDS pandemic has been raging in South Africa – a context within which the current study was conducted. The theoretical framework is divided into a clinical overview of HIV/AIDS (Chapter Three), its treatment (Chapter Four), as well as the side effects of ART (Chapter Five). Ototoxicity (Chapter Six), and an overview of ototoxicity monitoring methods (Chapter Seven) are also explored as

part of the theoretical framework of the current study. These chapters form a foundation and theoretical backdrop for the empirical study (Chapter Eight). The results are presented (Chapter Nine) and discussed in Chapter Ten in a manner consistent with the primary aim and specific objectives of the study, with conclusions, possible recommendations and limitations of the study highlighted in Chapter Eleven.

PART II - THEORETICAL FRAMEWORK OF THE STUDY

Chapter 2

HIV/AIDS IN THE GLOBAL AND SOUTH AFRICAN CONTEXT



Map of Africa coloured according to the percentage of Adults with HIV/AIDS (Retrieved from "http://en.wikipedia.org/wiki/AIDS" – 05, May, 2008)

CHAPTER TWO

HIV/AIDS IN THE GLOBAL AND SOUTH AFRICAN CONTEXT

2.1. Introduction

In its third decade, the acquired immune deficiency syndrome (AIDS) and the Human Immunodeficiency Virus (HIV) that causes it, continue to be one of the biggest challenges faced by South Africa today, alongside poverty, joblessness and other social ills that the South African Government is making a concerted effort to eradicate (Kotwal, 2004). South Africa has seen over ten years of democracy since the abolition of the apartheid regime. In these years, the democratically elected government has made much progress in instituting new and equitable policies and laws, and also in reforming the health sector and other social services to cover the majority of the South African population (Benatar, 2004; Posel et al., 2007). All these achievements, and many others, are recognized and acknowledged. However, poverty, inequality, and the incidence and prevalence of HIV/AIDS appear to be worsening.

Terreblanche (2003) and UNAIDS (2006) argue that even though South Africa has experienced a remarkable political transformation since 1994, there has been no parallel socioeconomic transformation; moreover, South Africa has experienced an increasing prevalence of HIV infection, contributing to a vicious cycle of illness, death, poverty and hardship. Hickey, Ndlovu and Guthrie (2003) assert that the severity and size of the pandemic make the fight against HIV/AIDS an unparalleled challenge. This assertion is echoed by Walker, Reid and Cornell (2004, p.12) who believe that HIV and AIDS "have Southern Africa by the throat". Despite having access to relatively adequate resources, South Africa has lagged behind

somewhat in its response to the HIV/AIDS epidemic. This chapter adopts a deductive approach by presenting the general incidence and prevalence rates of HIV/AIDS in the world and on a more global level and thereafter proceeding to look at the specific South African context.

2.2. Incidence and prevalence of HIV/AIDS

The true epidemiology of HIV/AIDS is almost impossible to confirm at any given point in time (both globally and for specific countries). Review of literature on the incidence and prevalence of HIV/AIDS exposed the lack of reliable, relevant and consistent statistical information. Information available seems to be heavily dependent on the institutional affiliation of the writer and the purpose of the report, creating some level of contradiction. To find the true epidemiological incidence and prevalence rates of HIV/AIDS for a population, a survey of an entire population would be required. In view of the practical and methodological limitations of such an approach, most epidemiological studies found relied significantly on estimates.

The nature of the disease, the stigma associated with testing and diagnosis, and the resistance of some sections of our society in acknowledging and accepting the existence of HIV/AIDS possibly exacerbate the situation even further as epidemiological studies rely on open disclosure and willingness to participate in tests and surveys. A further obstacle probably hindering attempts to confirm the true epidemiology of HIV/AIDS may be the fact that health care is not accessible to all of South Africa's citizens, particularly in rural areas, even though the government reports making all efforts to improve access to health care in all areas. With these limitations in mind, the following incidence and prevalence rates of HIV/AIDS are offered:

2.2.1. The Global epidemic today

The first descriptions of this disease appeared in the early 1980s, in New York and San Francisco, but since then, an estimated 38.6 million [33.4 million–46.0 million] people worldwide were reported to have been living with HIV by the end of 2005. An estimated 4.1 million [3.4 million–6.2 million] became newly infected with HIV and an estimated 2.8 million [2.4 million–3.3 million] lost their lives to AIDS. Overall, the HIV incidence rate (the proportion of people who have become infected with HIV) is believed to have peaked in the late 1990s and to have stabilized subsequently, notwithstanding increasing incidence in several countries (UNAIDS, 2006).

Favourable trends in incidence in several countries are thought to be related to changes in behaviour and prevention programmes. The observed declines in prevalence appear to be related to a combination of factors, especially reductions in casual sex relations with non-regular partners, along with increases in condom use and later sexual debuts (UNAIDS, 2005).

Changes in incidence along with rising AIDS mortality have caused global HIV prevalence (the proportion of people living with HIV) to level off. However, the numbers of people living with HIV have continued to rise, due to population growth and, more recently, the life-prolonging effects of antiretroviral therapy (UNAIDS, 2006). In sub-Saharan Africa, the region with the largest burden of the AIDS epidemic, data also indicate that the HIV incidence rate has peaked in most countries. However, the epidemics in this region are highly diverse and especially severe in Southern Africa, where some of the epidemics are still expanding (UNAIDS, 2006). Among the notable new trends are the recent declines in national HIV prevalence in two

sub-Saharan African countries (Kenya and Zimbabwe), urban areas of Burkina Faso, and similarly in Haiti, in the Caribbean (UNAIDS, 2006).

2.2.2. The African epidemic today

Africa remains the global epicentre of the AIDS pandemic (UNAIDS, 2006). Sub-Saharan Africa has been reported to be more severely affected by AIDS than any other part of the world since even though this region forms 10% of the world's population, it constitutes nearly 64% of the worldwide total of infected people (Claton, 2006). South Africa's AIDS pandemic - one of the worst in the world - shows no evidence of a decline (UNAIDS, 2006). Based on South Africa's extensive antenatal clinic surveillance system, as well as national surveys with HIV testing and mortality data from its civil registration system, an estimated 5.4 million people were reported to be living with HIV in 2005, with an estimated 18.8% of adults between the ages 15–49 years living with the virus in 2005. Almost one in three pregnant women attending public antenatal clinics were living with HIV in 2004 and trends over time show a gradual increase in HIV prevalence among this group (UNAIDS, 2006).

There are no clear signs of declining HIV prevalence elsewhere in southern Africa - including Botswana, Namibia and Swaziland, where exceptionally high infection levels are reported to continue (UNAIDS, 2006). In Swaziland, the national adult HIV prevalence is estimated at 33.4%. HIV prevalence among pregnant women attending antenatal clinics rose from 4% in 1992 to 43% in 2004. Botswana's epidemic is equally serious, with national adult HIV prevalence estimated at 24.1% in 2005. Lesotho's epidemic seems to be relatively stable at very high levels, with an estimated national adult HIV prevalence of 23.2% (UNAIDS, 2006).

On the eastern coastline, Mozambique is said to be developing a dynamic epidemic, where the estimated national adult HIV prevalence is 16.1% (UNAIDS, 2006).

In summary, sub-Saharan Africa's HIV epidemics are following divergent trends. There is evidence of diminishing or stable HIV spread in most east African and west African countries, along with signs of growing epidemics in a few countries. In southern Africa, only Zimbabwe presents evidence of a strong decline in national HIV prevalence (Dorrington et al., 2006). In several other countries - including South Africa - the epidemics do not yet show signs of abating.

2.2.3. The South African epidemic today

National sentinel surveys of public sector antenatal clinic attendees have been conducted in South Africa by the Department of Health since 1990. Antenatal sentinel surveys are internationally recognized as tools for estimating the magnitude, growth and spread of the pandemic over time (Dorrington et al., 2006). These surveys conducted each year, have provided the best available data in terms of HIV prevalence and are regarded as the cornerstone in tracking the progression of the HIV/AIDS pandemic in the country. Pregnant women presenting for antenatal care for the first time during their current pregnancies at selected sites are requested to participate in these anonymous and unlinked surveys. Recent antenatal clinic data show that several parts of Southern Africa have now joined Botswana with prevalence rates among women exceeding 30%, and that of men just over 25% (Dorrington et al., 2006).

In South Africa, some 5.4 million [4.9 million - 6.1 million] people, including 240 000 [93 000 - 500 000] children younger than 15 years, were living with HIV in 2005 (UNAIDS,

2006). HIV data gathered in the country's extensive antenatal clinic surveillance system suggest that HIV prevalence has not yet reached a plateau (DOH, 2006b). The latest data show a continuing, rising trend nationally in HIV infection levels among pregnant women attending public antenatal clinics: from 22.4% in 1999 to 30.2% in 2005 (a 35% increase) (DOH, 2006b). However, HIV prevalence among young people may be stabilizing. Antenatal surveillance suggests that HIV prevalence among 15 - 24-year-old pregnant women has remained relatively stable since 2000 at 14% - 16% among 15 - 19-year-olds and 28% - 31% among 20 - 24-year-olds (DOH, 2006b).

As in the rest of sub-Saharan Africa, the epidemic in South Africa has been noted to disproportionately affect more women than men as opposed to worldwide statistic that points to men being more infected (Claton, 2006). Young women (15 - 24 years) are four times more likely to be HIV-infected than are young men: in 2005, prevalence among young women was 17% compared with 4.4% among young men (Shisana & Simbayi, 2005). These infection levels were similar to those found in the 2003 national survey of 15 - 24-year-olds where 15.5% of young women and 4.8% of young men were found to be HIV-infected (Pettifor et al., 2004). One in three women aged 30 - 34 years were living with HIV in 2005, as were one in four men aged 30 - 39 years, according to the 2005 national HIV household survey. In addition, high infection levels were found among men older than 50 years, more than 10% of whom tested HIV-positive (Shisana & Simbayi, 2005).

Although it is reported that the HIV epidemic emerged a little later than most other HIV epidemics in the sub-region, South Africa's pandemic has now reached the stage where

increasing numbers of people are dying of AIDS (Statistics South Africa, 2006). The latest official mortality data show total deaths (from all causes) in South Africa increased by 79% from 1997 to 2004 (from 316 505 to 567 488) (Statistics South Africa, 2006). Death rates from natural causes for women aged 25 - 34 years increased fivefold between 1997 and 2004, and for males aged 30 - 44 they more than doubled over that period. A large proportion of the rising trend in death rates is attributable to the AIDS pandemic (Actuarial Society of South Africa, 2005; Bradshaw et al., 2004; Dorrington et al., 2002; Medical Research Council - MRC, 2005), and the increasing death toll has driven average life expectancy below 50 years in three provinces (Eastern Cape, Free State and KwaZulu-Natal) (Actuarial Society of South Africa, 2005).

Evidence suggesting that the HIV pandemic is extensive in South Africa comes from a variety of other sources over and above HIV tests of pregnant women attending public antenatal clinics. These sources include analysis of death certificates (MRC, 2001; Statistics South Africa, 2002) and surveys from a number of communities (Human Sciences Research Council – HSRC, 2002) and companies and institutions such as hospitals across the country (Colvin, Dawood, Kleinschmidt, Mullick & Lallo, 2001; Zwi, Pettifor, Soderlund & Meyers, 2000). None of these surveys, even taken together, can provide a precise estimate of the number of infected, dying or dead people, but they do imply a problem of pandemic proportions (Claton, 2006; Posel et al., 2007).

There are geographic variations with some provinces more severely affected than others (Claton, 2006). These differences also reflect background socio-economic conditions as demonstrated by the district level HIV surveillance data in the Western Cape (DOH, 2006b). In

this province in 2005, the average was the lowest in the country at 15,7%, but two metropolitan health areas of Khayelitsha and Gugulethu/Nyanga registered prevalence rates of 33,0% and 29,0% respectively, which are considerably above the national average. People living in rural and urban informal settlements seem to be at highest risk for HIV infection and AIDS (DOH, 2006b).

More recently Dorrington et al. (2006) provided current projections in South Africa based on a thorough analysis of a range of epidemiological and demographic data including the antenatal surveys and recorded deaths up to the year 2003. In addition, the projections these authors provide allow for the impact of major current interventions such as provision of antiretroviral drugs. According to the projections about 5.4 million people out of a total of nearly 48 million South Africans were HIV positive in the middle of 2006, giving a total population prevalence rate of slightly over 11%. Around 600,000 people are estimated to have reached the stage of being ill with AIDS (11%) (Claton, 2006). This is the percentage of the population that was targeted for this study as they are the group which receives ARV treatment in South Africa.

The projections also suggest that antiretroviral treatment could, even at this late stage of the disease, have a significant impact on reducing the number of AIDS deaths per year (Claton, 2006). Without ART, South Africa would have expected some 505 thousand deaths a year due to AIDS in 2010, but with ART this figure will be reduced to approximately 388 thousand a year – a difference of over 100 thousand deaths in a year (Dorrington et al., 2006). These authors raise the uncertainty about the coverage of the ART roll-out in the future and the number of AIDS deaths in 2010, which they believe could even be as low as 291,000 a year if 90% of people

progressing to AIDS were to receive treatment. It is estimated that by the middle of 2006 some 711 thousand people were in need of ART, while approximately some 255 thousand were receiving it (Dorrington et al., 2006). The number on treatment can be expected to rise, reaching at least 500 thousand by 2015 even if coverage fell to only 20%, furthermore, if coverage increased to 90% there would be over 2 million on treatment by 2015 (Dorrington et al., 2006).

The Department of Health, Actuarial Society of South Africa (ASSA) and the HSRC have all separately used the results from some of these surveys to estimate the size of the pandemic. This is a difficult task and involves making a number of assumptions. There is also quite a large margin for error. The three institutions calculate different pandemic sizes ranging from 4,8 million to 6,6 million. Clearly the differences are significant, but they all reach the same critical conclusion: the South African HIV pandemic is massive. Even if the size of the pandemic was as small as one million, there would still be an enormous amount to be done to mitigate its effects, including research into intervention strategies that the government is instituting - roll out of antiretroviral drugs being one of these.

2.3. The South African context

Great strides have been made in the past 10 years in uncovering the onset and development of the HIV/AIDS disease process, in public awareness campaigns regarding the disease, and in allaying the concerns of the general public with regard to the virus. However, much still needs to be done to dispel the many myths surrounding HIV/AIDS, as well as in terms of the provision and administration of antiretroviral drugs to slow down the course of HIV/AIDS in the South African population (Posel et al., 2007). To this end, it is imperative to provide the socio-political context within which this country has been waging the war against HIV/AIDS. It

is with this backdrop in mind that one can understand the current statistics of HIV/AIDS, and how the prevalence of HIV/AIDS has reached the pandemic proportions it has in this country. This section aims to orient the reader to this very context and endeavours to introduce the reader to other factors that are believed to play a significant role in how the HIV/AIDS pandemic is viewed and managed in this country.

South Africa is a fairly new democracy, with its first democratic elections dating back to 1994. It is a country that is emerging from and continues to struggle against a history of social dysfunction, racial and gender discrimination, associated with unjust and inequitable distribution of resources affecting the majority of its people, as a result of the apartheid regime which was the dispensation pre-1994 (Budlender, 2000; Claton, 2006). These factors have resulted in a country that is still struggling to establish stability in all sectors of its society and this is reflected in the burden of disease experienced by its citizens. Health problems such as poverty-related diseases of infection that include HIV/AIDS are believed to occur mainly in the previously disadvantaged communities (Adams, Claasens, Dikweni & Streak, 2001; Bradshaw, Groenewald, Laubscher, Nannan, Nojilana, Norman, Pieterse & Schneider, 2003).

As earlier reported, the first few cases of HIV and AIDS in this country were identified in the late 1980s (DOH, 2006a). As a result of the lack of a positive and definitive response from the government of the time, there was no discernible slowing down of this early phase (Posel et al., 2007). It is reported that it was not until leadership from the National Liberation Movement, led by the African National Congress in 1992 that there was a definitive programme to raise awareness in society of the disease (DOH, 2006a). This was however followed by a long period

of dissent from the highest office in the country of a connection between HIV and AIDS as well as an extended period of withholding provision of antiretroviral treatment to the infected (Posel et al., 2007). The fact that the South African President (President Thabo Mbeki) disputed the fact that HIV causes AIDS created turmoil in the country and caused confusion that could have had a negative effect on some of the prevention programmes that were being implemented at the time (Claton, 2006).

Posel et al. (2007) assert that with the country's President taking up a position of AIDS denialism and the Minister of Health (Manto Tshabalala-Msimang) sceptical about the merits of antiretroviral treatment (but instead promoting alternative therapies of vitamins, olive oil, lemon juice and beetroot), it is no wonder that there are many signs of uncertainty, confusion, and conflict over the nature and effects of HIV.AIDS in this country. Furthermore, it is believed that it was only because of the significant resistance and opposition from the Treatment Action Campaign (TAC) that more changes were executed by the South African government's Department of Health (Claton, 2006). The TAC and people living with AIDS were involved in court battles with the government, and Claton (2006) believes it was due to this pressure from the TAC that the South African government eventually implemented an antiretroviral treatment roll out programme that was instituted in the first quarter of the year 2004. The government's slow response in provision of ARVs is believed to have been a violation of the Bill of Human Rights (Posel et al., 2007).

Acclaimed internationally as one of the best pieces of Human Rights legislation, the Bill of Rights is one of the fundamental imperatives of the South African Constitution (Posel et al.,

2007). It is in the Constitution and the National Health Act of 2005 that the right of access to health care, to reproductive health and emergency medical services for all is embedded. The process of rectifying the imbalances of the past commenced in 1994 and is reported to be progressing well and with great dynamism and energy (Benatar, 2004). This is clearly seen, for example, in the transformation that one sees occurring in most provincial hospitals in the country where equity in respect of resources, direct improvement of services, the ongoing quality assurance (accreditation) programmes, are equitably implemented, emphasized and continually monitored. This statement flies in the face of recent scandals at Mt Frere and Mahatmah Gandhi Hospitals where unacceptably high numbers of infants allegedly died from poor nursing care and preventable infections. Several programmes to ensure access to education, health services, and reduction of poverty, provision of shelter, clean water and sanitation seem to be the thrust of today's government interventions (Benatar, 2004). As a prerequisite to ensuring sustained development, growing the economy and good governance are reportedly seen as the requirements by the current government (Bell, Devarajan & Gersbach, 2006).

As part of efforts to improve good governance, the South African government has had to also examine the role of women in society. Women in South Africa, particularly black women, have been at the bottom of the pyramid in terms of contribution to the economic, social, and political functioning of the country (Claton, 2006). They have for a long time, experienced racial, class, and gender discrimination, which the media sometimes describe as "triple oppression" (Adams et al., 2001). Given that the location of power in society is determined by these factors, the gender roles in South African society have arguably favoured men (Claton, 2006). Some practical challenges facing women and arising from these factors, relate to violence and abuse,

poverty, and the health status of women in general (DOH, 2006a). This gender inequality is believed to be one of the leading explanations for why HIV/AIDS seems to be affecting more women than men in the country (Claton, 2006). The current government, under the leadership of President Thabo Mbeki has made distinct efforts towards changing the gender imbalances in the country (Kotwal, 2004), as evidenced for example by the Deputy President (Deputy President Phumzile Mlambo-Ngcuka) of the country being a black woman, for the first time in the history of South Africa.

Since 1994, the current government has made many other advances towards empowerment of women, which is one of critical elements of the transformation agenda in the country (Kotwal, 2004). To date, the adoption of the Constitution, the setting up of an Office of the Status of Women in the Presidency and provincial Premier's office, the existence of gender units in each government department, and the creation of the Commission on Gender Equality are some of the reported significant developments that have been made by the South African government (DOH, 2006a). Access to parliamentary discussions and decision-making processes under the leadership of women chairpersons (1994-2004 speaker of national legislature was Dr Frene Ginwala and currently Ms Baleka Mbete) are examples of government acknowledgment of women being valuable and contributing members of the society. In the private sector more and more women are making their mark and being recognized for their impact on the economy as well as all other sectors of the country. Women's involvement in the country's economic development is believed to have contributed to the current economic climate that South Africa is experiencing.

According to the South African Minister of Finance (Manuel, 2007), the country's economy has and continues to experience the most unprecedented growth and is now one of the "largest and most popular emerging economies in the world". Although this may be true, the gap between the central actors in that economy and those at the periphery is still much too wide (Walker et al., 2004). A significantly large number of people without the necessary skills and financial expertise are yet to experience the full benefits of this economic "boom". These are the people most at risk for infections and diseases commonly referred to as diseases of poverty like HIV, AIDS, and Tuberculosis (Bollinger & Stover, 1999). Noring, Dubler, Birkhead and Agins (2001) and Claton (2006), believe that socially and economically disadvantaged populations are disproportionately affected by HIV infection and also have unequal access to treatment and that this inequitable access to HIV treatment poses a compelling ethical obligation for countries to examine their decisions regarding treatment.

Close monitoring of the yearly address by the South African Minister of Finance revealed that in the past decade of South Africa's democracy, some changes have been made as attempts towards meeting the basic needs of shelter, clean water and sanitation, food, security, the provision of health and other social services through social grants and other means of assistance – though much more work still awaits the government. The South African Department of Health believes that the many programmes that are currently being implemented to increase access to education, skills development, and preferential procurement, can contribute towards minimizing this economic gap between the "haves" and the "have nots" (DOH, 2006a). It is believed that these programmes, as they reduce the levels of poverty, will contribute towards the reduction of

vulnerability to medical conditions such as HIV/AIDS and TB (Adams et al., 2001; Barnett & Whiteside, 2002; Idasa, 2003).

The Government's Comprehensive HIV and AIDS management programme is firmly located within and aligned to all of these aforementioned development interventions. The beginning of a national coordinated response to HIV and AIDS dates back to 1992 with the formation of the National AIDS Coordinating Committee of South Africa (NACOSA). The goal of NACOSA was to mobilize sectors of society towards raising national awareness about HIV and AIDS (NACOSA. 1994). NACOSA was reviewed in 1997 and the need for a multisectoral approach to the HIV/AIDS problem was highlighted (DOH, 2006b). This focus therefore led to the development of the "National Strategic Framework for HIV and AIDS and STIs 2000-2005", and this policy has also recently been reviewed and updated to the current **"**Broad Framework for HIV & AIDS and STI strategic plan for 2007-2011" under the direct leadership of the Deputy President of the country (DOH, 2006a). The four priority areas outlined in these frameworks are:

- Prevention
- Treatment, Care and Support
- Legal and Human Rights
- Research, monitoring and surveillance

(DOH 2006a, 2006b)

During the implementation of the South African Strategic Framework, programmes have changed to take account of scientific developments and the availability and affordability of interventions against HIV and AIDS (DOH, 2006a). Currently, the National Comprehensive Plan

for the Management, Care, and Treatment HIV/AIDS is reported to guide the design and implementation of programmes. It reportedly highlights the centrality of prevention, the importance of nutrition and traditional medicines, and health care systems strengthening as the mandatory elements for a concrete and sustainable solution (DOH, 2006a). This policy is context specific, and it takes into account the factors that are present in this country that may not be so widespread in international developed countries – such as the high prevalence of poverty and the heavy reliance on and belief in traditional healers by the greater majority of the people in this country.

The Comprehensive HIV and AIDS Care, Management and Treatment Plan for South Africa is a significant milestone both as a health sector intervention and as a socioeconomic enhancement strategy (Claton, 2006). This Plan presents a unique approach to disease management and in particular to HIV and AIDS management. It recognizes the important role of preventing any further infections in South African society by laying emphasis on strengthened intervention strategies, although this plan has more emphasis on education than on provision of antiretroviral drugs to all infected (Jackson, 2002). It further recognizes that a traditional approach to disease management which ignores the contextual factors, including factors related to historic underdevelopment, the poor social environment and limited social facilities that confront the unwell and the healthy, is not optimal and impedes true advances in good health service provision. The Plan therefore closely integrates within it the broader social and development strategy. Another important paradigm within which the Plan was conceived and developed is the reality that singular problems including HIV and AIDS can only be addressed

successfully in a context where the entire health system is simultaneously being strengthened and developed to adequately sustain equitable and good quality programmes (DOH, 2006a).

Most of these programmes are incorporated into the broader primary health care system. As far as prevention of HIV/AIDS is concerned, programmes such as life-skills education for children and the youth, condom distribution, STI management, Prevention of Mother to Child Transmission (PMTCT), Voluntary Counselling and HIV Testing (VCT), are illustrations of some of the strategies for prevention of new infections (DOH, 2006a). As part of the Quality Assurance or Accreditation programmes cited earlier, work is being done on ensuring safe blood supplies, safe intravenous drug use, and infection control in health facilities to minimize the risk of occupational exposure to all blood-borne pathogens (McCoy, Besser, Visser & Doherty, 2002). Care, treatment and support services provided in health facilities and in the informal health sector mainly by Non-Governmental Organizations (NGOs) also validate the extent of the work done, steered and supported by Government (Claton, 2006; DOH, 2006a).

South Africa is currently implementing an accreditation process which is reported to have as one of its objectives ensuring that any public health facility, including those accredited to provide antiretroviral therapy act in accordance with a minimum set of standards that ensure good quality of care (DOH, 2006a). A specially designed accreditation tool is used to guide discussions with various representatives of the facilities and to also gather information that is used to make recommendations on the accreditation status. The facilities that do not comply with the minimum standards are required to develop plans for immediate implementation and are then accredited once the improvements have been made.

Through the implementation of the Comprehensive Plan, every health district in the country is reported to have a service point for the provision of a range of interventions (Gilson, Doherty, McIntyre, Thomas, Brijlal, Bowa & Mbatsha, 1999). These interventions are expected to include prevention, nutrition, management of opportunistic infections and treatment with antiretroviral drugs. Provision of these interventions is undoubtedly dependent on factors such as the upgrading in information management systems, the improved human resources management and capacity development, as well as the strengthening of laboratory services and referral system (Claton, 2006; Gilson et al., 1999). This implies that investments in the Health Department's functioning need to be extensive.

Investing in information management systems may be criticized by some sectors of the society who may not understand what impact these may have on HIV/AIDS management. It is apparent though that these information management systems would assist in accomplishing aspects of the Monitoring and Evaluation Framework for the Comprehensive HIV and AIDS Plan such as in collecting data used as indicators in order to establish:

- the cumulative number of patients assessed;
- the cumulative number of patients on treatment;
- the number of CD4 counts and viral loads measured; and
- the number of accredited health facilities

(DOH, 2006a)

Collection, analysis, and close monitoring of theses data are not only crucial for epidemiological purposes, but are also powerful research and monitoring tools for both scientists involved in management of HIV/AIDS, and for government planning and policy formulation.

The South African Department of Health (2006a) reports having great difficulty in achieving an appropriate information monitoring system. It acknowledges that there is generally a lack of a patient information systems, and where systems exist, there are challenges in implementing them. Therefore it is very difficult to collect data to monitor the indicators listed above. The existing monitoring system is reported to be in the process of being progressively strengthened and there are reports of an ongoing process to strengthen and expand the number of reported ART data elements to include indicators such as patients lost to follow-up, deaths, adherence, adverse events, ART regimens, and gender and age groups (DOH, 2006a).

Expenditure on HIV and AIDS activities has been seen to have increased substantially over the past five years when one compares the budget that has been allocated towards these activities on a yearly basis. The annual budget allocation for this programme increased from R264 million in 2001 to R1.5 billion in 2005. From the 2007 budget speech (Manuel, 2007), a general overall increase in the allocation towards health was evident. Over and above the general health budget allocation, health received a further R1,7 billion for this programme, presently being delivered through 272 sites (Manuel, 2007). Spending on dedicated HIV and Aids programmes by health, education and social development departments is envisaged to exceed R5 billion by 2009/10 (Manuel, 2007). The increasing budget allocation highlights the government's

commitment to management of HIV/AIDS – the specific use of this budget though may leave much to be desired, particularly when it comes to the provision of antiretroviral drugs.

The availability and provision of antiretroviral therapy in accredited public health facilities commenced in the first quarter of 2004 as part of the Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (Posel et al., 2007). The National Antiretroviral Treatment Guidelines, published in 2004, are used for the assessment, enrolment and management of persons who are eligible for ART (DOH, 2004). It was only in 2005 that the National Antiretroviral Treatment Guidelines for children were published. The first edition (2004) of the National Antiretroviral Treatment Guidelines stipulates the following patient eligibility criteria for adults and adolescents:

The medical criteria for commencement of ART are as follows: -

- CD4 count <200 cells/mm^3 irrespective of WHO stage, or
- WHO (World Health Organization) Stage IV disease irrespective of CD4 counts.

The Psycho-social considerations (not exclusion criteria) are as follows:

- Demonstrated reliability, i.e. patient has attended three or more scheduled visits to an HIV clinic.
- No active alcohol or other substance abuse.
- No untreated active depression.
- Disclosure: it is strongly recommended that patients have disclosed their HIV status to least one friend or family member OR have joined a support group.

- Insight: patients need to have accepted their HIV-positive status: They need to have insight into the consequences of HIV infection and the role of ART before commencing therapy.
- Patients should be able to attend the antiretroviral centre on a regular basis or have access to services that are able to maintain the treatment chain. Transport may need to be arranged for patients in rural areas or for those far away from the treatment site.

These guidelines stress the importance of informed consent and highlight the fact that the final decision to treat needs to be taken by the multi-disciplinary team at the ART centre that initiates treatment. The involvement of the patient or caregiver in the decision making is encouraged. At the beginning of February 2006, there were reportedly 204 facilities that were fully functional and providing ART services at the end of December 2005 (DOH, 2006a). All 53-health districts had at least one health facility providing ART services and 63% of the 252 sub-districts had full coverage (DOH, 2006a).

The Department of Health in South Africa carries a major responsibility for co-coordinating the response to HIV (Claton, 2006). Some of the activities include coordinating implementation of the National HIV, AIDS, STI and TB programmes as well as coordination of the Comprehensive Plan for HIV and AIDS Care, Management and Treatment and the provision of support grants as well as coordinating work done by other government departments (DOH, 2006b). All stakeholders in South Africa are reported to have embraced the National Strategic Plan (NSP) 2000-2005 as a guiding framework. It served to broaden the involvement of agencies beyond the Department of Health. However, stigma and discrimination remain unacceptably high and this has been a deterrent to the use of some of the services (Benatar, 2004). Also, it is

reported that implementation of programmes tended to be vertical, with some serious capacity deficits, especially in the previously disadvantaged rural communities (Claton, 2006; Gilson et al., 1999; May, 1998). This state of affairs does not come without challenges which have been well acknowledged and extensively reported (Whiteside & Sunter, 2000).

According to Claton (2006) and the Department Of Health South Africa (2006a), the following is the list of challenges which the South African government still faces and needs to continually address in order to reach the goals and targets set out in all the strategic plans and treatment programmes:

- Health system challenges remain amongst the most pressing and there is a need to address the shortage of health personnel in the public health sector in general and in the accredited service points.
- The shortage of scarce skills including doctors, pharmacists and nurses is a major challenge facing the public health sector in South Africa. Allied medical personnel including audiologists, social workers, occupational therapists and physiotherapists fall within the category of scarce skills personnel.
- The programme needs to be implemented in the context of a country that has recently emerged from institutionalized inequalities. Most of the communities are still challenged by poverty and underdevelopment.
- It is imperative to ensure that implementation of the plan strengthens health systems and improves quality of care. The implementation of the National Health Management Information System remains a major challenge.

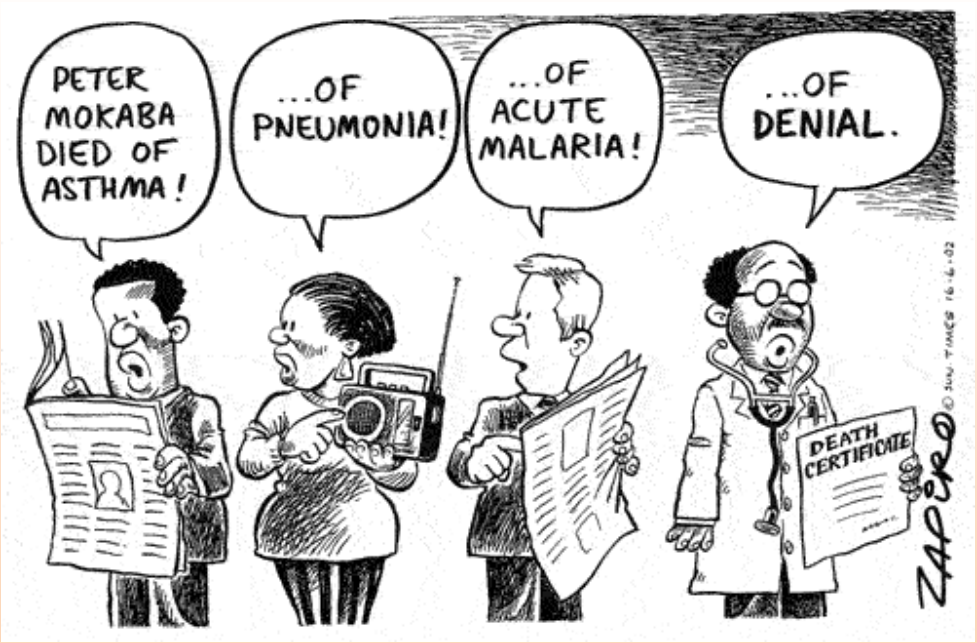
- It is necessary to integrate the Comprehensive HIV and AIDS services within the Primary Health Care approach.
- Management of African Traditional medicine (registration, training, referral systems and research) needs to take place.

(Claton, 2006; DOH, 2006a)

2.4. Summary

It is clear from the review of literature in this chapter that South Africa is facing a significant challenge in addressing the HIV/AIDS pandemic that is affecting every sector of its society. If the scourge of HIV/AIDS is not brought under control, the country's political, social, as well as financial gains achieved in the post apartheid period could all be in vain. The reported steady growth in financial indicators which in turn improve the general functioning of the country would be significantly impaired since this development relies heavily on a healthy and productive workforce. The treatment programmes that are currently being implemented need vigorous continual reviewing and monitoring to ensure that both prevention (education to those not yet infected, prevention of mother-to-child-transmission, and prevention of the spread of the virus) and treatment are provided early to ameliorate the negative impact that HIV/AIDS has on the population of this country.

HIV/AIDS - AN OVERVIEW



Chapter 3

CHAPTER THREE

HIV/AIDS - AN OVERVIEW

3.1. INTRODUCTION

It is currently understood and accepted that untreated HIV disease is a chronic progressive process that begins with viral infection. From the time of infection, the virus reportedly continuously and rapidly replicates, mutates, and as a result diversifies and evolves. Immune system damage also begins upon infection (Centers for Disease Control, 1992a). The burden of the virus and the bulk of this process is said to occur in lymphoid tissue, and the immune system struggles to hold the process in check. Slowly, but persistently, the process destroys essential components of the host immune system (Van Dyk, 2001). Eventually the host becomes increasingly susceptible to opportunistic infections and malignancies resulting from immune system dysfunction so that it eventually dies as a result of complications from these consequences of an impaired immune system (Mindel & Tenant-Flowers, 2001).

It is also well known and accepted that untreated HIV disease typically advances relentlessly in almost all infected persons from clinically silent infection measurable only by laboratory tests to severely impaired immunologic function, resulting in the acquired immunodeficiency syndrome (AIDS) (DOH, 2006a). Without treatment, HIV/AIDS is reported to progress over a median interval of about 10 years, although with vast individual variation, and eventually causes death (Hogg et al., 1994). During the course of HIV disease, a range of clinical syndromes may occur. Partly understood interactions between host, HIV, and environmental

factors seem to influence the particular clinical manifestations and rate of disease progression for each individual (Hogg et al., 1994; Walker et al., 2006).

However, contemporary and continual advances in basic and clinical research in HIV disease have dramatically changed the perspective of HIV infection as a treatable and potentially curable disease, rather than one that is persistently progressive and inevitably fatal (Hammer et al., 2006). In clinical trials and in individual patients, new anti-HIV drugs employed in potent combination regimens (HAART) have demonstrated impressive efficacy by both clinical and laboratory measures, and have provided evidence of the concept that the appropriate drugs can suppress HIV replication and disease manifestations (Mocroft et al., 2003; Noring et al., 2001). These authors report that HAART can increase the length and quality of life and reduce viral load, thus decreasing the likelihood of HIV transmission. Furthermore, HIV-related hospitalisations and death rates have reportedly declined since the widespread introduction of HAART. Hammer et al. (2006) insist that it is the new techniques for measuring HIV RNA that have allowed more intelligent and effective clinical management and prognostication, and they have also reduced from years to weeks the time required to accumulate evidence for drug efficacy in a clinical trial. All these advances and benefits may only be applicable in developed countries where these studies were conducted – as opposed to developing countries where issues of tuberculosis and poverty may play a significant role in disease management.

The discovery of the rapid replication rate of HIV in all stages of the disease together with the appreciation of progressive immune system damage from the beginning of HIV infection, have generated theories that now guide anti-HIV therapy. Indications of at least some

degree of immune recovery after response to potent antiretroviral therapy (Hammer et al., 2006; Noring et al., 2001) provide realistic hope that even more immune recovery and reconstitution can be achieved with knowledge gained in future research. Although much work still remains to be done and moreover more effort still needs to be placed on ensuring that the benefits of even these advances are made available to all individuals particularly in developing countries, nevertheless a realistic basis for optimism has been established.

All this new knowledge has answered many questions, but it has also created many more. Progress has produced new classifications, new recommendations for monitoring, staging and estimating prognosis, and new foci of research interest with side effects of ARVs being one of the major research thrusts. The objective of this chapter is to provide an overview of HIV disease as a preface to the contemporary thinking about pathophysiology and clinical management of the disease.

3.2. HISTORY OF THE PANDEMIC

When it first emerged, AIDS was recognized as a severe, previously unseen, immunodeficiency syndrome with an unknown aetiology. In 1981, early reports (Centers for Disease Control, 1981a) described the HIV epidemic in the United States as a clinical syndrome of immune deficiency well before research recognized and acknowledged HIV and showed it to be the cause of the syndrome. The Centers for Disease Control (CDC) introduced the name "acquired immunodeficiency syndrome" and devised a case definition by which clinicians and researchers could identify and report cases (Adler, 2001). It was only in the late 1980s that first few cases of HIV/AIDS were identified in South Africa (DOH, 2006a).

Since then, major risk groups have been identified and reported throughout the world. Epidemiologic studies have showed that major risk groups vary in various world populations (Adler, 2001; Mindel & Tenant-Flowers, 2001; Wilson, Naidoo, Bekker, Cotton & Maartens, 2004), and these differences are reported to be a sign of the predominant transmission mechanisms of the area. These transmission mechanisms are defined as three patterns of HIV transmission: types I, II, and III (Adler, 2001). Type I exists in North America, Western Europe, and Australia and leads to disease mainly in homosexual men, injection drug users and their sexual partners, and haemophiliacs and transfusion recipients. Type II exists in Africa, results in equally prevalent disease in males and females, and reflects predominantly heterosexual transmission. Type III refers to a few cases usually attributable to imported contaminated blood or contact with an infected person from outside the region (Adler, 2001). South Africa seems to be mainly experiencing the type II pattern of transmission, with type III having a limited effect.

Alongside the identification of major risk groups was the identification of minor syndromes that are linked to the disease (Mindel & Tenant-Flowers, 2001). Between 1981 and 1983, reports described two syndromes, generalised lymphadenopathy and "AIDS-related complex". These syndromes are now known to be manifestations of early and middle stages of HIV disease (Centers for Disease Control, 1982a).

The first syndrome, generalized lymphadenopathy (Abrams et al., 1984; Centers for Disease Control, 1982a, Metroka et al., 1983) became known most consistently as persistent generalized lymphadenopathy (PGL), but in the early literature was also referred to as gay lymph

node syndrome (GLNS), chronic lymphadenopathy syndrome (LAN, LAS, LNS), extended lymphadenopathy syndrome (ELAS), idiopathic lymphadenopathy syndrome (ILS), generalized persistent lymphadenopathy syndrome (GPL), chronic polyadenopathy, chronic lymphadenomegaly syndrome, and chronic unexplained lymphadenopathy syndrome (CUL). The second, more complex syndrome consisted of combinations of constitutional symptoms and minor indications of immune deficiency, such as oral candida, which did not qualify as CDC-defined AIDS. Many patients also had PGL. This second syndrome became known most consistently as AIDS-related complex (ARC) (Cohen, 1998).

As researchers began to describe the epidemiology and risk factors in a systematic way, many theories surfaced regarding the cause of the strange disease (Wilson et al., 2004). An infectious agent was proposed, and, in 1983, a novel human retrovirus was isolated as the alleged etiologic agent (Barre-Sinoussi et al., 1983; Gallo et al., 1984; Levy et al., 1984). That virus was eventually termed human immunodeficiency virus, or HIV (Coffin et al., 1986). This causal relationship between HIV and AIDS was (and still continues to be) a major source of criticism of the South African President (Mr Thabo Mbeki), and his Department of Health, in the early 2000's for his denialism stance on its existence.

Despite dramatic improvements and developments in basic virology and clinical management, HIV infection has developed into a worldwide pandemic, with millions of individuals infected by the virus and many millions more affected by it (Adler, 2001; DOH, 2006a). In South Africa, because of the extensive and widespread infection rate, the HIV/AIDS problem has been termed a pandemic (DOH, 2006a). Clinicians treating HIV are challenged by a

clinically complex illness with relatively restricted resources for treatment in the majority of settings, South Africa being one of these settings.

Besides the use of prophylaxis in clinical management of HIV disease, antiretroviral therapy has revolutionised and transformed the face of HIV intervention (Noring et al., 2001). In 1987, zidovudine (AZT, or azidothymidine) became the first drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of AIDS (Fischl et al., 1987). When the first approved antiretroviral drug became widely available, there was great optimism and enthusiasm. Unfortunately, this initial excitement was followed within several years by scepticism following the realization that zidovudine used alone ("zidovudine monotherapy") was of only short-term benefit in changing disease progression, and provided at best only minor clinical improvement in most cases (Shafer, Seitzman, & Tapper, 1989).

The occurrence of unfavourable adverse effects and the less than optimal response to zidovudine resulted in a climate of disappointment and cynicism about antiretroviral therapy - cynicism which is still rife in developing countries like South Africa (Benatar, 2004). Early excitement over the life-extending effects of the drug soon diminished, as patients treated with this single-drug therapy began to experience disease progression with negative side effects. However, understanding of the epidemiology, treatment, and prophylaxis of opportunistic infections (OIs) associated with HIV-induced immune deficiency led to significant life-saving innovations (Hammer et al., 2006; Shafer et al., 1989).

In the period of 1993 to 1996, several key developments significantly changed the negative and cynical view about the use of antiretroviral therapy internationally and re-established a sense of hope and optimism to patients, providers, and researchers in developed countries. These developments, credited to years of basic and clinical research in both the private and public sectors, include the following:

- Availability of HIV RNA measurements to monitor viral load
- Development and validation in clinical trials of potent antiretroviral drugs exemplified by the HIV protease inhibitors
- Validation, in clinical trials, of regimens of multiple anti-HIV drugs as a strategy to address HIV replication.

(Cohen, 1998; Hammer et al., 2006)

The result has been a comprehensive approach to highly active antiretroviral therapy (HAART) with combinations of anti-HIV drugs (Hammer et al., 2006; Sepkowitz, 1998, USPHS/IDSA, 1997). Although this has been available in developed countries for approximately two decades, developing countries like South Africa have only started implementing these treatment strategies in the recent past, and still have a long way to go with regard to establishing the effects and impact of contextual, environmental, and other host factors on the efficacy of treatment strategies.

The introduction of protease inhibitors (PIs) in the mid-1990s revolutionized the treatment of HIV (Hammer et al., 1997). Effective combination antiretroviral therapy (ART) became the standard of care in the United States and Western Europe (Palella et al., 1998). Very soon thereafter, countries in which effective ART was available began to note and report sharply

declining morbidity and mortality associated with HIV infection (Adler, 2001; Palella et al., 1998). Again, this positive benefit from the use of ART has not extended to developing poorer countries like South Africa.

Studies of patients receiving the new therapies shed light on HIV pathogenesis (Noring et al., 2001). These authors report that in their study patients treated with potent ART showed abrupt decreases in the amount of HIV RNA circulating in their serum, signifying interference with HIV replication. Additionally, after successful inhibition of viral replication, CD4 T-cell counts began to increase in treated individuals, indicating the capacity of the damaged immune system to restore and regenerate itself (Noring, et al, 2001).

Potent therapy was not without complications, however; and the code of belief of the late 1990s, "hit early, hit hard," (DOHHS & Henry J. Kaiser Family Foundation, 1998) became balanced by realization that long-term medication toxicity was to be expected among individuals who were now living longer, healthier lives with HIV infection. Once more, the model and standard of care of HIV treatment underwent revision, and treatment was from then on recommended primarily for individuals with more advanced disease (Dybul, Fauci, Bartlett, Kaplan, & Pau, 2002) or for all patients with symptomatic HIV disease (Hammer et al., 2006), the former being the treatment model that South Africa seems to have embraced and adopted, and on which its treatment protocols have been based on.

3.3. CLASSIFICATION SYSTEMS AND STAGING PROCEDURES

3.3.1. Pathophysiology and Classification of HIV Disease

Infection with the HIV is responsible for the development of AIDS. Jackson (2004) and Saltzman, Williams, Gelfand and Wilson (2005) describe the pathophysiologic process as follows:

- Once introduced into the bloodstream, the virus attaches to receptors on the host's CD4 lymphocytes where it releases its RNA.
- Reverse transcriptase, a unique enzyme characteristic to the HIV virus, incites the cell to synthesize copies of DNA complimentary to the viral RNA template (cDNA).
- The cDNA migrates into the nucleus of the infected cell and becomes a part of the chromosomal material of the host.
- Thus, the infected lymphocyte manufactures large numbers of new viral particles that are released back into the bloodstream to infect the other CD4 lymphocytes to levels low enough to lead to severe immuno-compromise.

Simply put, HIV appears to cause damage by:

- Weakening the CD4 or T4 response by invading the dendritic cells that stimulate the CD4 cells to respond to foreign organisms.
- Entering CD4 cells and joining the cells' own reproductive material. Numerous copies of the virus are produced, which eventually break out of the cells, killing them. They then find other CD4 cells to invade and the process starts again.
- Causing uninfected CD4 cells to clump around infected CD4 cells, thus immobilising them.

- Leading other types of cells dependent on CD4 cells to cease to function properly as the CD4 cells become depleted.
- Attacking various other cells important for immunity (monocytes and macrophages), and causing other damage.

The systematic depletion of CD4 cells from greater than 500 cells/mm^3 to less than 200 cells/mm^3 eventually causes profound host immunosuppression (CDC, 1993). Fundamental to the pathophysiology of AIDS is the inability of the immune system to compensate for the depletion of specific immune effector cells induced by HIV (Levine, Scadden, Zaia & Krishnan, 2001).

Because HIV damages the immune system, it leaves the infected person vulnerable to a variety of infections (called "opportunistic infections" to indicate that they arise in the setting of immune impairment) (Mindel & Tenant-Flowers, 2001; Pederson et al., 1989). This effect of HIV on the immune system is monitored by measuring the CD4 (helper) lymphocyte count in the blood. A normal CD4 count (between approximately 600 and 1,200 cells/mm^3) indicates that the immune system has not undergone sufficient damage to put the individual at risk for opportunistic illness (Dybul et al., 2002). Such individuals are unlikely to require treatment, however, CD4 counts less than 350 cells/mm^3 indicate that some impairment of immune function is present, and should prompt consideration of ART (Hammer et al., 2006). CD4 counts of less than 200 cells/mm^3 indicate imminent risk of serious opportunistic infections or other complications of HIV disease, and prompt treatment is recommended (Hammer et al., 2006).

Untreated HIV disease is chronic and progressive (Dybul et al., 2002). Primary HIV infection is followed by a period of clinical latency typically lasting several years, during which high levels of viral replication and CD4 cell turnover lead to progressive immune dysfunction, eventually resulting in clinical disease progression (Mindel & Tenant-Flowers, 2001). The distinction between "HIV infection" and "AIDS" seems to be important, as it has clinical and prognostic implications, as well as utility in research.

Besides the U.S. Centers for Disease Control and Prevention (CDC) definition of HIV/AIDS, the World Health Organization also developed a clinical staging system for HIV infection (WHO, 1993). This staging system relies more heavily on clinical rather than laboratory evaluation, and has been used widely in resource-constrained areas where laboratory testing is not widely available (Grant & De Cock, 2001). The CDC classification system, the CDC/WHO System, which emphasizes clinical presentations of HIV disease, (Centers for Disease Control, 1986, Centers for Disease Control, 1992a) is reported to be intended for public health purposes, (for example, disease reporting and surveillance, epidemiologic studies, prevention and control activities, and public health policy planning epidemiologic data), but it is thought to be of limited value for describing the progression of disease in an individual as must be done during clinical management or clinical research (Cohen, 1998; Jackson, 2002). Cohen (1998) and Jackson (2004) claim that in order to characterize disease in an individual for purposes of estimating prognosis, planning therapy, and establishing criteria for enrolment or endpoints in clinical trials, clinicians require the following information:

- how far the disease has progressed; and
- how rapidly it is progressing.

In untreated HIV disease, information regarding how far the disease has progressed currently is most usefully indicated by the CD4+ count, and information regarding how rapidly the disease is progressing is indicated by the plasma HIV RNA level, usually termed the "viral load" (Hammer et al., 2006).

Early in the AIDS epidemic, clinical manifestations were frequently categorized as those diagnoses meeting the surveillance case definition of AIDS and other less severe signs and symptoms collectively known as AIDS-related conditions or complex (ARC) (CDC, 1993). As more became known about the full spectrum of HIV-related disease, the term ARC was largely abandoned and the pathologic process from HIV infection to symptomatic disease was characterized with the more comprehensive phrase "HIV disease." A number of classification and staging systems have been proposed for HIV disease, most using a combination of the CD4 lymphocyte count and symptoms, but only the classification scheme constructed by the Centers for Disease Control and Prevention (CDC) has gained wide acceptance (Jackson, 2002; Mindel & Tenant-Flowers, 2001). The CDC proposed that it be used to guide clinical and therapeutic actions in the management of HIV-infected adolescents and adults (Centers for Disease Control, 1992b).

The definitions of the three CD4+ T-lymphocyte categories and the three categories of clinical conditions used follow:

- Category 1: > 500 cells/mm^3 (or CD4% > 28%)
- Category 2: 200-499 cells/mm^3 (or CD4% 14% - 28%)
- Category 3: < 200 cells/mm^3 (or CD4% < 14%)

These categories correspond to CD4+ T-lymphocyte counts per microliter of blood. The percentage of CD4+ T cells can be substituted for the count as indicated in parentheses (Centers for Disease Control, 1992a). The lowest accurate, but not necessarily the most recent, CD4+ T-lymphocyte count or percentage is used for classification purposes (Centers for Disease Control, 1992a; Hammer et al., 2006). Generally, persons with HIV/AIDS are loosely subsumed under the following categories of infection:

3.3.1.1. Primary HIV Infection

Primary HIV infection is defined as the time period from initial infection with HIV to the development of an antibody response detectable by standard tests (Mindel & Tenant-Flowers, 2001). Data from careful prospective evaluations of populations at risk for HIV infection demonstrate that up to 87% of individuals who acquire HIV may experience some symptoms of primary HIV infection (Schacker, Collier, Hughes, Shea, & Corey, 1996). Symptoms may be mild or severe and may last from a few days to several weeks, with the average duration being 14 days (Jackson, 2002; Schacker et al., 1996). The most common presenting symptom is fever, seen in over 75% of patients (Vanhems & Dassa, 1999).

Diagnosis of HIV during the acute sero-conversion phase requires not only high clinical suspicion but also an understanding of appropriate testing strategies. Routine HIV antibody testing may be negative for several weeks or even months after exposure in the so-called "window period" (Busch et al., 1995; Walker et al., 2004). CD4 counts and CD4 function may decline during primary HIV infection, occasionally to levels that allow opportunistic infections to develop (Gupta, 1993; Vento et al., 1993). Absolute CD4 count often rebounds after the

primary infection, but may not return to a normal baseline (Jackson, 2002; Rosenberg et al., 1997). These authors report that in patients with clinical progression of HIV disease, CD4 responses against HIV itself remain particularly impaired following primary infection.

3.3.1.2. Clinical AIDS

According to CDC criteria, AIDS is defined by either diagnosis of one of the AIDS-defining conditions, or by measurement of CD4 levels that are below 200 cells/mm^3 (Centers for Disease Control, 1992a). Progression to AIDS from time of infection occurs, on average, 2 years earlier when defined by laboratory criteria (CD4 levels <200 cells/mm^3) compared to clinical criteria (development of an opportunistic illness) (Jackson, 2002; Osmond, Charlebois, Lang, Shiboski, & Moss, 1994). Survival time from the development of AIDS varies according to the AIDS-defining event (Jackson, 2002). In the Multicenter Hemophilia Cohort Study, median survival after a single AIDS-defining condition ranged from 3 to 51 months for the 10 most common conditions (Gail, Tan, Pee, & Goedert, 1997). The mean survival time after diagnosis of AIDS in the United States prior to the availability of antiretroviral treatment was 10-12 months (Gail et al., 1997). This is expected to be different in developing countries like South Africa where a host of other factors such as poverty and diseases (such as TB) can have an added impact on the disease progression (Jackson, 2002; Walker et al., 2004). These reported mean survival times guided the current researcher in deciding the length of time that was deemed appropriate and feasible for the current longitudinal study.

Progression from seroconversion to the development of AIDS in Africa may be shorter than in industrialized countries, but there are insufficient data to be certain. Although the data are

not always directly comparable, survival after an AIDS diagnosis appears to be substantially shorter in African countries and this may be partly because of later diagnosis of AIDS in Africa, but may also be because of environmental factors such as increased exposure to pathogens of high virulence and lack of access to care (Grant, Djomand & De Cock, 1997; Jackson, 2002; Walker et al., 2006). In South Africa, tuberculosis and bacterial infections are the most important causes of morbidity and mortality among hospitalized patients with AIDS (DOH, 2002; Walker et al, 2006; Wilson et al., 2004). Tuberculosis is the single most important HIV-related opportunistic infection in African countries, but diagnosis, particularly of extrapulmonary disease, remains difficult (DOH, 2006a). Wilson et al. (2004) assert that HIV infection is the strongest risk factor for the progression of latent TB infection to active TB, and conversely, TB is the most common life-threatening HIV-related infection worldwide and is often the sentinel of illness of HIV infection. The lack of laboratory facilities makes the diagnosis of bacterial infections difficult in many parts of the continent (Jackson, 2002). Data available suggest that HIV-infected individuals in Africa develop opportunistic disease at broadly the same level of immunosuppression as do individuals in industrialized countries, but death occurs at a higher range of CD4 counts, although still in the range consistent with advanced disease (Grant et al., 1997, Jackson, 2002; Walker et al., 2006).

The concept of AIDS as end-stage immunodeficiency has been reported to be somewhat muddied by the advances in antiretroviral therapy which is known to produce improvement in immunologic function (Hammer et al., 2006; Redfield, Wright & Tramont, 1986). The AIDS-defining criteria, such as CD4+ count below 200 cells/mm^3, and an incidence of opportunistic conditions can be influenced by the use of antiretroviral drugs, and remaining immune system

deficits can be masked (Jackson, 2002). Nevertheless, there are classification systems and staging procedures that are utilized in order to estimate the risk of progression of HIV disease in the presence of ARVs (Hammer et al., 2006). These systems and procedures are necessary to describe the progression of HIV disease. This is considered critical for use in classification of clinical presentations for epidemiologic case reporting and in indicating progression during clinical management or clinical research, as well as in monitoring response to clinical management through the use of antiretroviral drugs (Hammer et al., 2006).

3.4. OBJECTIVE LABORATORY TESTING FOR HIV

3.4.1. HIV Antibody Testing

HIV infection is usually diagnosed by testing serum for antibodies to HIV using a commercially available enzyme-linked immunosorbent assay (ELISA or EIA) (Hammer et al., 2006). Because the ELISA test has been reported to be not entirely specific, positive results are confirmed with a Western blot assay, which identifies antibodies to specific components of HIV (Jackson, 2002; Schwartz, Dans, & Kinosian, 1988). Despite these reservations of accuracy of ELISA, the automated ELISA has been reported to be better and 99.9% accurate (i.e. fewer than 0.1% of HIV- negative individuals incorrectly score as positive by the ELISA test) (Hung et al., 2000). These authors, however, also support the use of the 2-step process as they also acknowledge that there are false positives to the ELISA test. The aforementioned 2-step process may mean that a patient must wait for a week or more to receive test results. These results are more accurate though since the Western blot test is believed to have a lower incidence of false positives that the ELISA (Hung et al, 2000; Wilson et al., 2004).

ELISA is reported to be quite sensitive in chronic HIV infection, but because antibody production does not occur immediately upon infection, an infected individual may test ELISA negative during a "window period" that varies in length from a few weeks to a few months after infection, depending on the individual case and assay used (Hammer et al., 2006; Jackson, 2002). Despite negative antibody testing during this window period, an individual may have high viral load and be at high risk of transmitting infection (Adler, 2001; Wilson et al., 2004).

Some methodologies allow antibody testing on saliva specimens (Emmons, Paparello, Dekker, Sheffield, & Lowe-Bey, 1995; Martinez et al., 1999) and urine specimens (Martinez et al., 1999; Tiensiwakul, 1998), although positive results still require to be confirmed with serologic testing (Hammer et al., 2006). Home testing methods are also reported (Colfax et al., 2002). Rapid HIV serum testing, with results available in 3-30 minutes, has shown 99-100% sensitivity and specificity compared to ELISA when tested in clinical settings (Ketema, Zeh, Edelman, Saville, & Constantine, 2001), including in resource-poor settings (Phili & Vardas, 2002; Ramalingam, Kannangai, Raj, Jesudason, & Sridharan, 2002; Respess, Rayfield, & Dondero, 2001). In recent years, with the availability of rapid tests such as OraQuick (Abbott Laboratories, Abbott Park, IL) and Reveal (MedMira, Halifax, Nova Scotia, Canada), rapid testing protocols are being implemented in many countries (Colfax et al., 2002; Walker et al., 2006).

3.4.2. "Detuned" Antibody Testing

Relatively recent infection (in which antibodies are present in lower concentrations and bind to HIV less effectively) can be distinguished from established infection (in which antibodies reach stable levels and have been selected for more avid binding to HIV) (Janssen et al., 1998; Wilson et al, 2004). These authors report that soon after infection (but after the window period) an individual tests positive on the standard ELISA, but may test negative on the less-sensitive ("detuned") test. After maturation of the antibody response, both tests will give a positive result. Such "sensitive/less sensitive" or detuned ELISA testing strategies are used to identify individuals who are in the early months of HIV infection and also help to identify incident infections in epidemiologic studies (Jackson, 2002; Janssen et al., 1998).

3.4.3. CD4 Testing

CD4 lymphocyte count or the CD4 lymphocyte percentage is generally acknowledged to follow closely the progression of HIV immune-suppression, and the CD4 lymphocyte count is currently the principal laboratory test used in clinical management of HIV infection (Hammer et al., 2006). Recommendations for both antiretroviral therapy and prophylaxis of opportunistic infections are based on CD4 lymphocyte count or percent. For example, frequent AIDS diagnoses, such as Pneumocystis carinii Pneumonia (PCP), are uncommon at CD4 counts above 200/mm3, (Phair et al., 1990) and other AIDS-defining conditions, such as toxoplasmosis and non-Hodgkin's lymphoma, are reported to typically occur at even lower CD4 counts (Jackson, 2002; Mindel & Tenant-Flowers, 2001).

The plasma CD4+ lymphocyte count (CD4+ count, T-helper cell count) has been used since the beginning of the HIV epidemic to indicate disease stage, although it has some limitations (Centers for Disease Control and Prevention, 1997; Jackson, 2002). Individual determinations may vary significantly (Centers for Disease Control and Prevention, 1997). Identifiable causes of variation that have been reported include time of day, short-term changes in health, and experience of the clinical laboratory performing the test (Centers for Disease Control and Prevention, 1997; Walker et al., 2006). Nevertheless, over many months, the decline in CD4+ cells reflects progression of untreated HIV disease (Hammer et al., 2006; Wilson et al., 2004)

The CD4+ count alone is reported not to always reflect the clinical status of an HIV-infected individual (CDC, 1997). It is reported that untreated individuals with similar CD4+

counts may have very different functional status, frequency of opportunistic infections, and constitutional symptoms and signs (Hammer et al., 2006). Moreover, the CD4+ cell numbers reflect only one aspect of immunocompetence. Normal CD4+ counts are in the range of 500 to 1300 cells/mm^3, and treatment with potent antiretroviral therapy often results in return of CD4+ counts to high levels that probably mask other immune system defects, thus somewhat complicating staging of disease (Jackson, 2002). Even in patients who have responded to antiretroviral therapy with markedly increased CD4+ counts, however, subsequent decline over time indicates continuing progression (Hammer et al., 2006). The CDC recommends CD4 testing every 3-6 months in all HIV-infected persons (CDC, 1992) but different intervals may be appropriate to each individual case (Hammer et al., 2006).

3.4.4. Therapeutic Drug Monitoring

The measurement of antiretroviral drug concentrations in patient serum has been reported to be useful in several clinical situations. This measurement has been reported to be useful in predicting toxicity (Nunez, Gonzalez-Requena, Gonzalez-Lahoz, & Soriano, 2003), maximizing efficacy of treatment (Mallon, Ray, & Cooper, 2003), assessing effects of drug-drug interactions (Dasgupta & Okhuysen, 2001; Molla et al., 2002; Wilson et al., 2004), and providing evidence regarding medication adherence (Hammer et al., 2006; Hugen et al., 2002).

Therapeutic drug monitoring (TDM) is said to require proper timing of sampling relative to dosing and meals (Hammer et al., 2006). In general, data on the efficacy of TDM in clinical practice are mixed. In certain circumstances, such as in pregnant or paediatric patients, TDM is reported to have the potential to provide data on drug concentrations that have not otherwise

been well characterized, but data from large studies are lacking to support its routine use in clinical care (Acosta & Gerber, 2002).

3.4.5. HIV RNA Levels (Viral Load Assays)

The words "HIV viral load" are used in several different ways. "HIV viral load" (or "HIV viral burden") is sometimes used to mean the quantity of HIV in all body tissues and fluids (Wong et al., 1997). Evidence indicates that if the viral load quantity is lower, there is less HIV replication and less risk of short-term progression of HIV disease (Jackson, 2002). Accumulating evidence supports the assumption that the quantity of HIV in the blood reflects the total body viral load (Cavert et al., 1997; Jackson, 2002).

Viral load measures have a reported significant use in management of HIV disease (Hammer et al., 2006; Jackson, 2002). HIV viral load measurements are believed to be a major advance in HIV disease management and are reported to have two major applications. The first application is in estimating the risk of progression (the prognosis) of the disease (Jackson, 2002), and the second, monitoring the effectiveness of anti-HIV drug therapy in clinical trials as well as in clinical practice (Hammer et al., 2006). Several studies have demonstrated a very strong correlation between a higher HIV viral load and a greater rate of progression of HIV disease (Fiscus et al., 1998; Hughes et al., 1997; Jackson, 2002; Lathey et al., 1998; Marschner et al., 1998; Mellors et al., 1997; O'Brien et al., 1997; Vlahov et al., 1998). Findings from these studies seem to be consistent regardless of the fact that these were conducted in different countries with vast differences in economic development.

3.4.6. Other HIV Testing Techniques

ELISA or HIV viral load testing of fluids other than blood (seminal and vaginal fluid, cerebrospinal fluid, urine, and saliva) are currently available and/or under investigation. The clinical applications of some of these methods are clearly demonstrated (i.e., diagnosis of HIV infection with saliva or urine ELISA testing [Martinez et al., 1999]), whereas for others it is less so (for example, testing of semen for use in in vitro fertilization [Dunne et al., 2003]).

3.5. TRANSMISSION AND RISK FACTORS

The primary method of spread of HIV infection worldwide is through sexual exposure (Adler, 2001; Claton, 2006). In the areas of highest HIV prevalence globally, heterosexual intercourse is the primary mode of transmission, accounting for approximately 70% of the overall sexual transmission (Gayle, 2000). In most developing countries such as South Africa, heterosexual transmission is the most dominant mode of spread, and mother to child transmission of HIV is much more common than in industrialized countries (Claton, 2006; Grant & De Cock, 2001). HIV has been isolated from blood, seminal fluid, pre-ejaculate, vaginal secretions, cerebrospinal fluid, saliva, tears, and breast milk of infected individuals (Adler, 2001; Geier et al., 1992; Ho et al., 1985; Hollander & Levy, 1987; Wofsy et al., 1986). HIV-1 viral concentrations in tears and saliva are comparatively low (Jackson, 2002). No case reports could be found of HIV infection documented to arise from contact with nonbloody saliva or tears.

Possibility of nonsexual HIV transmission is reported to be present where transfusion with contaminated blood products, injection drug use, occupational exposure, or accidental needle sticks occur (Adler, 2001). The risk from occupational needle sticks to health care

workers from known HIV-positive source patients in case series performed prior to the availability of potent ART was found to be 0.33-0.5% (Cardo et al., 1997; Leentvaar-Kuijpers et al., 1990), which seems significantly minimal. Factors increasing the risk of HIV acquisition from an occupational needle stick include deep injury, injury with a visibly bloody device, or injury with a device that had been previously used in the source patient's vein or artery (Cardo et al., 1997). Post exposure prophylaxis (PEP) has been associated with a reduction of HIV transmission after occupational needle stick events of approximately 80% (Cardo et al., 1997; CDCP, 1996).

HIV transmission through transfusion of contaminated blood products was recognized early in the epidemic. With current testing methods, the risk of acquiring HIV from a unit of transfused blood in the United States has been reported to be 1 in 676,000 (Schreiber et al., 1996) but may be significantly higher in many developing countries like South Africa where lack of resources may impact on the rigorous testing, preparation, and packaging of donated blood (Jackson, 2002).

In the absence of interventions, mother-to-child transmission reportedly occurs in approximately 25% of live births to HIV-infected mothers (Connor et al., 1994). Various regimens of antiretroviral drugs can reduce the rate of perinatal transmission by 50% or more (Chalermchokcharoenkit, et al., 2004; Connor et al., 1994, Guay et al., 1999; Lallemant et al., 2000; Shaffer et al., 1999). Breast-feeding is also a risk factor for HIV transmission (Richardson, John-Stewart et al., 2003). Approximately one-third of cases of mother-to-child transmission result from breast-feeding, and the risk increases with the duration of breast-feeding (Claton,

2006). This mode of transmission may be the exacerbating factor in developing countries such as Sub-Saharan Africa (Jackson, 2002). Thus, interventions to prevent mother-to-child transmission at delivery are largely negated when mothers are not provided with safe alternatives to breast-feeding (Hammer et al., 2006).

3.6. FACTORS AFFECTING HIV DISEASE PROGRESSION

Although the median time for progression from HIV infection to AIDS is reported to be approximately 10 years in untreated individuals (Mindel & Tenant-Flowers, 2001), there is tremendously vast variation within individuals (Claton, 2006). Some authors in the literature report on a few individuals who progress rapidly following the acute stage and develop AIDS and die within months, while at the other extreme, a few untreated individuals, called "long-term slow progressors" or "long-term non-progressors" (LTNP) (Buchbinder et al., 1994; Lefrere et al., 1997; Sheppard et al., 1993; Petrucci et al., 1997), remain well after more than 15 years of infection, without apparent clinical or laboratory signs of disease progression. It is obvious, therefore, that factors determining the rate of progression are important to understand for purposes of research as well as for clinical management of an individual. Identified factors include host genetic makeup (chemokine receptors, SDF-1 variants), host immune response (cytokine milieu, T cell dynamics, and cellular immune response), as well as HIV characteristics and replication dynamics (viral virulence, replication fitness, and genetic diversity) (Hammer et al., 2006; Mindel & Tenant-Flowers, 2001; Noring et al., 2001).

3.7. SPECIAL CONSIDERATIONS IN DISEASE PROGRESSION

3.7.1. Host Factors

A number of host factors influence HIV disease progression. For example, it is reported that individuals who acquire HIV at an older age tend to have more rapid disease progression (Moss et al., 1988) and shorter survival times (Bacchetti et al., 1988). Behavioral or psychological host factors may also influence HIV disease progression. More rapid HIV disease progression has been reported with unprotected anal intercourse (Vittinghoff et al., 2001), smoking (Royce et al., 1990) poor nutrition (Claton, 2006; Moseson et al., 1989; Walker et al., 2006), and depression (Burack et al., 1993); however, not all studies confirm these findings. Drug use might be expected to influence HIV disease progression, but studies exploring this factor have also produced mixed results (Veugelers et al., 1994; Vittinghoff et al., 2001). These host factors are critical in developing countries and may explain the more significant impact that HIV/AIDS seems to be having in developing countries when compared to first world countries.

3.7.2. Viral Factors

HIV virions infect human cells by first binding to the CD4 receptor on the cell surface. This alone is said to be insufficient for the virus to enter the host cell; however, binding to an additional co-receptor is also required. M-tropic viruses (Macrophage- or M-tropic viruses preferentially infect monocytes and macrophages) are frequently found in early HIV infection, and a switch to T-tropic strains (thymocyte- or T-tropic viruses preferentially infect T cells) in the course of disease is associated with rapid CD4 cell depletion (Connor et al., 1997; Shankarappa et al., 1999; Tersmette et al., 1988).

Other viral factors may be important as well. For example, faster rates of disease progression have been observed in Ugandan individuals infected with subtype D compared with subtype A isolates (Kaleebu et al., 2002).

3.7.3. Co-infections

The development of opportunistic infections during HIV disease not only indicates the degree of immunosuppression, but may also influence disease progression itself (Walker et al., 2006). When stratified by CD4 counts, patients with prior histories of OIs are reported to have higher mortality rates than those without prior histories of OIs (Saravolatz et al., 1996).

Hepatitis C co-infection (HCV) is common in HIV-infected patients, and is reported to be present in up to 40-50% of all patients in urban settings and in 90% of intravenous drug users (Sulkowski et al., 2000). HIV is said to lead to more rapid HCV disease progression; however, the effect of HCV infection on HIV progression is less clear (Greub et al., 2000). These authors report that in a study of the Swiss HIV Cohort, HCV co-infection was associated with poorer CD4 responses to ART, development of new AIDS-defining events, and increased mortality; however, other authors have not found these associations (Sulkowski et al., 2002). In South Africa, the most common co-infection is reported to be tuberculosis which has been associated with rapid spread of HIV/AIDS since both conditions compromise immunity (Walker et al., 2006).

3.7.4. Long-Term Nonprogressors

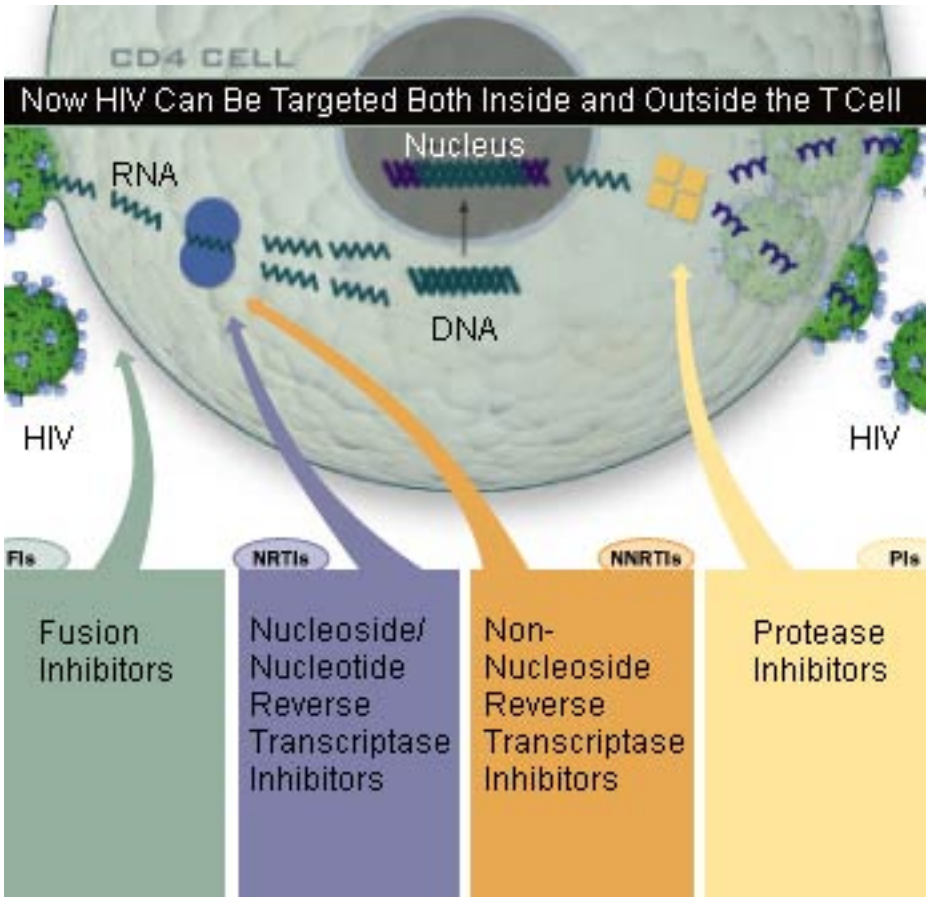
Reports of a small subset (approximately <5%) of individuals infected with HIV who remain asymptomatic, achieve good control of HIV viral replication, and maintain high CD4 counts in the absence of antiretroviral medications over many years of infection exist (Buchbinder & Kaslow, 1998). However, some individuals initially identified and recognized as long-term nonprogressors (LTNPs) have been documented to have experienced disease progression over time. In general, LTNPs have been reported to have strong cellular immune responses to a variety of HIV antigens (Kalams et al., 1999; Lisziewicz et al., 1999; Rosenberg et al., 1997).

3.8. Summary

Clinical care of patients with HIV requires familiarity with a wide range of medical, social, economic, and scientific issues. Despite the limitations of current forms of ART and financial limitations, it is clear that HIV replication can be effectively suppressed. Current challenges include improving upon existing antiretroviral therapies, developing new therapies to control and eliminate the virus and enhance the immune system, extending current and future therapies to all individuals in need of treatment worldwide, and developing effective strategies to prevent HIV infection. With regard to quality of life issues, pharmaco-vigilance in the form of monitoring all side effects of treatment modalities should not be sidelined – monitoring and managing effects of the disease itself and side effects of antiretroviral drugs should be one of the cornerstones of any successful and efficacious treatment plan. It is believed that monitoring and managing side effects of ART will enhance the success of the treatment programmes that the

government is implementing, since adherence to treatment has been shown to be closely linked to the side effects of the drugs.

Chapter 4



HIV/AIDS TREATMENT

CHAPTER FOUR

HIV/AIDS TREATMENT

4.1. INTRODUCTION

Management of HIV/AIDS is multifaceted and takes into account a significant and varied number of factors. The intervention is myriad in nature and covers not only the provision of antiretroviral drugs, but also incorporates general medical care as well as close monitoring of the patient's health status as a way of assessing the effect of both the disease on the individual as well as the effect of medications offered.

This chapter centres on treatment of HIV/AIDS including an array of intervention strategies such as the use of prophylaxis against opportunistic infections, and strategies to restore immune competence. A particular focus is placed on ART with details regarding the different regimens available and their effects, including mortality and morbidity associated with this kind of therapy. Information regarding time when ART is initiated as well as benefits and risks of early versus delayed initiation of treatment is provided. In addition, information about the effects of treatment interruptions as well as those of changing ART is also presented. Moreover, monitoring of ART and how ART impacts on quality of life is also considered in this chapter. Finally, HIV/AIDS treatment within the African context is considered with some attention also paid to complimentary and/or alternative treatment options in the form of African traditional medicine.

4.2. MANAGEMENT OF HIV/AIDS

Over and above routine health care maintenance in HIV/AIDS, interventions to alter the natural course of HIV disease include prophylaxis against opportunistic infections, antiretroviral therapy, and strategies to restore immune competence. Although dramatic advances in clinical treatment have been reported to have greatly improved the lives of many people with HIV/AIDS, many other patients are said to have no access to information about or access to these treatments because of healthcare providers' presumptive judgements about patients' ability to adhere to medical regimens (Noring et al., 2001). In South Africa, lack of adequate resources and the stigma attached to HIV/AIDS and its treatment may be contributing factors towards deferred benefit from these advanced treatment modalities.

4.2.1. Routine Health Care Maintenance in HIV Infection

All individuals, whether on ART or not, will have other health care needs, some related to HIV infection and some not. Individuals with HIV infection must be deemed to be at risk for other blood-borne pathogens and sexually transmitted infections (Mindel & Tenant-Flowers, 2001). Therefore, these authors recommend that all HIV-infected individuals be screened for viral hepatitis A, B, and C, and be immunized (against A and/or B) or treated as appropriate. Furthermore, routine screening for syphilis, chlamydia, gonorrhea, and other sexually transmitted diseases is also recommended based on the individual's risk behaviour (DOH, 2006).

Age- and gender-appropriate cancer screening is also suggested in HIV-infected individuals (Mindel & Tenant-Flowers, 2001), with special recommendations for increased screening for cervical and anal dysplasia associated with human papillomavirus (HPV) disease

(Feingold et al., 1990; Palefsky, 1991; Piketty et al., 2003). Annual screening for tuberculosis is also indicated, particularly in high incidence areas (DOH, 2006; Grant & De Cock, 2001). Similarly, because hyperlipidemia, glucose intolerance, and insulin resistance are reported common consequences of antiretroviral therapy (Carr et al., 1999; Vergis et al., 2001; Walli et al., 1998), the need for close monitoring and treatment of these conditions as part of general health management is generally indicated. Furthermore, with indications of potential increases in cardiac events among HIV-infected individuals, careful attention to modifiable cardiac risk factors is also recommended (Friis-Moller et al., 2003).

Other routine health measures such as blood pressure determination, depression and domestic violence screening, smoking cessation interventions, drug and alcohol counselling, and dental and ophthalmologic evaluation are reported to be just as important in HIV-infected individuals as with HIV-uninfected individuals (Noring et al., 2001). Furthermore, discussions and counselling sessions regarding sexual health also form part of the holistic medical management of HIV-infected individuals, and involve regular education to reduce risk of transmitting HIV to uninfected partners, preventing other sexually transmitted diseases, as well as discussions of contraceptive options and issues of family planning with individuals of reproductive potential, over and above adherence counselling for ART (Hammer et al., 2006).

4.2.2. Prophylaxis against Opportunistic Infections

Appropriate prophylaxis is reported to have been a part of the standard of care for HIV disease since early in the treatment of the epidemic (Noring et al., 2001). The reported impression is that these interventions improve quality of life, prolong survival, and decrease

hospitalizations. Prophylaxis in the form of routine prescription of antimicrobial medications against infections such as Pneumocystis carinii pneumonia and Mycobacterium avium complex are reported to be widely used for prevention or clinical suppression of these infections (Hammer et al., 2006). Furthermore, evidence exists that point to the fact that certain regimens in selected patients are beneficial against toxoplasmosis, bacterial infections, cytomegalovirus, herpes simplex, Mycobacterium tuberculosis, and fungal infections (Hammer et al., 2006).

Many commonly encountered opportunistic infections may be prevented by administering prophylactic antibiotics to those at risk based on pathogen-specific CD4 cell count thresholds (Kaplan, Masur & Holmes, 2002). In general, secondary prophylaxis (treatment to prevent recurrence of an OI) is provided as long as immune impairment persists (Hammer et al., 2006; Noring et al., 2001).

4.3. Antiretroviral Therapy defined

Antiretroviral therapy can be defined as the use of drugs that fight retroviruses such as HIV/AIDS (Jackson, 2002). Currently, the term "HAART", which is an abbreviation for highly active antiretroviral therapy is the preferred choice of treatment for HIV/AIDS (Hammer et al., 2006). HAART refers to any antiretroviral regimen capable of suppressing HIV replication to undetectable levels and sustaining this suppression for months or years in a significant number of individuals, by using a combination of reverse transcriptase inhibitors and protease inhibitors to treat patients (Hammer et al., 2006). While HAART is not a cure for AIDS (cannot eradicate HIV entirely from the body), it has greatly improved the health of many people with AIDS and it

reduces the amount of virus circulating in the blood to almost undetectable levels (Hammer et al., 2006).

As far as antiretroviral therapy is concerned, it is reported that in the 1980s, when HIV/AIDS first emerged, the medical fraternity and patients infected with the virus experienced the tremendous confusion of dealing with a complex immunologic disease that presented extreme variability from patient to patient in terms of disease presentation and progression. Doctors were initially powerless as the virus systemically destroyed HIV patients' immune systems, causing the inevitable opportunistic infections and cancers that in the early years of the pandemic predictably led to and ended in death (CDC, 1997). It was only after HIV was identified, and when the approval of zidovudine (AZT) in 1987 (initially identified and rejected in the 1960s as an anticancer compound, and later identified as a chemical that neutralized HIV in the test tube) that much hope emerged with regard to curbing the outbreak of the disease (Powderly, 2003). The identification of HIV and the emergence of therapeutic intervention in the form of AZT was a sign that HIV itself, and not just its consequences, might be controlled (Powderly, 2003).

The advent of this therapeutic intervention, along with those of some earlier drugs such as didanosine (ddI) and zalcitabine (ddC) encouraged the drug development companies to develop additional drugs. Powderly (2003) believes that the availability and use of these drugs, while having minimal impact on the progression of HIV disease and resulting in toxicities, did suggest that additional drugs could be developed that might be useful in halting immune system deterioration, or in potentially reconstituting the immune system. It possibly is against this

backdrop that clinicians are rigorously researching vaccine trials against HIV/AIDS in South Africa.

During the 1990s, more powerful drugs were approved and introduced by the Food and Drug Administration (FDA) for clinical management of patients with HIV/AIDS (CDC, 1997). These drugs included protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), other potent nucleoside reverse transcriptase inhibitors (NRTIs), and other classes of drugs. Concurrently (in the 1990s), the concept of combination therapy instead of single therapy became known (Powderly, 2003). The use of combination therapy is reported to have been followed by the use of highly active antiretroviral therapy (HAART), which is believed to have transformed and significantly altered HIV treatment, and HAART has therefore become the gold standard therapeutic strategy, despite problems of long-term adherence because of pill burden, complex drug regimens, and treatment-limiting toxicities (Hammer et al., 2006; Powderly, 2003).

Despite the many benefits of HAART, implementation of HAART is reported to have many limitations. These limitations include, but are not limited to the fact that it is not a cure, but that it is also not available to everyone on grounds of cost, adverse effects, or lack of knowledge about proper use (Adler, 2001; DOH, 2006a; Noring et al., 2001). HAART is also reported to not be effective in all cases (Sepkowitz, 1998; USPHS/IDSA, 1997). Nevertheless, documented research to date has provided support for the theory that appropriate medication can curb HIV replication with resulting dramatic clinical improvement. The remarkable clinical improvement

in patients successfully taking these regimens has instilled hope among clinicians and patients with AIDS, and has enhanced quality of life for many of these patients.

4.3.1. Current ARV regimens

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced substantial complexity into treatment regimens for persons infected with HIV. Antiretroviral regimens are complex, have serious side effects, pose difficulty with adherence, and carry serious potential consequences from the development of viral resistance because of non-adherence to the drug regimen or sub-optimal levels of antiretroviral agents (Noring et al, 2001). For these reasons, patient education and involvement in therapeutic decisions is critical (DHHS, 2003).

Antiretroviral drugs are categorized into groups according to how the drug interferes with retroviral reproduction. Retroviral activity may be impeded in a number of different ways; however the primary mechanism typically involves interference with one or more of the enzymes required for retroviral reproduction (Larsen, 1998). Two targets of therapeutic intervention of HIV replication that have been exploited with success have involved the HIV enzymes reverse transcriptase (RT) and protease (Bankaitis & Schountz, 1998). As such, antiretroviral medications specifically developed to disable HIV may be classified into two general categories: RT inhibitors, and protease inhibitors (Bankaitis & Schountz, 1998).

New antiretroviral medications that are in development include improved formulations of currently approved drugs (to enhance bioavailability, increase half-life, or reduce adverse

effects); new drugs in the same classes as currently approved drugs (such as PIs or NNRTIs with fewer adverse effects or unique resistance patterns); and drugs with novel mechanisms of action (e.g., integrase inhibitors, entry inhibitors, and HIV co receptor blockers) (Cohen, 1998; Hammer et al., 2006).

Management of patients with HIV infection is one of the rapidly changing and dynamic clinical fields in medicine today. With over 20 antiretroviral drugs currently available, one can easily construct a potent 3- to 4-drug treatment regimen that can durably suppress viral replication, enhance immunity, and delay or prohibit clinical deterioration (Hammer et al., 2006). Among patients who take their prescribed therapy, successful and sustained treatment responses as high as 90 - 95% have been reported (Murphy, 2000). The biggest challenge for clinicians today is choosing an effective treatment regimen to which an individual patient will adhere, and experience as minimal negative side effects of the treatment as possible (Murphy, 2000). The following is a list of antiretroviral regimens that are used, with their recommended combinations. These drugs have not previously been available to the South African population in government hospitals and clinics until as recently as April 2004.

- **Fusion Inhibitors:** block HIV from fusing with a cell's membrane to enter and infect it.
- **Nonnucleoside Reverse Transcriptase Inhibitor–Based Regimens (NNRTI):** target construction of viral DNA by inhibiting activity of reverse transcriptase. These include the use of *Efavirenz + (zidovudine or tenofovir or stavudine) + lamivudine* as preferred initial NNRTI-based regimens (except for pregnant women). *(Efavirenz + didanosine + lamivudine)* (except for pregnant women) or *nevirapine-based regimen* can be used as an

alternative. Three NNRTIs (namely, delavirdine, efavirenz, and nevirapine) are currently marketed for use by patients.

- **Protease Inhibitor-Based Regimen (PI):** target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new virons. These include the use of *lopinavir/ritonavir + (zidovudine or stavudine) + lamivudine* as preferred PI-based regimens**.** There are alternative PI-based regimens documented in the literature.
- **Triple NRTI Regimen:** a 3-NRTI regimen consisting of *abacavir + zidovudine (or alternately, stavudine) + lamivudine* is only used when an NNRTI-based or a PI-based regimen cannot or should not be used as initial therapy (e.g. for important drug-drug interactions). Although easy for patients to take and with less drug-drug interactions than some other combinations, various clinical trials have shown that 3-NRTI regimens that have been studied are less potent virologically than NNRTI- or PI-based regimens.

(DHHS, 2003; Hammer et al., 2006)

How HAART drugs work:

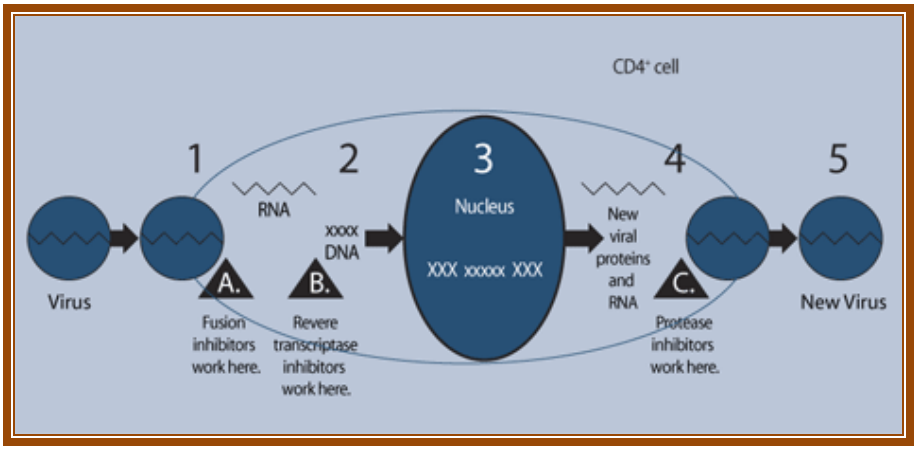


Illustration of **(1)** the virus entering the cell, **(2)** conversion of viral RNA to DNA using the reverse transcriptase enzyme, **(3)** incorporation of the viral genome into the DNA of the host cell, **(4)** viral proteins cleaved by protease for assembly of new viral particles, and **(5)** new virus particles budding from the surface of the host cell. It also shows the steps in the viral life cycle that are interrupted by **(A)** fusion inhibitors **(B)** reverse transcriptase inhibitors and **(C)** protease inhibitors. Source: National Institutes of Health. Available at www.niaid.nih.gov/publications/discovery/hiv.htm. Accessed May 05, 2008

4.3.2. Effects of HAART

Striking and significant subjective and objective clinical improvement has been reported as common in patients with clinically significant HIV disease, including many with AIDS and CD4+ counts below 100 cells/mm^3, who begin an appropriate HAART regimen, adhere successfully to it, and do not experience significant adverse medication effects (Cohen, 1998). In patients who respond well to HAART, subjective signs reported and observed by the current researcher often include increased appetite, weight gain, increased energy, improved sleep, and a general feeling of greatly improved well being (Sepkowitz, 1998). Often, there is reported resolution or significant improvement of minor problems, such as seborrheic dermatitis, molluscum contagiosum (Hicks, Myers & Giner, 1997), or recurrent thrush; and reports describe resolution of more significant conditions such as cytomegalovirus (CMV) (Reed et al., 1997),

Kaposi's sarcoma (Murphy et al., 1997), microsporidiosis, and cryptosporidiosis (Carr et al., 1998).

Objective clinical improvement from the use of HAART in patients with advanced disease has been reported and noted with CD4+ counts that commonly rise dramatically, often by several hundred cells per microliter, to levels characteristic of the clinically quiescent middle stage of HIV disease (Noring et al., 2001). Furthermore, HIV RNA levels drop to levels undetectable by standard commercial assays (Cohen, 1998). Cohen (1998) believes that in patients with middle-stage disease, the changes may be less dramatic, although some increase in CD4+ T cells and subjective sense of well being is common. Use of combination antiretroviral therapy has been reported to correlate temporarily with decreases in HIV-related deaths, reported AIDS cases, and hospitalizations in centres where such therapy is widely available (Centers for Disease Control, 1997; Noring et al., 2001; Palella et al., 1998).

Unfortunately, the desired response to HAART does not occur or is not sustained similarly in all patients (Hammer et al., 2006). Besides the side effects of the treatment, in some patients, an initial response occurs, but eventually signs of advancing HIV disease re-emerge, while in others, the response is minimal (Deeks et al., 1997). This varied response to treatment is thought to be due to several factors. Factors associated with a poor response include a high baseline viral load; very advanced disease; poor adherence to the medical regimen; and previous exposure to antiretroviral treatment with suboptimal regimens (Fatkenheuer et al., 1997). In patients who fail HAART, the clinical picture may eventually return to that characteristic of untreated disease (Deeks et al., 1997).

With a significant number of antiretroviral medications currently available, it is clear that the design of effective HIV therapy requires strategic thinking and modification of drug regimens to deal with toxicity and cross-resistance. Furthermore, with HIV infection rates not showing any signs of decreasing in South Africa one can argue that such evidence is providing yet another reason for implementation of feasible treatment options that will be adhered to, with minimal side effects. The side effects are believed to be one of the leading causes of poor adherence, and this does not refer to major side effects only (Powderly, 2003). Powderly (2003) highlights the fact that it is often the minor but more immediate side effects of the antiretroviral drugs (e.g. diarrhoea, rash) that deter patients from taking the correct amount, rather than the major long term side effects such as cardiovascular consequences. Although it has been suggested that hearing impairment may be one of the side effects of ART, at this point, it is not clear where the possible hearing changes may fall in terms of time of onset.

Data from the Centers for Disease Control offer evidence that the incidence of opportunistic infections, the main causes of AIDS-related deaths, has significantly decreased (Noring et al., 2001). Improved survival is felt by most experts to be due primarily to the use of protease inhibitor-based treatments, although other factors (better access to care and adequate opportunistic infection prophylaxis) play a role (Hammer et al., 2006). Treatment with potent antiretroviral regimens is reported to have resulted in immune reconstitution; infections that were previously impossible or difficult to treat such as cryptosporidiosis, azole-resistant thrush, cytomegalovirus retinitis, mycobacterium avium intracellular infections, and progressive

multifocal leucoencephalopathy have changed their naturally relentless courses (Tebas et al., 2001).

The process of clinical management of HIV/AIDS through the use of antiretroviral drugs is not without problems. All of the components of potent antiretroviral regimens are reported to potentially have major acute and long-term toxicities that are only partially understood (Behrens et al., 1999; Brinkman, ter Hofstede, Burger, Smeitink & Koopmans, 1998; Carr et al., 1999; Carr, Miller, Law & Cooper, 2000; Deeks, Smith, Holodniy & Kahn, 1997; Eastone & Decker, 1997; Henry et al., 1998; Lo, Mulligan, Tai, Algren & Schambelan, 1998; Visnegarwala, Krause & Musher, 1997; Yarasheski et al., 1999). These drugs may be difficult to take, may require tight schedules and dietary restrictions, and are expensive. All these factors are serious considerations and may have a major impact in the South African context particularly given the high levels of poverty and low levels of education among certain sectors of the population. Nevertheless, guidelines (Anon, 2000; Carpenter et al., 2000) suggest a very aggressive management of HIV-infected individuals, although the long-term clinical and virologic implications of this approach are said to be unknown (Tebas et al., 2001).

4.3.3. ART mortality and morbidity

There is ample evidence that the use of potent antiretroviral therapy has dramatically changed the morbidity and mortality rates of HIV infection (Cameron et al., 1997; Hammert al., 1997; Hammer et al., 2006; Palella et al., 1998; Tebas et al., 2001). This evidence shows broader populations with significant mortality reductions and suggests that a system of care and support that gives access to potent antiretroviral therapy can benefit diverse populations of people with

HIV disease. Nonetheless, there are numerous reasons for caution regarding current ART regimens.

It is reported that in the best of circumstances, the goal of maximal virus suppression is achieved in only 50% of patients (Noring et al., 2001). The reason for this relatively low success is thought to be the fact that HAART regimens are often complex. Adverse events are common and may lead to discontinuation of therapy, dose interruption, and significant morbidity leading to reductions in quality of life – which could possibly include hearing loss due to the potential effects of the drugs on the inner ear (Max & Sherer, 2000).

Adherence may be compromised because of adverse events, and adherence is increasingly recognized and reported as an important determinant of successful antiretroviral therapy. Because adverse events are common with all available antiretroviral agents (DHHS, 2003), it is critical to anticipate, detect, recognize, and manage these adverse events when providing primary care for HIV-infected patients. With regard to adverse events, patients should be informed of potential side effects (such as possible ototoxicity in the form of hearing loss, tinnitus, or vertigo) during consideration of the first regimen, options for subsequent regimens, and possible management strategies in case of adverse events (Max & Sherer, 2000). In the case of ototoxicity, several preventative measures could be put in place to either delay the onset and progression of the hearing loss, or to stop further inner ear damage from occurring due to other causes such as concomitant noise exposure.

4.3.4. Initiating Treatment

Review of the literature on time of treatment initiation revealed that not all HIV-infected individuals require ART at a given point in time. For those whose CD4 count and clinical assessment indicate a low risk of imminent disease progression, the potential adverse effects of immediate treatment are usually expected to outweigh any potential benefit (Hammer et al., 2006). Other HIV-infected patients may have psychosocial barriers to adherence that rule out effective ART, at least in the short term, until conditions related to these issues can be improved (e.g., through stable housing, substance abuse counselling, or treatment of medical or psychiatric conditions, psychosocial counselling, and so on) (Noring et al., 2001).

Because incomplete adherence can rapidly lead to lasting resistance against available antiretroviral drugs, it is reportedly worthwhile and advisable to address issues that are likely to impair adherence before initiating ART. Still other individuals may opt for complimentary/alternative medicine (CAM) for management of their disease (Hsiao et al., 2003) – this could be in the form of traditional healing in the South African context. In one large population-based study, 3% of individuals with HIV chose to use CAM as a substitute for standard therapy. Unfortunately, there is no convincing evidence that CAM is effective in improving clinical status or survival in HIV infection. The same can be said about proven positive effects of traditional medicine on managing the signs and symptoms of HIV/AIDS in South Africa. In South Africa, widespread use of CAM in the form of *"ubhejane"* has been reported (Bateman, 2006). "*Ubhejane"* is a potion that contains 89 herbal ingredients from all over Africa which was created by Mr Zeblon Gwala following a dream that he had – and clients using this potion have to choose between it and ARVs (Bateman, 2006). Bateman (2006) reports

that Gwala claims that if ARVs are taken together with *"ubhejane",* ARVs aggravate negative HIV/AIDS symptoms.

Internationally, unlike in South Africa, antiretroviral guidelines are heavily based on the principle of 'hit early, hit hard' (Ho, 1995) that was popularized after the introduction of HIV protease inhibitors (Hammer et al., 2006). Most experts advocate that all HIV-infected patients should be treated sooner rather than later, which is an aggressive approach that is based on three assumptions (Tebas et al., 2001):

- First, through continued mutations and recombination, HIV diversity increases with time in any individual. Fully suppressing viral replication with therapy should therefore be easier in patients with early-stage disease, when the viral population is less diverse, and less likely to have developed resistant mutants.
- Second, although complete viral suppression with aggressive therapy prevents disease progression, it may not reconstitute lost immunologic function; therefore, therapy should be started early to minimize damage to the immune system.
- Third, there was the hope that maintenance of maximal viral suppression for a period of time, initially calculated to be 3 to 4 years, would result in eradication of the infection.

(Tebas et al., 2001)

Several lines of evidence have put all the aforementioned stated assumptions into question. First, although several studies have demonstrated that patients with very advanced disease (CD4+ lymphocyte count less than 50X106 cells/l) have lower probability of response to a given antiretroviral regimen, the same assumption cannot necessarily be made for patients with

moderately advanced disease (absolute CD4+ cell count greater than 200X106 cells/l) (Tebas et al., 2001). In such patients, the most important predictor of response to an antiretroviral regimen is the baseline plasma HIV RNA (viral load). The viral load of a patient remains relatively constant over time until the late phases of the disease (Tebas et al., 2001). Second, there is ample evidence that the use of HAART is associated with clinical and laboratory evidence of immune reconstitution for opportunistic pathogens even in patients with advanced disease (Gorochov et al., 1998, Hammer et al., 1997; Pakker et al., 1998; Palella et al., 1998). Third, several studies have demonstrated that HIV can be cultured from lymphocytes obtained from patients that have been maximally suppressed for several years (Tebas et al., 2001). This confusion may apply internationally and may influence decision-making when it comes to when to initiate treatment, the situation is however not the same in South Africa since this country does not subscribe to the 'hit early, hit hard' principle – ARVs are only provided at the very late and advanced stage of the disease.

Individuals for whom initiation of ART is not indicated are monitored closely for changes in immune status (e.g., CD4 counts) that might signal increased risk of OIs and thus trigger initiation of ART, OI prophylaxis, or other intervention (Kaplan et al., 2002; USPHS/IDSA, 2000). Factors considered when initiating antiretroviral therapy include:

1. The patients' willingness and readiness to begin therapy;
2. The assessment of adherence potential;
3. The patients' preference regarding pill burden, dosing frequency, and food and fluid considerations;

4. Severity of HIV disease according to the baseline CD4+ T-lymphocyte count, viral load, and presence or history of AIDS-defining conditions;

5. Potential adverse drug effects;

6. Co-morbidity or conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, chemical dependency, pregnancy, and family planning status; and

7. Potential drug interactions with other medications (DHHS, 2003).

4.3.5. ART: benefits and risks of early versus delayed initiation of treatment

The U.S. Department of Health and Human Services (DHHS, 2003) recommends that treatment should be offered to all patients with symptoms attributed to HIV infection. Recommendations for offering antiretroviral therapy among asymptomatic patients require analysis of real and potential risks and benefits (Hammer et al., 2006). Recommendations are that treatment should be offered to persons who have <350 CD4+ T cells/mm^3 or plasma HIV ribonucleic acid (RNA) levels of >55,000 copies/mL (DHHS, 2003; Hammer et al., 2006). It is recommended that treatment of asymptomatic patients should be based on the willingness and readiness of the person to begin therapy; the degree of existing immunodeficiency as determined by the CD4+ T cell count; the risk for disease progression as determined by the CD4+ T cell count and level of plasma HIV RNA; the potential benefits and risks of initiating therapy in an asymptomatic person; and the likelihood, after counselling and education, of adherence to the prescribed treatment regimen (DHHS, 2003). These guidelines would clearly be different country to country depending on a host of factors. In developing countries; financial factors may play a more defining role than in developed countries.

The DHHS, (2003) put forward a list of potential benefits and risks for early therapy as well as potential benefits and risks of delayed therapy, and this creates more confusion as to whether early treatment is the best way to go or not. However, this list affords the patients with the ability and the opportunity to make informed decisions based on awareness and recognition of a balanced view of treatment initiation options. The list is provided in Table 2 below.

Table 2: Benefits and Risks of Early and Delayed ARV treatment as adapted from DHHS (2003)

	Early Treatment	Delayed treatment
Benefits	-Earlier suppression of viral replication -Preservation of immune function -Prolongation of disease-free survival -Lower risk of resistance with complete viral suppression -Possible decrease in the risk of HIV transmission	-Avoid negative effects on quality of life -Avoid drug-related adverse events -Preserve future treatment options -Delay in development of drug resistance
Risks	-Drug-related adverse effects on quality of life -Drug-related serious toxicities -Early development of drug resistance due to sub-optimal viral suppression -Risk of transmission of virus resistant to antiretroviral drugs (if sub-optimal suppression) -Limitation of future treatment options -Unknown durability of current available therapy	-Possible risk of irreversible immune system compromise -Possible greater difficulty in viral suppression -Possible increased risk of HIV transmission

The aforementioned list only focuses on the medical benefits and risks for the individual, and fails to include global benefits and risks such as, for example, the benefit of prolonging a life may lead to the individual staying a productive member of the society, hence benefitting the country in economic terms. Furthermore, reduction in AIDS deaths may benefit the society by reducing the number of AIDS orphans who may need government financial support.

4.3.6. Treatment Interruption

Situations arise when interruption of therapy is necessary in a given patient. Factors that contribute to interruption of treatment include toxicity, severe illness, and other circumstances that make adherence impossible (DHHS, 2003). In these situations, it is advisable that clinicians and patients should be aware of the recommendations that have been put forward stating that all antiretroviral drugs should be stopped at once (or possibly staggered according to each drug's half-life) to minimize the possible emergence of resistance (Dybul et al., 2002; Hammer et al., 2006; Tremblay et al., 2003).

Intentional supervised (or structured) treatment interruption (STI) presents several theoretical benefits: minimizing drug exposure, possibly decreasing short- and long-term adverse effects; "autovaccinating" individuals with their own virus in hopes of boosting the host immune control of HIV; allowing reversion of resistant virus to a wild type, potentially creating a more drug-sensitive target for salvage therapy; and reducing the cost of therapy (Dybul et al., 2002; Hammer et al., 2006).

Studies conducted thus far demonstrate that supervised (or structured) treatment interruption does not increase HIV-specific immune response by acting as "autoimmunizations," and does not lead to persistent control of viremia (Fischer et al., 2003; Garcia et al., 2001; Lori et al., 2000; Ortiz et al., 2001; Ruiz et al., 2000; Ruiz et al., 2001;). In general, studies of the safety and efficacy of STIs do not support their use in routine care, and STIs cannot be recommended outside of a research setting (Dybul et al., 2002).

4.3.7. Changing ART

Antiretroviral regimens may fail to suppress viral replication for a number of reasons, including incomplete adherence, poor absorption, toxicity leading to missed or lowered doses, pharmacokinetic interaction, suboptimal antiviral potency, and pre-existing drug resistance (Dybul et al., 2002; Hammer et al., 2006). Virologic failure has been reported in as many as 63% of patients in population-based studies (Ledergerber et al., 1999; Lucas et al., 1999).

At the time of changing antiretroviral regimens, careful assessment of the reasons for changing is strongly recommended. Understanding the factors of adherence, toxicity, and resistance that prompted the switch reportedly aids in designing subsequent regimens and optimizing patient outcomes (Noring et al., 2001). Patients who have failed multiple regimens or who have highly drug-resistant viruses may require a more complicated "salvage" regimen (Hammer et al., 2006). Such regimens may contain more drugs, may involve more complicated dosing schedules and may include experimental agents. Complete viral suppression may not be an achievable goal in some patients; hence, decisions to change or continue treatment should take into account immunologic and clinical stability (Deeks et al., 2003; Hammer et al., 2006).

4.3.8. Monitoring ART

The efficacy of an antiretroviral regimen should be monitored by regular determinations of HIV viral load and CD4 count (DOH, 2006a). The first indication of successful treatment is a decline in viral load (Hammer et al., 2006). The decline in viral load is reported to be biphasic in nature (Perelson et al., 1997). The first (fast) decay phase occurs during the first 2 weeks of treatment for most patients, and a second (slow) phase of decay is evident thereafter. The first

phase may result primarily from antiviral effects of medications, whereas immune factors such as cytotoxic T lymphocytes (CTL) antiviral activity may contribute to the elimination of virally infected cells in the second phase (Wu et al., 1999). The kinetics of response are variable among individuals, and do not appear to be entirely determined by adherence or drug levels. Moreover, although viral decay rates are not entirely predictive of subsequent virologic failure (Wu et al., 1999), virologic response at 4 weeks of treatment has been shown to correlate with response at 48 weeks (Powderly et al., 1999). As a rule of thumb, it is believed that in a successful regimen the viral load should decline by at least 1 log by 4 weeks after treatment initiation; where slower rates should prompt closer assessment of patient adherence, viral resistance, and possible drug-drug interactions (Hammer et al., 2006). It is reported, however, that even a successful regimen may take 4-6 months or even longer to attain undetectable viral loads (Hammer et al., 2006; Powderly et al., 1999).

As viral load declines, the number of circulating CD4 cells reportedly begins to increase (Noring et al., 2001). Initial increases in CD4 count during the first 1-3 months of therapy are believed to be caused primarily by a redistribution of cells trapped from lymphoid tissue (Pakker et al., 1998). The subsequent rate of improvement in CD4 levels is said to be variable among individuals, and gradual CD4 count increases may continue for many years with therapy that effectively suppresses HIV replication (Kaufmann et al., 2000; Smith et al., 2003; Staszewski et al., 1999). Individuals with lower nadir CD4 counts may have a slower and less complete CD4 recovery, whereas those who start therapy with higher CD4 counts and maintain continued viral suppression with antiretroviral medications may reach CD4 counts similar to those of HIV-uninfected individuals (Smith et al., 2003).

4.3.9. ART in Africa – South Africa

In recent years, AIDS has helped drive a global revolution in the delivery of complex therapy in resource-limited settings such as South Africa. The 2001 Declaration of Commitment on HIV/AIDS embraced equitable access to care and treatment as fundamental to an effective global HIV response (UNAIDS, 2006). On World AIDS Day in 2003, WHO and UNAIDS released a detailed and concrete plan to reach the 3 by 5 target of providing antiretroviral treatment to three million people living with AIDS in developing countries and those in transition by the end of 2005. This was a vital step towards the ultimate goal of providing universal access to AIDS treatment to all those who need it. Since then, the "3 by 5" initiative, the US President's Emergency Plan for AIDS Relief, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and initiatives such as employer programmes have definitively demonstrated the feasibility of delivering HIV treatment in resource-limited settings (UNAIDS, 2006). Between 2001 and 2005, the number of people on antiretroviral therapy in low- and middle-income countries is reported to have increased from 240 000 to approximately 1.3 million with the number of sites providing antiretroviral drugs having increased from roughly 500 in 2004 to more than 5000 by the end of 2005 (UNAIDS, 2006). Despite these efforts, a significant number of people in Africa, and in South Africa are still without ART.

Provision of antiretroviral therapy has expanded dramatically in sub-Saharan Africa, with more than one million [930 000–1.15 million] people reported to have been receiving antiretroviral treatment by June 2006, representing a tenfold increase since December 2003 (UNAIDS, 2006). Efforts towards the increase in the rate of provision of ARTs have been noted to be especially strong of late in a few countries, including Botswana, Kenya, Malawi, Namibia,

Rwanda, South Africa, Uganda and Zambia (UNAIDS, 2006). However, the sheer scale of need in this region means that a little less than one quarter (23%) of the estimated 4.6 million [4 - 5.4 million] people in need of antiretroviral therapy in this region are receiving it – which is clearly not an ideal situation (UNAIDS, 2006).

There is a growing demand for antiretroviral treatment amongst people living with HIV and AIDS in South Africa. Guidelines and procedural arrangements have been developed at national and provincial levels to accelerate the rollout of ARV treatment in the public sector (Ndlovu & Daswa, 2006). At its inaugural launch, the Joint Civil Society Monitoring Forum (JCSMF, 2004) noted that political and managerial oversights as well as overall commitment to the ARV treatment plan varied from province to province. The JCSMF also reported that there was a lack of systematic national management. The most serious problems identified were:

- Severe human resource (HR) shortages in clinics and hospitals across the country.
- Wealthier provinces such as Gauteng and the Western Cape were increasing the rate of provision of ART much more speedily when compared to poorer provinces such as the Eastern Cape.
- Gaps in communication and information sharing: these appeared to be mainly between the national and provincial health departments as well as between the national department, provincial health departments and civil society organizations. Examples of these gaps were with regard to data collection and management, patient outcomes, patient numbers, gender and age breakdowns of people on treatment, treatment literacy and community awareness initiatives.

- Good outcomes of ARV treatment for children were dependent on timely initiation of treatment and implementation of proper and holistic subsidiary care programmes for children living with HIV.
- On budgetary aspects of the Operational Plan, there was a lack of clarity on the extent to which provinces were using conditional grants allocated by the National Treasury or using funds from their own budgets to implement the ARV treatment plan.
- Due to lack of agreement and lack of comprehensive reporting in HIV and AIDS expenditure reporting, it is difficult to monitor how the ARV budgets are spent on ARVs and other treatment-related spending areas (e.g. laboratory services). This is important to monitor because there still remains a need to prioritize other areas of HIV and AIDS spending such as prevention and care and support (Ndlovu & Daswa, 2006).

The South African government has consistently stressed the importance of addressing nutritional issues in its treatment plan for HIV/AIDS, and this approach has been viewed with scepticism by the general population. Ndlovu and Daswa (2006) report on how it is common knowledge that medical treatments require nutritional support for them to be effective. Nutritional supplements are even more important among people living with HIV and AIDS because they boost the general functioning of the immune system. However, neither nutrition nor ARV treatments are self-sufficient – both need to be provided simultaneously to improve the health of people living with the disease (Ndlovu & Daswa, 2006). To achieve this protocol, the Department of Health needs to ensure that ARV provision is supported with sufficient and appropriate nutritional supplements in a sustainable manner. Ndlovu and Daswa (2006) believe that the provision of HAART in itself is not sufficient as there are a variety of other socio-

economic variables that impact on successful treatment of HIV and AIDS. The South African department of health also needs to be clear on its stance regarding the use of alternative/complimentary medicines in the form of traditional medicines such as "ubhejane" in the treatment of HIV/AIDS. This form of traditional medicine by Mr Gwala is reportedly chosen by some patients as an alternative to ARVs since Gwala advocated that if taken in a complimentary manner with ARVs, ARVs can aggravate the negative HIV/AIDS symptoms (Bateman, 2006). Gilbert, Selikow and Walker (2002) estimated that eight out of every ten Black South Africans consult with traditional healers as complimentary or alternative medicine.

The use of complementary and alternative medicine has been reported in patients with HIV/AIDS. This form of treatment is documented to be used by patients to improve general health, prevent opportunistic infections, treat symptoms, and reduce side effects from biomedical treatments (MacIntyre & Holzemer, 1997). Although there is debate about what constitutes "alternative" versus "traditional" medicine, the consensus is that this type of treatment is that which does not fall under the traditional western medicine which in prescribed by doctors working in the mainstream health care facilities. *"Ubhejane"* can be considered as both an "alternative" therapy and a "traditional" form of intervention in South Africa. James (1996) maintains that a large proportion of the world's people use their traditional medicine as primary health care since it is a low cost and effective form of treatment.

The use of traditional medicine as either complimentary or as an alternative to ARVs is seen to have a negative influence on the wide scale provision of ARVs in South Africa (Opie, 2005). Complementary and alternative medicine therapy has been defined as that form of therapy not

generally provided by most clinics and hospitals (Eisenberg et al., 1993), or as practices that do not form part of the dominant system for managing health and disease (MacIntyre, Holzemer & Philippek, 1997). Although it is true that not all HIV-infected individuals require or consent to antiretroviral therapy at a given point in time – several factors have been reported by adherence counsellors as barriers to enrolment and adherence to ART such as unstable housing, substance abuse, financial constraints influencing nutritional status, and psychiatric conditions to add to this problem. Opie, in (2005), also reported that many confused HIV-positive patients refuse ARVs as a result of the South African government's misinformation about the benefits of ARVs. The Health Minister of South Africa (Dr Manto Tshabalala-Msimang) has actively highlighted the benefits of nutrition (notably garlic, lemon, beetroot and olive oil) rather than promoting the use of ARVs. Cullinan (2005) believes that this stance from government has resulted in AIDS patients being reluctant to take HAART because they fear it is 'poisonous', and it has also created the space for alternative remedies to compete with HAART even though their clinical effects have not been established.

Patients with HIV/AIDS have been reported to take advantage of the abundance of alternative forms of therapy (MacIntyre & Holzemer, 1997). These authors claim that these alternative therapies are usually not generally sought for their antiretroviral properties, but rather for their ability to strengthen the immune system and to treat symptoms that patients present with such as wasting, nausea, sleep disturbance, and pain. The specific findings about benefits of "ubhejane" have been reported by Bateman (2006) to include stimulating appetite and enhancing patients' feelings of well-being while remaining non-toxic. Other reasons commonly cited for the use of alternative or complimentary medicine by patients with HIV/AIDS include expectation of

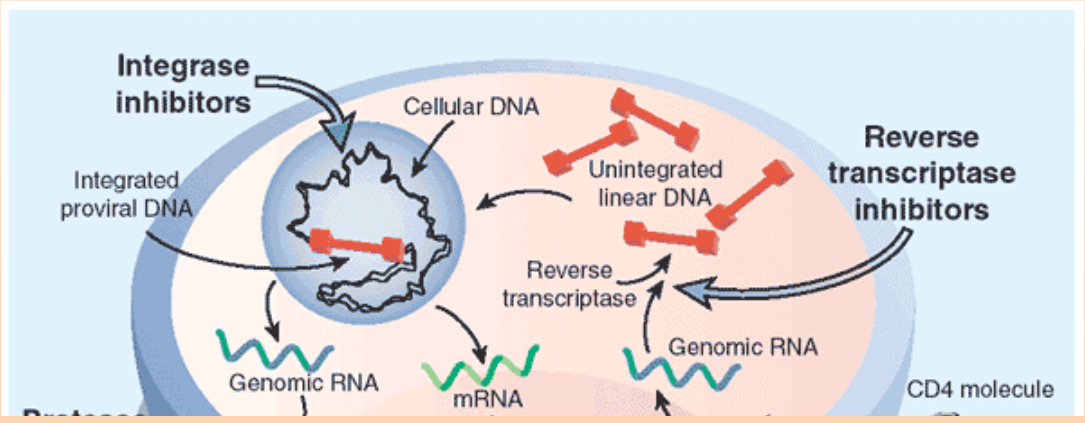
cure (Duggan, Peterson, Schutz, Khuder & Charkraborty, 2001), reduction of symptoms from the disease (Anderson, O'Connor, MacGregor & Schwartz, 1993) or desire for increased control over the disease process (Fryback & Reinert, 1997). In South Africa, scientists and practitioners are encouraged to establish and monitor the growing effects and contributions of alternative and complementary medicines in the management of HIV/AIDS. While research into this topic is needed, audiologists need to focus their research thrusts on the impact of this therapy singly or in combination with ARVs on hearing function.

One large population-based study conducted by Hsiao et al. (2003) indicated that 3% of individuals with HIV choose to use alternative medicine as a substitute for standard therapy. Duggan et al. (2001) believe that the use of complimentary and alternative therapies is widespread in many chronic illnesses, including HIV/AIDS. The use of unorthodox or non-Western medical practice is reported by these authors to range anywhere from 30% to 80% of patients. Furthermore, the use of this form of therapy is reported to be common among patients with HIV, even those with good virologic response (Duggan et al., 2001). Limited published research exists with regard to convincing evidence of the positive effects of alternative medicine in improving the clinical status or survival in HIV infection. This paucity of research in this area needs to be addressed as use of this medicine among HIV- infected patients may not diminish even with the availability and accessibility of increasingly effective ARV therapy, particularly in a country like South Africa where a majority of its people are still reported to believe in traditional healing.

4.4. Summary

It is clear that successful and efficacious management of HIV/AIDS is influenced by a number of factors. Factors such as the population's belief and trust in western medicine and their reliance on CAM play a significant role in the success of a treatment programme. Combination therapy with three or more drugs has been reported to generally improve the health and survival of HIV-infected patients. However, concerns about drug interactions, adherence, drug resistance, side effects, and toxicities have influenced and modified the way these drugs are used and prompted more caution about concomitant medications and monitoring. It is believed that as the number of drugs continues to increase, the antiretroviral (ARV) picture is likely to become far more complex. It is with this knowledge that efforts to improve access to treatment as well as to monitor the effects of the drugs and the quality of life of people on these drugs should be intensified globally – with more focus in areas where the disease has reached pandemic proportions, South Africa being one of these areas.

TOXICITY & SIDE EFFECTS OF ANTIRETROVIRAL DRUGS



Chapter 5

CHAPTER FIVE

TOXICITY AND SIDE EFFECTS OF ANTIRETROVIRAL DRUGS

5.1. INTRODUCTION

Eradication of HIV infection has proved elusive, and permanent lifelong treatment must be administered to fight against viral replication. Although highly active antiretroviral therapy (HAART) has often been acclaimed as effective in maintaining suppression of viral replication, potentially adverse consequences of long-term exposure to antiretroviral agents have been increasingly regarded as cause for concern. This concern may be reflected, in part, in a shift toward a more conservative position on when to initiate antiretroviral therapy. Issues of long-term toxicity are at the forefront of patient management, with increased focus on drug side effects and their potential to compromise adherence. This chapter explores these side effects in more detail, focusing on general physiological side effects rather than side effects specific to the ear.

The advent of HAART has dramatically decreased rates of AIDS-related morbidity and mortality, even in advanced disease (Palella et al., 1998). However, every available anti-HIV drug class has been associated with major toxic effects that can significantly compromise quality of life and, in some cases, jeopardize survival. Powderly (2002) states that major long-term toxic effects associated with antiretroviral therapy fall into three categories: nucleoside analogue–associated toxic effects (i.e., neuropathy, myopathy, pancreatitis, hepatic steatosis, lactic acidosis, and possibly lipoatrophy), metabolic complications (i.e., fat redistribution, insulin resistance, and hyperlipidemia), and bone disease (i.e., osteopenia and/or osteoporosis). This

therefore implies that optimal patient management should consistently revolve around the development of strategies to maximize sustained treatment efficacy while minimizing the potential for serious side effects (Murphy, 2000).

Antiretroviral toxicity is an increasingly important issue in the management of HIV-infected patients. With the sustained major declines in opportunistic complications, HIV infection has become a more chronic disease, and so more drugs are being used in more patients for longer periods. Hence it is of critical importance that audiologists establish the potential for ototoxicity and document all the antiretroviral medications used as part of therapy provided to patients.

5.2. Why explore toxicity of HAART?

It is well reported that all biologically active substances exhibit some kinds of detrimental and undesirable effects. The history of a new drug frequently is marked by early enthusiastic endorsements and approval of its therapeutic value followed by condemnations because of its adverse side reactions. This phenomenon has been observed with initial use of some antiretroviral drugs. The obvious goal in drug research is to recognize the harmful effects of newly developed drugs by laboratory tests before any injury is experienced by human participants. Unfortunately, experimental methods have not been standardized, and therefore final analyses are not always entirely dependable (Cummings, 1993). More importantly, audiological assessments and ototoxicity monitoring does not always form part of the initial experimental methods where the harmful effects of the drug being developed are established.

Bankaitis and Schountz (1998) report on the drug development process which highlights the critical need to ensure that all drugs used are monitored in terms of their efficacy and negative side effects. Because the discovery of HIV and subsequent appreciation of the biology of the virus led to the development of experimental drugs, the Food and Drug Administration (FDA) may have hastily approved experimental/investigation drugs for clinical trials involving human participants. Approval of experimental drugs has implications for research into audiological function.

Standard clinical trials must be performed on any new experimental drugs; however, several exceptions have been made for drugs specifically developed for serious illnesses. In response to political and social pressures surrounding the AIDS epidemic, in 1987, the FDA created an exception to the standard clinical trial procedure to expedite the evaluation process of promising experimental drugs in cases of life-threatening illnesses (Blaschke et al., 1995). In other words, the FDA could rapidly approve HIV drugs in as little as 3 years, prior to the completion of all standard clinical trials. In addition, the FDA definition of a "safe" drug was modified according to the severity of the disease that the drug was developed to treat. As stated by Shipp and Nabors (1993), "No drug is completely safe, and investigators and the FDA are willing to accept more severe side effects from a drug used to treat a life-threatening disease, such as HIV infection….."(p.233) Drug-induced hearing loss may not qualify as a "more severe side effect"; however it does require some attention by the research community.

If the FDA approves investigational drugs for clinical testing, clinical trials are conducted in four FDA mandated phases, each phase taking approximately 1 to 2 years to complete (AIDS

Research Information Center [ARIC], 1996a). The first three phases must be completed before the FDA will consider approving the experimental drug (Blaschke, Nies, & Mamelok, 1995)

- Phase I trials involve a small number of volunteers and are designed to document biological effects and determine safe dosage ranges for humans (Shipp & Nabors, 1993).
- As an extension of phase I, phase II clinical trials focus on short-term effects of investigational drugs on a larger pool of participants.
- Phase III trials usually involve 500 to 3000 selected patients to determine drug efficacy, long-term side effects, intolerance, resistance, and other major problems (ARIC, 1996a; Blaschke et al.,1995).
- Lastly, Phase IV trials involve tracking a drug's efficacy and long term side effects on many thousands of patients. This phase of the clinical trials is often conducted after FDA approval has been granted.

However, an extensive literature search yielded a paucity of information relating to ototoxicity monitoring as part of the above four phases; even though significant literature exists on the other adverse events that are the focus of this chapter.

The standard-of-care therapy for HIV/AIDS (HAART) can result in near-complete suppression of HIV-1 replication, hence the reported reductions in morbidity and mortality (Carr & Cooper, 2000). Several factors are, however, linked to HAART, and it is these combined factors that have increased researchers' attention to the toxicity of HAART:

- Firstly, since HIV-1 eradication seems unlikely with current therapy, HAART needs to be indefinite for clinical benefits to be preserved.

- Secondly, the severity of the HIV pandemic has led to accelerated licensing of many antiretroviral agents, often with very little known about long-term safety.
- Thirdly, the sustained benefits of HAART have led to far greater numbers of HIV-1-infected patients receiving at least three drugs for greater periods of time. Moreover, drug-related toxicity is being increasingly recognized because of the declining incidence of HIV-1 associated opportunistic diseases.
- Lastly, there are many antiretroviral drugs available in four drug classes and so the number of possible HAART combinations is extensive. Choosing between these various combinations is, therefore, increasingly dependent upon knowledge of antiretroviral toxicities.

(Carr & Cooper, 2000)

Combination therapy with at least three antiretroviral agents has been shown to have a significant effect upon morbidity and mortality in HIV disease (Grabar et al., 2002). These positive responses are mediated through suppression of HIV replication, preservation of immune function and reconstitution of specific immune responses (Louie & Markowitz, 2002). Viral load reduction to below the limit of detection usually occurs within the first 8-24 weeks of therapy; however, maintenance of optimal treatment response is highly variable (DHHS, 2003). The time of onset of audiological sequelae in the form of ototoxicity has not been documented. It is also likely to be extremely variable from patient to patient, and therefore needs to be monitored closely and documented. This type of information is likely to provide audiologists with knowledge about when and how audiological habilitation should be instituted.

The South African Department of Health emphasizes the importance of research, monitoring, and surveillance into antiretroviral drugs as one of the priority areas in their comprehensive drug roll-out programme (DOH, 2000). The importance of conducting regular surveillance in the form of pharmacovigilance is likely to strengthen the system which monitors the efficacy of drugs being used as well as any adverse reaction to the drugs, thereby highlighting the potential value of ototoxicity monitoring. The specific aims of the DOH's antiretroviral pharmacovigilance programme are:

- To determine the burden of drug-related morbidity and mortality in patients with HIV and AIDS, particularly associated with ARV use, and develop measures to minimize their impact.
- To provide training and information to health personnel and patients on the safe use of antiretroviral medications and other medicines commonly used in HIV infected and AIDS patients.
- To develop systems to assess the risks and benefits of treatments commonly used in patients with HIV, Sexually Transmitted Infections (STI) and TB, including over the counter (OTC) medication / phyto-therapeutic agents.
- To identify, assess and communicate any new safety concerns associated with the use of antiretroviral medications and other HIV medicines.
- To support regulatory and public health decision-making through an efficient, national post-marketing surveillance system, monitoring the quality, benefits and risks or harm associated with ARVs and other medicines currently used in the health sector.
- To minimize the impact of misleading or unproven associations between adverse events and ARV therapy.

- To detect, assess, and respond to safety concerns related to complementary and traditional medicines used in HIV- infected patients.
- To establish an early warning system for resistance to antimicrobials commonly used in HIV, including, but not limited to, antiretroviral medications.
- To respond to unfounded and unsubstantiated claims of efficacy of untested products and treatment modalities.

(DOH, 2000)

The above aims are critical in formulating research questions and research priorities in the area of HIV/AIDS, and form a cornerstone for the rationale for the current study.

The South African Government is taking advantage of new developments to enhance the country's comprehensive response to HIV and AIDS. The government, as matter of urgency, started implementing a programme to provide anti-retroviral treatment (ART) in the public health sector. The comprehensive programme includes prevention, treatment and care, research and human rights. Provision of ART is limited to those symptomatic patients who have moved on to develop AIDS with low CD4+ counts (below 200 cells/mm^3). The Department emphasizes the importance of fully informing patients about the benefits of restoring immune function and improving the quality of life and about serious side effects that may result from treatment with these drugs.

5.3. Side Effects of Antiretroviral Therapy

Antiretroviral drugs have dramatically changed the survival rate of patients with HIV/AIDS. They are also a complicated group of medications with significant side effects, toxicities, and

drug interactions (Zapor et al., 2004). Several potential adverse events associated with antiretroviral agents, with the exception of audiological function, have been reported and include the following:

- **Skin Rash:** Skin rash occurs most commonly with the NNRTI class of drugs. The majority of cases are mild to moderate, occurring within the first weeks of therapy. Certain experienced clinicians recommend managing the skin rash with antihistamine for symptomatic relief without drug discontinuation, although continuing treatment during such rashes has been questioned (Fagot et al., 2001).
- **Osteonecrosis, Osteopenia, and Osteoporosis:** Avascular necrosis and decreased bone density are now recognized as emerging metabolic complications of HIV infection that might be linked to HAART regimens. Both of these bone abnormalities have been reported among adults and children with HIV infection who are now surviving longer with their disease in part because of HAART (Mora et al., 2001; Scribner et al., 2000).
- **Increased Bleeding Episodes among Patients with Haemophilia:** Increased spontaneous bleeding episodes among patients with haemophilia A and B have been observed with Protease Inhibitors (PI) use (Racoosin & Kessler, 1999). Reported episodes have involved joints and soft tissues; however, serious bleeding episodes, including intracranial and gastrointestinal bleeding, have been reported. Bleeding episodes occurred a median of 22 days after initiation of PI therapy. Certain patients received additional coagulation factor while continuing PI therapy.
- **Fat Maldistribution:** HIV infection and antiretroviral therapy have been associated with unique fat distribution abnormalities. Generalized fat wasting is common in advanced HIV disease, and localized fat accumulations have been reported with NRTI mono-

therapy (Mulligan et al., 2001). However, the recognition and observation of fat maldistribution syndromes have increased in the era of combination antiretroviral therapy characterized by fat wasting (lipoatrophy) or fat accumulation (hyperadiposity).

- **Hyperlipidemia:** HIV infection and antiretroviral therapy are associated with complex metabolic alterations, including dyslipidemia. Cachexia, reduced total cholesterol, and elevated triglycerides were reported before the availability of potent antiretroviral therapy (Coodley et al., 1994; Grunfeld & Feingold, 1992).
- **Lactic Acidosis/Hepatic Steatosis:** Chronic compensated hyperlactatemia can occur during treatment with NRTIs (John et al., 2001). Although cases of severe decompensated lactic acidosis with hepatomegaly and steatosis are rare (estimated incidence of 1, 3 cases/1,000 person-years of NRTI exposure), this syndrome is associated with a high mortality rate (Boxwell & Styrt, 1999; Boubaker et al., 2001; ter Hofstede et al., 2000). Severe lactic acidosis with or without pancreatitis, including three fatal cases, were reported during the later stages of pregnancy or among postpartum women whose antiretroviral therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents (Fortgang et al., 1995; Luzatti, Del Bravo, Di Perri, Luzzani & Concia, 1999). Other risk factors for experiencing this toxicity include obesity, being female, and prolonged use of NRTIs, although cases have been reported with risk factors being unknown (Fortgang et al., 1995).
- **Hepatotoxicity:** Hepatotoxicity, which is defined as a 3–5 times increase in serum transaminases with or without clinical hepatitis, has been reported among patients receiving HAART. All marketed NNRTIs and PIs have been associated with serum transaminase elevation. The majority of patients are asymptomatic, and certain cases

resolve spontaneously without therapy interruption or modification (denBrinker et al., 2000). Among the NNRTIs, nevirapine has the greatest potential for causing clinical hepatitis. An incidence of 12,5% of hepatotoxicity among patients initiating nevirapine has been reported, with clinical hepatitis diagnosed for 1,1% of these patients (Martinez et al., 2001).

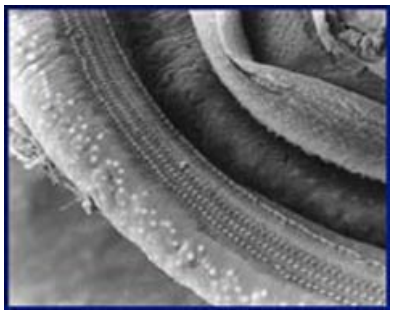
- **Hyperglycemia:** Hyperglycemia, new-onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of pre-existing diabetes mellitus have been reported among patients receiving HAART (Dube, 1998; Eastone & Decker, 1997; Visnegarwala et al., 1997). These metabolic derangements are strongly associated with PI use (Mulligan et al., 2000), though they can occur independently of PI use (Behrens et al., 1999).
- **Other mitochondrial toxicities:** myopathy (zidovudine), neuropathy (stavudine, didanosine) (Carr & Cooper, 2000).
- **Other toxicities:** nausea, headache, diarrhoea, mouth ulcers, central nervous stimulation, perioral paraesthesiae, reflux oesophagitis, retinoid effects, hypersensitivity (Carr & Cooper, 2000).

Although peripheral neuropathy, myopathy, lactic acidosis, and fat redistribution are the most commonly described complications of NRTI use, other adverse effects have also been reported. These include hematopoietic toxicity (culminating in anemia, neutropenia, or thrombocytopenia) (Freund et al., 2002; Gallicchio, Hughes & Tse, 1993), and myriad other drug interactions. The above effects highlight the critical need to have hearing function monitored in the form of ototoxicity studies. As the armamentarium of HIV medicines expands, so must our awareness of the myriad drug interactions and side effects (Zapor et al., 2004).

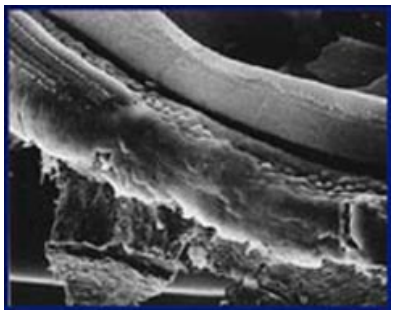
5.4. Summary

Understanding the toxicities and side effects of antiretroviral drugs forms the basis of ensuring efficacious management of patients with HIV/ADS. Exploring general physiologic toxicity of ARVs highlights the crucial need for close monitoring of those on these medications and also raises the importance of establishing other toxicities that may not have been previously thoroughly explored nor reported. It is well understood that treating patients with AIDS with antiretroviral drugs is effective in prolonging the lives of people who would have rapidly progressed to the end stage of the disease. However, the treatment of patients with antiretroviral drugs is relatively new and not a simple matter. The drugs do not cure people - they merely arrest the progression of the disease. The drugs can be toxic and have adverse side effects that may make patients temporarily more ill. In some cases, for several reasons, the drugs do not work. A robust monitoring system can potentially help to ensure an early warning system to detect the adverse drug events, including drug-induced hearing loss should it be one of the side-effects of ART.

Normal hair cells



Damaged hair cells



www.hearingprofessionals.co.nz/faq.htm

Chapter 6

OTOTOXICITY

CHAPTER SIX

OTOTOXICITY

6.1. Introduction and ototoxicity defined

Ototoxicity may be defined as a tendency for certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear and especially of the end organs and neurons of the cochlea and vestibular divisions of the eighth cranial nerve (Cummings, 1993; Hawkins, 1976). It refers to medication-caused auditory and/or vestibular system dysfunction resulting in hearing loss or disequilibrium. Damage to the cochlea or vestibular apparatus occurs due to exposure to a chemical source, resulting in hearing loss or disequilibrium. Drugs and other chemicals that damage the cochlea – the organ of hearing in the inner ear – do so by destroying sound sensitive hair cells, usually starting at the basal turn and progressing towards the apical turn (Campbell, 2007). These drugs may also damage the end organs of balance in the semicircular canals, utricle and saccule (vestibular apparatus) (Smith & MacKenzie, 1997). The propensity of specific classes of drugs to cause ototoxicity has been well established. The list includes certain antibiotics, certain antineoplastic agents, salicylates, and loop diuretics (Campbell, 2007; Kalkanis, 2002; Ludman & Wright, 1998). However, antiretrovirals as a class of drugs have not been extensively studied. This chapter explores ototoxicity by defining ototoxicity, providing an overview of factors that influence ototoxicity, clinical features of ototoxicity, and finally a brief re-look at ototoxicity associated with ART.

It is well established that many drugs, such as the aminoglycoside antibiotics and the chemotherapeutic drug cisplatin, are capable of inducing both nephrotoxicity and ototoxicity. The factors that selectively predispose the kidney and inner ear to the toxic effects of these agents as well as the mechanism by which damage is produced are not well defined. However, it has been established that the two organs reportedly differ greatly in their exposure to these toxic agents (Walker, Fazekas-May, & Bowen, 1990). The kidney is said to have an abundant vascular supply and tends to selectively concentrate a number of drugs within the renal cortex or medulla, often to toxic levels (Levine et al., 2001). The vascular supply of the inner ear is apparently not as extensive, and the stria vascularis of the cochlea can act as a functional regulator of drug entry into inner ear fluids (Walker et al., 1990).

Reports in the literature indicate that drug-induced ototoxicity and nephrotoxicity can be explained on a cellular level (Walker et al., 1990). These authors report on studies using radiolabeled gentamicin that suggest that binding mechanisms of the drug to the plasma membrane of the outer hair cells of the cochlea and vestibular apparatus and to the brush border receptors of the renal proximal convoluted tubules are similar. This suggests that the same receptor sites for aminoglycosides may occur in otic and renal organs. Aminoglycosides reportedly concentrate within the lysosomes of renal proximal tubular cells, and they also may concentrate in lysosomes within the cells of cochlea and vestibular structures. This information forms part of the data that established a link between renal toxicity and ototoxicity (Walker et al., 1990).

In HIV infected patients, very limited information exists on the link of ARVs to ototoxicity on a physiologic level although the aforementioned renal-toxic link has not been refuted. Several reports in the literature on ARV toxicities that could contribute towards a link between ARVs and ototoxicity were found. Lactic acidosis and or hepatic steatosis have been reported as a side effect of NRTIs (Fortgang et al., 1999; John et al., 2001), and hepatotoxicity has also been reported with the use of HAART (denBrinker et al., 2000; Martinez et al., 2001). Furthermore, Simdon et al. (2001) propose an explanation that suggests that reductions in mitochondrial DNA content induced by NRTIs, as well as mitochondrial DNA mutations associated with aging and HIV-1 infection, all may contribute to auditory dysfunction in older patients with HIV-1 infection.

6.2. Factors that influence ototoxicity

Ototoxicity came to the forefront of clinical attention with the discovery of streptomycin in 1944, which was used successfully in the treatment of tuberculosis (Edmunds et al., 2006). Ever since then, several other medications have been added on to the list of ototoxic agents. The ototoxicity of these agents is usually related to the blood levels of the drugs and the duration of utilization, however, toxic effects have been noted in some patients after only a few doses (Edmunds et al., 2006). In other patients the toxic effects have progressed even after the drug has been discontinued (Cohn, 1981). Site and extent of ototoxic damage to the cochleovestibular system vary according to a number of risk factors, including the type of drug, drug interactions, dosage, method of administration, duration of treatment, and presence of physical conditions which exaggerate the drugs' adverse effects (Campbell, 2007; Moore, Smith & Lietman, 1984; Wofford, 1981).

Ototoxic drugs reach the inner ear primarily through the bloodstream, and it is believed that the higher the concentration of the drug in the serum, the higher the risk of damage to inner ear structures (Bergstrom & Thompson, 1984). An increased dosage or increased length of administration time of the drug presumably results in increased serum levels, and ototoxicity is thus said to be dose-related (Bergstrom & Thompson, 1984). Patients who may be particularly susceptible to ototoxic damage, who should be targeted for audiological monitoring as part of their therapeutic treatment, include those patients in poor general medical condition with low levels of red blood cells or serumen proteins, status of renal function (i.e. patients with poor renal function), interactions with other medications and treatment modalities (e.g. patients who are receiving potentially harmful agents such as furosemide), and length and dose of treatment (e.g. patients receiving large or prolonged doses of antibiotics) (Campbell, 2007). It is generally reported that once - daily treatment is considered safer than the conventional twice or three times a day regimen, since the uptake of the ototoxic agent, such as aminoglycosides, in the inner ear tissues is greater with continuous infusion rather than a single dose (Tran Ba Huy, Bernard & Schacht, 1986). Questions arise regarding the impact of ARV medications in adults where the treatment is not taken once-daily (Stavroulaki et al., 1999).

Factors such as age may also increase an individual's susceptibility to ototoxicity (Lonsbury-Martin & Martin, 2001; Konrad-Martin, Wilmington, Gordon, Reaves & Fausti, 2005). For example, it is generally accepted among clinicians that infants and young children are less susceptible to the ototoxic effects of aminoglycosides than adults (Crifo, Antonelli,

Gagliardi, Lucarelli, & Marcolini, 1980; Finitzo-Hieber, McCracken, & Brown, 1985; McCracken, 1986). It has not been firmly established whether the same applies with ART.

Generally, the factors that have been associated with a higher risk of incidence of ototoxicity have included duration of therapy where the administration of an ototoxic agent continues for more than 14 days; cumulative dose; total daily dose; peak and trough serum drug concentrations; concurrent diuretic therapy as well as simultaneous exposure to multiple ototoxic agents; underlying disease states; previous exposure to an ototoxic agent; increased age; impaired renal function and compromised hepatic function; exposure to noise; pre-existing sensorineural hearing loss; and genetic factors (Bauman, 2003; Campbell, 2007; Singer, Smith & Krieff, 1996; Vasquez & Mattucci, 2003). These factors clearly indicate the difficulty that one would experience in trying to establish ototoxicity of a new drug since so many other variables could have an influence.

6.3. Clinical features of ototoxicity

Early ototoxicity investigations involving animals demonstrated that initial detection of ototoxicity typically corresponded with damage to hair cells in the basal region of the cochlea, where higher frequency sounds are perceived (Campbell, 2007). Histopathological studies have shown that the outer hair cells are the cochlear components most susceptible to injury from ototoxic drugs like aminoglycosides (Stavroulaki et al., 1999). The most consistent histological finding of gentamicin ototoxicity, for an example, is degeneration of outer hair cells with a predilection for the basal parts of the cochlea with the inner hair cells being more resistant but they may also be affected by very high doses (Probst, Lonsbury-Martin & Martin, 1991). This

damage is reported to progress from high to low frequencies (Fausti et al., 2005). It is for this reason that hearing assessments and monitoring at the highest audible frequencies (ultrahigh frequencies) and the use of otoacoustic emission measures for each patient are recommended. This type of monitoring would not only allow for early identification of ototoxic changes but is also critical for the detection of hearing changes before the lower frequencies necessary for understanding speech are affected (Fausti et al., 2005).

Whatever drug is the cause of suspected ototoxicity, the clinical features have been reported by Ludman and Wright (1998) to be much the same, differing only in the severity of the symptom, the timing of onset and the duration of the effect. These authors further report that the cardinal symptoms are tinnitus, sensorineural hearing loss, and vertigo; with a feeling of pressure in the ears being a frequently added complaint. The reported tinnitus is typically described as intense and high pitched, ranging from 4 kHz to 6 kHz (Schwade, 2000).

Ototoxicity typically is associated with bilateral high-frequency SNHL and tinnitus. Hearing loss is initially evident in the high-frequency range, and as it progresses or becomes more severe, all audiometric frequencies may become affected (Campbell, 2007). In a hearing loss involving all frequencies, a characteristic high-frequency slope configuration is usually evident (Fausti et al., 2005). When the mid-frequency or high-frequency range is affected, auditory discrimination ability is also impaired (Bergstrom, et al., 1984). Hearing loss can be temporary, but it is usually irreversible with most agents (Campbell, 2007). Generally, antibiotic-induced ototoxicity is bilaterally symmetrical, but it can also be asymmetrical (Ludman & Wright, 1998). The usual time of onset is often unpredictable, and marked hearing loss can occur

even after a single dose. In addition, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy (Ludman & Wright, 1998). Generally, the symptoms can present after the initial course of treatment or be delayed for days or months, and are often progressive (Konrad-Martin et al., 2005). This may not be true for antiretroviral drugs, and therefore, their specific clinical features need to be established.

The reported incidence of ototoxic hearing loss varies widely, and this wide discrepancy is most likely due to diverse testing methodologies, different populations studied and varying regimens of drug dosage and duration – however, clinical features seem consistent throughout.

6.4. Ototoxicity and antiretroviral therapy

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced substantial complexity into treatment regimens for persons infected with human immunodeficiency virus. Drugs interfere, in one way or another, with the chemical system that governs the homeostatic mechanisms of an organism. To be useful, drug-induced changes must do one or more of the following:

- normalize pathologic functions;
- alleviate disease symptoms;
- prevent disease;
- combat infections or;
- enhance performance (Cummings, 1993, p. 255)

Unwanted adverse events such as drug induced hearing loss do not contribute positively towards patients' quality of life, and therefore need to be well monitored, documented, and managed

timeously (Campbell & Durant, 1993). Eradication of HIV infection cannot be achieved with available antiretroviral regimens, chiefly because the pool of latently infected CD4+ T cells is established during the earliest stages of acute HIV infection (Chun et al. 1998; Hammer et al., 2006) and persists with a long half-life, even with prolonged suppression of plasma viremia to <50 copies/mL (Chun et al., 1997; Finzi et al., 1997; Finzi et al., 1999).

The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and preservation of immunologic function; reduction of HIV related morbidity and mortality, and improvement of quality of life (Hammer et al., 2006). Hearing loss due to opportunistic infections constitutes HIV related morbidity, and morbidity due to possible side effects of antiretroviral medications needs to be established and documented as it can exert a significant impact on the patients' quality of life (DHHS, 2003). Patient education in terms of these side effects and involvement in therapeutic decisions is therefore critical. This education should include information on anticipated hearing changes and monitoring of these changes as part of providing efficacious treatment to patients infected by HIV/AIDS. Therefore ototoxicity monitoring of patients on antiretroviral drugs can potentially contribute to both theoretical knowledge and is likely to impact directly on patient management.

There is a wide range of drugs which are capable of causing deafness and/or dizziness, either by producing toxic degeneration of the inner ear, or of the higher centres of hearing and equilibrium. Many ototoxic drugs have no apparent chemical similarity (for instance thalidomide, ethacrynic acid and the arsenical compound atoxyl), but most ototoxic antibiotics belong to the 'useful but unruly' family of basic streptomyces antibiotics (Hawkins, 1976), or

aminoglycoside antibiotics and the so-called 'loop diuretics' (Kerr, 1997). In audiology literature, antiretroviral drugs have not been clearly defined in as far as their potential ototoxicity levels are concerned. Drugs regimens specifically developed to combat HIV in the HIV-infected population often involve potentially ototoxic, government-approved antiretroviral medications along with experimental antiretroviral drugs with undocumented or unknown side effects (Marra et al., 1997; Simdon et al., 2001). In addition, a variety of known ototoxic medications are also prescribed either as a prophylaxis or treatment for opportunistic infections (Bankaitis & Schountz, 1998). In contrast with these findings on the ototoxic effects of treatment regimens for HIV/AIDS infected patients, Chandrasekhar et al. (2000) report that the hearing loss as found in their study did not correlate with routine medications used in the outpatient management of HIV in their participants. This was however a cross sectional study with no longitudinal follow up of patients and limited control over extraneous variables that are known to impact on hearing function.

Although a variety of adverse effects have been attributed to treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) for HIV-1 infection, only a small number of cases of ototoxicity have been reported in the literature. Simdon et al. (2001) describe three cases of possible NRTI-associated ototoxicity in HIV-1 infected patients, all of whom were aged >45 years, had a history of noise-induced hearing loss, and reported tinnitus and deterioration in hearing following initiation of antiretroviral therapy. These authors suggest that reductions in mitochondrial DNA content induced by NRTIs, as well as mitochondrial DNA mutations associated with aging and HIV-1 infection, all may contribute to auditory dysfunction in older patients with HIV-1 infection. They highlight the fact that prospective studies are necessary to

determine the incidence of tinnitus and hearing loss among HIV-1 infected patients and their relationship to the use of NRTIs (Simdon et al., 2001).

Several cases of ototoxicity have been reported in HIV-infected patients treated with zalcitabine (Martinez & French, 1993; Monte, Fenwick & Monteiro, 1997; Powderly, Klebert & Clifford, 1990); didanosine (Colebunders, Dipraetere, Van Wanzeele & Van Gehuchten, 1998); zidovudine (Simdon, Watters, Bartlett & Connick, 2001); and combinations of zidovudine and didanosine (Christensen et al., 1998); stavudine and lamivudine (Simdon et al., 2001); stavudine, lamivudine, didanosine, and hydroxyurea (Simdon et al., 2001); and post exposure prophylaxis with stavudine, lamivudine, and nevirapine (Rey et al., 2002). Moreover, a study of 99 HIV-infected individuals who received antiretroviral drugs showed that hearing loss was common in this population. Hearing loss was significantly associated with being 35 or older and with a history of ear infection, and there was a trend toward an association with documented receipt of therapy with antiretroviral drugs in the preceding 6 months (Marra et al., 1997). A possible mechanism involved in ototoxicity of ARVs could be mitochondrial damage caused by nucleoside analogues (Brinkman, & Kakuda, 2000; Seidman et al., 1996).

While hearing loss in HIV-infected people after beginning nucleoside reverse transcriptase inhibitors (NRTIs) has been described (Kakuda, 2000), there have been extremely limited prospective studies, with one example of a prospective study by Schouten et al. (2006). This study assessed hearing changes longitudinally in treatment-naïve HIV-infected subjects following initiation of regimens containing NRTIs. The goal of their study was to perform a prospective assessment of the contribution of zidovudine (ZVD) and didanosine (ddI) to hearing

loss. Changes in hearing levels at all frequencies and in low and high frequency pure tone averages were measured at baseline, 16, and 32 weeks after initiating antiretroviral therapy. In the aforementioned study (Schouten et al., 2006); treatment with ZVD and ddI did not result in loss of hearing, even after taking into account noise exposure, immune status and age. The results of this prospective pilot study did not support the view that treatment with nucleoside antiretroviral drugs damages hearing. This is a contradictory notion when compared to other cross-sectional studies and case reports that have indicated that hearing loss may be common among HIV-infected people (Marra et al., 1997; McNaghten et al., 2001; Simdon et al., 2001). Hearing loss may be linked with HIV infection itself, opportunistic infections, or ototoxic drug therapy (Khoza & Ross, 2002; Marra et al., 1997). However, in up to 50% of HIV-infected people with hearing loss, no cause can be identified (Lalwani & Sooy, 1992). The results of the prospective study by Schouten et al. (2006) did not corroborate this relationship and are consistent with the report from the Adult/Adolescent Spectrum of HIV Disease Project Group that demonstrated no association between hearing loss and age. Of note, however, that study was centred on a retrospective chart review for International Classification of Diseases (ICD) -9 coding for hearing loss and not on formal audiometry (McNaghten et al., 2001).

Prior cross-sectional studies and case reports have shown an association between hearing loss and NRTI therapy (Marra et al., 1997; McNaghten et al., 2001; Simdon et al., 2001). There have been two case reports of hearing loss in subjects receiving ART regimens that included NRTIs and a second class of antiretroviral drugs; one with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Nevirapine) and one with a protease inhibitor (PI) (lopinavir/ritonavir) each combined with NRTIs, (both these subjects were also receiving stavudine and lamivudine). One

case reported sudden hearing loss two weeks subsequent to the person completing one month of post-exposure prophylaxis which resulted in long-term hearing loss (Rey et al., 2002). The other case described hearing loss in a subject with extensive HIV pre-treatment, and suggested a possible relationship with the protease inhibitor, although there were other possible explanations noted in Simdon's reply to this case report (Simdon et al., 2001; Williams, 2001). Simdon reported three subjects who experienced ototoxicity, all of whom were over the age of 45 and received combination ART with 2-3 NRTIs plus a NNRTI or a PI. All three of the subjects had prior hearing problems, prior exposure to occupational noise and all developed significant tinnitus (Simdon et al., 2001). The authors suggested that NRTIs should be used cautiously in patients with pre-existing hearing loss.

Internationally, iatrogenic hearing loss has been associated with many of the drugs used to treat HIV/AIDS and its associated complications. Antineoplastic medications such as vincristine, antifungal agents including amphotericin B, immune modulators, aminoglycoside antibiotics, erythromycin, and azidothymidine (AZT) are all widely used in the management of HIV and are all associated with significant ototoxicity or decreased hearing (Bankaitis & Keith, 1995; Campbell, 2007; Gold & Tami, 1998; Kohan et al., 1990; Lalwani & Sooy, 1992). Moreover, the use of experimental medications with relatively unknown toxicity as well as the use of ototoxic drugs in combination adds to the overall effect on hearing (Simdon et al., 2001). In a study by Marra et al. (1997), hearing loss was seen in 29 participants (29%). It was significantly associated with age and history of ear infection and tended to be more common in participants who were prescribed antiretroviral agents. An interaction existed between age and antiretroviral therapy; the association between hearing loss and antiretroviral therapy was

significant for participants aged 35 years or older, but not for participants younger than 35 years, that is hearing loss was common among HIV-infected individuals and was associated with antiretroviral therapy in those aged 35 years or older (Marra et al., 1997). Again, the cross sectional nature of their study limits the reliability of the findings.

The potential for a drug-induced hearing loss in an HIV-infected individual at any stage of the disease is relatively high (Bankaitis & Schountz, 1998). With all the medications that individuals with HIV are taking and the continual developments in HIV therapies, it is challenging to acquire and maintain a comprehensive knowledge base of HIV-related drugs and associated ototoxicity. Although the side-effects of many antiretrovirals are yet to be determined, HIV-infected individuals are often prescribed medications as a prophylaxis or treatment of opportunistic infections that have been long associated with the development of audiological and vestibular changes. For example, common antifungal agents for candidiasis include Amphotericin B, flucytosine, and ketoconazole. These medications are associated with hearing loss, tinnitus and vertigo. Frequently administered medications for PCP (Pentamidine, TMP/SMX, Primaquine) may cause tinnitus, vertigo, dizziness, auditory disturbances, deafness, decreased hearing, hearing loss, and otalgia (Bankaitis & Schountz, 1998)

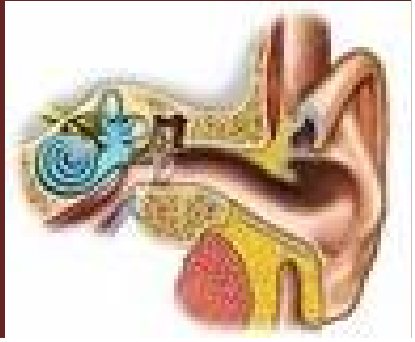
In South Africa, one of the most frequently administered treatments to the HIV/AIDS population is that of TB treatment. South Africa, like many sub-Saharan countries, witnessed a dramatic upsurge of TB cases over the past decade (Clarke, Dick & Bogg, 2006). This upsurge in the number of TB cases is expected to continue, largely due to co-infection with the Human Immuno-Deficiency Virus (HIV), with the emergence of drug resistant TB (Aziz et al., 2006)

also being reported. This co-occurrence of HIV/AIDS and TB raises serious implications for the audiologist with regard to the association between TB treatment and ARVs. Because some of the drugs used in the treatment of TB fall under the umbrella term 'aminoglycosides' (Smith & MacKenzie, 1997), interactions between these treatments need to be explored. Examples of these aminoglycosides include amikacin, gentamicin, kanamycin, netimicin, paromomycin, streptomycin, tobramycin, and apramycin (Cohn, 1981). These antibiotics are most notorious for being ototoxic, primarily targeting the renal and cochleo-vestibular system (Campbell, 2007).

6.5. Summary

As illustrated in this chapter, ototoxicity can be influenced by a variety of factors. Regardless of the variance in contributing factors, clinical features of ototoxicity seem to be consistent with high frequency sensorineural hearing loss with varying ranges of severity from patient to patient. Moreover, this chapter demonstrated that ototoxicity of ART does exist, although minimal reporting of this ART related morbidity is available in the academic literature. Documented information on ART ototoxicity is mainly of case reports, and where bigger samples are described, the studies are based on retrospective cross sectional data review and many have not utilized sensitive audiological monitoring tools. Moreover, these reports have mainly been international reports, with none found from Africa. It is clear though that ototoxicity can have significant negative effects on the patients' quality of life, hence early detection, monitoring and management is of paramount importance.

Chapter 7



OTOTOXICITY MONITORING METHODS – AN OVERVIEW

CHAPTER SEVEN

OTOTOXICITY MONITORING METHODS – AN OVERVIEW

7.1. Introduction

The need for audiometric testing to identify early changes in hearing thresholds resulting from drug therapy is widely recognized. Life-threatening conditions may require treatment with highly ototoxic agents, and the risk of hearing loss may well be unavoidable. In many cases, however, alternative drugs, reduced dosages, or altered treatment regimens are options if ototoxicity is detected early in the treatment period (Vaughan et al., 2002). Prospective monitoring of high-frequency auditory function permits the physician the opportunity to contemplate and balance the merits of alternative treatment before the loss of hearing sensitivity progresses into the speech communication range. In contrast, the absence of evidence of ototoxicity can justify prolonged and chronic or more aggressive treatment. Monitoring hearing threshold changes can also forewarn the audiologist, family and the patient of possible drug-induced hearing loss and alert them to the potential for the concomitant need for early amplification assistance. Consequently, strict use of, and adherence to a routine test protocol for early detection of hearing loss caused by therapeutic ototoxic drug treatment is imperative.

There is no doubt that it is important to prevent ototoxicity because the adverse effects of the majority of the drugs resulting in a hearing loss are irreversible. Thus, the only certain method of preventing incapacitating ototoxicity is to detect it as early as possible in the treatment regimen so that ototoxic medications can be replaced with less ototoxic drugs, altered dosages,

and/or the mode of administration changed (Lonsbury-Martin & Martin, 2001). Ototoxicity monitoring is therefore the focus of this chapter with a general overview of audiological behavioural monitoring methods, with more specific attention paid to Distortion Product Otoacoustic Emissions (DPOAEs) as a sensitive monitoring tool of choice in the current study.

7.2. Ototoxicity monitoring history

Until recent years, ototoxicity could only be monitored in clinical and scientific conditions by conventional pure tone audiometry (PTA). Although objective measures such as the Auditory brainstem response (ABR) have been researched and recommended for ototoxicity monitoring (Bernard, Pechere & Herbert, 1980; Piek, Lumenta & Bock, 1985), far too many disadvantages of this measure as an ototoxicity monitoring tool have limited its widespread use. These disadvantages include the fact that the click-evoked ABR has sensitivity that is limited to 4 kHz and below, hence hearing loss can progress to the point of communication impairment before being detected by ABR. Although high frequencies can be targeted through the use of tone-bursts as a way of identifying ototoxic changes (Fausti et al., 1991; Fausti et al., 1992a), this test is lengthy, could lack frequency specificity depending on how it is measured, and response interpretation at ultrahigh frequencies is variable and subjective (Campbell, 2007). Resource constraints with regard to time, personnel, availability of ABR machines, and so on seem to have been the most commonly cited reasons why conventional audiometry has been the method of choice over other measures.

Despite the widespread use of conventional audiometry for monitoring hearing function, Stavroulaki et al. (1999) argue that conventional audiometry also normally detects hearing loss at

a late, irreversible stage when inner ear function is already permanently impaired. This view is very different to that of Fausti et al. (1999), who, based on both their retrospective study and preliminary prospective data, contend that identifying and behaviourally testing a small range of frequencies for each patient on ototoxic medication provides sensitive early detection capability to audiologists (Fausti et al., 1999).

In addition, a study by Vaughan et al. (2002) demonstrates that an uppermost target frequency for a limited frequency range can be determined for each individual with a rapid and efficient protocol. Their study concluded that the use of smaller frequency steps during behavioural audiological assessment could provide increased sensitivity for early detection of ototoxicity at frequencies within the speech range that are not usually included in routine clinical threshold testing. These authors' proposed approach can be seen as an addition to the usual and most commonly used international approach of focusing on high frequency monitoring, which can be best done by utilizing OAEs. Ototoxicity monitoring seems to have been enhanced and dramatically advanced by the use of OAEs as a monitoring tool and this appears to have led to earlier identification of hearing loss due to toxic substances (Vaughan et al., 2002). Early identification of ototoxic effects could be beneficial, allowing for possible preservation of hearing in the frequency range that can affect communication abilities in the middle and lower frequencies.

7.3. Otoacoustic emissions defined

OAEs are defined as energy emitted from the cochlea and measured in the ear canal (Kemp 1978). The primary purpose of OAE tests is to determine cochlear status, specifically hair cell function, and this function is based on the premise that the normal cochlea does not only receive sound, but also produces low-intensity sounds (OAEs) (Campbell, 2007). The presence of cochlear emissions was hypothesized in the 1940s on the basis of mathematical models of cochlea nonlinearity; however, OAEs could not be measured until the late 1970s, when technology created the extremely sensitive low-noise microphones required for recording these responses (Campbell, 2002).

While pure tone audiometry is believed to measure throughout the outer ear, middle ear, cochlea, vestibular-cochlear nerve, and central auditory system, OAEs measure exclusively the peripheral auditory system, which includes the outer ear, middle ear, and cochlea (Campbell, 2007). The response only emanates from the cochlea, but the condition and function of the outer and middle ear is crucial as these structures must be able to transmit the emitted sound back to the recording microphone (Hall, 2000). OAE testing is often used as a screening tool to determine the presence or absence of cochlear function, although closer and more detailed analysis can be performed for individual cochlear frequency regions for diagnostic purposes (Campbell, 2002).

7.3.1. Otoacoustic emissions: types

There are two general categories of OAE – spontaneous and evoked (Hall, 2000). Spontaneous OAEs (SOAEs) occur without any external acoustic stimulation. These emissions are reported to consist of energy at one or more frequencies produced by the normal ear and recorded in the ear canal with an exceptionally sensitive microphone. The clinical value of SOAEs has been and is still limited, as they are not always emitted by normal ears. To be precise, this point means that the absence of SOAEs does not automatically imply cochlea dysfunction. Furthermore, the possibility of SOAE even in normal ears is much higher for females than for males. This significant gender influence on SOAEs invariably decreases the clinical value of this test (Hall, 2000).

Three types of OAEs are elicited or evoked with some kind of acoustic stimulus. This allows for some degree of control by the examiner on how the response is obtained. These evoked OAEs are the stimulus frequency, the transient evoked, and the distortion product OAEs (Hall, 2000). Stimulus frequency OAEs (SFOAEs) are evoked with a constant pure-tone stimulus presented at a low intensity level and generally swept or changed slowly across a region of frequencies. Although SFOAEs are supposedly better than SOAEs, they are, by far, the least studied experimentally and clinically. Moreover, there are no commercially available devices for recording SFOAE; hence they are also of limited clinical benefit (Katz, 2002). And finally, the two other types of OAEs that seem to be widely applied clinically are the transient evoked OAEs (TEOAEs) and the distortion product OAEs (DPOAEs) (Hall, 2000). These two measures have gained significant acclaim as part of an audiological test battery and have been widely used for early identification of hearing loss, particularly in the paediatric population as part of the

universal newborn hearing screening campaigns that all countries are aiming to achieve (Katz, 2002).

Since no behavioural response is required from the patient, OAEs can be obtained even from patients who are comatose. For a quiet and cooperative patient, recordings usually require less than 5 minutes (Campbell, 2002). This again makes them ideal for monitoring the hearing of the large numbers of patients going through a busy provincial government hospital where resources such as time and manpower are a problem.

7.4. Distortion Product OAEs defined

When two continuous acoustic pure tones, close in frequency, are presented simultaneously, acoustic distortion products at frequencies not present in the acoustic stimuli are produced (Hall, 2000). The two frequencies (known as primaries) activate the cochlea in the same region of the basilar membrane. The lower frequency portion of the travelling wave for the higher frequency stimulus actually overlaps with the higher frequency portion of the travelling wave for lower frequency stimulus. One or more additional frequency components, the DPOAE(s), is (are) emitted at another frequency (or frequencies). These distortion products can be detected in the ear canal by a sensitive microphone and are referred to as DPOAEs (Dreisbach et al., 2006). Because DPOAEs have been extensively studied and distinctly characterized, they have become widely recognized and respected, and hence DPOAE testing has become a quick, non-invasive, and objective test used in hospitals and hearing clinics to determine the status of the cochlea (Campbell, 2007). In contrast to SOAEs, the prevalence of DPOAE in normally functioning cochleas is close to, but slightly less than, 100% (Hall, 2000). This, therefore, makes

DPOAEs extremely useful in assessing integrity of the cochlea, and hence makes them of significant value in ototoxicity monitoring.

The DPOAE recording is achieved by inserting a soft probe tip in the ear canal to obtain a hermetic seal, in the same way to immittance audiometry. Multiple responses are averaged and analysis, as in all other OAEs, is performed by looking at responses relative to the noise floor. This reliance on the noise floor for analysis therefore highlights the reduction of physiologic and acoustic ambient noise as being critical for valid and reliable recordings (Campbell, 2007).

7.4.1. DPOAE recording parameters

Several variables are known to affect the presence and magnitude of DPOAEs, including the test frequencies (F1 and F2), test frequency separation or ratio (F2/F1), the nature and degree of auditory pathology, the absolute sound pressure levels of the primary tones (L1 and L2), the relative levels of the two primaries (L1+L2) (Beattie & Jones, 1998; Harris, Lonsbury-Martin, Stagner, Coats & Martin, 1989; Norton & Stover, 1994; Whitehead, McCoy, Lonsbury-Martin & Martin, 1995) and the number of stimulus repetitions (sweeps) that are averaged (GSI 60DPOAE User Manual, 1996).

As in every objective test procedure, for an accurate and reliable recording, several recording parameters have to be closely observed as failure to monitor these parameters could greatly influence the reliability and validity of the results obtained. Most importantly, for all OAEs, an optimal probe fit is critical (Hall, 2000). For DPOAEs, the other important recording parameters that require close monitoring are stimuli, intensity and frequency of measure

(Dreisbach & Siegel, 2001). Stimuli consist of 2 pure tones at 2 frequencies (i.e. f1, f2 [f2>f1]) and 2 intensity levels (i.e. L1, L2). The relationship between L1-L2 and f1-f2 dictates the frequency response. To yield an optimal response, it is recommended that one should set intensities so that L1 equals or exceeds L2. Lowering the absolute intensity of the stimulus renders the DPOAEs more sensitive to abnormality. A setting of 65/55 dB SPL L1/L2 is frequently used. Responses are usually most robust and recorded at the emitted frequency of 2f1-f2; however, they generally are charted according to f2 because that frequency approximates the cochlear frequency region generating the response (Campbell, 2002; Dreisbach & Siegel, 2001).

The most appropriate stimulus intensity for evoking DPOAE in most clinical applications is in the range of 50 to 70 dB SPL (Hall, 2000). With higher stimulus intensities, there is a chance that passive (versus active) responses will be recorded, responses that do not always reflect outer hair cell activity. On the other hand, lower intensities are reported to often fail in generating a detectable DPOAE, even from persons with reasonably normal hearing sensitivity. There is currently clear experimental evidence that DPOAE amplitude is slightly larger and, more importantly, sensitivity to cochlea dysfunction is enhanced, when the intensity of the F_2 primary (referred to as L_2) is lower in intensity than the F_1 primary (L_1) (Hall, 2000).

The acoustic activity picked up by the microphone contains DPOAEs as well as other unwanted noises. These noises originate within the patient, as well as from external sources, and the relationship between these noises and the signal has an effect on the DPOAE obtained. Hence; controlling the noise is of crucial importance in ensuring that the response measured is a reliable one. Internal sources may include blood circulation, breathing, coughing, spontaneous

OAEs and movement (especially jaw and neck) noise (Beattie & Ireland, 2000; Katz, 2002). External sources originate outside the subject and may include electromagnetic radio signals, power line radiation, ambient noise, probe tip movement and instrument noise (Arlinger, 1981; Baer & Hall, 1992; Jacobson & Hyde, 1985; Popelka, Karzon & Clary, 1998).

External noises are especially problematic if testing is not conducted in a sound-treated room and if there is not a good probe fit to reduce ambient noise (Baer & Hall, 1992; Campbell, 2007; Popelka et al., 1998). These noises may obscure OAEs which typically are much smaller than the various noises combined. This challenge therefore requires the audiologist to employ methods of enhancing the signal to noise ratio (S/N). Methods of increasing the S/N during the test procedure include artifact rejection and signal averaging and instructing the patient to relax as much as possible (Beattie & Ireland, 2000; Katz, 2002). Signal averaging is a powerful tool for increasing the S/N and, thus, detectability of DPOAEs (GSI 60DPOAE User Manual, 1996).

7.4.2. Interpretation of DPOAEs

Interpretation of OAEs is based on the presence or absence of an emission as well as the size of the emission in relation to the noise floor. Because several studies have established the prevalence rates of the different types of OAEs, the presence of OAEs is usually regarded as a sign of good cochlea health. For example, Spontaneous OAEs have been reported to occur in only approximately 40% of individuals who have normal hearing, and it is precisely this fact that has rendered this type of OAE not clinically relevant. This prevalence rate is however very different for DPOAEs since they are reported to be present in essentially all (100%) normally functioning ears (Hall, 2000). Most clinicians use the presence of a DPOAE in a particular

octave band to suggest that hearing sensitivity should be 50 dB HL or better, unless a functional or neural component is present (Campbell, 2002).

DPOAEs are plotted in one of two ways. The most common format is the DPgram (Hall, 2000). The DPgram is a graph of DPOAE amplitude as a function of the stimulus frequency. The stimulus frequency, usually represented as the f_2 primary in Hz, is plotted along the horizontal axis. The DP amplitude is plotted in dB SPL on the vertical axis. To be considered a valid DPOAE, the DP amplitude must exceed the noise floor value by at least 3dB (Hall, 2000).

Generally it is not easy to obtain OAEs in subjects with hearing thresholds >30dBHL (Campbell, 2002; Probst, Lonsbury-Martin, Martin & Coats, 1987). The stimulus is reduced going in because of the hearing impairment, and the response is also eliminated or reduced because of poorly functioning hair cells of the cochlea. In Bonfils and Uziel, (1989), DPOAE responses were recordable and found in only 6,7% of the population studied when hearing loss exceeded 30dB. Moon and Jung (1998) further state that DPOAEs are completely immeasurable when the hearing threshold exceeds 50dBHL. Therefore, if hearing loss is greater than 50dBHL and DPOAEs are present, it is believed that this may mean either that the hearing loss has a neural base or the patient may be malingering (Hall, 2000; Robinette & Facer, 1991).

7.5. DPOAEs versus behavioural audiometry in ototoxicity monitoring

Ototoxicity has been reported to affect the higher frequencies of hearing before the lower frequencies (Fausti et al., 1999). Serial monitoring of behavioural auditory thresholds is a conventional method for detection of hearing decrease during treatment with a potentially ototoxic drug (Campbell, 2007). Human auditory testing programs monitoring drug-induced hearing loss with conventional audiometers have shown that the highest frequencies evaluated are the first to be affected (Katz, 2002; Meyerhoff, Malle, Yellin & Roland, 1989; Skinner, Pearson, Amineddine, Mathias & Craft, 1990). If ototoxicity originates in the basal portion of the cochlea where the highest frequency energy is transduced, detection of ototoxicity using conventional audiometry (0.25 – 8 kHz) requires damage progression into the region of the cochlea corresponding to frequencies affected early (high frequencies through to 20 kHz). Behavioural pure tone audiometry in the form of extended high frequency audiometry has been recommended in the audiological assessment of patients exposed to noxious agents such as noise and ototoxic medications. Studies that have monitored in the high frequency range have indicated that high frequency thresholds generally appear to be affected first, with spread of hearing loss into the conventional frequency range throughout the course of treatment (Campbell, 2007; Dreschler, van der Hulst, Tange & Urbanus, 1989; Fausti et al., 1992; Fausti et al., 1994).

Traditionally, a person's hearing is only tested behaviourally up to 8 kHz due to equipment limitations and the variability of high frequency hearing thresholds across subjects (Dreisbach, Long & Lees, 2006). However, using commercially available equipment, it has been determined that high frequency hearing thresholds (>8 kHz) tested behaviourally are repeatable

over time within a subject, making this type of test reliable and clinically useful (Fausti et al., 1990; Frank, 1990). Consequently, it has been recommended that an individual's conventional (0.25 to 8kHz) and high frequency hearing thresholds be monitored behaviourally to determine if a significant change has occurred that is due to ototoxic therapies (American Speech-Language-Hearing Association, 1994; Campbell, 2007). The major drawbacks with behavioural testing in a clinical population are that it is time consuming and requires the active participation of the patient, who can be too sick or too young to provide reliable responses (Dreisbach et al., 2006). When monitoring ill patients, however length of time can have significant effects in test reliability. In these cases, evaluation of hearing in a more limited frequency range may be necessary. Over and above this limitation, Feghali and Bernstein (1991) also highlight the effect that the transducer (i.e. headphones, insert phones) can have on the reliability of this monitoring method. These authors assert that thresholds obtained at ultra-high frequencies through the use of headphones tend to be more variable than at conventional audiometric frequencies – this variability stabilises when custom-made earmolds are used. This test-retest variability was also reported by Frank (1990) for frequencies 10 – 20 kHz while trying to establish normative data for a group of young adults between the ages of 18 and 28 years.

Nevertheless, several studies have been conducted to determine the benefit of using behavioural pure tone testing in the high frequencies versus DPOAEs as monitoring measures for cochlea damage. Recent reports that examined the feasibility of using DPOAE measures to assess and monitor patients exposed to noise and ototoxic drug treatments (Hall & Lutman, 1999; Mulheran & Degg, 1997; Ress et al., 1999; Stavroulaki et al., 2001) found that hearing loss predominantly occurred at high frequencies (especially 12kHz) for young patients with

chronic renal failure having haemodialysis and that DPOAE levels were decreased whether patients did or did not have hearing loss up to 4kHz versus age-matched controls. These authors suggested that DPOAE measures might possibly be more predictive in the case of substantial threshold shifts for a given frequency before a measurable sensitivity loss, i.e. before the hearing loss is indicated on the audiogram. This is contrary to Ress et al. (1999) who claimed that DPOAEs were as sensitive as ultra-high-frequency (UHF) audiometry for detecting changes in hearing due to cis-platinum ototoxicity, but that DPOAEs were superior to UHF audiometry as an ototoxic screening tool (Dreisbach et al., 2006).

Stavroulaki et al. (2001) argued that DPOAE measures were more sensitive than behavioural audiometry in revealing cochlea dysfunction. These authors also concluded that DPOAE levels were sensitive indicators of cochlea damage and were superior to pure tone audiometry (up to 8 kHz) based on their results when examining children who received a first cis-platinum infusion. One needs to acknowledge that sensitivity of a test may be different in paediatric patients when compared to adults since there are variables that are present in adults that may not be present in paediatric patients (for example, presbycusis, noise exposure, previous use of ototoxic drugs and so forth). Given that ototoxicity initially causes damage in the high frequencies (>8kHz), as noted in changes of hearing sensitivity measured with pure-tone audiometry (Fausti et al., 1999), and ultra-high-frequency hearing influences DPOAEs at significantly lower frequencies (Arnold, Lonsbury-Martin & Martin, 1999), Dreisbach et al. (2006) believe that it is not surprising therefore that DPOAE measures were more sensitive to change than pure tone results at frequencies less than 8kHz in their study.

Because high-frequency hearing (>8kHz) is affected first by ototoxic agents and DPOAE measures have been shown to be repeatable and sensitive to cochlea damage, high-frequency DPOAE measures are therefore recommended as a method of choice for the monitoring of patients exposed to noise or ototoxic agents that are not able to reliably respond to traditional behavioural measures of high frequency hearing (Dreisbach et al., 2006). These authors based their recommendation on the results of their study which demonstrated that high-frequency DPOAEs are repeatable over four trials.

Arnold et al. (1999) investigated the relationship between hearing in the extended high-frequency region (11 to 20 kHz) and DPOAE levels at lower frequencies for a group of fifty normal-hearing human subjects. The results, evaluated using multiple regression analyses, demonstrated that extended high-frequencies contributed significantly to the variance of DPOAE levels from 4 to 8 kHz. From the results of their study on high-frequency hearing and its influences on lower-frequency DPOAEs, Arnold et al. (1999) found from simple regression analysis that the 4 to 8kHz DPOAE levels were significantly correlated with the PTA from 11 to 20kHz. However, the PTA for 4 and 8 kHz were also significantly correlated with the PTA for UHF hearing. These findings suggest that UHF hearing influences DPOAEs at significantly lower frequencies because emissions are sensitive to subtle changes in outer hair cells not yet detected by pure tone thresholds in this region or because alterations in the basal cochlea affect the generation of lower-frequency DPOAEs originating from more apical cochlear regions (Arnold et al., 1999). This was found to be true not only for DPOAEs since in a study by Avan, Elbez and Bonfils, (1997), results indicated that poorer ultrahigh frequency hearing (8-16 kHz) correlated with reduced TEOAE amplitudes evoked at much lower frequencies (1-5 kHz).

However, in this study, age and UHF hearing levels were also correlated and, therefore, it was not possible to exclude aging as the primary cause of the relationship between TEOAEs and UHF hearing. Both these findings support the sensitivity of utilizing conventional pure tone audiometry and DPOAEs as a monitoring protocol – as in the current study.

It is now well established that OAEs measures are more sensitive to inner ear dysfunction than conventional PTA or auditory brainstem responses (Arnold et al., 1999; Biro, Baki, Buki, Noszek & Jokuti, 1997; Ress et al., 1999). In their study, Stavroulaki et al. (2002) demonstrated DPOAEs were significantly affected at the higher frequencies following recent exposure to gentamicin. Stavroulaki et al. (2002) concluded that tests for DPOAEs seemed to be more frequency sensitive for determining minor cochlea dysfunction when compared to another type of OAEs (TEOAEs). Furthermore, these authors assert that for monitoring purposes, DPOAEs would also seem preferable to TEOAEs because DPOAEs are known to have a more extensive range regarding hearing loss and can be measured over a broader frequency range with more sensitive frequency-specific responses (Campbell, 2007; Franklin, McCoy, Martin & Lonsbury-Martin, 1992). These authors further assert that decreased emissions in the presence of normal behavioural hearing may indicate an underlying pathologic condition, which, if allowed to continue, might result in a clinically significant hearing loss.

7.6. DPOAEs and test-retest reliability

The relative merits of DPOAEs have been widely discussed. Essentially, DPOAEs allow greater frequency specificity and can be used to record at higher frequencies than the other types of OAEs. Therefore, DPOAEs have been put forward as best for particular early detection of cochlea damage as evidenced with ototoxicity and noise-induced ear damage. Formal studies addressing the reliability of DPOAEs have been conducted because the intra-subject and inter-subject variability in DPOAE amplitudes is reportedly high. Reliability of DPOAEs has been reported to be greatest above 1000Hz, and this report significantly enhances the validity of ototoxicity monitoring methods since ototoxicity monitoring is usually performed on frequencies higher than 1000Hz (Campbell, 2002).

One of the proposed uses of DPOAEs is to monitor cochlea function over time within individuals (Hall, 2000; Hunter et al., 1994; Katz, 2002; Kimberly et al., 1997; Yardley et al., 1998). For example, clinicians may obtain baseline DPOAE measurements prior to the administration of potentially ototoxic drugs and then repeat DPOAE measurements during the course of treatment in an effort to identify early warning signs of toxicity, so that corrective action can be taken before there is permanent damage to the auditory system. This decision requires that clinicians know how much of a difference in the DPOAE is necessary before they can be reasonably certain that the DPOAE change is attributable to a change in the auditory system, and is not simply due to measurement error. Answering that question requires reliability estimates that define the degree of confidence that can be placed in an individual DPOAE or in differences between DPOAEs. Significant debate has been documented regarding the frequency specificity as well as test-retest reliability of OAEs. Publications have appeared supporting both

sides of the argument. The disparity in findings may depend primarily on methodologies employed and on patient populations studied. Using current technology, most researchers and clinicians find a correlation between frequency-specific analysis DPOAEs and cochlear hearing loss. Moreover, test-retest reliability measures have been established for short term as well as long term DPOAE repeats for monitoring purposes.

DPOAEs have been subjected to vigorous scrutiny in the research laboratory regarding their reliability and validity in measuring cochlea changes. Furthermore, research on test-retest reliability of DPOAEs in identifying slight cochlear dysfunction has been conducted. As mentioned earlier, reliability is an essential aspect of any clinical procedure, because it provides a measure of the degree of confidence that can be placed in an individual DPOAE or between DPOAEs. Reliability may improve with increases in the signal-to-noise ratio (S/N), and may decrease as the time interval between the test and retest increases (Campbell, 2007). This decrease due to increased time interval is due to a variety of factors including changes in cochlea functioning following ear exposure to damaging agents such as noise and ototoxic medications (Zhao & Stephens, 1999). DPOAE frequency sweeps have been found to be repeatable over short and long periods of time (Beattie & Bleech, 2000; Beattie, Kenworthy & Luna, 2003; Cacace, McClelland, Weiner & McFarland, 1996; Franklin et al., 1992; Roede, Harris, Probst & Xu, 1993; Shehata-Dieler, Dieler, Teichert & Moser, 1999; Zhao & Stephens, 1999) allowing a patient's inner ear function to be monitored before, during, and after exposure to noise or ototoxic therapies (Campbell, 2007).

A review of literature on test-retest reliability of DPOAEs revealed that test-retest reliability is expected to approach a maximum when the retest immediately follows the test: this is what Beattie, Kenworthy and Luna (2003) refer to as *immediate test retest reliability*. Maximal reliability is said to be expected because the short time interval minimizes the likelihood of changes in hearing, environmental noise or subject noise, procedures, probe tip position, or equipment (Franklin et al., 1992; Hall, 2000; Marshall & Heller, 1996; Prieve et al., 1993; Roede et al., 1993; Zhao & Stephens, 1999). All these factors have been reported by these authors to have a significant negative effect on test-retest reliability. A longer time frame between test repeats is said to further influence reliability (Beattie et al., 2003). For example slightly poorer test retest reliability may be expected when the retest follows a 10 to 20 minute break and involves probe tip removal and replacement. Beattie et al. (2003) attribute these slightly poorer reliability results measured under these conditions to the variable probe tip placement and to the fact that the 10 to 20-minute time interval allows more opportunity for changes in hearing (e.g. swallowing or coughing may alter middle ear pressure), environmental noise or subject noise, or equipment. For example, Zhao and Stephens (1999) state that changing the position of the probe tip may affect:

- the level of background noise in the ear canal, particularly at the low frequencies
- acoustic leakage, and
- the interaction of the ear canal resonances and the acoustic stimuli.

Roeder et al. (1993) also state that middle ear changes in fluid or air pressure can affect DPOAEs and will have more effect on low-frequency DPOAEs than on the higher frequencies. Beattie et al. (2003) further state that retesting subjects 5 to 10 days after the initial test may result in even greater test retest variability. These studies highlight the need for extreme caution in interpreting

DPOAE results obtained for monitoring purposes, and emphasize the necessity for closer scrutiny of results before one can conclude that changes obtained in retest measures represent cochlea function changes, and are not just due to expected variability in test-retest measures.

It is auspicious however that the variability problems reported in the literature are said to mainly influence low frequencies and not high frequencies (and high frequencies are the main focus of ototoxicity monitoring studies). Somewhat poorer reliability is expected at the lower frequencies (approx 550Hz) than at higher frequencies because of the more variable immittance and variable background noise typically measured at the lower frequencies, and because immittance changes tend to affect mostly frequencies below 1000Hz the most (Beattie et al., 2003; Hall, 2000). Beattie et al. (2003) examined immediate and short term reliability of DPOAEs, and their results indicated that short-term differences between two DPOAEs must exceed approximately 14dB at 550Hz and 7dB at 1000-4000Hz to be statistically significant at the 0.05 level of confidence.

Cacace et al. (1996) examined time-of-day effects on DPOAE levels measured with equal level primary tones (55 and 75dBSPL) over the f2 frequency range of 1 to 6kHz and found that individual results were reliable over a 24hr period and that time of day did not affect the results significantly. Participant size in this study was not thought to be large enough to allow ease of generalizability of results. Beattie and Bleech (2000) explored short term DPOAE repeatability and found that the differences between two DPOAE frequency sweeps at frequencies between 0.5 and 4kHz must exceed approximately 6dB to be statistically significant when tested in the same trial (immediate test-retest). Again, this is not the frequency range that one monitors for

ototoxicity – hence, test retest data for this frequency range is not as essential as data on higher frequencies. More recently, Beattie et al. (2003) determined the immediate and short-term (5 to 10dB) reliability of DPOAE frequency sweeps between 1 and 4kHz and concluded that the difference between two DPOAE measures must exceed approximately 7dB to signify a change in cochlea status. Based on these studies, Dreisbach et al. (2006) concluded that a change in DPOAE level of 6 to 7dB would be considered significant when examining short-term DPOAE repeatability using equal level primary tones for frequencies between 0.5 and 6 kHz. This change in DPOAE level that is significant for DPOAE repeatability has also been studied in measures occurring over longer periods of time.

Typically, monitoring for hearing loss occurs for the duration of exposure to the damaging agent (noise or ototoxic drugs). As early as 1992, Franklin et al. reported that DPOAE frequency sweeps were repeatable over consecutive days and weeks using equal level primary tones (55, 65, and 75dBSPL) over the 2f1-f2 frequency range of 1 to 8kHz. In their study, some individuals were reported to have demonstrated greater variability, but in general there was less than 2dB of variation in the DPOAE level when the individuals underwent repeat testing. These authors concluded from the results of their study that DPOAE frequency sweeps can be used to monitor stable, as well as progressive and fluctuating hearing losses with the expectation that only 5% of the population will have greater than a 4dB change in DPOAE level during monitoring. Their results were later extended and confirmed by Roede et al. (1993), utilizing a paradigm similar to Franklin et al. (1992) where they concluded that a change of more than 6 to 9dB in DPOAE level would constitute a significant change in cochlea status based on monitoring over a 6 week period. More recently, Dreisbach et al. (2006) suggested that when examining

short- or long-term DPOAE repeatability for frequencies <=8 kHz using equal level primary tones, a 4 to 9dB change in DPOAE level would be considered significant. Although these studies have all been conducted with over a decade in between them with different equipment technologies, different populations, different sample sizes, and so on – the results seem consistent.

There is considerable evidence that DPOAEs are generated from specific cochlear sites. This cochlear specification of DPOAEs may lead to a frequency-specific relationship to cochlea function (Gaskill & Brown, 1990; Hall, 2000). The implication of the frequency-specific properties of DPOAEs is that each part of the cochlea can be characterized by examining the amplitude of the DP-gram. The general results on reliability of DPOAEs have shown that the shape of the DP-gram is often unique for an individual, and is highly reproducible over time (Zhao & Stephens, 1999).

The main factors affecting the variability of DPOAEs, including parameters of measurement, the placement of the probe, test procedure, instrument and environment (e.g. background noise and subject-generated noise) are well recognized (Campbell, 2007). Among these factors, the short-term variability reflects the inherent variability, which is caused by instrumental errors and subject noise. Any other component of DPOAE variability is introduced by probe placement because of the stimulus levels varying as a function of an interaction between the individual characteristics of each ear and the placement of the probe (Zhao & Stephens, 1999). This therefore raises important clinical implications when utilizing DPOAEs for ototoxicity monitoring. For clinical monitoring, Katz (2002) recommends that the subtle

changes in the cochlea status be reduced to a minimum by controlling the influencing components, such as environmental and subject noise. Moreover, Hall (2000) suggests that monitoring the ear canal volume may reduce the variance due to the degree of fit of the probe in the ear canal. This, they believe, will reduce changes of the background noise level in the ear canal, which mainly contaminates DPOAEs at the low frequencies. At the same time, it will also reduce changes due to the resonances of the ear canal.

Because DPOAE recording has the advantages of being simple, objective and non-invasive and can be used under physiologically normal conditions, DPOAE frequency analysis may objectively reflect physiological irregularities of the cochlea (Campbell, 2007).

7.7. Prerequisites for obtaining OAEs

To improve response accuracy and reliability, certain prerequisites for obtaining OAEs have been documented (Campbell, 2002; Campbell, 2007; Hall, 2000; Katz, 1994). The following are some of the aforementioned prerequisites:

- A quiescent patient: excessive movement or vocalization may preclude recording. This may be difficult to maintain in a very ill patient who may have cognitive impairments (e.g. Aids Related Dementia) who may be unable to follow instructions.
- Relatively quiet recording environment: a sound booth is not required, but a noisy environment may preclude accurate recording. This may lead to extreme difficulties in monitoring of patients in the wards or general outpatient clinics as noise levels may be too high to allow for reliable recordings.
- Unobstructed outer ear canal

- Hermetic seal of the ear canal with the probe
- Optimal positioning of the probe
- Absence of middle ear pathology: pressure equalizing (PE) tubes alone have been reported to probably not have significant effects on OAEs
- Functioning cochlea outer hair cells

Presence of these prerequisites enhances the response signal and improves chances of obtaining a clear and reliable as well as repeatable OAE (Hall, 2000). However, this process is known to be influenced by several factors known to affect OAEs.

7.8. Factors that affect OAEs

There are factors that have been documented to have a negative impact on OAEs. These factors include non-pathologic factors and pathologic factors. These factors are reported to diminish or cause an absence of OAEs (Campbell, 2002; Hall, 2000). To record OAEs, the cochlear response must be able to travel efficiently through the middle ear and tympanic membrane to the recording microphone in the ear canal. Even in the presence of normal cochlear function, OAEs generally may be absent in the presence of these pathologic and non-pathologic factors. Pathologic problems have been differentially divided into the different parts of the ear from the outer ear to the cochlea. These factors are listed in the following Table 3:

Table 3: Non-pathologic and pathologic factors that have an effect on OAEs:

Non-pathologic factors	Pathologic factors
Poor probe tip placement or poor seal Standing waves Cerumen occluding the canal or blocking a probe port Debris and foreign objects in the outer ear canal Vernix caseosa in neonates: this is common immediately after birth Uncooperative patient: usually this impedes recordings from being obtained.	Outer ear: Stenosis, External otitis, Cyst, Abnormal middle ear pressure Tympanic membrane: Perforation of the eardrum (Pressure Equalizing tubes have been reported to not necessarily prevent good recordings) Middle ear: Otosclerosis, Middle ear disarticulation, Cholesteatoma, Cyst, otitis media Cochlea: Exposure to ototoxic medication or noise exposure (including music) and any other cochlear pathology.

(Campbell, 2002; Hall, 2000)

7.9. Effects of gender on DPOAEs

According to a review by McFadden (2001), profiles of OAEs exhibit gender differences similar to those observed for hearing sensitivity. In general, hearing sensitivity is better in women than in men. Similarly, OAEs are stronger in women than in men (Schmuziger, Probst & Smurzynski, 2005).

It is surprising that gender differences have been reported in DPOAE measures, despite lack of reported significant behavioural differences. These findings lead to the assumption that some other process may be contributing to DPOAE gender differences when using both lower and higher frequency stimuli. The effect of gender on tests of the auditory system has long been of interest to both researchers and clinicians. Gender differences have been consistently found in ABR wave amplitude and latency values (Don, Ponton, Eggermont & Masuda, 1993; Jerger & Hall, 1980) and have lead to the practice of establishing separate norms for females and males in clinical settings (Katz, 2002). This practice is in contrast to most behavioural findings, which have consistently not found significant differences between genders, and therefore normative data do not exist separately for the conventional frequency range (Dunckley & Dreisbach, 2004).

Hence it is very important to determine what effect gender may have on DPOAE measurements and how these differences may affect DPOAE use in clinical settings.

Gender differences have been found in other tests of the auditory system at high frequencies, as well as measurements using low frequency stimuli to evoke DPOAEs. Gender differences have been reported in studies of evoked potentials (Barrett & Fulfs, 1998; Don et al., 1993), middle ear immittance (Hall, 1979, 1982; Jerger, Jerger & Mauldin, 1972) and low frequency otoacoustic emissions (Ferguson, Smith, Davis & Lutman, 2000; Kimberley, Brown & Eggermont, 1993), including an increased prevalence of spontaneous otoacoustic emissions in females (Bilger, Matthies, Hammel & Demorest, 1990; Cacace et al., 1996). Studies using lower frequency stimuli (<=9kHz) to evoke DPOAEs have found differences between male and females in group delay, the slope of the phase versus frequency curve, level (Cacace et al., 1996; Shehata-Dieler, Dieler, Teichert &Moser, 1999) and growth behaviour using input/output functions (Lonsbury-Martin et al., 1990).

As early as 1978, Stockard, Sharbrough, and Tinker discovered that females had smaller central nervous system dimensions, which may account for the shorter wave V latency values found in females for auditory evoked potentials. The fact that the two gender groups have different wave V latencies, presumably due to anatomic differences, leads to the speculation that additional anatomic differences may be causing differences in OAE measures. In 1996, Cacace et al. reported on statistically significant differences in DPOAE levels across gender. These authors' results revealed significant DPOAE level differences, where female levels were greater than male levels at 2.4kHz and higher, which they attributed to the increased prevalence of

SOAEs in females. Later in 1999, Shehata-Dieler et al. published results from their study which revealed absolute DPOAE levels that were significantly larger for females in the 2-6 kHz region, and larger for males below 2 kHz. Furthermore, Bowman, Brown and Kimberley (2000) also found DPOAE differences between males and females. Levels were very similar across gender below 3.3 kHz; however, at high frequencies (>3.3 kHz), females tended to have larger emissions but not at a statistically significant level. Most recently, Dunckley and Dreisbach (2004) found significant differences between gender and DPOAE level but only at the higher frequencies. With varying methodologies and different populations studied, all these findings are consistent with regard to the fact that high frequency variability exists between males and females.

7.10. Effects of age on DPOAEs

Besides gender, age also seems to have an effect on OAEs. Murray and LePage (1993) showed that the TEOAEs decreased as function of age in the whole age span. While most of the age-related changes in OAEs can be attributed to changes in hearing sensitivity (Campbell, 2002; Karzon, Garcia, Perercio & Gates, 1994; Prieve & Falter, 1995; Stover & Norton, 1993; Strouse, Ochs & Hall, 1996) some studies suggest that there are small changes even after controlling for hearing thresholds (Arnold, Lonsbury-Martin & Martin, 1996; Dorn, Piskorski, Keefe, Neely & Gorga, 1998; Engdahl, 2002). Engdahl (2002) believes that while these changes are small and therefore of minor clinical importance, they could be of interest in epidemiological studies. An early decline in OAEs that is not reflected in hearing thresholds would favour the use of OAEs when probing effects of age and exposure, as suggested by Murray and LePage (1993). Generally, there is a constant decline in DPOAE level over the whole age span (Hall, 2000). In a

study by Oeken, Lenk and Bootz (2000) results revealed that DPOAEs could be found in nearly all ears at all frequencies in the younger age group; however in the older age groups, the percentage of occurrence of DPOAEs was much lower. Furthermore in this study, particularly in those subjects over 70 years of age, DPOAEs were found only sporadically. When one interprets these findings, one needs to consider other factors that influence hearing function besides age which an older person might have been exposed to (which were however not considered by these researchers) such as noise exposure, chronic medication use (medication that might be ototoxic), and so on.

7.11. Effects of right/left ear on DPOAEs

There seems to be small effect also of ear side, although this is infrequently reported in studies of small samples. Schmuziger, Probst and Smurzynski (2005) report that hearing sensitivity is better in right than in left ears and that OAEs are stronger in right than in left ears. Right ears may be more likely to have SOAEs (Bilger et al., 1990; Burns, Hoberg-Arehart & Campbell, 1992) and a slight tendency for higher TEOAEs and DPOAE levels has been reported (Cheng, 1998). The ear side difference in hearing sensitivity has been attributed both to the left ear receiving more noise exposure in right-handed subjects and to a fundamental difference in the bilateral organization of the human auditory system (Engdahl, 2002; McFadden, 1993). Left ears are also suggested to be more vulnerable to noise than right ears (Job, Grateau, & Picard, 1998). Even though the small right-left difference does not seem to have any clinical significance, its noting and close scrutiny could be of some interest.

7.12. DPOAEs as a predictor of ototoxicity

It is patently clear that OAEs provide valuable information on auditory function and make an important and unique contribution to early detection of cochlea impairment and to diagnostic audiological assessment. Because of their sensitivity to disruptions in metabolic processes within the cochlea, OAEs are extremely well-suited for monitoring the cochlea function of patients treated therapeutically with potentially ototoxic drugs (Campbell, 2007). At least three principles of ototoxicity are very relevant to the meaningful clinical application of OAEs:

- First, the incidence of ototoxic effects varies among drugs and even for specific drugs among patients. A variety of factors can influence the strength or likelihood of ototoxicity, especially concomitant exposure to other drugs, renal function, and age. The age variable is extremely important clinically. There is a growing body of evidence indicating that sensitivity to ototoxicity is increased during periods when cochlea function is developing.
- Second, the deleterious effects of ototoxic drugs on auditory status, including OAEs, may be delayed after administration, or may persist for days and even weeks after the drug therapy is discontinued.
- Third, DPOAE abnormalities in ototoxicity, particularly for high-frequency stimuli, may be detected prior to changes in auditory-evoked responses and the pure-tone audiogram.

(Hall, 2000, pp.463-464)

The DPOAE is a versatile and effective tool in the assessment of hearing and in the hearing scientist's laboratory. Like any hearing assessment tool, it must be used correctly to ensure appropriate evaluation and interpretation of test outcome. When conducted in an optimal

manner, with a clear understanding of interpretation, DPOAEs add significantly to the auditory assessment battery and provide a means of detecting hearing loss in difficult-to-test patients. An equally beneficial application of the DPOAE is in its use as a scientific tool to explore the cochlea (Hall, 2000). The DPOAE provides a non-invasive window into the cochlea and allows for frequency-specific exploration of cochlear auditory function. Dysfunction (versus destruction) of some outer hair cells is likely to be reflected by less than normal motility and reduced OAE amplitude, without affecting hearing sensitivity for steady state (pure tone) signals at audiometric frequencies (Katz, 2002). Abnormal OAE findings may be recorded in a variety of patient populations with normal audiograms yet some cochlear dysfunction, including patients with ototoxicity (Hall, 2000).

7.13. Summary

Until recent years, ototoxicity could only be monitored in clinical conditions by conventional pure tone audiometry (PTA). However, this method normally detects hearing loss late, at an irreversible stage when inner ear function is permanently impaired. Early identification of ototoxic effects could be beneficial, allowing for possible preservation of hearing in the frequency range that can affect communication abilities (middle and lower frequencies). The use of OAEs seems to be one of the current methods of choice for objective ototoxicity monitoring. This chapter therefore explored these ototoxicity monitoring tools in detail, presenting both advantages and disadvantages of each tool. The non-invasive nature of OAEs recording, coupled with their accuracy and objectivity in assessing cochlea function, outer hair cell function in particular, suggest potential clinical application in the form of identification of sensorineural damage caused by ototoxic drugs, hence a major focus of this chapter.

Stavroulaki et al. (2001) concluded that DPOAE measures are more sensitive than behavioural audiometry in revealing cochlear dysfunction. From their study, these authors also concluded that DPOAE levels are sensitive indicators of cochlea damage and are far superior to pure tone audiometry (up to 8 kHz). Given that ototoxicity initially causes damage in the high frequencies (>8kHz), as noted in changes of hearing sensitivity measured with pure-tone audiometry (Fausti, Henry, Helt et al., 1999), and ultra-high-frequency hearing influences DPOAEs at significantly lower frequencies (Arnold et al., 1999), it is not surprising that DPOAE measures are reported to be more sensitive to change than pure tone results less than 8kHz (Dreisbach, Long & Lees, 2006). The reliability indicators of DPOAEs are also good (Dreisbach et al., 2006), which is a crucial feature when performing monitoring studies.

Regardless of the fact that typically once damage has occurred, the cochlea cannot recover, early identification is still crucial. Unfortunately, because primary prevention is not always feasible, early detection of hearing loss becomes of paramount importance. Along with primary prevention, early detection of hearing loss is important for providing management options. The physician might have the option of adjusting the therapy to potentially less ototoxic regimen. Likewise, early indications of a threshold shift would be useful for planning audiological management and counselling (Stavroulaki et al., 2002). For severe hearing loss, amplification may be the only treatment option.

No therapy is currently available to reverse hair cell damage. Basic awareness of ototoxic medications and use of appropriate monitoring during treatment are important to preserve

hearing. Throughout therapy, it is recommended that baseline hearing evaluations followed by periodic testing be performed (Campbell & Durant, 1993; Campbell, 2007; Kalkanis, 2002; Ludman & Wright, 1998). This protocol is not routinely followed locally for patients on antiretroviral drugs since their effect on hearing has not been firmly established yet. Although a variety of adverse effects have been associated with the use of these agents, ototoxicity has been rarely researched and/or reported with limited reports of monitoring through the use of sensitive monitoring tools such as OAEs and ultra high frequency audiometry described in this chapter.

PART III – EMPIRICAL RESEARCH

EMPIRICAL RESEARCH METHODOLOGY

Chapter 8

CHAPTER EIGHT

RESEARCH METHODOLOGY

8.1. PRIMARY AIM OF THE STUDY:

The main aim of the current study was to investigate and monitor the auditory status in a group of adult patients with AIDS receiving ART and other therapies in a hospital outpatient clinic in Gauteng, South Africa.

8.2. *SPECIFIC OBJECTIVES:*

1. To estimate the prevalence of hearing loss and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth)
2. To assess the type, degree and configuration of the hearing loss
3. To explore the type of hearing symptom onset (e.g. sudden or gradual/progressive onset)
4. To document case history data such as signs and symptoms of each participating participant and to identify any associations between obtained signs and symptoms and hearing loss
5. To document the names of all medications used to establish their possible impact on hearing function, specifically ototoxicity monitoring
6. To compare the results of the experimental group with those of a control group.

The null hypothesis was that the participants' auditory function before and after antiretroviral drug-use would remain the same. The alternative hypothesis was that it would not remain the same, that is, participants would present with changes in their auditory function (Newell & Burnard, 2006; Rosenthal & Rosnow, 1991; Stein & Cutler, 1996).

8.3. DESIGN OF THE STUDY:

As an extensive literature search yielded a paucity of both South African and internationally published data on this topic, the study was exploratory and longitudinal in nature. The design utilized was a repeated measures, quasi-experimental design with pre- and post-treatment testing, and a control group (Devore, 1999). A quasi-experimental design is reported to be the best design where there are practical and ethical barriers to conducting randomized controlled trials (Grimshaw, Campbell, Eccles & Steen, 2000). In the current study, although there was manipulation of the independent variables (the antiretroviral drugs) and a control group, there was no random allocation of participants, which led to the study being quasi-experimental instead of experimental in nature (Newell & Burnard, 2006). In addition, the fact that the control group of the current study was not a true control group in that there were confounding variables that may have had an effect on the analysis and results further contributed to the quasi-experimental nature of the study.

In this repeated measures design, each participant served as his or her own control, allowing for the difference in performance associated with the use of antiretroviral drugs and other therapies to be observed despite differences in individual baseline performance. Because participants acted as their own controls, subject variability was accounted for (i.e. since the same participants took part in each testing session, no subject variability occurred) (Newell & Burnard, 2006). More importantly, this design offered within-subject comparison which is reported to offer greater statistical power relative to sample size (Devlin, 2006; Huck & Cormier, 1995). In view of the fact that in a repeated measures design, each participant acts as their own control, it was not critical to have a control group as part of the design in the current study, however

because of the confounding variables found in this population (e.g. co-use of other medications), the researcher felt that having a control group that was not on ARVs would aid in improving the statistical power of the data obtained. Furthermore, this design was thought to be appropriate for the current study as there was no randomization of participants and there was also limited control over some confounding variables such as co-occurring diseases (e.g. TB) (Schiavetti & Metz, 2002). Therefore, the use of the control group that was not on ARVs was adopted as an attempt to determine the possible effects, if any, of ARVs on auditory status.

The antiretroviral medications and other therapies were the independent variables, with the audiological measures (otoscopy, impedance audiometry, pure tone audiometry, otoacoustic emissions) featuring as dependent variables. The aim was to investigate and monitor the auditory status in a group of adult patients with AIDS receiving ART and other therapies before and during antiretroviral treatment – with measures taken before commencement of ARVs, 3 months after initiation of treatment and 6 months into therapy. All of the objectives were examined at baseline (before initiation of ARVs) and with repeated measures (at 3 and 6 months into treatment) for both the control and experimental group. A comparison of results of control group and experimental group was done for all objectives.

8.4. DESCRIPTION OF PARTICIPANTS:

8.4.1. Selection criteria - Participant Inclusion Criteria

For baseline measures, all (150) participants from the research site who volunteered to participate in the study were assessed. However, because one of the aims of the study was to attempt to specifically isolate the impact that antiretroviral drugs may have on hearing, it was crucial to apply a rigid set of participant inclusion criteria after baseline measures had been taken (i.e. for all participants that were going to participate in session 2 and 3 of testing). Given the fact that little, if any, published research has been conducted on this aspect of HIV/AIDS in South Africa, the researcher believed that it was crucial to have a high degree of control over variables which could confound the results of the study (e.g. noise exposure, syphilis, and so forth) (Devore, 1999; Schiavetti & Metz, 2002).

Consequently, the participant inclusion criteria that were adopted following baseline testing were (for session 2 and 3 of testing):

- All participants' HIV/AIDS status needed to be confirmed by serology studies, as the study was aimed at patients infected with HIV/AIDS.
- For the experimental group, participants were required to be on antiretroviral treatment, and co-administration of other ototoxic agents (such as loop diuretics) was monitored and recorded. A variety of factors can influence the strength or likelihood of ototoxicity, especially concomitant exposure to other drugs, and renal function (Hall, 2000). For the control group, participants were not supposed to be on antiretroviral treatment.
- All participants had to be between the ages of 18 and 50 years. The reason for choosing a lower limit of 18 years was related to the fact that there is a growing body of evidence

indicating that sensitivity to ototoxicity is increased during periods when cochlear function is developing (Hall, 2000). Furthermore, the presentation of the virus is reported to be different in adults when compared to children (Matkin, Diefendorf, & Erenberg, 1998). The reason for selecting 50 years as the upper age limit was because hearing loss associated with presbycusis needed to be excluded from the study (Katz, 2002). Furthermore, age extremes are reported to be a risk factor that has been identified for development and potentiation of aminoglycoside ototoxicity (Bankaitis & Schountz, 1998; Campbell, 2007), as well as antiretroviral ototoxicity (Marra et al., 1997; Simdon et al., 2001).

Presbycusis is reported to be dependent on many factors. Endogenous effects, such as hereditary factors or disease states (e.g. diabetes and hypertension) as well as exogenous factors, such as nutrition, stress impact, and noise might play a role. As far as disease states are concerned, Campbell (2007) believes that many of the diseases that the elderly experience change the way normal physiologic systems function and therefore also change how the body responds to drugs. In pure tone audiometry, presbycusis starts with a hearing loss at high frequencies, before low frequencies are also affected. Degeneration of outer and inner hair cells, reduction in the number of spiral ganglion cells, reduction in the number of neurons in the cochlear nuclei and temporal lobe as well as degenerative changes of efferent fibres have been shown (Oeken, Lenk & Bootz, 2000). In a study reported by Oeken et al. (2000) DPOAEs could be found in nearly all ears at all frequencies in the younger age group. In the older age groups, the percentage of occurrence of DPOAEs was much lower, especially in those subjects over 70 years of age, where DPOAEs were found only sporadically.

- All participants needed to be alert, oriented, able to provide informed consent, and able to participate in an audiological assessment.
- All participants had to have an air-bone gap of less than 15dB with hearing thresholds that were better or equal to 25dBHL at baseline testing in order to qualify for the monitoring phases of the study. This criterion was designed to provide the researcher with a clear indication of subtle hearing changes should they occur.

The aforementioned discussed criteria are summarised in Table 4 below.

Table 4: Summary of participant Inclusion Criteria following baseline measures

Criterion	Experimental group	Control group
HIV/AIDS positive serology	**Yes**	**Yes**
On ARVs	**Yes**	**No**
Age between 18 and 50 years	**Yes**	**Yes**
Alert and oriented	**Yes**	**Yes**
Normal pure tone audiometry (thresholds better or equal to 25dBHL)	**Yes**	**Yes**

8.4.2. Selection criteria - Participant Exclusion Criteria

The following criteria were strictly observed for persons who participated in the repeated measures following baseline:

- Participants with excessive noise/music exposure at baseline testing, where results found could be attributed to noise damage rather than antiretroviral drugs, were excluded from the study. Chronic and consistent exposure to noise has been documented to cause a hearing loss particularly in the high frequencies (generally seen as a dip at 4000 Hz) (Cummings, 1993; Katz, 2002; Schuknecht, 1993; Stephens, 1997). It was felt that this condition could confound the results of the study since ototoxicity is also typically high frequency in nature.

- Participants with a recent (less than 3 years) or current history of TB treatment and those who had undergone radiotherapy were excluded as these interventions are known to have an effect on hearing (Katz, 2002; Schuknecht, 1993). Radiotherapy is an effective method of treatment for various head and neck tumours (HNT). Participants with a positive history with normal results at baseline testing were not excluded from the research; however their history was carefully recorded and used during the analysis phase of the study.

There are contradictory opinions in clinical practice and literature regarding incidence, type, severity, and the time of onset of hearing loss as a complication of radiotherapy. The available literature appears to support the notion that otitis media and sensorineural hearing loss can occur as complications during or shortly after radiotherapy. These complications may arise as a result of radiation damage to neighbouring structures. However, there is little or no convincing evidence to support the notion that hearing loss that develops several years after radiation is causally related to radiation therapy (Morawski, Namyslowski, Skladowski & Golen, 2001).

- Participants with positive clinical or serological evidence of syphilis at the time of the study were excluded as this disease is known to cause hearing loss (Cummings, 1993; Darmstadt & Harris, 1989; Stephens, 1997).
- Participants with middle ear pathology at baseline testing were excluded as normal middle ear function is reported to be a prerequisite for obtaining OAEs. To record OAEs, the cochlear response must be able to travel efficiently through the middle ear and tympanic membrane to the recording microphone in the ear canal. Even in the presence of normal cochlea function, OAEs generally are absent in the case of middle ear pathology (Hall, 2000; Katz, 2002).

- Participants presenting with tinnitus at baseline testing were excluded. Otoacoustic emissions are reported to be characteristically abnormal, or not detectable, in the frequency region of the tinnitus, even among persons with clinically normal audiograms. Distortion product OAE (DPOAE) amplitudes have been found to be consistently reduced among patients with tinnitus, even those with audiometrically normal hearing (Hall, 2000).
- Participants who had a recent history (less than 3 years) of prior use of antiretroviral drugs were also excluded from participation in the study.
- Participants who showed evidence of newly acquired noise exposure, TB, radiotherapy, syphilis and/or middle ear pathology after the baseline testing were excluded from the ototoxicity monitoring phase of the study.

The summary of the participant exclusion criteria discussed above is tabulated in Table 5 below.

Table 5: Summary of participant Exclusion Criteria following baseline measures

Criterion	Experimental group	Control group
Noise exposure	**Yes**	**Yes**
Recent (less than 3 years) or current history of treatment for TB and radiotherapy	**Yes**	**Yes**
Positive clinical or serological evidence of syphilis	**Yes**	**Yes**
Middle ear pathology	**Yes**	**Yes**
Presence of tinnitus	**Yes**	**Yes**
Recent (less than 3 years) history of previous ARV use	**Yes**	**Yes**

8.4.3. Recruitment and Sampling Procedure

A nonprobability convenience sampling technique was utilized in the study since the sample was restricted to a part of the population that was readily available (Devore, 1999; Schiavetti & Metz, 2002), and true random sampling would have been difficult to achieve. Time,

cost, and equipment limitations were considerations that prohibited the researcher from obtaining clearance and permission to recruit participants from other facilities, and these factors have been reported to prevent most researchers from employing probability sampling methods (Devlin, 2006; Portney & Walkins, 1993).

A major limitation of the convenience sampling technique is that generalization of the results is significantly influenced by the fact that the sample may not be representative of the population studied and the fact that participants volunteer to participate in the study i.e. the volunteer effect (where volunteers have been found to have different characteristics from non-volunteers) (Schiavetti & Metz, 2002; Stein & Cutler, 1996). Stein and Cutler (1996) state that an eager volunteer may perform better when evaluated than would a participant who is not interested in the study. For the current study, the volunteer effect could possibly have affected the pure tone audiometry results as these rely on participants' cooperation in providing responses. However, the other measures (tympanometry and DPOAEs) could not have been influenced by this effect since they are objective measures that do not rely on the participants' active responses.

Advantages of the convenience sampling technique include the fact that the participants are readily available to the researcher; and that the technique is easy, fast and usually the least expensive (Schiavetti & Metz, 2002). Hence, participants attending the HIV/AIDS clinic at Johannesburg Hospital volunteered to have their hearing status evaluated in response to notices that were posted in the clinic inviting them to participate in the study, and in response to the researcher's verbal and written explanations of the purpose of the project at this clinic.

Participants for the control group were recruited from the wellness section of this clinic where patients that refuse treatment are seen by Dieticians and Social Workers. At the time of the study, the researcher was already providing a service to patients at this clinic as she is on an honorary appointment as an Audiologist at the Johannesburg hospital.

8.4.4. The Sample

The patients selected for this study were recruited from the Johannesburg Hospital's Adult HIV/AIDS clinic. Patients attending this clinic have already been diagnosed with HIV/AIDS and are seen there for general medical management as well as antiretroviral treatment and monitoring. The antiretroviral therapy programme was only instituted at this clinic in April 2004, when an antiretroviral drug roll-out programme was introduced by the South African government. At the time of the study all patients with CD4+ counts below 200 cells/mm^3 had access to ARV treatment, at this clinic - and this is the group that was targeted for the experimental group.

Johannesburg Hospital is situated in Parktown, Johannesburg and is one of the biggest government and academic teaching hospitals within the Gauteng Province, South Africa. This hospital is designated a Central hospital with 1088 beds serving patients from across Gauteng and neighbouring provinces, as well as other regions in Africa. Up until 2006, Johannesburg Hospital used to offer inpatient and specialist outpatients services mainly at level three (tertiary) and level two (secondary), with 20% of the services rendered at level one (primary). The hospital's professional and support staff exceeds 4000 people. The hospital is also the main teaching hospital for The University of the Witwatersrand, Faculty of Health Sciences, and

provides the service base for under graduate and post-graduate training for all health professions. The joint staff produces world-class research and collaborates with several universities on the continent and abroad (S. Pillay, personal communication, June 07, 2007).

As from September 2006 Johannesburg Hospital started to function as a strict tertiary institution, i.e. patients seen at the hospital are patients who come to the institution as emergencies or are referred from an appropriate lower level facility. The hospital offers a full range of tertiary and highly specialized services. The cost of providing these services to the population of Gauteng Province as well as the neighbouring provinces is funded by a National Tertiary Services Grant as well as a Provincial budgetary allocation. Like all state funded hospitals in the country, Johannesburg hospital runs under severe resource constraints including but not limited to financial resources, as well as personnel restrictions. The hospital is located in Parktown and serves as a referral hospital for a number of hospitals in its referral chain (S. Pillay, personal communication, June 07, 2007).

8.4.5. Sample Size and Distribution of Participants

The sample size was determined by logistical reasons such as availability of volunteering participants, time length of the study, and the resources available to collect data from participants (Newell & Burnard, 2006). The aim was to have as many participants as possible to accommodate for anticipated attrition, as well as to increase the likelihood that the sample was as representative as possible of the population studied.

A total of 150 participants, including both males and females, comprised the research sample at baseline. The experimental group (those patients that had consented to enrolling in an ARV programme) comprised 104 participants at baseline (with 54 participants on regimen 1 as the final ototoxicity monitoring sample size) and the control group (those patients that had refused to enrol in an ARV programme) comprised 46 participants at baseline (with 16 participants as the final sample size). The 150 participants tested at baseline were all at Stage 3 of HIV/AIDS according to their CD4+ T-cell counts, as patients with this CD4 count were the ones that were offered antiretroviral treatment in provincial hospitals in South Africa at the time of the study.

Because of the repeated measures design nature of the study, some participants did not attend all 3 sessions of testing for various reasons. All participants' data were analysed for the descriptive analysis phase of the study, however not all participants' data were included in the inferential statistics phase of analysis. This had an influence on the total number of participants at each stage of the analysis. The following table (Table 6) illustrates the process that led to the final sample size of 54 participants in the experimental group (who were analysed through inferential statistics) and 16 in the control group.

Table 6: The sample size process illustrating how the sample was handled

Experimental Group (n=104)			**Control Group (n=46)**		
Referred to ENT	**DNA/DTR**		**Referred to ENT**	**DNA/CTR**	
	22 DNA	**6 DTR**		**16 DNA**	**8 CTR**
12 at session 1 1 at session 2	19 missed 1 session only (18 missed session 2 only and 1 missed session 3 only) 9 attended 1 session only (baseline)		3 at session 1 3 at session 2	23 missed 1 session only (21 missed session 3 only) 1 attended 1 session only (baseline) 1 missed session 2 only	
Total: 13	Total: 28		Total: 6	Total: 24	
Total excluded from the repeated measures analysis					
41 who had not attended all 3 sessions			30 who had not attended all 3 sessions		
Total number not on regimen 1 excluded					
9			0		
Total included in the repeated measures analysis					
54 who had attended all 3 sessions and on regimen 1			16 who had attended all 3 sessions		

Key: ENT = Ear, nose and throat specialist; DNA = did not arrive; DTR = Defaulted treatment; CTR = Commenced treatment

The data of those participants, who did not attend all three sessions of testing, were included in the descriptive analysis phase of the study. However their data were excluded in the inferential statistics phase as this required data for all three sessions. Furthermore, 9 participants were excluded from the experimental group because they were on the ARV regimen that was not taken by the majority of the sample. Hence, due to attrition factors such as missing appointments and defaulting/commencing ART; the final sample size comprised 54 participants in the experimental group and 16 participants in the control group. The discrepancy in the sizes of the two groups is acknowledged as one of the methodological limitations of the current study. The researcher experienced difficulties in recruiting participants who were diagnosed with AIDS (those who were at stage 3 of HIV/AIDS according to CD4+ count) who were not on ART at the

research site. This therefore led to a smaller sample size for the control group which is acknowledged as a limitation of the study since typically, different sample sizes are reported to lead to different accuracies of measurement – with larger sample sizes leading to increased precision in estimates of various properties of the population (Newell & Burnard, 2006).

The final sample size for the experimental group (54 participants, 108 ears) was deemed large enough and appropriate for the current study, however that of the control group (16 participants, 32 ears) was deemed small following attrition. Although the small control group sample size was noted as a limitation to the study, the repeated measures design of the study which allowed within-subject comparisons was thought to have sufficient statistical power to allow for the statistical tests to accurately test the null hypothesis and to detect a difference within subjects where one existed (P. Fridjhon, personal communication, March 26, 2007; K. Otwombe, personal communication, April 30, 2008). Furthermore, the probability level of significance (0.05) that was used in the current study also contributed to the statistical power of the data obtained as the power of a test (indicating the ability to reject the null hypothesis) has been reported to increase when the researcher is willing to accept a higher probability of error such as 0.05 (Devlin, 2006; Stein & Cutler, 1996). What this level means is that the researcher was willing to accept more error in interpreting the statistical results.

8.5. TEST PROTOCOL:

The time frame for the completion of the test protocol was approximately 3 years. Data collection for the current study commenced in November of 2004 and ended in April 2007. It took the researcher this length of time to recruit participants and adopt a longitudinal approach to following up the set number of participants required for the current study. Personnel who were involved in the research project were the researcher and a nursing sister who played the role of a research assistant whose job was to recruit interested participants and refer them to the researcher for participating in the research process. As part of ethical considerations, ethical clearance to conduct the study was granted provided the researcher was the only person directly involved in testing the patients in order to protect the patients' confidentiality.

All measures were taken before commencement of ARVs, 3 months after initiation of treatment and again at 6 months into therapy. This timeframe for assessments was chosen as this is usually the time when patients' CD4+ testing is done following CDC recommendations (CDCP, 1992), and it was also deemed appropriate in order to minimize attrition which was an anticipated risk in the population studied. The mean survival time after diagnosis with AIDS without ARVs has been reported to be 10-12 months in developed countries (Gail et al., 1997) and shorter in developing countries (Grant et al., 1997). No time variability was allowed for the baseline measures as all participants were tested on the day that they were enrolled onto ARVs (before the treatment commenced); however a slight time variability of approximately a maximum of two weeks was allowed for sessions 2 and 3 of testing. This repeated measures nature of the study may have posed a significant threat to participant recruitment as it required more effort on the part of the participants to commit to multiple visits.

Baseline data were collected from assessing participants' dependant variables before administration of ARV therapy. These baseline data were then compared to two other measures that were taken three and six months after commencement of therapy. The same procedures were followed for the control group. For those participants who did not attend all three sessions of testing, their data were included in the descriptive analysis phase of the study, however they were excluded from the inferential statistical analysis as this required data from all three sessions. This contributed to the attrition rate. Furthermore, some participants were excluded from the inferential statistics phase of the study because they were on ARV regimen that was not used by the majority of the participants. Eighty six percent of the participants were on regimen 1 of ARVs, and hence these were the participants analysed for ototoxicity monitoring – as an attempt to improve the homogeneity of the sample for determination of possible ototoxic effects of ARVs. One methodological limitation of the current study related to the time when the last measure was carried out (6 months after treatment). This could have limited the type of results obtained since ototoxicity may present long after six months; however the researcher proposed this time in an attempt to control for variables such as: patients changing medications, participant attrition via patients leaving the study for various reasons, and so forth.

A case history form that targeted the signs and symptoms of auditory manifestations was utilized in order to gather all the important case history information, audiological data and some medical variables that could have exerted an impact on the results of the study. To improve reliability of the case history data obtained, for information on the diagnosis of HIV/AIDS; the clinical stage of the disease; antiretroviral medications the participant was taking; co-occurring

diseases (e.g. tuberculosis, syphilis); and Ear, Nose and Throat Specialists' reports; patients' medical records were reviewed as opposed to participant self-reports. Blood test results for T-cell subtest (CD4+) and syphilis serology were also obtained from patients' records. The only information obtained from patient self-reports was confined to demographic information, history of noise exposure, family history, and history and presence of auditory symptomatology. Self reported medical history was validated by medical record reviews as variability in reliability of these reports has been reported to exist (Chang, Smedby, Hjalgrim, Glimelius & Adami, 2006).

8.5.1. Material

The following testing materials were used during the study:

- A case history form
- A Welch Allyn otoscope and its accessories
- Inter-Acoustic AC 40 diagnostic audiometer
- Inter-Acoustic AZ26 audiotympanometer and its accessories
- Biologic Scout Otoacoustic emissions meter with its accessories
- AMILO personal computer notebook with Microsoft Windows XP
- Medtex non-sterile Latex examination gloves
- All necessary hygiene, infection control solutions
- NCSS Statistical Programme

Some of the testing materials were provided by the Audiology Clinic at Johannesburg Hospital, while other material was derived from the researcher's own equipment.

8.5.2. Testing Procedures

The testing procedure was conducted in 3 sessions:

8.5.2.1. Session 1 – (Pre-treatment: Basic audiometry)

Before the audiological testing commenced; the researcher ensured that ethical considerations, ethical clearance, obtaining permission from relevant authorities, recruitment of participants, and collection of case history information were all addressed.

i. Ethical considerations

Participants were asked to volunteer to be part of the study. The researcher spoke to each group of patients attending the HIV/AIDS clinic. She described the study and what the testing involved. She also explained their rights as research participants and invited them to participate in the study. On the arrival of participants at the Hearing Clinic, the researcher explained the study to the participants again to ensure informed consent. Once the participants confirmed their willingness to participate in the study, the Participant Information and Consent Forms (Appendix G) were signed by both the participants and the researcher. Participants were assured that they would be allowed to withdraw from the study at any time should they wish to do so. Written permission to undergo testing was obtained from participants, with an understanding that confidentiality would be maintained. Care was taken to ensure that ethical practice conformed to the internationally accepted guidelines. The researcher conformed to the following ethical principles during the study:

- *Confidentiality*: Participants were assured that confidentiality would be maintained as the names of participants were not going to be published.

- *Autonomy*: Participants' autonomy was respected and participants were given the opportunity to discontinue participation in the study at any point should they wish to do so.
- *Beneficence and Non- maleficence*: The researcher ensured that benefit to the participants was optimal while the risks were reduced to a minimum. The researcher conducted her research for her Master's degree at the HIV/AIDS clinic and subsequently established audiology services at this clinic, and therefore had become familiar with the functioning of the clinic and was already providing a service to patients attending the clinic. Where patients presented with a hearing loss in the study, they were managed in the form of appropriate referrals to Ear, Nose and Throat Specialists, provision of amplification or auditory training, and/or audiologic monitoring following clinic protocols. These procedures were conducted in order to ensure that participants received direct benefits from participating in the study.
- *Justice*: The principle of justice establishes special protection for vulnerable persons and therefore excludes the use of vulnerable groups. Justice forbids exposing one group of people to the risk of research solely for the benefit of another group. Although the HIV/AIDS population can be regarded as a vulnerable population, the fact that the researcher utilised the convenience sampling technique where participants volunteered to participate in the study contributed towards implementing the principle of justice in the current study.

(Council for International Organizations of Medical Sciences - CIOMS, 2000; South African Medical Research Council, 2003).

Over and above adhering to the aforementioned ethical principles, the current researcher observed the ten provisions of the Nuremberg Code (Newell & Burnard, 2006) throughout the research process. These are presented in Table 7 below:

Table 7: The Nuremberg code of ethics observed in the current study

Synopsis of the Nuremberg Code of ethics in research
Voluntary consent is important
Study should produce fruitful findings for the good of society
Previous results should give good reason for the study
Study should avoid all unwarranted physical and mental anguish and injury
No study should be conducted if it is believed death or disabling injury will occur
The degree of risk should never surpass potential benefit of the study
Participants should be protected against even remote possibilities of injury, disability or death
The study should be conducted only by qualified persons
Participants should be free to withdraw at any time
The person conducting the study must be prepared to stop the study if a continuation is likely to cause harm

ii. Obtaining Ethics Clearance

Prior to commencement of the study, permission to conduct the research project was sought from the University of the Witwatersrand Human Research Ethics Committee (Medical) which gave unconditional ethical clearance in the form of protocol number M041131 (Appendix E).

iii. Obtaining Permission from Relevant Authorities

Permission to conduct the study at the Johannesburg Hospital was obtained from Hospital management and from the Heads of the Audiology and HIV/AIDS clinics. These documents are set out in Appendices A, B, C and D.

iv. Recruitment of participants

After obtaining the necessary permission required before conducting the study, the researcher discussed details regarding the project with the medical team at the HIV/AIDS clinic, and enlisted their co-operation in informing their patients about the study. Notices inviting patients to volunteer for the study were posted at the clinic and help was sought from a nursing sister who acted as a research assistant. The researcher discussed the study with groups of patients at the clinic, explaining the aim and the methods as well as the time frame to be employed in the study. Participants who were interested in participating in the study volunteered by approaching the researcher directly or the nursing sister who played the role of research assistant.

v. Collection of Case History Information

To enhance reliability of the information obtained from case history collection, self-reports were kept to a minimum by relying more on medical record reviews than on participants' reports. Self reports have been found to be flawed by the fact they are subject to participants' moods and changes of views and opinions (Newell & Burnard, 2006). The researcher therefore obtained some of the case history information (specifically demographic information, history of noise exposure, family history, and history and presence of auditory symptomatology) through an interview conducted in a quiet office at the Hearing Clinic which ensured privacy and confidentiality. No one else, beside the staff involved in the direct management of the patients, was made aware of the participants' HIV/AIDS status.

The case history information was obtained individually as an initial part of the audiologic evaluation that the participants underwent. Persons who could read and write, self-administered

parts of the case history form (demographic information, noise exposure, tinnitus, vertigo, and hearing status sections), while the remaining information was obtained by the researcher from medical record reviews. The researcher interviewed all participants who were illiterate as well as those who could not read English. The researcher later completed the medical history section of the case history form as information required could only be obtained reliably and accurately from the medical records (e.g. medical diagnosis of HIV/AIDS, serology information, the clinical stage of the disease and blood test results for T-cell subtest (CD4+) counts, names of antiretroviral drugs that the participants were taking as well as dosage, co-occurring diseases (e.g. Tuberculosis, Syphilis); and Ear, Nose and Throat Specialists' reports). Where participants provided medical history, this information was validated by medical record reviews.

The case history form (Appendix H) was utilized to gather relevant medical and ear-related history that was thought to be possibly related to hearing and HIV/AIDS. This was completed and updated at every session with each participant. The information obtained about the patient's history has been reported to be useful in testing, assessing validity of the results, and explaining the results to the patient (Katz, 2002). The case history form emphasized the names of the different medications that the patient was taking/had taken; the dosage and frequency of use; and the length of time on the medication. It is acknowledged that information obtained from patients directly such as history of use of other medications (not documented in the hospital file) including the use of traditional medicine, may not have been truly reliable as patients may have forgotten the names of the medications or may not have been willing to share that information with the researcher. For example, it has been documented in the literature that patients who utilize the services of traditional healers often do not share this information with western health

care professionals for fear of being reprimanded by persons who do not approve of such practices (Dagher & Ross, 2004).

The case history form used was a slightly modified version of a case history form previously used in an earlier study by Khoza and Ross (2002), with changes to accommodate the treatment options history that had been omitted from the earlier study. The format of the case history form fostered quick and easy completion with sections that were completed from a review of participants' medical records. The case history form was not pre-tested for the current study as it had previously been pre-tested on a similar sample (Khoza & Ross, 2002) and found to be adequate. However, the treatment options history section, which was completed by the researcher for all patients, had not been previously pre-tested. The case history form consisted of the following sections:

- *Demographic information:* This section included information about participants' ethnic group. Age and gender were documented on the audiogram record forms.
- *History of Noise exposure:* This section was included so as to differentiate between noise-induced hearing loss and HIV/AIDS related hearing loss. Chronic and consistent exposure to noise has been documented to cause a hearing loss particularly in the high frequencies (generally seen as a dip at 4000 Hz) (Cummings, 1993; Katz, 2002; Schuknecht, 1993; Stephens, 1997). History of and current exposure to chronic noise was also of concern as noise exposure is known to exacerbate ototoxicity in patients who either have a history of noise induced cochlear pathology or who are exposed to noise while taking potentially ear toxic agents.

- *History and presence of tinnitus and vertigo:* These are the associated signs and symptoms of hearing loss. They form part of a standard case history interview conducted for every adult audiological assessment (Jacobsen & Northern, 1990; Katz, 2002). These associated signs were also included as they are reported to form part of the presentation of ototoxicity.
- *Hearing status:* This section covered family history of hearing impairment, previous audiologic assessments, time of onset and type of onset of hearing loss, progression of the hearing loss, current hearing status, and laterality of the hearing loss. These are again standard case history questions that form part of every adult audiologic case history taking (Bess & Humes, 1990; Hodgson, 1985; Katz, 2002; Schuknecht, 1993).
- *Medical history:* This section covered the aspects listed below. The following medical history was recorded for each participant:
    - The participants' clinical or serological evidence of syphilis (from medical records) was recorded as this disease is known to cause hearing loss (Cummings, 1993; Darmstadt & Harris, 1989; Stephens, 1997). All participants who presented with this diagnosis at any stage of the research were excluded from ototoxicity monitoring.
    - Case history factors that may have contributed to a hearing loss (e.g. history of prior ear disease; of industrial noise exposure; head trauma; and familial deafness, etc); were noted (Friedman & Arnold, 1993; Jacobson & Northern, 1990; Katz, 2002; Lalwani & Sooy, 1992; Stephens, 1997). Participants who presented with any of these factors were excluded from ototoxicity monitoring.
    - The history of participants' treatment that was known or even suspected to cause hearing loss was recorded. Specific medications that the participants were taking were

recorded including antiretroviral drug names and dosage. Additional treatments such as history and exact time and duration of radiation treatment and TB treatment were also recorded. Radiation may have an impact on the overall presentation of the symptoms in these patients while TB treatment is known to be ototoxic (De Lima et al., 2006; Gold & Tami, 1998; Larson, 1998). De Lima et al. (2006) reported on high frequency sensorineural hearing loss in 75% of TB patients they evaluated in their study. These authors report that when patients discontinue their TB treatment, they are often forced to resume taking the medication, using more toxic drugs for even longer periods of time. This increases the chances of ototoxicity. All participants who presented with a recent history (less than 3 years) of these treatments with abnormal baseline audiometric assessment results were excluded from the current study.

The participants were divided into the experimental group (those who were commencing ARV treatment) and the control group (those that were not on ARV treatment).

vi. Audiological Testing

Following infection control measures proposed by Kemp and Roeser (1998), all testing was conducted in a sound-proof booth. Basic audiological testing followed by Distortion Product Otoacoustic Emission (DPOAE) measurements for all participants was undertaken and systematically recorded (Appendix I). The researcher assessed the participants' hearing via a test battery that consisted of otoscopy; tympanometry; pure tone audiometry; and DPOAE testing. DPOAE testing for ototoxicity monitoring was conducted in order to determine possible outer hair cell damage due to medications used (Hall, 2000; Katz, 2002). One methodological limitation of the current study was that ultra-high-frequency audiometry did not form part of the

ototoxicity monitoring protocol due to lack of equipment available at the time of the study. Ultra-high-frequency testing has been reported to be sensitive to ototoxicity.

The objective of Otoscopic Evaluation through the use of a Welch Allyn otoscope was to assess the condition of the outer ear and the status of the tympanic membrane. The researcher evaluated the participants' ears for the presence of impacted wax; otitis externa; possible otitis media; perforated tympanic membranes; collapsed ear canals; presence of any growths and any other ear disorders (Friedman & Arnold, 1993). These otoscopic abnormalities are reported to have a significant effect on DPOAE and therefore needed to be documented before testing commenced (Hall, 2000).

Impedance audiometry in the form of tympanometry was utilized to assess the status and integrity of middle ear functioning – through the use of Inter-Acoustic AZ26 audiotympanometer. Standard single frequency tympanometry using an 85dB SPL tone set at 226Hz was done. The primary purpose of impedance audiometry was to determine the status of the tympanic membrane and middle ear via tympanometry. This test can potentially identify the following pathologies of the peripheral auditory system: middle ear effusion, perforation of the tympanic membrane (including whether the pressure equalization tubes are patent or not), tympanosclerosis, hypermobidity of the tympanic membrane, Eustachian tube dysfunction, glue ear, otosclerosis, and ossicular chain discontinuity (Campbell, 2002; Jerger, 1970) – all of which are reported to have a significant effect on DPOAEs (Hall, 2000). The researcher ensured that all participants undergoing DPOAE testing had normal tympanometry results.

Tympanometry has been reported to be superior to routine otoscopy in correctly predicting the presence or absence of middle ear effusions (Silman & Silverman, 1991). These authors believe that otoscopic evaluation relies on subjective assessment and therefore may lead to high inter-tester variability in results. The present researcher however believes, [and is supported by Wiley and Fowler (1997)], in the use of both assessment procedures in a complementary fashion where results from both assessment procedures are combined to provide valuable information that can be utilized to arrive at an accurate diagnosis. The procedure followed in the current study included the assessment of the status and mobility of the tympanic membrane; pressure within the middle ear; presence of fluid behind the tympanic membrane; functioning of the ossicles; and Eustachian tube functioning (Hall, 2000; Katz, 1994; Wiley & Fowler, 1997).

The tympanogram results were analyzed according to the documented Jerger system types of tympanograms (A –A_s, A_d; B; C; D); with the type A regarded and reported as normal and all other types as abnormal (Campbell, 2002; Chandrasekhar et al., 2000; Hodgson, 1985; Jacobson & Northern, 1990; Katz, 1994). The Jerger system was adopted because it is the most commonly used classification for tympanograms. Participants presenting with the other types of tympanograms besides a type A were excluded from the ototoxicity monitoring phases of the study.

Conventional (250Hz-8000Hz) pure tone audiometry was performed on all persons who participated in the study – through the use of Inter-Acoustic AC 40 diagnostic audiometer. Pure tone audiometry is a behavioural test measure used to determine hearing sensitivity (Mullin-Derrick, 2002; Stach, 1998). This measure involves the peripheral and central auditory systems.

Pure tone thresholds indicate the softest sound audible to an individual at least 50% of the time. These thresholds were established by both air conduction (using standard TDH-39 circumaural headphones) and bone conduction (using model B71 bone conductor) utilizing the ascending-descending technique in 5dB steps. The criteria used to define normal hearing, was that of pure tone thresholds of 25dBHL or lower across all frequencies, with the absence of an air-bone gap (Martin & Clark, 2003). Where pure tone air conduction and tympanometry were abnormal at any test frequencies, at pre-treatment phase, participants were excluded from continuing participating in the study, and were referred to Ear, Nose and Throat Specialists for assessment and management, and were subsequently offered appropriate audiological rehabilitation. Participants presenting with normal pure tone audiometry at baseline were advanced to session two and three of the study where ototoxicity monitoring was conducted.

The usual primary purpose of pure-tone tests is to determine the type, degree, and configuration of hearing loss; however in this study another purpose was to monitor any changes that might occur to the participants' hearing status, particularly in the high frequencies since this region is the one that is documented to be prone to drug-induced hearing loss (Hall, 2000). Using pure tone data, a change in the hearing level of 10 dB at one or more frequencies is commonly taken to be indicative of some significant change, hence this protocol was followed in the current study (Ludman & Wright, 1998).

Ultra high frequency (UHF) testing, though it is the recommended behavioural method of choice for ototoxicity monitoring, was not possible in the current study due to equipment limitations. Dreisbach et al. (2006) also highlight a major drawback with this form of

behavioural testing in a clinical population in that it is time consuming and it requires the active participation of the patient, who can be too sick or young to provide reliable responses. Ress et al. (1999) reported that DPOAEs were as sensitive as UHF audiometry for detecting changes in hearing due to cis-platinum ototoxicity, but that DPOAEs were superior to UHF audiometry as an ototoxic screening tool; hence this methodology was followed in the current study.

8.5.2.2. Session 1 – (Pre-treatment: DPOAEs)

All participants with normal middle ear functioning (type A tympanogram) underwent DPOAE measurements, as the crucial aspect of ototoxicity monitoring, through the use of a Biologic Scout Otoacoustic emissions meter. The primary purpose of OAE tests is to determine cochlea status, specifically hair cell function. This is based on the premise that the normal cochlea does not just receive sound; but it also produces low-intensity sounds called OAEs. These sounds are produced specifically by the cochlea and, most probably, by the cochlear outer hair cells as they expand and contract (Hall, 2000). OAE testing is often used as a screening tool to determine the presence or absence of cochlear function, and analysis can be performed for individual cochlear frequency regions, therefore they are regarded an excellent tool for early detection of cochlea damage due to ototoxicity (Campbell, 2007; Hall, 2000).

OAEs are considered to have clinical utility as a sensitive measure of cochlea function, being generated only when the cochlea is functioning normally or near normally (Engdahl, 2002). Screening and monitoring of cochlea function have been the two most important areas of clinical application of OAEs (Robinette & Glattke, 1997). Because OAEs are objective, easy and

provide rapid measures using non-invasive commercially available methods, they are thus ideal for large-scale population testing, as in the current study.

Clinical applications of OAEs and their rationale for monitoring ototoxicity have been documented by Hall (2000, pp. 27-28), and these were used as the motivation for selecting OAEs as part of the test battery. Firstly, OAEs are site-specific for cochlear (sensory) auditory dysfunction, which affords the researcher the opportunity to determine site of lesion due to ototoxic drugs. Secondly, ototoxic drugs exert their effect on outer hair cell function and OAEs are dependent on outer hair cell integrity. Thirdly, OAE recording is electrophysiological and not dependent on patient behavioural responses, and can be recorded from patients who, due to their medical condition, are unable to perform behavioural audiometry tasks, and this was crucial for the current study. Lastly, OAEs can detect cochlear dysfunction before it is evident on pure tone audiometry, and in ototoxicity monitoring this factor is critical since the main aim of monitoring is early detection of adverse effects of the drug before it causes clinical damage (Campbell & Durant, 1993; Campbell, 2007; Hall, 2000). This latter point was critical for the current study where changes in DPOAE levels could directly imply changes in cochlear function a significantly long time before this change is denoted on the audiogram.

As far as DPOAEs are concerned, the current study only monitored frequencies up to 8000Hz - and this was an acknowledged methodological limitation as literature has indicated greater sensitivity when using higher frequencies in ototoxicity monitoring. DPOAEs elicited with high-frequency stimuli would be a rapid objective test for monitoring, however, performance of these measures was hindered by equipment limitations. A decline in high-

frequency cochlear function, which usually precedes damage in the conventional frequency range, could potentially be identified objectively using high-frequency DPOAE measures. If damage could be identified at the higher frequencies this could be beneficial in preventing further damage to lower frequency hearing which is vital to speech production and perception (Dreisbach et al., 2006).

For recording, a soft probe tip was inserted in the ear canal to obtain a hermetic seal, similar to immittance audiometry. All OAEs are analysed relative to the noise floor, therefore, reduction of physiologic and acoustic ambient noise was ensured as this condition is critical for good recordings. For a quiet and cooperative patient, recordings were easily obtained bilaterally in less than 5 minutes. The following prerequisites for obtaining OAEs which are advocated by Hall (2000) were observed:

- Unobstructed outer ear canal
- Hermetic seal of the ear canal with the probe
- Optimal positioning of the probe
- Absence of middle ear pathology
- Functioning cochlea outer hair cells (pre-treatment phase)
- A quiescent patient as excessive movement or vocalization may preclude recordings
- Relatively quiet recording environment.

The following DPOAE test protocol was employed:

Test parameters	*Diagnostic /High frequency*
• Stimuli	
o Intensity level	L_1-L_2= 10dB (e.g. L_1=65dB, L_2=55dB)
o Ratio	f_2/f_1 = 1.22
o Frequency range	750 to 8000 Hz

The Biologic Scout Otoacoustic emissions meter provided both DPOAE and noise amplitude. The presence of the DPOAE was determined by comparing the amplitude of the DPOAE to that of the noise floor to calculate the size of the emission. A DP amplitude that exceeded the noise floor by at least 7dB across all frequencies measured was regarded as indicative of a normally functioning cochlea (Hall, 2000). The size of the emission at the different frequencies measured was then monitored over the three testing sessions.

8.5.2.3. Sessions 2 & 3 – (Post-treatment: Basic audiometry)

All participants who had presented with normal hearing and normal DPOAE results at baseline testing were re-tested after having been on antiretroviral drugs for 3 months and again at 6 months. The control group followed the same protocol but they were not on ARV drugs. Repeat updates of case history, otoscopy, tympanometry and basic audiometric testing were carried out and results compared to baseline measures to determine any difference in auditory function post commencement of treatment.

8.5.2.4. Sessions 2 & 3 – (Post-treatment: DPOAEs)

Repeat DPOAE testing was conducted 3 and 6 months later for both experimental and control groups and the results were then compared to baseline measures. Careful repeat measures of middle ear function were obtained to ensure normal middle ear function before repeat DPOAEs were re-assessed as middle ear status has been shown to have a significant effect on otoacoustic emissions.

All data were entered on to the researcher's AMILO personal computer notebook for proper management on an EXCELL spreadsheet (Appendix J). The NCSS Statistical Programme was used to statistically analyze the data.

8.6. VALIDITY AND RELIABILITY:

In the current study validity was viewed as a measure of the ability of a test to detect the disorder for which it was designed, while reliability was defined as a measure of intra-examiner and inter-examiner consistency of a test (Roeser, Valente & Hosford-Dunn, 2000). These authors argue that, in audiology, test reliability can be controlled and maintained at a high level by standardizing test administration, ensuring proper equipment calibration, and controlling patient variables. The current researcher ensured that all these three procedures were undertaken in the current study. To this end, the following specific procedures were put in place to enhance reliability of the measures employed in the current study.

For all audiological assessments precautionary measures advocated by Bess and Humes (1990) and Hall (2000) were followed in terms of proper maintenance and calibration of the equipment; optimizing testing environment; correct earphone and bone vibrator placement, and proper probe placement for DPOAE. To ensure accurate threshold measurement and accurate emission detection, the researcher adopted the necessary precautions to eliminate variables that could influence the testing. Specifically, all testing was conducted in a soundproof booth or sound-treated room with equipment that was calibrated on an annual basis, with biologic calibration conducted before every test session. All participants were tested by the same researcher using the same test procedure at all 3 sessions. Furthermore, all patients were tested in

the mornings to reduce the effect that fatigue can have on patients' responses to behavioural audiometry testing.

Reliability of all case history data was enhanced by ensuring that important aspects of the data were obtained from medical record reviews instead of relying on participants' self reports. Specifically, information such as the names of the different medications that the patient was taking/had taken, the dosage and frequency of use, and the length of time on the medication, CD4 count, and so on was obtained from record reviews; while information such as demographic details, family history of hearing loss, signs and symptoms of auditory pathology, and history of noise exposure, was obtained directly from patients. Furthermore, because Newell and Burnard (2006) argue that performing a series of interviews with the same people improves reliability of self-reports; this was undertaken in the current study since the same participants were assessed more than once.

To improve the reliability and validity of the audiological measures employed in the current study, the researcher utilised a test battery approach that allowed for the cross-check principle to be adhered to throughout the assessments (Jerger & Heyes, 1976). The cross-check principle, though originally introduced by Jerger and Hayes in 1976 for paediatric audiology measures, has been utilized throughout the audiologic test battery including that of adults (Katz, 2002; Turner, 2003). This principle emphasizes that the results of a single test be cross-checked by an independent test measure to improve reliability and validity of the findings.

For reliability and validity of otoscopic findings, the researcher employed the cross-check principle by using results of tympanometry to confirm otoscopic evaluation findings. This approach allowed the researcher to exclude those participants who did not qualify to be included in the ototoxicity monitoring phase of the study. Abnormal otoscopic findings were also cross-checked against the findings of the Ear, Nose and Throat Specialists following referrals to them for suspected outer and middle ear pathologies. The cross-check principle within the test battery approach adopted in the current study was also used to validate the results obtained from tympanometry and pure tone audiometry (air conduction and bone conduction thresholds). For illustration, if otoscopy revealed suspicious findings, these findings would have had to be cross-checked against tympanometry – which would have had to reveal abnormal tympanograms which in turn would have had to be confirmed by the Ear, Nose and Throat Specialist's report. Furthermore, tympanometry would be cross-checked against pure tone audiometry to confirm type of hearing loss. Type of hearing loss was determined by comparing air conduction thresholds to bone conduction thresholds.

For reliability and validity of DPOAEs, the researcher ensured reduction of physiologic and acoustic ambient noise as these conditions are critical for good recordings (Campbell, 2007). Moreover, the researcher consistently monitored and verified the intensity of the stimulus being presented, verified that noise levels (noise floor) were not excessive in the ear canal compared to normal expectations, and she consistently monitored each of these parameters visually on the computer screen as the DPgram was being performed. All of these aspects were carried out after the prerequisites for obtaining OAEs advocated by Hall (2000) listed earlier were observed and adhered to. Most importantly, reliability of the DPOAE recordings was enhanced by ensuring

that the participant's middle ear status was normal ensuring that the participant obtained a type A tympanogram before the measurement was conducted.

In summary, in the current study, attempts to enhance validity were achieved by:

- Standardizing administration of all test and research procedures for all participants
- Having regard for environmental and patient factors that could distort the results
- Having a control group to eliminate the Hawthorne effect. It is acknowledged that the control group used in the current study did not qualify as a true control group since it was subject to influences other than the lack of ARV (e.g. other medications used). However, the current researcher is of the opinion that the experimental group was also plagued by the same influences, with the specific difference in the two groups being that of ARV drugs use
- Matching the experimental group to the control group to ensure that there were no significant differences in variables such as age, CD4 count, hearing status/level following baseline
- Having baseline measures of pre-test to ensure that the experimental group and the control group were equivalent in terms of hearing levels
- Having post-test measures that were compared to pre-test measures to control for the placebo effect
- With the exception of pure tone audiometry, all measures used were objective in nature; hence participants' level of active participation did not play a significant role in the results.

(Devlin, 2006; Newell & Burnard, 2006; Stein & Cutler, 1996)

However, threats to validity in the current study were present, and they included:

- The study was not a double-blind study as the researcher was aware of which participants were in the control group and which were in the experimental group.
- There was no random selection of participants to reduce bias in the sample.
- There was limited control over confounding variables such as interaction of ARVs with previous exposure to ototoxic drugs, and interaction of ARVs with other routine medications and supplements that were being prescribed at the time of the study.
- The subjective nature of pure tone audiometry could have had an influence on the participants' responses since this test required active participation from participants. Controlling for practice effects was suboptimal (participants' familiarity with the test procedures was thought to have played a minimal role).

(Grimshaw et al., 2000; Newell & Burnard, 2006)

Finally, due to the sample size and the fact that the data were collected in one hospital in Gauteng, South Africa, the researcher's ability to generalize the results from the sample studied to the total population of adults with AIDS in South Africa is limited.

8.7. DATA ANALYSIS AND STATISTICAL PROCEDURES:

Before any statistical analysis of the data was conducted, a description of the sample was carried out where factors including age, gender, CD4 count, and attendance rate of participants were examined. While examining the attendance rate, attrition factors were considered and documented.

CD4 count monitoring and analysis was seen as important in the current study as a measure of immunologic status as well as an indicator of adherence to treatment for the experimental group – although this measure was not obtained for all participants at all 3 sessions due to the fact that some of the participants were followed up clinically (general health and physical indicators) rather than serologically (blood tests) at the research site at the time of the study. For the current study, all participants had CD4 counts done at baseline testing; however the same was not the case for sessions 2 and 3. Literature reports objective clinical improvement to be common in patients with clinically significant HIV disease once they enroll in an appropriate HAART regimen (Palella et al., 1998). Furthermore, these patients are expected to adhere successfully to treatment, and to not experience significant adverse side effects of medication (Palella et al., 1998). Objective clinical improvement from the use of HAART in patients with AIDS has been noted with CD4+ counts that are said to commonly rise drammatically, often by several hundred cells per microliter – to levels characteristic of clinically quiescent middle stage of HIV disease (Palella et al., 1998). The length of time for the current prospective study (six months) may not have allowed for this quiescent stage to be observed, yet another acknowledged limitation of the current study.

It is acknowledged that positive response to ARV treatment should also have been determined by measurements of viral loads. Literature indicates that the first indication of successful treatment is a decline in viral load (Perelson et al., 1997). This decline is reported by these authors to occur as early as the first two weeks of treatment for most patients. As viral load declines, the number of circulating CD4+ cells are reported to increase – the initial increases in CD4 count during the first 1-3 month/s of therapy are believed to be caused primarily by a redistribution of cells trapped from lymphoid tissue (Pakker et al., 1998). This monitoring and analysis of viral load could not be carried out in the current study as many of the participants did not have this measure taken at the time of the study.

Subsequently, following baseline measures, participants' results (Appendix J) were descriptively analysed and classified as either normal or abnormal – with those participants presenting with abnormal auditory function being eliminated from proceeding to the ototoxicity monitoring phase of the study (session 2 and 3). Normal hearing was taken as normal tympanometric results in the presence of normal otoscopic findings with pure tone responses at or better than 25 dB HL, with abnormal results being thresholds worse than 25dB HL with air-bone gaps greater than 10dB (Bess & Humes, 1990; Katz, 2002; Silman & Silverman, 1991). This stage of analysis aimed at determining the prevalence of hearing loss in the sample evaluated. The prevalence was determined at baseline and the same process was conducted on the sample at the end of the study (at six months). Occurrence of hearing loss in the control group and experimental group was analysed at each testing session in order to be able to determine the final prevalence rate at 6 months.

For all participants presenting with abnormal auditory function, abnormal hearing was further categorized into type of hearing loss; severity or degree of the loss; and type of onset of the hearing loss. Determination of type of hearing loss was conducted in order to determine anticipated management options and requirements for AIDS patients with hearing loss, and to anticipate communication prognosis for this population group. The management options may include Ear, Nose, and Throat Specialists' assessment and management; as well as diagnostic audiological assessment and management (in the form of both amplification and aural rehabilitation services). The hearing losses were classified into the three well-documented types of hearing losses (conductive - CHL; mixed - MHL; and sensorineural - SNHL) (Bess & Humes, 1990; Jacobson & Northern, 1990; Katz, 2002). SNHL was not further differentiated into cochlear (sensory) versus retrocochlear (neural), and this is acknowledged as another limitation of the current study. The test procedures employed, though appropriate for ototoxicity monitoring which was one of the objectives of the current study, were not appropriate for purposes of a complete detailed site of lesion evaluation.

The degree of hearing loss was determined using Silman and Silverman's (1991) classification of Magnitude of Hearing Impairment. This classification is reported by the authors to be the commonly employed system for describing the degree of hearing loss in adults, and is the researcher's preferred classification used at the Johannesburg Hospital's Hearing Clinic. This classification system, in line with Bess and Humes (1990), Gilbert, Smith and Stayner (2003), and Katz (1994) proposes that impaired hearing function begins at an average hearing level of 25 dB HL, and is categorized as seen in Table 8.

Table 8: System of classification of hearing loss in terms of degree of loss (Silman and Silverman, 1991) used in the current study

Average Hearing Level dB	Description
< 26 dB	Normal range
26dB – 40 dB	Mild hearing loss
41dB – 55 dB	Moderate hearing loss
56dB – 70 dB	Moderately severe hearing loss
71dB – 90 dB	Severe hearing loss
>91 dB	Profound hearing loss

Furthermore, in classifying the degree of the hearing loss, the researcher looked at the configuration of the loss and added categories depicting this change in degree of loss at frequency ranges (i.e. mild-moderate; severe-profound).

Configuration of hearing loss was established by describing the pure tone results as depicting flat, irregular, rising (low frequency), sloping (high frequency) configuration (Katz, 2002). Configuration was of particular importance in the current study as a configuration consistent with ototoxicity had to be determined. The initial stages of auditory toxicity are reported to involve selective destruction of the outer hair cells of the organ of Corti (Singer et al., 1996). In this early stage of toxicity, the damage is usually limited to the higher frequency levels (4000 to 8000Hz) (Bergstrom et al., 1985; Fausti et al., 1999; Schwade, 2000) particularly at the initial stages of the hearing loss (Konrad-Martin et al., 2005). The frequencies utilized in conversational hearing are reported to be commonly unaffected at this early stage (Garrison, Zaske & Rotschafer, 1990).

Symmetry of hearing loss was also examined where the researcher established whether the hearing loss was unilateral or bilateral, and whether it was symmetrical or asymmetrical (Katz, 2002). Bilateral hearing loss is reported to impact more severely on communication than unilateral hearing loss, and therefore requires prompt diagnosis and management (Hodgson,

1985; Stephens, 1997). Furthermore, binaural hearing is reported to be important in detecting the direction of a sound source, solving the problem of echoes as well as extracting information from multiple sound sources (Kidd, 2002). Early intervention in terms of medical management and/or amplification would enhance patients' communication abilities, allowing them an improved chance of correctly following their required medical treatment. Therefore, determining symmetry of hearing loss in this population would not only lead to enhanced communication, potential improvement in the patients' quality of life socially, academically, and vocationally; but it would potentially make a contribution in terms of their general health.

The type of onset of hearing symptoms was also analysed where descriptors such as gradual, gradual/progressive, sudden, and sudden/progressive onset were used to define the manner in which the symptoms presented, based on patient reports. Several studies have reported on sudden SNHL in patients with HIV/AIDS (Khoza & Ross, 2002; Real et al., 1987; Solanellas et al., 1996; Timon and Walsh, 1989). Smith and Canalis (1989) state that the otologic symptoms can include unilateral or bilateral SNHL; which can occasionally be of a sudden onset in nature, but is commonly rapidly progressive. Khoza and Ross (2002) reported the sudden onset of the hearing loss to be more prevalent in participants with more severe SNHL than in conductive or mixed hearing loss. Related to the type of onset, an analysis was undertaken of all participants who presented with clinical hearing loss with regard to the time (during the three sessions of testing) of identification of the clinical hearing loss.

All significant case history factors and Ear, Nose and Throat Specialists' reports were recorded and analyzed along with the audiological results in order to obtain a comprehensive

assessment and to ensure that participants presenting with hearing loss deemed (based on Ear, Nose and Throat Specialists' reports) to be opportunistic infection related were excluded from proceeding to the ototoxicity monitoring phase of the study. The abnormal hearing results were further compared to the different testing sessions to determine time of onset of hearing impairment as well as to identify any relationship between hearing loss and the use of ARVs and other therapies. For the researcher to be able to perform this comparison, an analysis of the medications that participants were taking was conducted for both the control group and the experimental group with a careful analysis of the different ARV regimens that were being prescribed. Dosing of the medication was also analysed at this stage to determine the amount, frequency, and length of time that the participants were on the medications for. Besides the dosing schedules of ARVs which were consistent and uniform, the dosing schedules for all other medications taken were so varied and inconsistent that this information proved impossible to meaningfully collate, and this is an acknowledged limitation of the current study. The risk of ototoxicity has been reported to be determined by factors such as amount and length of dosage, for example ototoxicity has been associated with large or prolonged doses of antibiotics (Konrad-Martin et al., 2005).

For the 54 participants who were on regimen 1 from the experimental group and the 16 from the control group (who attended all three testing sessions), the results from the pre-treatment phase were compared to the post-treatment phases (Keller & Warrack, 2000). This was carried out in order to determine if any changes occurred during the period when the experimental group was receiving ARVs. All participants in this group had normal middle ear functioning, based on otoscopic and tympanometric results, for them to be able to be evaluated

through the use of DPOAEs, and hence be part of this analysis. Statistical comparison was done basing the results on the average change from baseline. Each frequency's mean change from baseline for the ears individually was computed and then combined for both pure tone audiometry and distortion product otoacoustic emissions. Repeated-measures analysis of variance was used to compare the mean change from baseline for the control group and that of the experimental group from session to session. In the analysis of the DPOAE data, the baseline DPOAE levels in decibels SPL for each f2 value tested were compared with the corresponding session 2 and 3 measurement. The signal-to-noise difference was used as the measure of DPOAE amplitudes. The DPOAE values for the right and left ears were considered separately and combined. For pure tone audiomerty data, the baseline thresholds in decibels HL for each frequency were compared with the corresponding session 2 and 3 results as well. Similarly to DPOAEs, the pure tone data were also considered separately and combined. Data were analysed separately for each ear as one of the objectives of this study was to determine symmetry of auditory symptoms.

Because the research hypothesis had been formulated, close consultation with statisticians followed where statistical tests to be used were selected. The null hypothesis was that the participants' auditory function before and after antiretroviral drug-use would remain the same. The alternative hypothesis was that it would not remain the same, that is, participants would present with changes in their auditory function (Devlin, 2006; Newell & Burnard, 2006). The statistical tests were selected based on the data meeting the following statistical assumptions for both the control group and the experimental group (Newell & Burnard, 2006; Stein & Cutler, 1996):

- scale of measurement used in the study was interval (with comparison of means)
- the data were deemed to be normally distributed, and
- there was homogeneity of variance within the group scores

Normality of distribution was checked by visually viewing the distribution plots, an acknowledged limitation to the statistical analysis of the current study. Furthermore, data obtained were checked to ensure that the above assumptions were not significantly violated, and to ensure that where violations occurred, appropriate measures of corrections for violation (such as the Geisser-Greenhouse correction/Adjustments) were exercised. Tests of group differences in the form of Wilk's Lambda, Hotelling-Lawley Trace, Pillai's Trace, and Roy's Largest Root were conducted - with the understanding that where sample sizes are unequal (as in the current study), these tests would not be robust if the assumption of homogeneity of variances and covariances (homoscedasticity) was violated (Hand & Taylor, 1987; Zar, 1999). Box's M test for assumption of homoscedasticity was also conducted as this is appropriate for MANOVA's assumption of homoscedasticity where p (M) <.05 implied significant differences in covariances (Bray, James & Scott, 1985). Furthermore, because in a repeated measures design, univariate ANOVA tables may not be interpreted properly unless the variance/covariance matrix of the dependent variable is circular in form (Huynh & Mandeville, 1979); the Mauchly's test of sphericity was also performed. This was conducted particularly because authors such as Bray, James and Scott (1985) assert that when there is a violation of the assumption of sphericity in a repeated measures design, MANOVA rather than multiple univariate ANOVA tests should rather be used. MANOVA also provided the advantage of being sensitive not only to mean differences but it also does not require the assumption of orthogonality (lack of correlations) among the contrasts (Bray, James & Scott, 1985) – as opposed to using multiple univariate ANOVA tests

(when contrasts of groups means are correlated with each other), which may fail to reject the null hypothesis of no group differences because of the fact that ANOVA tests differences in means under assumptions of independence (Zar, 1999).

In the current study, results of the abovementioned tests of statistical validity were inconsistent for frequencies assessed for both pure tone audiometry and DPOAEs. For the control group, findings were mostly not significant for both pure tone audiometry and DPOAEs – and where departures from the assumptions occurred, the F tests were robust; however, this was not the case with the experimental group. For the experimental group's MANOVA, findings for pure tone audiometry were not statistically significant ($p>.05$) [with the exception of 8000Hz (left and right ears)], and those for DPOAEs indicated violations at 750Hz and 1000Hz (left and right ears), and 8000Hz (left ear). In repeated measures ANOVA, results were not statistically significant [with the exception of violations in DPOAEs at 750Hz, 4000Hz, 6000Hz (left and right ears), and 8000Hz (right ear). The fact that homogeneity of variance was not consistently met at all frequencies tested is an acknowledged limitation to the study, and should be taken into consideration when interpreting results of the study.

To statistically test the hypothesis, a significance level or a threshold P value (alpha) of 0,05 was selected, which meant that there would be a 95% confidence level that results were not due to chance (Devlin, 2006). This is an important step in clinical research as it ensures that the probability or the risk of making a type I error (rejection of the null hypothesis when it should be accepted) in the research is established (Stein & Cutler, 1996). The use of parametric tests was chosen because in terms of power, Motulsky (1999) maintains that there is a minor difference

between nonparametric and parametric tests if the samples are large; but with small samples, nonparametric tests have little power to detect differences. Therefore in the current study, because the control group was small, parametric tests were selected. With very small groups, nonparametric tests have zero power – the P value will always be greater than 0, 05 (Driscoll, Lecky, & Crosby, 2000).

Variables were rank ordered and the sizes of the differences between the variables were quantified and compared. The variables were categorized into both categorical (male/female; yes/no) and numerical variables with the latter falling into the continuous random variables (based on audiological measurements). Inferential statistical analysis testing for differences in the data was performed utilizing the repeated-measures analysis of variance [within group - (MANOVA – 1x3 ANOVA)] since the design employed was the repeated-measures design (where the researcher measured a variable in each participant before, during and after an intervention) where controlling for unwanted differences was important, and determination of time (treatment) effects was an objective (Newell & Burnard, 2006). Repeated measures ANOVA assumes that each measurement is the sum of an overall mean, a treatment effect (the average difference between subjects given a particular treatment and the overall mean), an individual effect (the average difference between measurements made in a certain subject and the overall mean) and a random component. Furthermore, it assumes that the random component follows a normal distribution (Motulsky, 1999). All these analysis were conducted at each frequency separately for the pure tone thresholds, and at each frequency separately for the DPOAE amplitudes.

These analysis methods were chosen because the same participants were measured repeatedly yielding three groups of scores for each participant. Motulsky (1999) insists that repeated measures tests should be applied strictly when treatments have been given repeatedly to one subject – and this was the case in the current study. Although the sample size of the control group was significantly smaller than that of the experimental group, statistical tests chosen were able to produce reliable results since when assuming the population has a normal distribution, and is able to invoke the central limit theorem, a sample size of ten or so is reported to be generally enough (Motulsky, 1999). The control group had 16 participants (32 ears).

Following statistical analysis through the use of the NCSS statistical programme, the ANOVA tables were studied. These tables offered information about the P value. The P value is a probability, with a value ranging from zero to one. If the P value is small, one can conclude that the difference between sample means is unlikely to be a coincidence, but can instead conclude that the populations have different means (Driscoll, Lecky & Crosby, 2000). Motulsky (1999, p.12) provides a classification system for statistical significance which can be used to further describe results that are statistically significant – and this classification was the one used in the current study. This classification states that if the P value is greater than 0,05 it is not significant; between 0,01 and 0,05 (significant); between 0,001 and 0,01 (very significant); and less than 0,001 (extremely significant).

Over and above determining the P value with repeated measures ANOVA, two sources of variability: between rows (individuals – in the current study this is referred to as 'within group' analysis) and random (residual), were obtained from the ANOVA tables (Motulsky, 1999).

Furthermore, the ANOVA table also adjusts for the number of groups and number of subjects (expressed as degrees of freedom) to compute F ratios; therefore this data was also studied and presented with the results because F ratios test the null hypothesis. The F ratio is expected to be near 1.0 if the null hypothesis is true. If F is large, the P value will be small, and hence the null hypothesis is rejected (Driscoll, Lecky & Crosby, 2000; Newell & Burnard, 2006).

Lastly, as part of statistical analysis of the data, a post-test in the form of the Tukey-Kramer multiple-comparison post-test was conducted. This test was conducted to compare pairs of group means so as to identify where, precisely, statistically significant changes occurred along the time continuum (baseline to 6 months) – if they did. This was deemed an appropriate post-test since it is a test for comparing three or more pairs of group means, and was particularly applicable in the current study as it contains an extension by Kramer to allow for unequal sample sizes (Greenstein, 2003; Motulsky, 1999). This post-test was used particularly to determine when, with regard to the three testing sessions, statistically significant changes occurred [with 0 indicating baseline (session1 before ARVs); 3 indicating three months (session 2); and 6 indicating six months (session 3)].

Lastly for the purposes of the current study, clinical significance (changes that are deemed significant enough to indicate structural and functional changes on the ear) as opposed to statistical significance was examined. There is a growing recognition that assessing an intervention's effect should not only focus on the statistical significance of the differences between the experimental and control group, but should also focus at the relevance or importance of these outcomes (Middel, 2002). Motulsky (1999, p. 11) argues that "just because a difference

is *statistically significant* does not mean that it is biologically or clinically important or interesting". This view is supported by Greenstein (2003) who asserts that it is problematic to rely only on statistical significance because it is possible to obtain statistically significant changes while the result may not be clinically significant or relevant.

Traditionally, a significant number of researchers who have evaluated the efficacy of care-related interventions have based their decisions on the statistical significance of the intervention-related change over time or any statistically significant difference in change from repeated measurements between experimental and control groups. These studies are based on the underlying hypothesis that the experimental group should show a higher mean change compared to the control group (Middel, 2002). Middel asserts that in some cases, for an example, investigators eager for results are likely to detect a statistically significant (but very small) change in scores related to the intervention, simply due to large sample sizes. Consequently, even if statistically significant (though trivial in magnitude) change is detected, the $p < 0,05$ doctrine unwittingly pushes the question of how meaningful, important, relevant, or substantial that change is, into the background (Greenstein, 2003; Middel, 2002). It was to avoid this dilemma that the next step of analysis (that of clinical significance) was included in the current study. The current researcher is of the opinion that clinical significance is also just as important as statistical significance when dealing with patients and particularly in the era of financial constraints where evidence-based practice informs budgets and policy formulation.

Kingman (1992) stated that statistical significance should become a necessary condition for clinical significance and that both statistical and clinical significance should coincide. In

support, Killoy (2002) indicated that clinical significance is a subjective evaluation of significance by the clinician and that before a finding can be clinically significant, it must have achieved statistical significance – and this stance is supported by the current researcher. For the current study, this change was that of changes found between measures at baseline and at six months after initiation of ARVs.

As far as pure tone audiometry is concerned, according to the "Guidelines for the audiologic management of individuals treated with cochleotoxic drug therapy" formulated by the American Speech-Language-Hearing Association (ASHA, 1994), using pure tone data, a clinically significant change in the hearing level is confirmed if the following criteria exist:

- 20dB or more pure tone threshold change at one test frequency
- 10dB or more pure tone threshold change at two adjacent test frequencies
- Loss of responses at three consecutive test frequencies where responses were previously obtained, and
- Threshold change must be confirmed by retest

Most often a change of 10dB at one or more frequencies is commonly taken to be indicative of some significant change (Ludman & Wright, 1998) – and this was the protocol followed in the current study. In that way short term reliability changes due to factors such as fatigue, concentration levels, time of day, and so forth are accounted for.

As far as DPOAEs are concerned, change is only regarded as significant in DPOAE measures if there is a change of at least more than 6 to 9dB in DPOAE level between consecutive measures (Dreisbach et al., 2006; Roede et al., 1993). In this way short and long term reliability

effects due to factors such as subject noise, probe tip placement/position, equipment, changes in middle ear pressure, etc (Franklin et al., 1992; Marshall & Heller, 1996; Roede et al., 1993; Zhao & Stephens, 1999) are accounted for. Absence of clinically significant changes in DPOAEs confirm intact cochlear functioning and the absence of evidence of cochlea damage, even microcochlear pathology – which is often evident on OAEs long before being depicted on the pure tone audiogram (Hall, 2000).

During exploratory data analysis, it was discovered that there were participants in the experimental group who presented with changes on DPOAE measures without changes in pure tone audiometry. This presentation of results necessitated an additional analysis step where these participants (referred to as the subclinical hearing loss group) were analysed separately; hence this formed an additional set of results. "Subclinical" (without clinical manifestations) is defined by Jackson (2002) as referring to the early stage of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests or of a very mild form of an infection or other disease or abnormality. In the current study, "subclinical" referred to microcochlea pathology which had not manifested clinically by observable and measurable audiological signs on audiogram. This was opposed to clinical hearing loss which was defined in the current study as observable and measurable audiological changes – hearing changes observable on audiogram.

Those participants in the experimental group who presented with normal pure tone audiometry results at all three sessions were closely analysed since DPOAEs are reported to be more sensitive to cochlea damage than pure tone audiometry. Changes in DPOAE results have

been reported in the absence of changes in pure tone audiometry as a sign of damage to the cochlea. Closer analysis of this group was therefore aimed at ensuring that the changes as well as the differences in the changes between PTA and DPOAE were examined separately. Eliminating those participants that presented with clinical hearing loss was carried out to ascertain that the changes found in DPOAE results were not due to clinical hearing loss. Analysis of the results for this subgroup of the experimental group involved comparing the results of all measures at all three assessment sessions in order to determine if any changes occurred during the period when the patients were receiving ARVs.

The following table (Table 9) provides a summary of all collection material and test procedures used in this study.

Table 9: A summary table of collection materials and test procedures used in the current study

Equipment	Function	Pass criteria	Fail criteria
Case history form	Gather important case history data	Refer to inclusion and exclusion criteria	Refer to inclusion and exclusion criteria
Welch Allyn Otoscope	Visual inspection of the ear	Clear outer ear with normal and tympanic membrane	Obstruction; abnormal tympanic membrane, pathologies of the outer and middle ear
AZ26 Interacoustic tympanometer	Middle ear functioning assessment	Type A tympanogram	Other tympanograms but type A
AC40 Diagnostic audiometer	Conventional pure tone audiometry (250 – 8000Hz) Monitoring function	Thresholds at and better than 25dBHL and no Air-Bone Gap No 10dB threshold change at one or more frequencies over time	Thresholds worse than 25dBHL A change of 10dB at one or more frequencies over time
Biologic Scout OAE machine	Diagnostic DPOAE measurement Ototoxicity monitoring	Greater than 7dB DP amplitude at frequencies assessed No DPOAE level change of more than 6 to 9dB between consecutive measures	Less than 7dB DP amplitude Change of more than 6 to 9dB in DPOAE level between consecutive measures

In summary, data analysis included the following:

1. An analysis of the prevalence of hearing status and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth).
2. An analysis of the type, degree and configuration of the hearing loss
3. An exploration of the type of hearing symptom onset (e.g. sudden or gradual/progressive onset)
4. Documentation of case history data such as signs and symptoms of each participating participant and identification of any associations between obtained signs and symptoms and hearing loss

5. Documentation of the names of all medications used to establish their possible impact on hearing function, specifically ototoxicity monitoring
6. A comparison of the results of the experimental group with those of a control group
7. An analysis of the group with subclinical hearing loss

The research process employed in the current study is illustrated in the flow diagram on the next page (Figure 1):

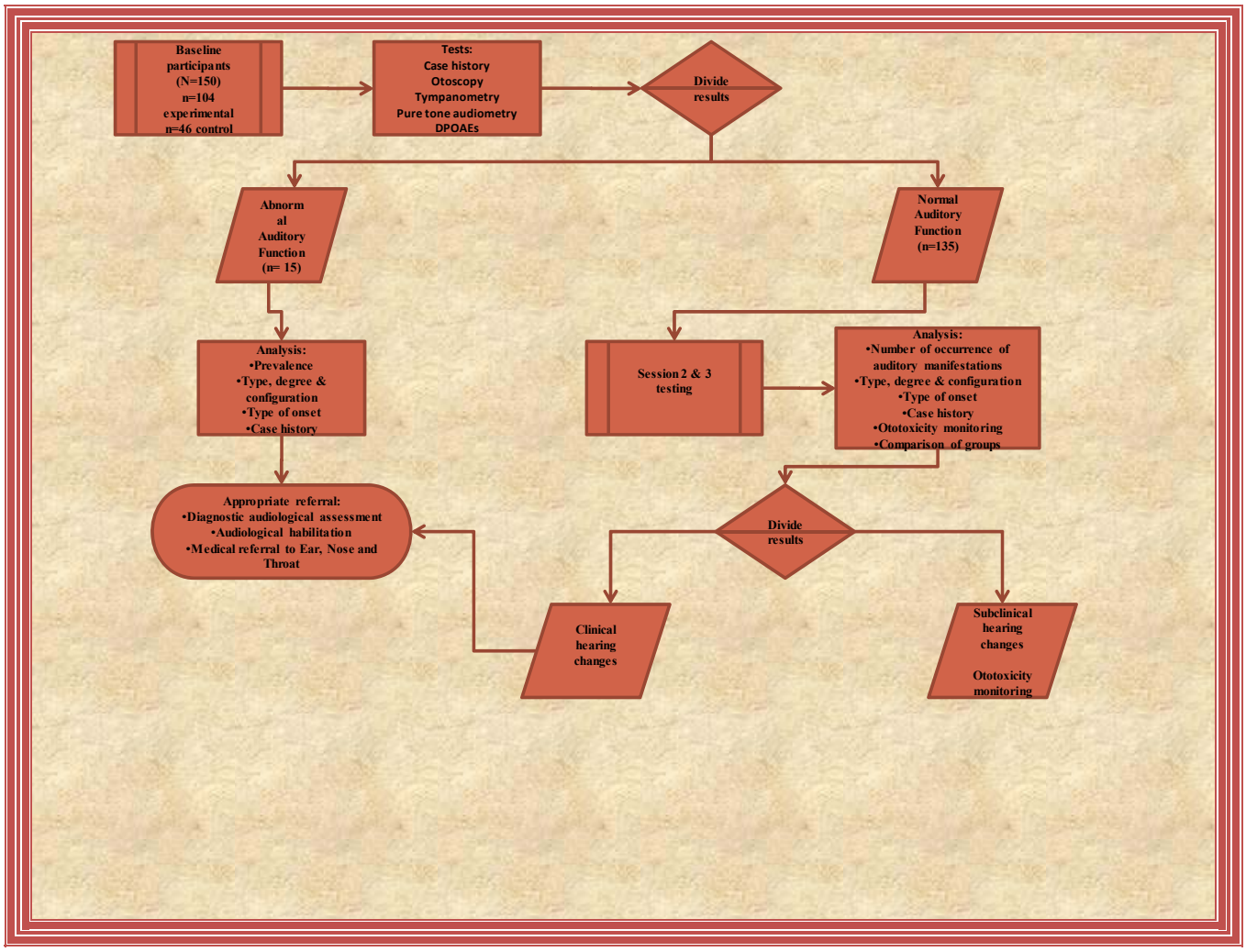


Figure 1: An illustration of the research process followed in the current study

8.8. Summary

The current study was conducted on 150 adult participants who volunteered to participate in the study at baseline. This number was analysed descriptively, however, for the repeated measures analysis phase of the study, this number decreased to 54 participants in the experimental group and 16 in the control group. All participants underwent a case history interview with medical record reviews, otoscopic evaluation, immittance measures, pure tone audiometry, as well as DPOAE measures at 3 sessions that included a baseline (pre-treatment) measure and the other two measures at 3 and 6 months into treatment with ARVs. The control group underwent the same assessment protocol with the difference being that they were not on ARVs at the time of the study. Those that commenced ARVs during the study were subsequently excluded from the repeated measures analysis section of the study. Attrition due to factors such as death, poor adherence to treatment, missed appointments, commencement of treatment for some of the participants in the control group etc was evident. These factors exerted a more significant impact on the control group than the experimental group in terms of the total numbers that formed part of the final inferential repeated measures analysis stage of this study. The fact that it was ethically unacceptable to influence members of the control group, in terms of choosing whether or not to go on to ARVs at a later stage, further contributed to attrition in the control group. The following chapter focuses on the statistical analyses and the results obtained with discussion of the results presented separately.

PART IV – PRESENTATION, ANALYSIS AND DISCUSSION OF FINDINGS

Chapter 9

RESULTS OF THE STUDY

CHAPTER NINE

RESULTS OF THE STUDY

The results arising from the investigation and monitoring of the auditory status of a group of adult patients with AIDS on antiretroviral drugs and other therapies attending a hospital outpatient clinic in Johannesburg are presented in this chapter in accordance with the specific aims of the study. This chapter presents the results of the total sample at baseline (before initiation of antiretroviral treatment), followed by the results of the control group and the experimental group presented concurrently. A continuous comparison of the experimental and control group is presented with a comparison table provided towards the end of the results section. Thereafter, an additional set of results (in respect of participants who presented with subclinical hearing changes) is presented at the end of the results section. Each section of the results is preceded by a detailed description of the participants.

9.1. RESULTS OF THE TOTAL SAMPLE AT BASELINE

9.1.1. Description of Participants

The study at baseline (Table 10) comprised 150 participants (104 in the experimental group and 46 in the control group). The sample included 53 (35%) males and 97 (65%) females between the ages of 20 and 46 years with a mean age of 33.9 years. All of the participants had been diagnosed with HIV/AIDS and were all at the AIDS stage of the disease. The average CD4+ count at baseline was 124 cells/mm^3 which was consistent with the CD4+ requirement that persons need to have before they can be enrolled in an ARV programme in South Africa (i.e. CD4+ has to be below 200 cells/mm^3). It is acknowledged that the unequal number of

participants in the control group and the experimental group represented a threat to generalization of the results – however this could not be controlled for since at the time of the study it was extremely difficult to find participants who did not wish to enrol for an ARV treatment programme at the research site.

Table 10: Demographic and baseline CD4 count data of participants for the whole sample at baseline (N = 150)

FACTOR	SUB-CATEGORY	NO.
Age (Years)	Range Mean	20-46yrs 33.9yrs
Gender	Male Female	53 (35%) 97 (65%)
Ethnic Group	Black White Coloured Indian	141 (94%) 0 9 (6%) 0
CD4+ Count (cells/mm^3)	Mean Standard deviation	123.5133 69.00294

The small number of control group participants (46) that participated at baseline decreased significantly to a total number of 16 participants who attended all 3 sessions of testing required for the completion of the current study. Attrition factors (Table 11) in the control group included commencement of antiretroviral treatment, over and above other general factors, such as failure to attend or inconsistency in attending follow up appointments, death, clinical hearing loss that was due to other causes, and so forth. Similar attrition factors applied to the attendance of persons in the experimental group. Even though the experimental group started with 104 participants at baseline, the numbers significantly declined to a total of 54 participants on regimen 1 who attended all 3 sessions of evaluations for ototoxicity monitoring. Unlike in the control group where some participants dropped out because they commenced ARV treatment, in

the experimental group, some participants were excluded when they defaulted from their treatment (Table 6).

Table 11: Reasons for attrition in both the experimental and control groups throughout the study

Reasons for attrition	
Experimental group	**Control Group**
No show in follow up	No show in follow up
Death	Death
Failure to adhere to treatment	Commenced ARV treatment
Relocated	Relocated
Defaulted treatment	
Hearing loss due to various causes e.g. middle ear pathology, syphilis, meningitis	Hearing loss due to various causes e.g. middle ear pathology, syphilis
	1 person had renal failure
	1 person had breast cancer and chemotherapy
	1 person had Lupus and TB

9.1.2. The prevalence rate of hearing loss

The first objective was to estimate the prevalence of hearing loss and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth).

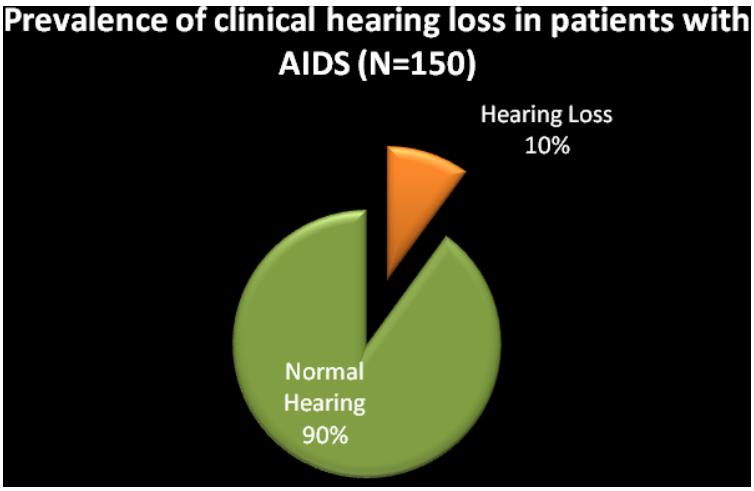


Figure 2: The prevalence rate of hearing loss in the sample of patients with AIDS evaluated at baseline (N = 150)

Of the total sample of 150 participants evaluated, 135 (90%) had normal hearing, and 15 presented with a clinical hearing loss at baseline (Figure 2). This finding indicates that of the total sample of 150 adults with AIDS that was evaluated, 10% of participants had clinical hearing loss with tinnitus and vertigo in varying degrees and combinations when evaluated at baseline (before initiation of ARVs).

However, the aforementioned prevalence of hearing loss changed after 6 months of longitudinal follow up of adults with AIDS (Figure 3). Of the total sample of participants

evaluated 42 (28%) presented with clinical hearing loss while 72% had normal hearing function as depicted by pure tone audiometry.

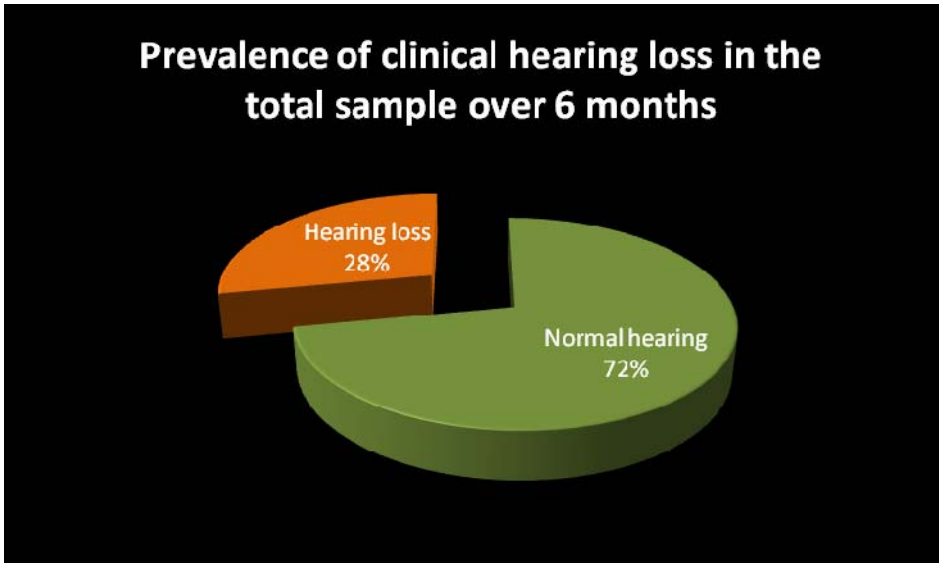


Figure 3: The prevalence rate of hearing loss in the sample of patients with AIDS evaluated after 6 months of monitoring (N = 150)

Over and above changes in audiological function, participants with clinical hearing loss in the current study also presented with associated symptoms of hearing loss in the form of tinnitus and dizziness at baseline (Figure 4). Ten (67%) of the participants presented with associated tinnitus, 4 (27%) experienced dizziness, and 4 (27%) had simultaneous experience of dizziness and tinnitus. Of note (Appendix J) is the fact that of the group with normal hearing function, some participants in the experimental group also presented with tinnitus and/or vertigo in the absence of hearing impairment. Nine participants presented with vertigo at session 2, however this was reduced to only 1 participant presenting with vertigo by session 3 of testing. Moreover, tinnitus was found in 1 participant, in the absence of hearing loss, at session 1 with an increase to five participants in session 3. The presence of associated signs in the absence of hearing loss was only seen in the experimental group and not in the control group, and this could

imply some impact that ARVs used in the current study may have on auditory function. However, Carr and Cooper (2000) do report on dizziness, which subsides with time in some patients who present with this symptom early in the treatment, as a side effect of ARVs.

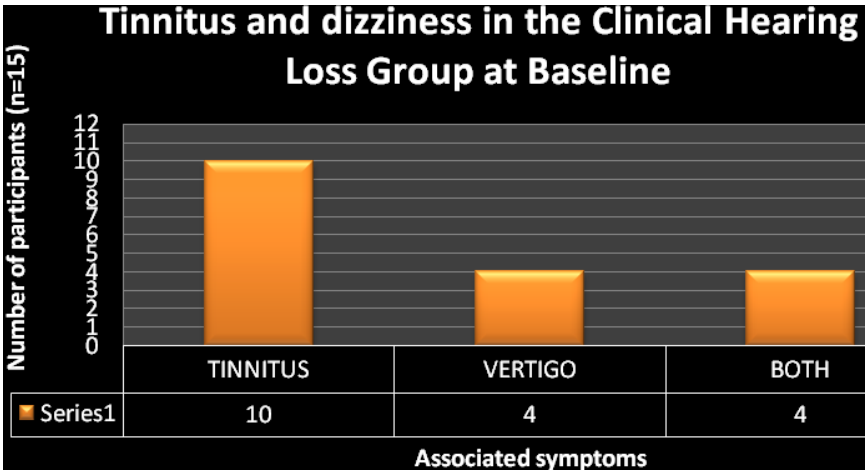


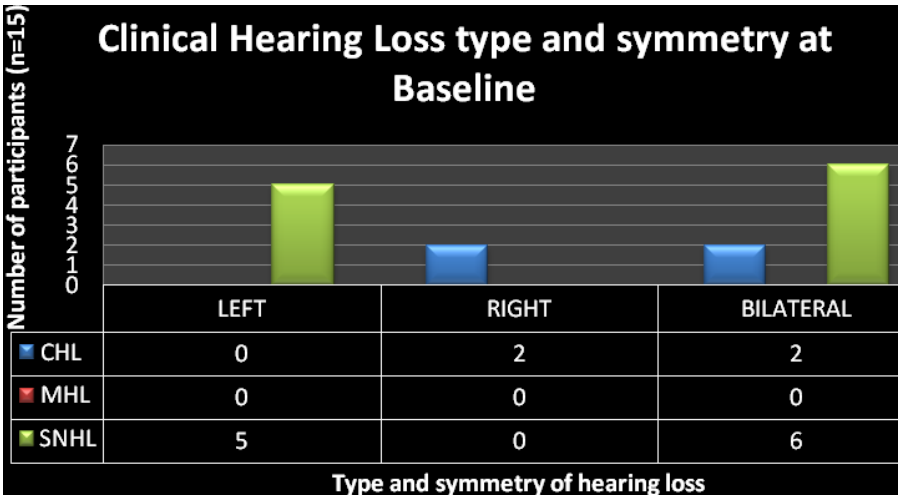
Figure 4: The occurrence of tinnitus and dizziness in the group of participants with clinical hearing loss at baseline (n=15)

9.1.3. Assessment of the type, degree, configuration, and symmetry of the hearing loss at baseline

The second objective was to assess the type, degree, configuration, and symmetry of the hearing loss.

9.1.3.1. Types of hearing loss

Of the 15 participants with clinical hearing loss at baseline, 11 (73%) had sensorineural hearing loss (SNHL); 4 (27%) had conductive hearing loss (CHL); and none had mixed hearing loss (MHL) (Figure 5).

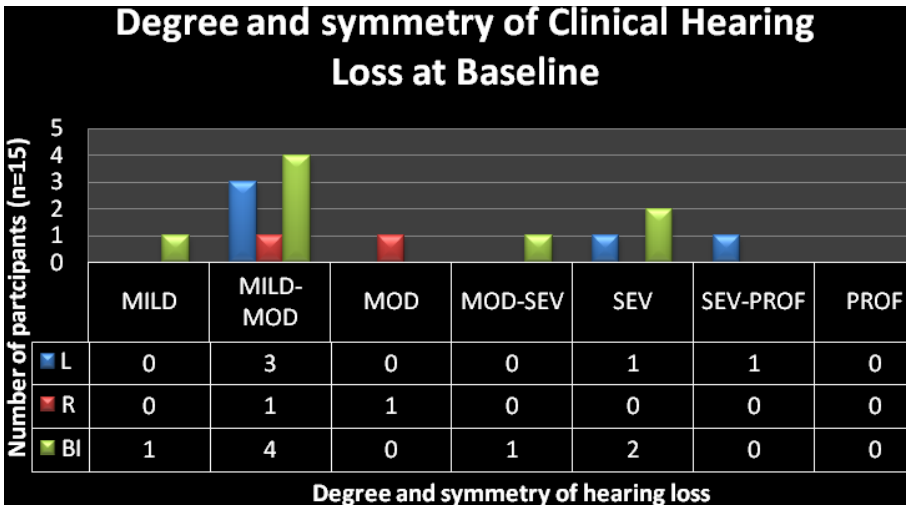


Key: CHL = Conductive hearing loss; MHL = Mixed hearing loss; SNHL = Sensorineural hearing loss

Figure 5: Types of hearing loss in the sub-sample of participants with clinical hearing loss at baseline (n =15)

9.1.3.2. Degree of hearing loss

Following the classification of degree of hearing loss previously reported; it became evident that the hearing loss could occur in any degree of severity as depicted in Figure 6. However, the most prevalent degree of severity of hearing loss was the mild-moderate hearing loss followed by the severe degree of hearing impairment. Of the 15 participants, 8 (53%) presented with mild to moderate hearing loss while 3 (20%) presented with severe hearing loss.



Key: Mod = Moderate; Sev = Severe; Prof = Profound; L = left; R = right; Bi = bilateral

Figure 6: Degree and symmetry of hearing loss in the sub-sample of participants with clinical hearing loss at baseline (n = 15)

9.1.3.3. Configuration of hearing loss

No typical pattern of configuration of hearing loss could be established at baseline before antiretroviral treatment was instituted. In the total sub-sample (n = 15) of patients with abnormal hearing at baseline, 5 (33%) participants presented with a sloping/high frequency hearing loss while the remaining 67% presented with flat and/or irregular audiograms with an equal chance of involvement of all frequencies.

9.1.3.4. Symmetry of hearing loss

Of the total sub-sample of 15 participants with abnormal hearing, 7 (47%) had unilateral hearing impairment while 8 (53%) presented with bilateral hearing loss (Figure 5 & Table 12). Although there appears to be a dearth of reported data in respect to symmetry of hearing loss in

adults infected with HIV/AIDS, the current study demonstrated that the hearing loss can be unilateral or bilateral, and can also be bilaterally symmetrical or asymmetrical (Table 12).

9.1.4. Type of onset of hearing symptoms

The third objective was to explore the type of hearing symptom onset (e.g. sudden or gradual/progressive onset).

Of the entire sample with abnormal hearing at baseline, all the participants (100%) presented with gradual/progressive hearing loss with no participant presenting with sudden onset of symptoms.

9.1.5. Case history information

The fourth objective was to document case history data such as signs and symptoms of each participating participant and to identify any associations between obtained signs and symptoms and hearing loss

Table 12: Case history and medical information for participants with clinical hearing loss at baseline (n=15)

Participant	Age (yrs)	Type of Hearing Loss	Medical History	Ear History
Participant 44s	30	Bilateral severe conductive hearing loss	Otitis media	Perforated tympanic membrane; Chronic suppurative otitis media
Participant 45s	41	L-mild-moderate sloping SNHL	Unknown	None
Participant 53	24	R-mild moderate CHL	Otitis media	Otitis media with effusion
Participant 54	32	Bilateral mild SNHL	? otosyphilis	None
Participant 61	46	L-Mild moderately severe SNHL	Unknown	History of otalgia
Participant 80	39	R-mild-moderate CHL	Otitis media	Perforated tympanic membrane; Chronic suppurative otitis media
Participant 83	33	Bilateral moderate severe SNHL	Otosyphilis	None
Participant 88	46	Bilateral moderate severe SNHL	Meningitis	None
Participant 89	41	L-moderate severe SNHL	Unknown	Hearing loss
Participant 97	29	Bilateral mild moderate sloping SNHL	TB treatment and syphilis treatment	None
Participant 102	20	L-severe profound SNHL	Syphilis & Viral meningitis	Hearing loss
Participant 104	39	Bilateral mild moderate SNHL	Unknown	None
Participant 2c	29	Bilateral sloping mild moderate SNHL	Herpes	None
Participant 44c	30	Bilateral severe CHL	Otitis media	Perforated tympanic membrane; Chronic suppurative otitis media
Participant 45c	41	L- mild moderate sloping SNHL	TB treatment and noise exposure	None

Key: s = study (experimental); c = control; L = left; R = right

Detailed analysis of the audiologic evaluation results together with the documented case history information where medical diagnoses had been confirmed by Ear, Nose and Throat Specialists (Tables 12 and 13) at baseline revealed the following:

- Patients who presented with SNHL had documented medical histories of meningitis; infections (syphilis and otosyphilis); and histories of ototoxic medication used in the treatment of TB and other opportunistic infections. Four participants had unknown causes of hearing loss.
- Patients who presented with CHL had a history of chronic suppurative otitis media, and otitis media with effusion.

Table 13: Summary of case history data and results for participants with clinical hearing loss at baseline (n=15)

FACTOR	SUB-CATEGORY	NO.	PERCENTAGE
Gender	Female Male	8 7	53 47
Age CD4+	Average Age Average CD4+	33.9yrs (Range 20-46yrs) 123.5 (Range 2-265 cells/mm^3)	Not applicable
Hearing Function	Hearing loss	15	10
Type of Hearing Loss	Conductive Hearing Loss Sensorineural Hearing Loss Mixed Hearing Loss	4 11 0	27 73 0
Type of onset of Hearing Loss	Sudden Gradual	0 15	0 100
Symmetry of Hearing Loss	Unilateral Bilateral	7 8	47 53
Possible aetiology of Hearing Loss *	Meningitis Oto/syphilis Otitis Media Herpes TB Treatment Unknown Noise exposure	2 4 4 1 2 4 1	13% 27% 27% 7% 13% 27% 7%
Degree of Hearing Loss (n=15)	Mild Mild-moderate Moderate Moderate-severe Severe Severe-profound Profound	1 8 1 1 3 1 0	7 53 7 7 20 7 0
Tinnitus	Present Absent	10 5	67 33
Vertigo	Present Absent	4 11	27 73
Tinnitus & Vertigo	Present	4	27

***% Scores do not add up to 100% as some participants presented with more than one possible aetiological factor.**

Of the 150 participants at baseline (104 experimental group and 46 control group), a significant number of participants were excluded from the inferential statistics phase of the study for various reasons. Eventually, only 54 participants were left in the experimental group, and 16

in the control group. The participants in this group of participants were the ones that were able to attend all 3 evaluation sessions that was the methodological requirement of the current study. For the experimental group, these were also the participants that were on regimen 1 of ART. Therefore, all participants (discussed in this section of the chapter) who presented with clinical hearing loss at baseline (15 in total, comprising 12 from the experimental group and 3 from the control group) were eliminated and excluded from participation in subsequent testing sessions (session 2 & 3). All participants with clinical hearing loss were referred appropriately to Ear, Nose and Throat Specialists, as well as for diagnostic and rehabilitative audiological services at the Johannesburg Hospital.

Despite the attrition experienced in the study, the demographic profile of the participants included in the analysis was thought to still be fairly representative of persons with AIDS in the local area at the time of the study. Furthermore, the adherence behaviour and attendance rate were also felt to be fairly representative of patients at the hospital where the data were collected. Participants were evenly balanced with regard to baseline hearing status, demographic characteristics, and CD4+ counts in the experimental group versus the control group.

Of the total sub-sample of the group with normal hearing at baseline testing, the pure tone audiometry as well as distortion product otoacoustic emissions results conformed to the criteria stipulated in the methodology section of this thesis. The criteria stipulated that the average pure tone results for all frequencies tested needed to be above 25 dB, indicating normal hearing in this population, and that the DPOAE mean (DPOAE-NF mean) for all frequencies assessed needed to be above 7dB, indicating the presence of cochlear emissions implying normal cochlea

functioning of the participants at baseline. These were the participants that continued in the ototoxicity monitoring sessions that ensued.

9.1.6. Medications used in the study

The fifth objective was to document the names of all medications used to establish their possible impact on hearing function, specifically ototoxicity monitoring

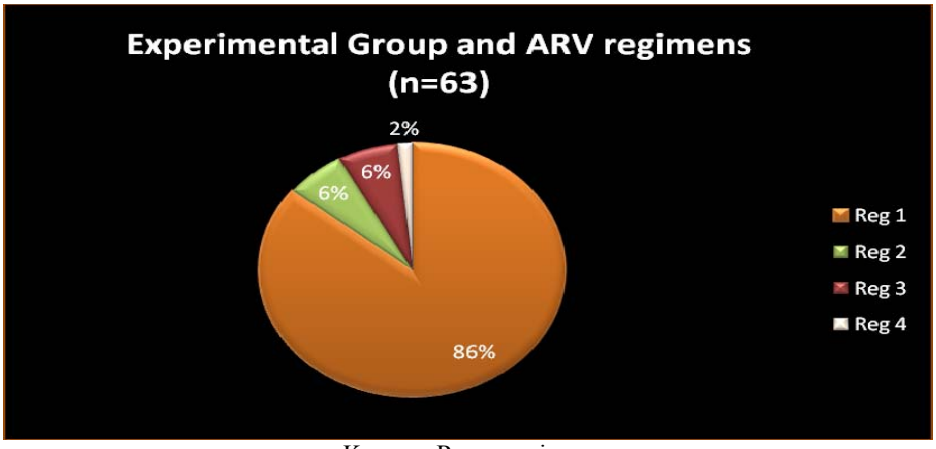
The following (Table 14) is the list of medications that the participants were utilizing during the current study. Interventions to alter the course of the disease and to treat opportunistic infections included antiretroviral therapy and general health management.

Table 14: List of medications that were used during the study

MEDICATIONS USED		
	Experimental group only	**Control Group & Experimental Group**
Reg 1	**3TC 150mg daily** **D4T 30 to 40mg daily** **Stocrin 600mg daily**	**Bactrim** **Vit Bco** **Vit C** **Amoxil** **Facticin** **Acyclovir** **Allergex**
Reg 2	**nevirapine 200mg daily** **3TC 150mg daily** **D4T 40mg daily**	**Fluconaze** **Mycostatin suspension** **Augmentin** **Diflucan** **Amphotericin B lozengez**
Reg 3	**AZT 300mg daily** **3TC 150mg daily** **Stoctrin 600mg daily**	**Flagyl** **Brufen** **Photophane** **Tryptanol**
Reg 4	**AZT 300mg daily** **3TC 150mg daily** **Nevirapine 500mg daily**	
Additional		**Ubhejane**

Key: Reg = regimen; mg = milligram

As can be noted on this list (Table 14), antibiotics, anti-depressants, antifungals, antivirals, analgesia, as well as traditional medicine were among the list of medications that were used in various combinations by both groups with the experimental group's distinct difference being the additional use of antiretroviral drugs. Review of literature on the adverse as well as minor side effects of all these drugs, if taken in recommended dosages, yielded side effects that were generally whole body related (e.g. headache, loss of appetite, diarrhoea, fatigue, disturbed sleep, nausea and vomiting; stomach or bowel problems, changes in sight or taste, and so on) (Canadian AIDS Treatment Information Exchange – CATIE, 2008), and no information could be obtained that linked any of these drugs to hearing function, or side effects relating specifically to the ear. The only medication on this list that could indirectly cause hearing function changes through its negative effects on the kidneys was Amphotericin, if ingested in extremely large amounts for prolonged periods of time (Gallis, 1996). Besides the supplements, all other medications on this list were used for short periods of time for symptom management, in recommended dosages.



Key: Reg = regimen

Figure 7: Percentage numbers of participants in the experimental group on the different antiretroviral treatment regimens in the study

As can be seen from Figure 7, of all participants that attended all 3 sessions in the experimental group (total 63), the majority (86%) were on regimen 1 (which consisted of 3TC-lamivudine, D4T-stavudine, and stocrin), with the remainder (9 participants) being on the other ARV regimens. The group on regimen 1 was the group (54 participants) that formed the analysis sample for ototoxicity monitoring. Participants in this group were also taking other medications for general health management (other than ARVs) in various combinations (as listed in Table 14). "*Ubhejane"* is a form of African traditional medicine that some of the participants also reported on using either as a form of complimentary (as in the experimental group) or as an alternative (as in the control group) to antiretroviral medications.

After elimination of the nine participants that were not on regimen 1 of ARVs for ototoxicity monitoring, the list of medications that were used is depicted in Table 14a.

Table 14a: List of medications that were used during the study

MEDICATIONS USED			
	Experimental group only	**Control Group & Experimental Group**	
Reg 1	**3TC 150mg daily**	**Bactrim**	**Allergex**
	D4T 30 to 40mg daily	**Amoxil**	**Vit Bco**
	Stocrin 600mg daily	**Acyclovir**	**Vit C**
		Flagyl	**Brufen**
		Facticin	**Photophane**
		Augmentin	**Tryptanol**
		Mycostatin suspension	**Fluconaze**
		Amphotericin B lozengez	**Diflucan**
		Ubhejane	

Key: Reg = regimen; mg = milligram

The nine participants that were on regimen 2, 3, and 4 were eliminated in an attempt to improve the homogeneity of the experimental group sample.

9.2. RESULTS IN RESPECT OF THE CONTROL GROUP AND EXPERIMENTAL GROUP

9.2.1. DESCRIPTION OF PARTICIPANTS

9.2.1.1. Control group participants

The control group comprised 46 participants which included 18 (39%) males and 28 (61%) females between the ages of 23 and 46 years with a mean age of 33 years (Table 15). All of the participants had been diagnosed with HIV/AIDS and were all at the AIDS stage of the disease. The average CD4+ count at baseline was 159 cells/mm^3.

Table 15: Demographic and attendance profile of participants in the control group (N = 46)

FACTOR	SUB-CATEGORY	NO.
Age (Years)	Range Mean	23-46yrs 33yrs
Gender	Male Female	18 (39%) 28 (61%)
Ethnic Group	Black White Coloured Indian	43 (93%) 0 3 (7%) 0
Attendance	Session 1 Session 2 Session 3 All 3 sessions	46 (100%) 40 (87%) 18 (39%) 16 (35%)

Although 46 participants enrolled to participate in the current study, by the end of the study only 16 participants comprised the control group, due to attrition factors stated earlier. The attrition rate was noted to be higher in the control group than in the experimental group (35% of the total number of participants that had enrolled in the control group was included in the analysis at the end of the study) (Table 15, Figure 8).

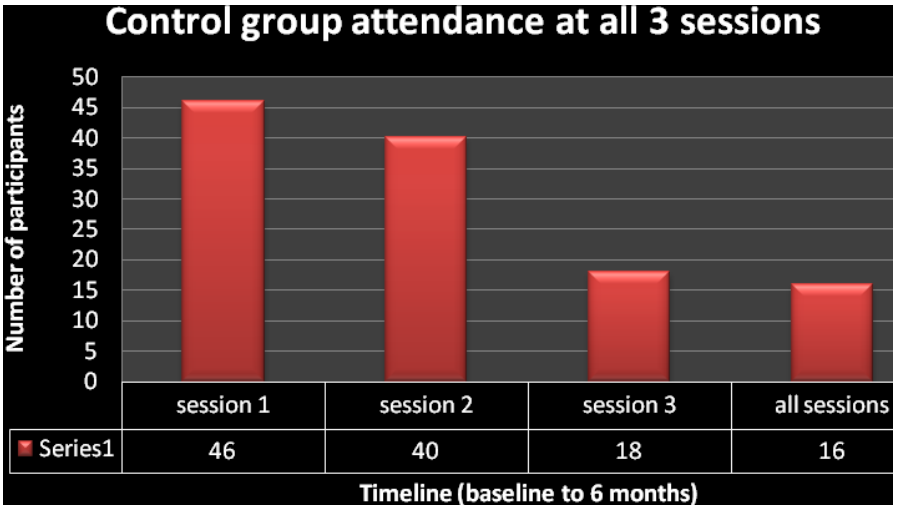


Figure 8: Number of the control group participants who attended each session and those that attended all 3 sessions of testing

9.2.1.2. Experimental group participants

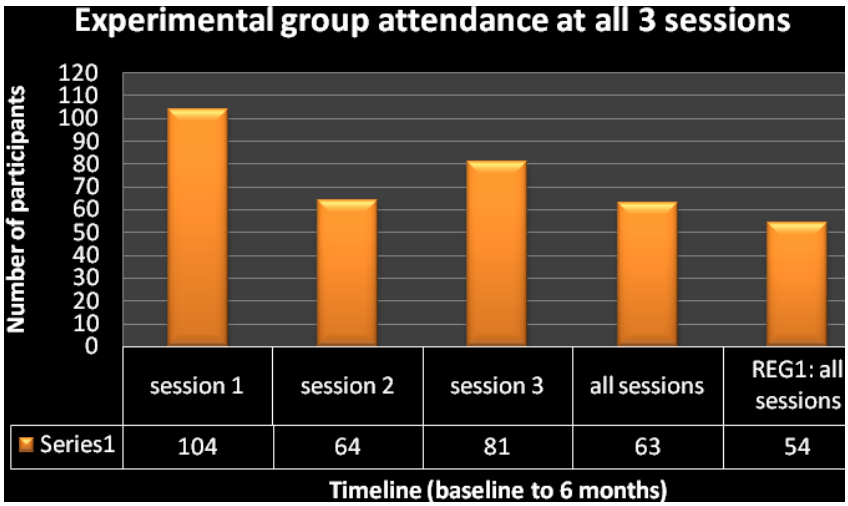
The study comprised 104 participants in the experimental group. The experimental group sample comprised 35 (34%) males and 69 (66%) females between the ages of 20 and 46 years with a mean age of 34.3 years (Table 16). All of the participants had been diagnosed with HIV/AIDS and were all at the AIDS stage of the disease. The average CD4+ count at baseline was 108 cells/mm^3.

Table 16: Demographic and attendance profile of participants in the experimental group (N = 104)

FACTOR	SUB-CATEGORY	NO.
Age (Years)	Range Mean	20-46yrs 34.3yrs
Gender	Male Female	35 (34%) 69(66%)
Ethnic Group	Black White Coloured Indian	98 (94%) 0 6 (6%) 0
Attendance	Session 1 Session 2 Session 3 All 3 sessions All 3 sessions on regimen 1	104 (100%) 64 (62%) 81 (78%) 63 (61%) 54 (52%)

As noted earlier, although 104 participants enrolled to participate in the current study, only 54 participants comprised the experimental group that was analysed for ototoxicity monitoring. The attrition rate was seen to be significantly higher in the control group than in the experimental group (only 35% of the participants comprised the analysis at the end of the study in the control group, as opposed to 52% of the participants in the experimental group) (Table 16 and Figure 9). This finding indicates that 65% of participants in the control group were lost while 48% of participants in the experimental group discontinued participation in the study. It is

acknowledged that the unequal number of participants in the control group and the experimental group was a threat to generalization of the results, and makes comparison of the results of the two groups difficult.



Key: Reg1 = participants on regimen 1 who attended all 3 sessions

Figure 9: Number of the experimental group participants who attended each session and those that attended all 3 sessions of testing

9.2.2. THE PREVALENCE RATE OF HEARING LOSS

The first objective was to estimate the prevalence of hearing loss and the presence of other otologic effects over and above hearing impairment (tinnitus, aural fullness, disequilibrium, and so forth)

9.2.2.1. Prevalence of hearing loss in the Control Group

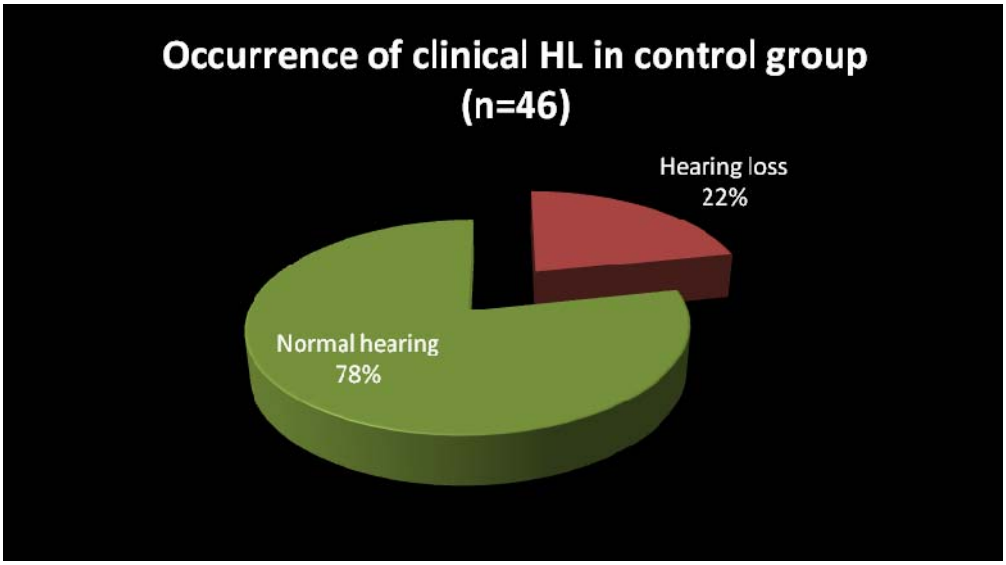


Figure 10: The occurrence rate of hearing loss in the control group (N = 46)

Of the total sample of 46 participants that were tested in the control group, 36 (78%) had normal hearing, and 10 presented with a clinical hearing loss (Figure 10) at different sessions of testing. This finding indicates that of the total sample, 22% of participants had clinical hearing loss with tinnitus and vertigo in varying degrees and combinations.

Of the 10 participants with clinical hearing loss, 80% presented with tinnitus, while only 10% presented with dizziness as associated signs of hearing impairment (Figure 11).

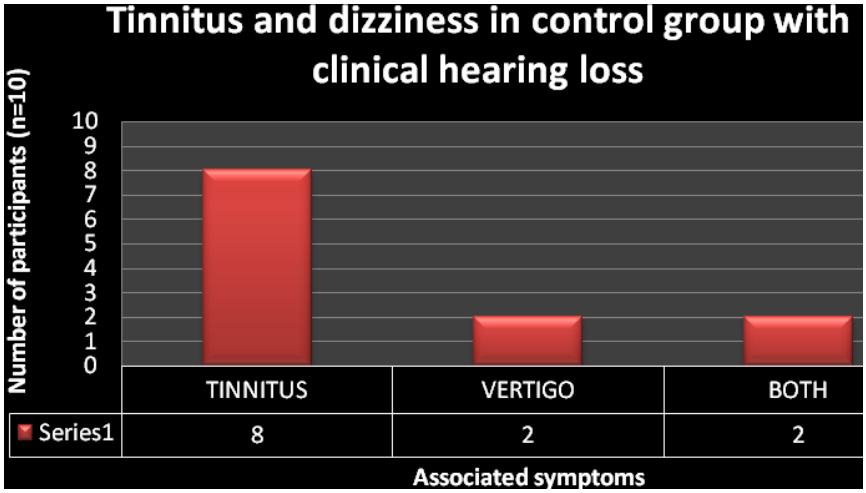


Figure 11: The occurrence of tinnitus and dizziness in the control group with clinical hearing loss at baseline (n=10)

9.2.2.2. Prevalence of hearing loss in the Experimental group

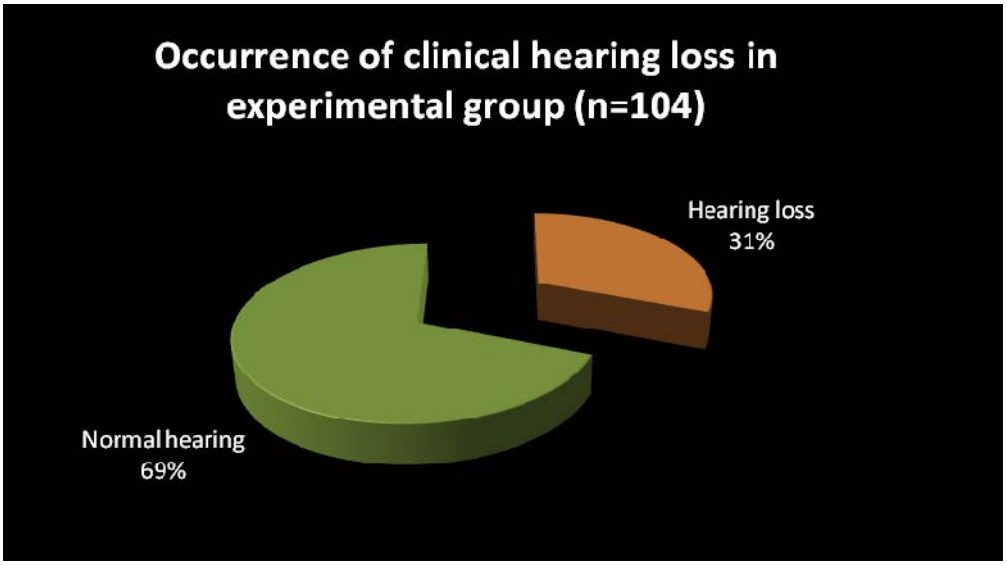


Figure 12: The occurrence rate of clinical hearing loss in the experimental group (N = 104)

Of the total sample of 104 participants evaluated for the experimental group, 72 (69%) had normal hearing, and 32 presented with a clinical hearing loss (Figure 12). This finding

indicates that of the total sample, 31% of participants had clinical hearing loss with tinnitus and vertigo in varying degrees and combinations at the 3 different testing sessions.

Of the 32 participants with clinical hearing loss, 44% presented with tinnitus, and 19% presented with dizziness as associated signs of hearing impairment (Figure 13).

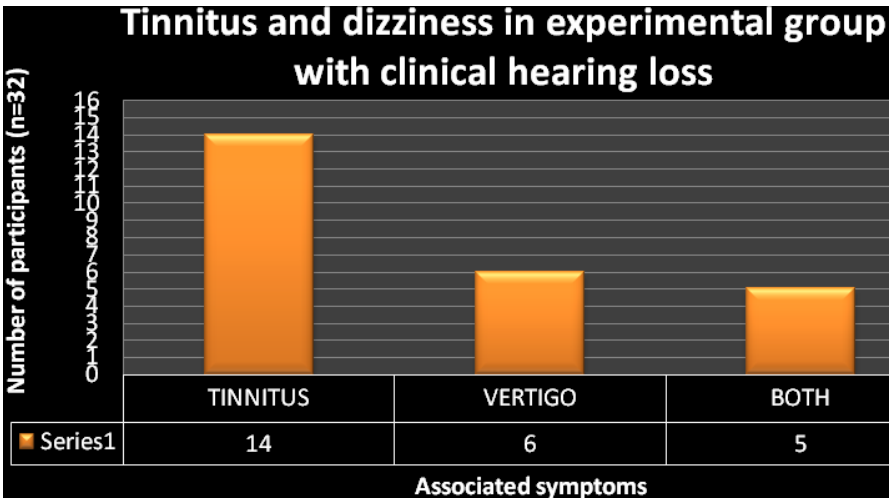


Figure 13: The occurrence of tinnitus and dizziness in the experimental group with clinical hearing loss at baseline (n=32)

9.2.3. ASSESSMENT OF THE TYPE, DEGREE, CONFIGURATION, AND SYMMETRY OF THE HEARING LOSS

The second objective was to assess the type, degree, configuration, and symmetry of the hearing loss.

9.2.3.1. Types of hearing loss

a) Types of hearing loss in the Control group

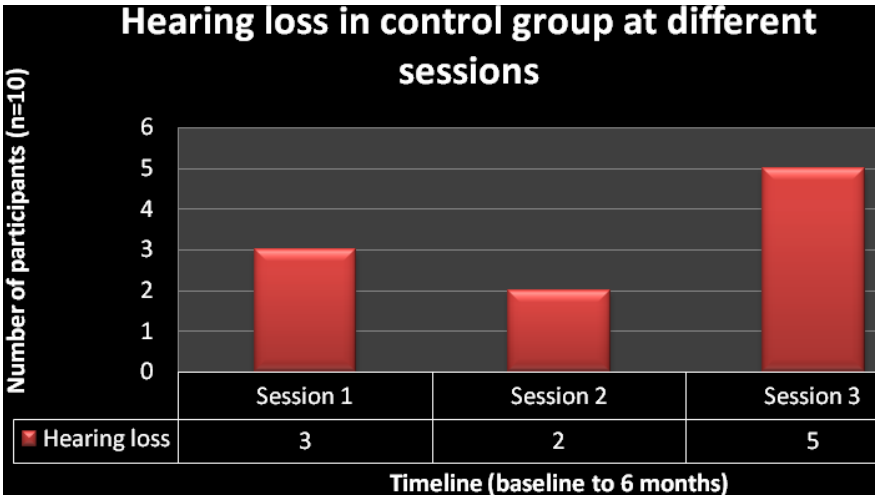
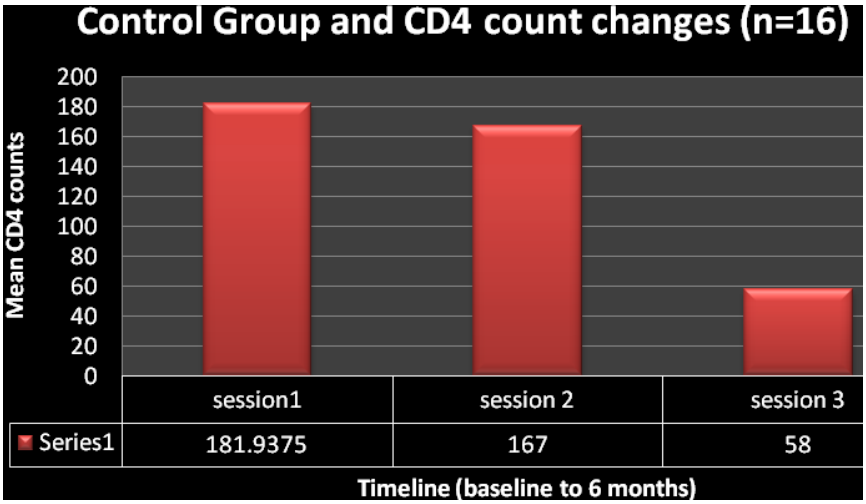


Figure 14: Number of participants in the control group who presented with clinical hearing loss at the 3 different sessions (n=10)

Figure 14 depicts the time of identification of the clinical hearing loss in all participants with hearing loss in the control group. Of the 10 participants with clinical hearing loss, 3 were excluded from participation in the study at session two as they presented with hearing loss at baseline. The majority (50%) of the participants in the group with clinical hearing loss presented

with hearing loss at session 3. However, this was expected as hearing loss has been associated with declining immune status in HIV/AIDS (Khoza & Ross, 2002) – and the declining immune function was evident in the control group's monitoring of CD4+ count (Figure 15). The mean CD4+ count of the control group declined significantly from 182 cells/mm^3 to 58 cells/mm^3 – representing a decrease of approximately 70% in immunologic function as measured by CD4+ count in 6 months without ART.

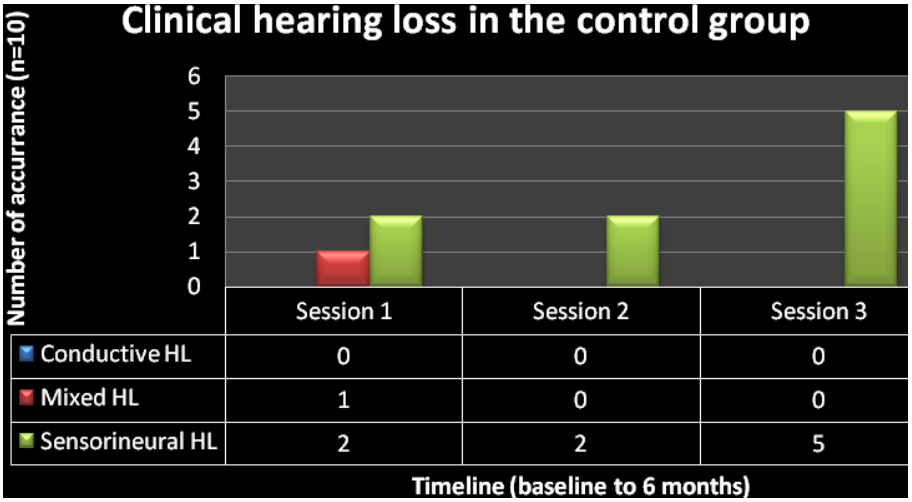


SD	**34.47602**	**48.08326**	**46.4227**

Key: SD = standard deviation

Figure 15: CD4+ count changes and the standard deviations in the control group at the 3 different sessions (n=16)

The results demonstrating clinical hearing loss were analysed to determine the types of hearing loss that the sample presented with (Figure 16). Of the 10 participants with clinical hearing loss, 1 (10%) had mixed hearing loss (MHL) and 9 (90%) had SNHL (Figure 16). No participants presented with a purely conductive hearing loss.



Key: HL = hearing loss

Figure 16: Types of hearing loss in control group with clinical hearing loss at the 3 different sessions (n =10)

b) Types of hearing loss in the Experimental group

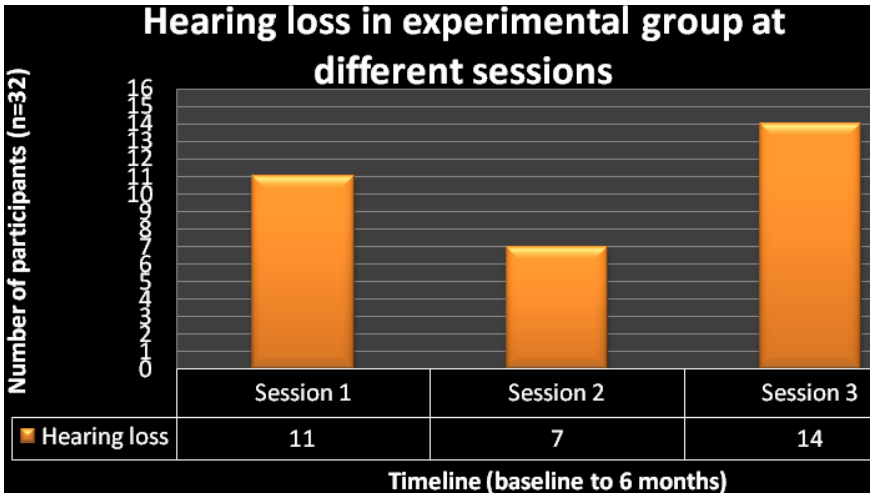
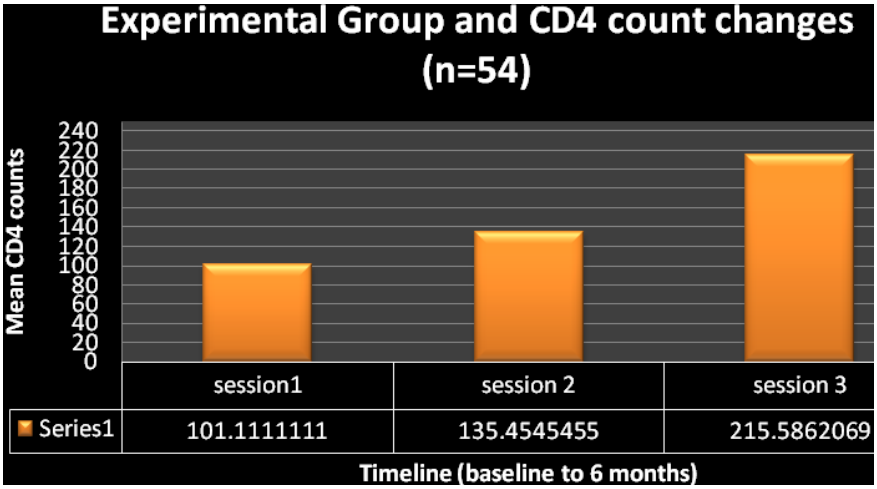


Figure 17: Number of participants in the experimental group who presented with clinical hearing loss at the 3 different sessions (n=32)

The time of identification of the clinical hearing loss in all participants with hearing loss in the experimental group is depicted in Figure 17. Of the 32 participants with clinical hearing loss 11 were excluded from participation in the study at session two as they presented with hearing loss at baseline (before initiation of ART). Furthermore, of the 32 participants with clinical hearing loss, 21 (66%) presented with hearing loss after initiation of ARV use, of which a substantial proportion (44%) of them presented with hearing loss at session three. This was, however unexpected and surprising as hearing loss has been associated with declining immune status in HIV/AIDS (Khoza & Ross, 2002). Although the declining immune status was seen in the control group, the same was not evidenced in the experimental group since the monitoring of CD4+ counts indicated improving rather than deteriorating immune status (Figure 18). Striking improvement in CD4+ counts were found in the experimental group from baseline to 6 months. The mean CD4+ count of the experimental group significantly improved from 101 cells/mm^3 to 216 cells/mm^3 – doubling to approximately 50% increase in immunologic function as measured by CD4+ count in six months of taking ART (taking the standard deviation into consideration).

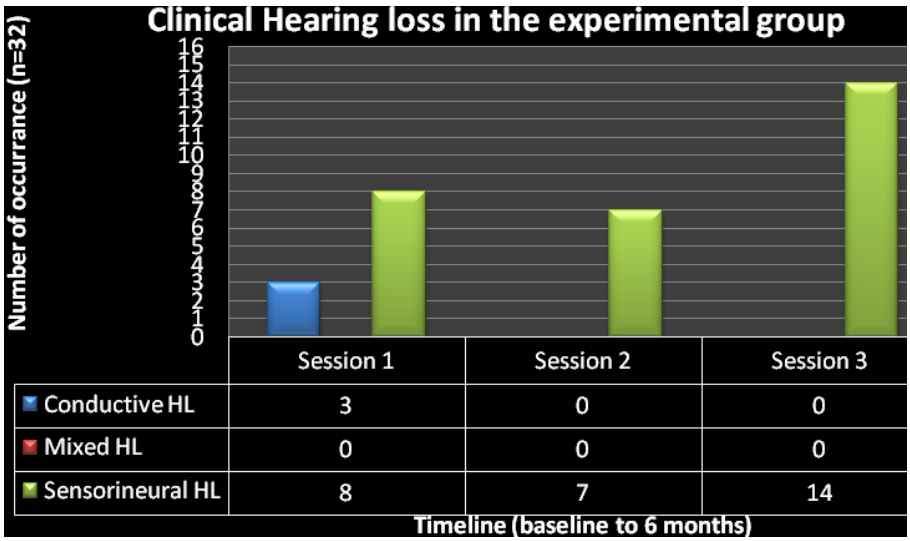


SD	**61.68804**	**71.80395**	**120.1725**

Key: SD = standard deviation

Figure 18: CD4+ count changes and the standard deviations in the experimental group at the 3 different sessions (n=54)

The results demonstrating abnormal hearing in the experimental group were analysed to determine the types of hearing loss that the sample presented with (Figure 19). Of the 32 participants with abnormal hearing function, no participants presented with mixed hearing loss (MHL), 3 (9%) had conductive hearing loss (CHL) at session 1; and the rest 29 (91%) had sensorineural hearing loss (SNHL) (8 at session 1 before ART, and 21 after commencement of ART) (Figure 19). Of the 21 participants with SNHL post ART, the majority (14) presented with clinical hearing loss at session 3 (at 6 months after initiation of ART).



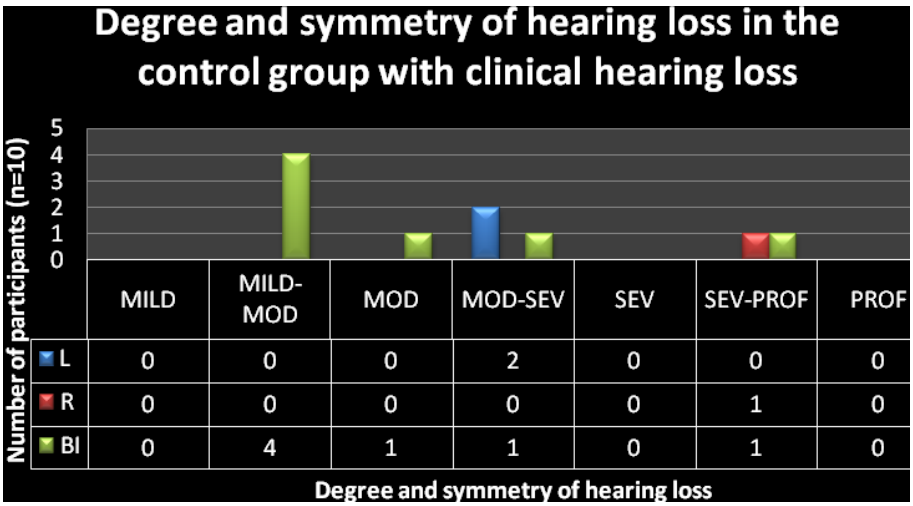
Key: HL = hearing loss

Figure 19: Types of hearing loss in the experimental group with clinical hearing loss at the 3 different sessions (n=32)

9.2.3.2. Degree of hearing loss

a) Degree of hearing loss in the Control group

Following the classification of Magnitude of Hearing Impairment described earlier, it became evident that the hearing loss could occur in any degree of severity as depicted in Figure 20. However, the most prevalent degree of severity of hearing loss was the mild to moderate hearing loss followed by the moderate to severe degree of hearing impairment. Of the 10 participants with clinical hearing loss, 4 (40%) presented with mild to moderate hearing loss while 3 (30%) presented with moderate to severe hearing loss.

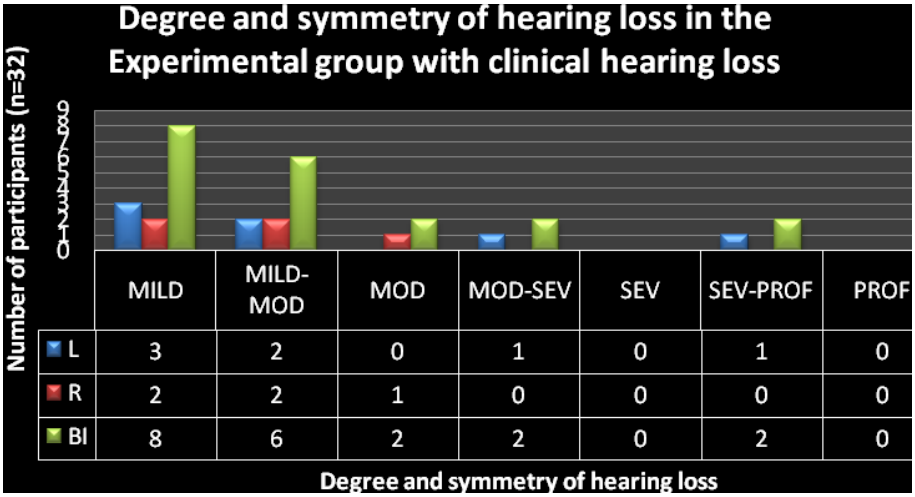


Key: Mod = Moderate; Sev = Severe; Prof = Profound; L = left; R = right; Bi = bilateral

Figure 20: Degree and symmetry of clinical hearing loss in control group with clinical hearing loss (n =10)

b) Degree of hearing loss in the Experimental group

Results of the experimental group also revealed that the hearing loss could occur in any degree of severity as depicted in Figure 21. However, the most prevalent degree of severity of hearing loss was mild hearing loss followed closely by mild-moderate degree of hearing impairment. Of the 32 participants with hearing loss, 13 (41%) presented with mild hearing loss while 10 (32%) presented with mild-moderate hearing loss. The occurrence of severe to profound degree of hearing impairment was not high, with only 3 (9%) participants presenting with this degree of hearing impairment. Furthermore, the degree of the hearing loss tended to be mild in the experimental group when compared to the control group.



Key: Mod = Moderate; Sev = Severe; Prof = Profound; L = left; R = right; Bi = bilateral

Figure 21: Degree and symmetry of clinical hearing loss in the experimental group with clinical hearing loss (n = 32)

9.2.3.3. Configuration of hearing loss

a) Configuration of hearing loss in the Control group

No typical pattern of configuration of hearing loss could be established in the control group. In the sample of patients with clinical hearing loss, only 2 (20%) participants presented with a sloping/high frequency hearing loss. The remaining 80% presented with flat and/or irregular audiograms with an equal chance of involvement of all frequencies (Table 17).

b) Configuration of hearing loss in the Experimental group

Unlike in the control group where no typical pattern of configuration of hearing loss could be established, in the experimental group a large number 15 (47%) of participants presented with a sloping/high frequency hearing loss (Table 19). The remaining 53% presented with flat and/or irregular audiograms with an equal chance of involvement of all frequencies.

9.2.3.4. Symmetry of hearing los

a) Symmetry of hearing loss in the Control group

Of the total control sample of 10 participants with clinical hearing loss, 3 (30%) had unilateral hearing impairment while 7 (70%) presented with bilateral hearing loss (Figure 20 and Table 15).

b) Symmetry of hearing loss in the Experimental group

Of the total experimental sample of 32 participants with clinical hearing loss, 12 (38%) had unilateral hearing impairment while 20 (62%) presented with bilateral hearing loss (Figure 21 & Table 17).

9.2.4. TYPE OF ONSET OF HEARING SYMPTOMS

The third objective was to explore the type of hearing symptom onset (e.g. sudden or gradual/progressive onset).

9.2.4.1. Type of onset in the Control group

Of the total sample with clinical hearing loss, all presented with gradual/progressive hearing loss. No participants reported sudden onset of auditory symptoms.

9.2.4.2. Type of onset in the Experimental group

Consistent with the findings in the control group regarding the type of onset of hearing loss, of the total sample with clinical hearing loss, all participants presented with gradual/progressive hearing loss.

9.2.5. CASE HISTORY INFORMATION

The fourth objective was to document case history data such as signs and symptoms of each participating participant and to identify any associations between obtained signs and symptoms and hearing loss

9.2.5.1. Case history data for the Control group

Table 17: Case history and medical information for participants in the control group with clinical hearing loss (n=10)

Participant	Age (yrs)	Type of Hearing Loss	Medical History	Ear History
Participant 2	29	Bilateral moderate-severe SNHL	Unknown	Hearing loss
Participant 6	32	L-moderate-severe SNHL	Meningitis	Hearing loss
Participant 11	37	R-severe-profound SNHL	Syphilis	Hearing loss
Participant 12	26	Bilateral mild-moderate SNHL	Otosyphilis	None
Participant 27	46	Bilateral mild-moderate SNHL	Syphilis	History of otalgia
Participant 40	37	Bilateral moderate-severe SNHL	Unknown	Hearing loss
Participant 43	30	Bilateral moderate SNHL dip at 2000Hz	Unknown	None
Participant 44	30	Bilateral severe-profound MHL		Otitis media
Participant 45	41	L-moderate severe sloping SNHL	Unknown	Hearing loss
Participant 46	43	Bilateral mild moderate sloping SNHL	TB treatment and syphilis treatment	None

Key: Participants with sloping/ high frequency SNHL; L = left; R = right

Table 18: Summary of results for participants in the control group with clinical hearing loss (n=10)

FACTOR	SUB-CATEGORY	NO.	PERCENTAGE
Hearing Function	Hearing loss	10	22
Type of Hearing Loss	Conductive Hearing Loss	0	0
	Sensorineural Hearing Loss	9	90
	Mixed Hearing Loss	1	10
Type of onset of Hearing Loss	Sudden	0	0
	Gradual	10	100
Symmetry of Hearing Loss	Unilateral	3	30
	Bilateral	7	70
Possible aetiology of Hearing Loss *(n=10)	Meningitis	1	10
	Oto/syphilis	4	40
	Otitis Media	1	10
	TB Treatment	1	10
	Unknown	4	40
Degree of Hearing Loss (n=10)	Mild	0	0
	Mild-moderate	4	40
	Moderate	1	10
	Moderate-severe	3	30
	Severe	0	0
	Severe-profound	2	20
	Profound	0	0
Tinnitus	Present	8	80
	Absent	2	20
Vertigo	Present	2	20
	Absent	8	80
Tinnitus & Vertigo	Present	2	20

***% Scores do not add up to 100% as some participants presented with more than one possible aetiological factor.**

Detailed analysis of the audiologic evaluation results together with the documented case history information where medical diagnoses had been confirmed by Ear, Nose and Throat Specialists (Tables 17 and 18) revealed consistency of findings with the results of the total sample at baseline with respect to the possible causal factors of the hearing loss in this group with clinical hearing loss. Major causes were oto/syphilis (40%) and unknown causes (40%), with meningitis, otitis media and TB treatment being the other possible causes found.

9.2.5.2. Case history data for the Experimental group

Table 19: Case history and medical information for participants in the experimental group with clinical hearing loss (n=32)

Participant	Age (yrs)	Type of Hearing Loss	Medical History	Ear History
Participant 15	22	Bilateral mild-moderate SNHL	Previous meningitis & syphilis once on ARVs	None
Participant 23	46	Bilateral mild-moderately severe sloping SNHL	Previous TB treatment & history of syphilis	None
Participant 32*	44	Bilateral mild SNHL @ 8kHz	Previous ARV use in 1998	None
Participant 33	38	Bilateral mild SNHL @ 8kHz	None (?current ARV use)	None
Participant 36	40	Bilateral mild SNHL @ 8kHz	None (?current ARV use)	None
Participant 40	39	Bilateral mild SNHL @ 8kHz	None (?current ARV use)	None
Participant 42	46	Bilateral moderate severe SNHL	Syphilis history Previous TB treatment	Hearing loss
Participant 43	30	Bilateral moderate SNHL @ 2kHz	Unknown	None
Participant 44	30	Bilateral severe-profound CHL	Otitis media	Otitis media
Participant 45	41	L mild moderately severe sloping SNHL	Otosyphilis	History of otalgia
Participant 46	43	Bilateral mild-moderate SNHL	Previous TB treatment	None
Participant 51	34	L mild SNHL	None (?current ARV use)	None
Participant 53	24	R mild moderate CHL	Lupus & previous TB treatment	Otitis media
Participant 54*	32	Bilateral mild SNHL	None (?current ARV use)	None
Participant 57*	40	L- mild sloping SNHL in high frequencies	None (?current ARV use)	None
Participant 60	46	bilateral mild sloping SNHL in high frequencies	Diabetes	None
Participant 61	46	R mild moderate SNHL	Previous TB treatment	None
Participant 62	46	Bilateral mild-moderate SNHL at high frequencies	Noise exposure after ARV initiation & previous TB treatment	None
Participant 63	44	L rising SNHL	Vascular disease, diabetic &hypertensive	None
Participant 71*	32	L mild SNHL @ 8kHz	None (?current ARV use)	None
Participant 72	35	R mild-moderate SNHL @ 8kHz	None (?current ARV use)	None
Participant 74	27	R moderate-severe SNHL @ 8kHz	Previous TB treatment & previous ARV use	None
Participant 76	26	Bilateral mild SNHL @ 8kHz	Previous TB treatment	None
Participant 80	39	Bilateral mild-moderate CHL	Otitis media	Chronic suppurative otitis media

Participant 83	33	Bilateral mild-moderately severe SNHL	Syphilis	None
Participant 85	44	R mild SNHL @ 8kHz	Previous TB treatment	None
Participant 88	46	Bilateral moderate-severe SNHL	None (?current ARV use)	None
Participant 89	41	Bilateral mild-moderately severe SNHL	Previous TB treatment & previous noise exposure	None
Participant 97	29	Bilateral mild-moderately severe SNHL	None (?current ARV use)	None
Participant 101	32	L moderate-severe SNHL	None (?current ARV use)	None
Participant 102	20	L severe-profound SNHL	None (?current ARV use)	None
Participant 104	39	Bilateral mild-moderate SNHL	None (?current ARV use)	None

Key: Participants with sloping/ high frequency SNHL; * = participants not on regimen 1 excluded from inferential statistics

Table 20: Summary of results for participants in the experimental group with clinical hearing loss (n=32)

FACTOR	SUB-CATEGORY	NO.	PERCENTAGE
Hearing Function	Hearing loss	32	31
Type of Hearing Loss	Conductive Hearing Loss	3	9
	Sensorineural Hearing Loss	29	91
	Mixed Hearing Loss	0	0
Type of onset of Hearing Loss	Sudden	0	0
	Gradual	32	100
Symmetry of Hearing Loss	Unilateral	12	38
	Bilateral	20	62
Possible aetiology of Hearing Loss *	Meningitis	1	3
	Oto/syphilis	5	16
	Otitis Media	3	9
	Previous ARV use	2	6
	Possible interaction with previous TB Treatment	10	31
	Unknown	1	3
	Other (noise exposure, diabetes)	4	13
	Current ARV use	13	41
Degree of Hearing Loss (n=32)	Mild	13	41
	Mild-moderate	10	32
	Moderate	3	9
	Moderate-severe	3	9
	Severe	0	0
	Severe-profound	3	9
	Profound	0	0
Tinnitus	Present	14	44
	Absent	18	56
Vertigo	Present	6	19
	Absent	26	81
Tinnitus & Vertigo	Present	5	16

***% Scores do not add up to 100% as some participants presented with more than one possible aetiological factor.**

Tables 19 and 20 revealed findings that were different to those of the control group with regard to the possible causal factors of the hearing loss in this group with clinical hearing loss. The major possible causes (Table 20) were current ARV use (41%), possible synergistic relationship of ARVs with previous TB treatment (31%) and oto/syphilis (16%), with meningitis, otitis media and other factors (diabetes, noise exposure after ART) being the additional possible aetiological factors.

9.3. RESULTS OF OTOTOXICITY MONITORING THROUGH REPEATED MEASURES ANALYSIS

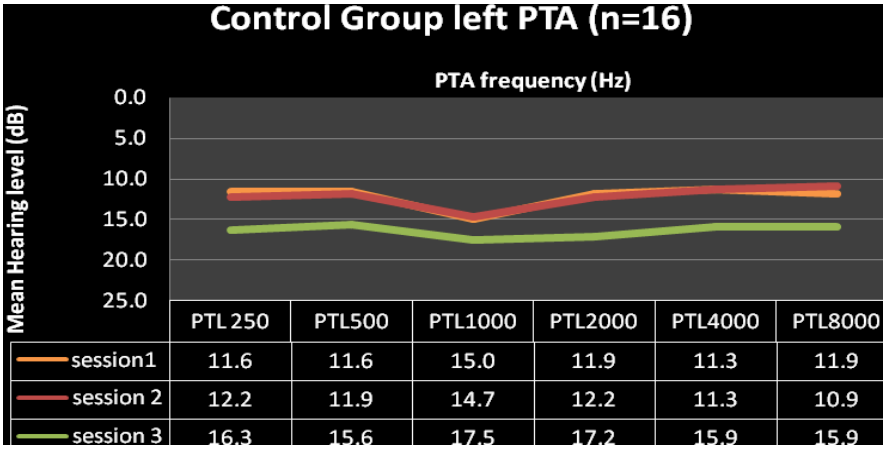
The fifth objective of the study was to document all medications used to establish their possible impact on hearing function, specifically ototoxicity monitoring.

In this section, the individual results (depicting 'within group' effects) of the control group and those of the experimental group, are discussed separately. All participants in both groups had normal middle ear functioning, based on otoscopic and tympanometric results, for them to be able to be evaluated through the use of DPOAEs. Furthermore, participants in both groups were excluded if they showed evidence of newly acquired noise exposure, TB, radiotherapy, syphilis and/or middle ear pathology after the baseline testing.

9.3.1. Ototoxicity monitoring in the Control group

Analysis of the results for the control group (n=16) involved comparing the results of all measures at all 3 assessment sessions in order to determine if any changes occurred during the period when the experimental group was receiving ARVs (in the form of 3TC and D4T with Stocrin).

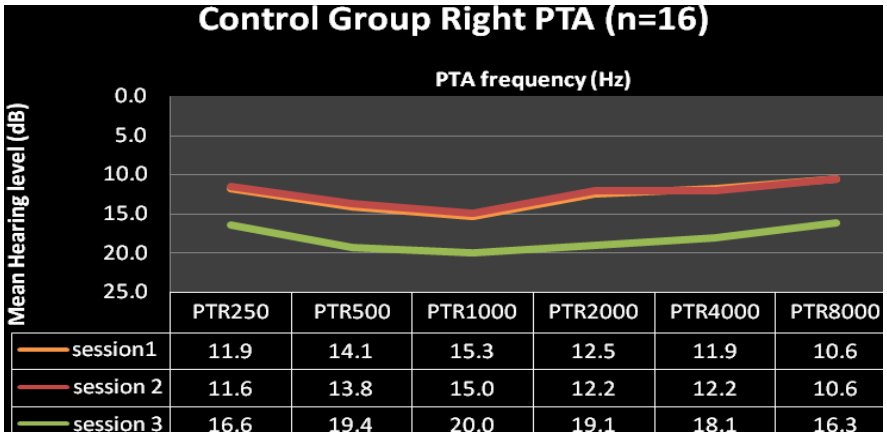
The pure tone audiometry results, in the form of means and standard deviations, are depicted in Figures 22, 23, and 24.



SD	PTL250	PTL500	PTL1000	PTL2000	PTL4000	PTL8000
Session1	5.7	4.4	3.7	5.1	4.3	4.8
Session2	5.5	4.0	3.9	4.8	4.3	4.2
Session3	10.2	13.0	9.7	13.4	12.1	11.0

Key: PTL = pure tone left ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

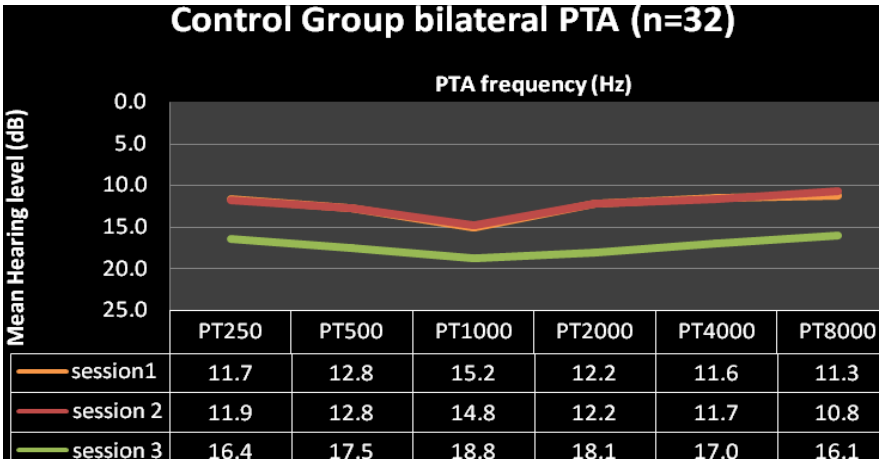
Figure 22: Mean Left pure tone audiometry results (in dBHL) and their standard deviations for the control group at the 3 different sessions (n=16)



SD	PTR250	PTR500	PTR1000	PTR2000	PTR4000	PTR8000
Session1	5.7	4.6	4.6	4.8	4.4	4.4
Session2	4.4	5.0	4.8	4.8	4.1	4.0
Session3	13.5	15.9	15.4	15.8	15.8	15.3

Key: PTR = pure tone right ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 23: Mean Right pure tone audiometry results (in dBHL) and their standard deviations for the control group at the 3 different sessions (n=16)



SD	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Session1	5.0	4.6	4.1	4.9	4.2	4.6
Session2	4.9	4.6	4.3	4.7	4.1	4.0
Session3	11.8	14.4	12.7	14.4	13.9	13.1

Key: PT = pure tone; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 24: Mean bilateral pure tone audiometry results (in dBHL) and their standard deviations for the control group at the 3 different sessions (n=32 ears)

Close inspection of the results either unilaterally (Figures 22 and 23) or bilaterally (Figure 24) for pure tone audiometry revealed hearing within normal limits with the average PTA being above the level regarded as indicative of normal hearing across all frequencies evaluated. These mean results were normal for all 3 sessions. However, when the standard deviation was taken into consideration, the results indicated normal hearing only for sessions 1 and 2 with slight hearing changes at session 3 at all frequencies tested.

Results of statistical analysis of pure tone audiometry through the use of MANOVA [within group (time)] are depicted in Table 21. All results for the 'within group' analysis demonstrated no statistically significant changes ($p > .05$) across all frequencies tested. These

results did not support the rejection of the null hypothesis for all frequencies tested in pure tone audiometry (i.e. hearing status did not change before and after ARV initiation).

Table 21: Results of MANOVA for pure tone audiometry results for the control group indicating levels of significance for 'within group' analysis

Frequency	P	F	α	Frequency	P	F	α
PTL250	**0.532590**	**0.22**	**>0.05**	PTR250	**0.571763**	**0.91**	**>0.05**
PTL500	**0.513221**	**0.74**	**>0.05**	PTR500	**0.889191**	**0.39**	**>0.05**
PTL1000	**0.971620**	**0.23**	**>0.05**	PTR1000	**0.987251**	**0.36**	**>0.05**
PTL2000	**0.737270**	**0.53**	**>0.05**	PTR2000	**0.689390**	**0.11**	**>0.05**
PTL4000	**0.422379**	**0.55**	**>0.05**	PTR4000	**0.955172**	**0.24**	**>0.05**
PTL8000	**0.560012**	**0.61**	**>0.05**	PTR8000	**0.155160**	**1.29**	**>0.05**

Key: PTL = pure tone left; PTR = pure tone right; P = P value; F = F ratio; Statistical significance = alpha (α) less than 0.05; *df* = 2(time); *df* = 15(participants)

In the control group, analysis of the aforementioned pure tone audiometry changes for clinical significance demonstrated that none of the changes found were audiologically clinically significant (Table 22). None of the changes were equal to 10dB HL and more (Ludman & Wright, 1998)

Table 22: Mean changes in bilateral pure tone audiometry indicating clinically significant changes over session 1 and 3 for the control group (n=32 ears)

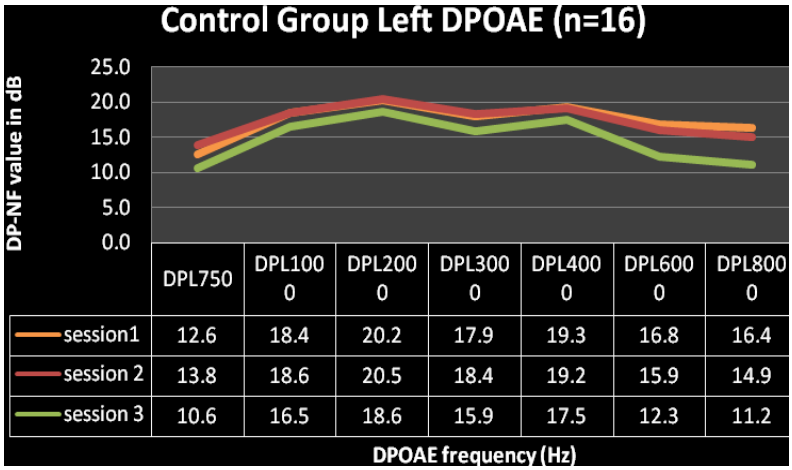
Frequency	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Mean change	4.7	4.7	3.6	5.9	5.5	4.8

Key: PT = pure tone in dBHL; Clinical significance = 10dB HL or more

All the aforementioned results imply that, from a statistical perspective, the null hypothesis which was that the participants' hearing status before and after antiretroviral drug-use

would remain the same was accepted in all the frequencies evaluated; even from the clinical significance perspective.

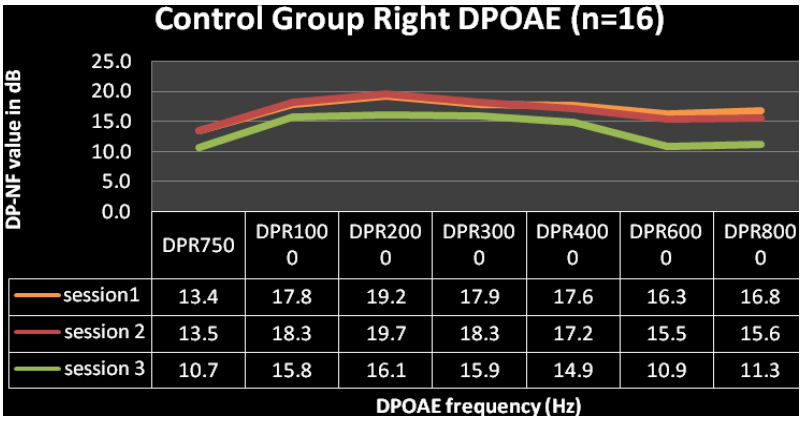
A similar analysis was conducted on the DPOAE results. These results, in the form of means and standard deviations, are depicted in Figures 25, 26, and 27.



SD	DPL750	DPL1000	DPL2000	DPL3000	DPL4000	DPL6000	DPL8000
Session1	4.5	5.9	6.9	5.8	5.4	7.6	5.3
Session2	4.8	6.4	7.3	6.1	5.7	7.3	6.1
Session3	8.0	7.8	8.4	7.3	7.2	9.3	7.9

Key: DPL = distortion product left ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

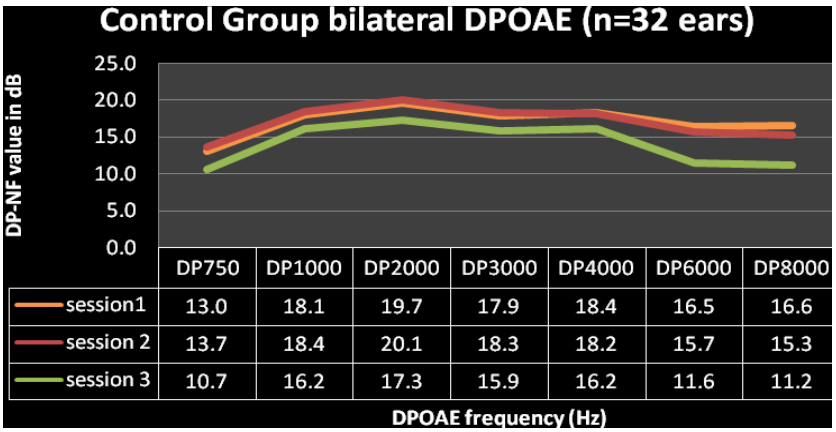
Figure 25: Mean Left distortion product otoacoustic emission results (in dBSPL) and their standard deviations for the control group at the 3 different sessions (n=16)



SD	DPR750	DPR1000	DPR2000	DPR3000	DPR4000	DPR6000	DPR8000
Session1	5.2	7.4	7.0	6.7	4.9	6.1	5.6
Session2	4.8	7.7	6.4	6.5	5.5	6.7	6.9
Session3	7.2	9.9	9.5	8.8	8.1	8.6	7.8

Key: DPR = distortion product right ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 26: Mean Right distortion product otoacoustic emission results (in dBSPL) and their standard deviations for the control group at the 3 different sessions (n=16)



SD	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Session1	4.8	6.6	6.9	6.2	5.2	6.8	5.4
Session2	4.7	6.9	6.8	6.2	5.6	6.9	6.4
Session3	7.5	8.8	8.9	7.9	7.6	8.8	7.7

Key: DP = distortion product; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 27: Mean bilateral distortion product otoacoustic emission results (in dBSPL) and their standard deviations for the control group at the 3 different sessions (n=32 ears)

Similarly, close inspection of the results either unilaterally (Figures 25 and 26) or bilaterally (Figure 27) for distortion product otoacoustic emissions revealed cochlear functioning to be within normal limits with average DPOAE emission size being above the level regarded as indicative of normally functioning cochlea across all frequencies evaluated (the DP amplitude exceeded the noise floor by at least 7dB across all frequencies measured) (Hall, 2000). These results were normal for all 3 sessions; however, when the standard deviation was taken into consideration; these results were below the norm for 500Hz, 6000Hz, and 8000Hz for bilateral DPOAE results.

Results of statistical analysis of DPOAE results through the use of MANOVA [within group (time)] are depicted in Table 23. These results were not statistically significant ($p > .05$) for all frequencies assessed for the 'within group' analysis, providing support for the acceptance of the null hypothesis (cochlea function remains the same before and after ARV initiation).

Table 23: Results of MANOVA for DPOAE results for the control group indicating levels of significance for 'within group' analysis

Frequency	P	F	α	Frequency	P	F	α
DPL750	**0.503001**	**1.21**	**>0.05**	DPR750	**0.300010**	**1.77**	**>0.05**
DPL1000	**0.188000**	**1.48**	**>0.05**	DPR1000	**0.610003**	**1.37**	**>0.05**
DPL2000	**0.800023**	**0.69**	**>0.05**	DPR2000	**0.440002**	**1.44**	**>0.05**
DPL3000	**0.700231**	**1.64**	**>0.05**	DPR3000	**0.910001**	**2.11**	**>0.05**
DPL4000	**0.244002**	**1.65**	**>0.05**	DPR4000	**0.503004**	**0.75**	**>0.05**
DPL6000	**0.116502**	**1.34**	**>0.05**	DPR6000	**0.880001**	**1.44**	**>0.05**
DPL8000	**0.900321**	**2.64**	**>0.05**	DPR8000	**0.130020**	**1.56**	**>0.05**

Key: DPL = distortion product left ear; DPR = distortion product right ear; P = P value; F = F ratio
Statistical significance = alpha (α) less than 0.05; *df* = 2(time); ***df*** **=** 15(participants)

Analysis of the aforementioned DPOAE changes for clinical significance indicated that none of the changes found were audiologically clinically significant (Table 24).

Table 24: Mean changes in bilateral DPOAEs indicating clinically significant changes over session 1 and 3 for the control group (n=32 ears)

Frequency	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Mean change	2.4	1.9	2.3	1.9	2.2	4.9	5.4

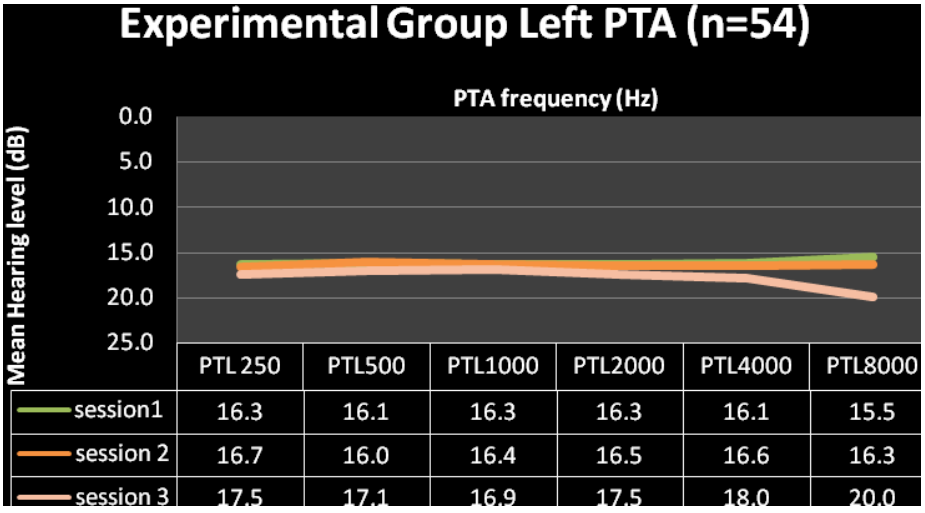
Key: DP = Distortion Product OAE in dBSPL; Clinical significance = 6 to 9dB change or more

Change is only regarded as significant in DPOAE measures if there is a change of at least 6 to 9dB in DPOAE level between consecutive measures (Roede et al., 1993; Dreisbach, Long & Lees, 2006). In the control group, none of the mean changes in DPOAE results were greater than 6dB – indicating that no clinical changes occurred in the cochlea function.

All the above results for DPOAEs imply that, from a statistical perspective, the null hypothesis which was that the participants' hearing status before and after antiretroviral drug-use would remain the same was accepted for the 'within group' analysis. Again, from the clinical significance perspective; the changes were not clinically significant.

9.3.2. Ototoxicity monitoring in the Experimental group

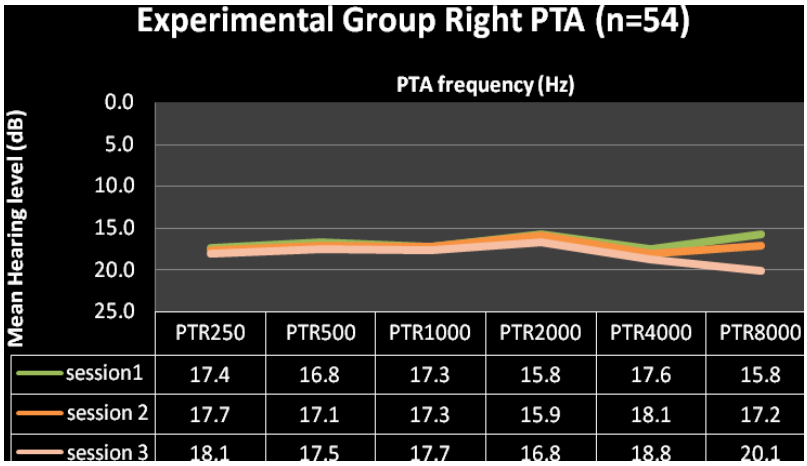
Analysis of the results for the experimental group (n=54) also involved comparing the results of all measures at all three assessment sessions in order to determine if any changes occurred during the period when they were receiving ARVs. The pure tone audiometry results, in the form of means and standard deviations, are depicted in Figures 28, 29, and 30.



SD	PTL250	PTL500	PTL1000	PTL2000	PTL4000	PTL8000
Session1	5.0	5.3	5.6	5.2	6.9	6.8
Session2	5.5	5.7	5.6	5.4	7.6	8.4
Session3	6.4	7.1	6.7	7.6	9.7	14.1

Key: PTL = pure tone left ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

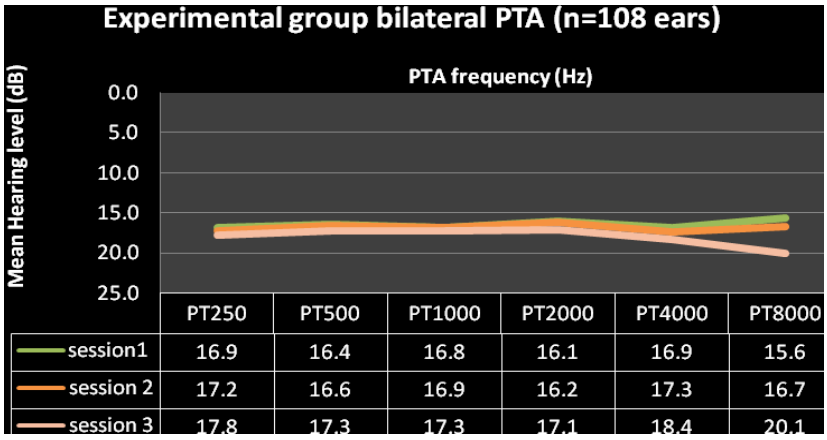
Figure 28: Mean Left Pure Tone audiometry results (in dBHL) and their standard deviations for the experimental group at the 3 different sessions (n=54)



SD	PTR250	PTR500	PTR1000	PTR2000	PTR4000	PTR8000
Session1	4.4	5.2	4.8	4.8	6.1	7.8
Session2	4.7	5.5	5.0	5.0	6.8	10.4
Session3	5.3	6.0	5.3	7.0	8.3	14.3

Key: PTR = pure tone right ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 29: Mean Right Pure Tone audiometry results (in dBHL) and their standard deviations for the experimental group at the 3 different sessions (n=54)



SD	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Session1	4.7	5.3	5.2	5.0	6.5	7.3
Session2	5.1	5.6	5.3	5.2	7.2	9.4
Session3	5.9	6.6	6.0	7.3	9.0	14.2

Key: PT = pure tone; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 30: Mean bilateral Pure Tone audiometry results (in dBHL) and their standard deviations for the experimental group at the 3 different sessions (n=108ears)

Close inspection of the results either unilaterally (Figures 28 and 29) or bilaterally (Figure 30) for pure tone audiometry revealed hearing within normal limits with average PTA being above the level regarded as indicative of normal hearing across all frequencies evaluated at session 1 (baseline) and session 2. This however changed when the standard deviations were taken into consideration at session 3 – hearing changes were observed for frequencies 4000 and 8000Hz.

Results of statistical analysis of pure tone audiometry through the use of MANOVA [within group (time)] are depicted in Table 25. All results for the 'within group' analysis demonstrated no statistically significant changes ($p > .05$) across all frequencies tested except for statistically significant changes at 8000Hz [Left ear ($p=0.04$)]. These results did not support the rejection of the null hypothesis for all frequencies tested in pure tone audiometry (hearing status did not change before and after ARV initiation, except at 8000Hz in the Left ear). The significant change occurred throughout the 3 sessions with means mean pure tone results increasing from session 1 to session 3.

Table 25: Results of MANOVA for pure tone audiometry results for the experimental group indicating levels of significance for 'within group' analysis

Frequency	P	F	α	Frequency	P	F	α
PTL250	**0.540015**	**0.62**	**>0.05**	PTR250	**0.751763**	**0.29**	**>0.05**
PTL500	**0.583521**	**0.54**	**>0.05**	PTR500	**0.789911**	**0.24**	**>0.05**
PTL1000	**0.791120**	**0.23**	**>0.05**	PTR1000	**0.897215**	**0.11**	**>0.05**
PTL2000	**0.587277**	**0.53**	**>0.05**	PTR2000	**0.698796**	**0.36**	**>0.05**
PTL4000	**0.472379**	**0.75**	**>0.05**	PTR4000	**0.677171**	**0.39**	**>0.05**
PTL8000	**0.042590**	**3.21**	**<0.05**	PTR8000	**0.151562**	**1.91**	**>0.05**

Key: PTL = pure tone left; PTR = pure tone right; P = P value; F = F ratio; Statistical significance = alpha (α) less than 0.05; *df* = 2(time); *df* = 159(participants)

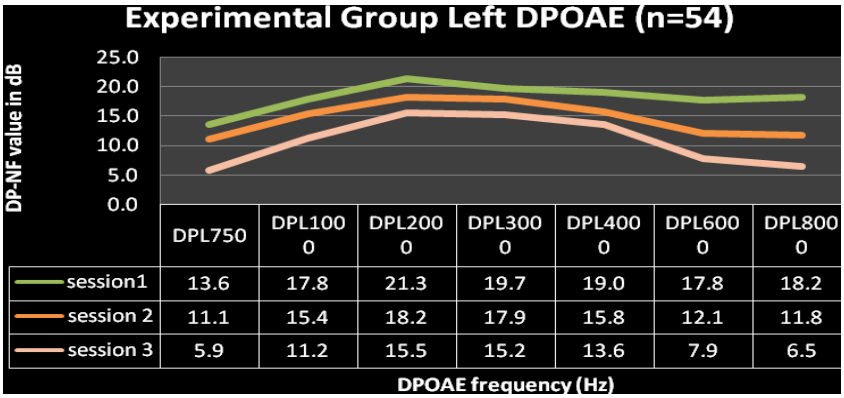
In the experimental group, analysis of the aforementioned pure tone audiometry changes for clinical significance showed that none of the changes found were audiologically clinically significant (Table 26). None of the changes were 10dB HL and more.

Table 26: Mean changes in bilateral pure tone audiometry indicating clinically significant changes over session 1 and 3 for the experimental group (n=108 ears)

Frequency	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Mean change	0.9	0.9	0.5	1.0	1.5	4.5

Key: PT = pure tone in dBHL; Clinical significance = 10dB or more

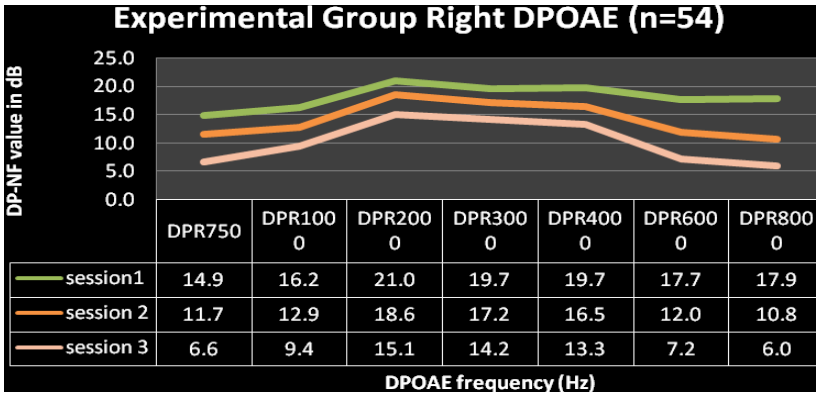
The same process was followed in the experimental group as in the control group where the pure tone results were not examined in isolation but rather compared to those of the DPOAE results. The DPOAE results, in the form of means and standard deviations, are depicted in Figures 31, 32, and 33.



SD	DPL750	DPL1000	DPL2000	DPL3000	DPL4000	DPL6000	DPL8000
Session1	6.3	6.3	7.1	6.5	5.7	5.0	4.4
Session2	5.4	6.2	6.8	6.5	5.5	5.5	5.3
Session3	9.0	8.2	7.9	6.5	7.2	7.4	7.0

Key: DPL = distortion product left ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

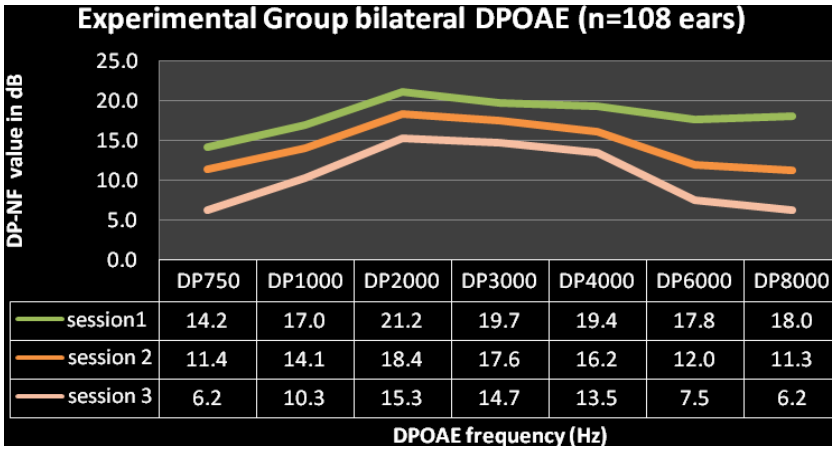
Figure 31: Mean Left DPOAE results (in dBSPL) and their standard deviations for the experimental group at the 3 different sessions (n=54)



SD	DPR750	DPR1000	DPR2000	DPR3000	DPR4000	DPR6000	DPR8000
Session1	6.2	6.8	5.2	5.0	5.3	5.1	5.8
Session2	5.5	6.7	5.9	5.7	4.7	4.6	5.7
Session3	7.9	8.7	8.1	7.8	6.9	6.2	7.1

Key: DPR = distortion product right ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 32: Mean Right DPOAE results (in dBSPL) and their standard deviations for the experimental group at the 3 different sessions (n=54)



SD	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Session1	6.3	6.6	6.2	5.8	5.5	5.0	5.1
Session2	5.4	6.6	6.3	6.1	5.1	5.0	5.5
Session3	8.5	8.5	8.0	7.2	7.0	6.8	7.0

Key: DP = distortion product; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 33: Mean bilateral DPOAE results (in dBSPL) and their standard deviations for the experimental group at the 3 different sessions (n=108 ears)

Similar to the control group, close inspection of the results either unilaterally (Figures 31 and 32) or bilaterally (Figure 33) for distortion product otoacoustic emissions revealed cochlea function to be normal at sessions one and two at all frequencies evaluated with declining DPOAE values at repeated measures. These changes were found to occur at all frequencies evaluated but were more pronounced at 750, 6 and 8 kHz bilaterally. When taking standard deviations into consideration, these three frequencies presented with results that were below normal.

Results of statistical analysis of DPOAE results through the use of MANOVA [within group (time)] are depicted in Table 27. These results were extremely statistically significant ($p < .001$) for all frequencies assessed for the 'within group' analysis, providing support for the rejection of the null hypothesis (cochlea function changed after ARV initiation). For all statistically significant results for DPOAEs (Table 27), the Tukey-Kramer test indicated that all the significant changes occurred throughout the 3 sessions of testing with mean DPOAE amplitudes at month 0 being larger than those of months 3 and 6 of follow up.

Table 27: Results of MANOVA for DPOAE results for the experimental group indicating levels of significance for 'within group' analysis and Tukey-Kramer test indicating time when significant changes occurred

Frequency	P	F	α	Tukey	Frequency	P	F	α	Tukey
DPL750	0.000001	21.11	<0.05	0>3 0>6 3>6	DPR750	0.000000	25.77	<0.05	0>3 0>6 3>6
DPL1000	0.000000	14.48	<0.05	0>3 0>6 3>6	DPR1000	0.000003	13.07	<0.05	0>3 0>6 3>6
DPL2000	0.000092	9.69	<0.05	0>3 0>6 3>6	DPR2000	0.000002	14.34	<0.05	0>3 0>6 3>6
DPL3000	0.000271	8.64	<0.05	0>3 0>6 3>6	DPR3000	0.000003	12.71	<0.05	0>3 0>6 3>6
DPL4000	0.000002	13.35	<0.05	0>3 0>6 3>6	DPR4000	0.000000	20.75	<0.05	0>3 0>6 3>6
DPL6000	0.000000	43.00	<0.05	0>3 0>6 3>6	DPR6000	0.000000	58.44	<0.05	0>3 0>6 3>6
DPL8000	0.000000	60.42	<0.05	0>3 0>6 3>6	DPR8000	0.000000	55.60	<0.05	0>3 0>6 3>6

Key: DPL = distortion product left ear; DPR = distortion product right ear; P = P value; F = F ratio
Statistical significance = alpha (α) less than 0.05; *df* = 2(time); *df* = 159(participants)

When comparing DPOAE results at session 1 to those at session 3, some clinically significant changes were noted across all frequencies (with the exception of 3000Hz) with a particularly significant change at 6000 and 8000Hz (Table 28). The changes at these frequencies were found to be 6dB and greater bilaterally. These results imply subclinical hearing loss which is particularly significant at high frequencies.

Table 28: Mean changes in bilateral DPOAEs indicating clinically significant changes over session 1 and 3 for the experimental group (n=108 ears)

Frequency	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Mean change	8.0	6.7	6.0	5.0	6.0	10.3	11.8

Key: DP = Distortion Product OAE in dBSPL; Clinical significance = 6 to 9dB change or more

9.4. COMPARISON OF THE EXPERIMENTAL AND CONTROL GROUPS

The sixth objective was to compare the results of the control group with those of the experimental group.

These comparisons are illustrated in Table 29 below.

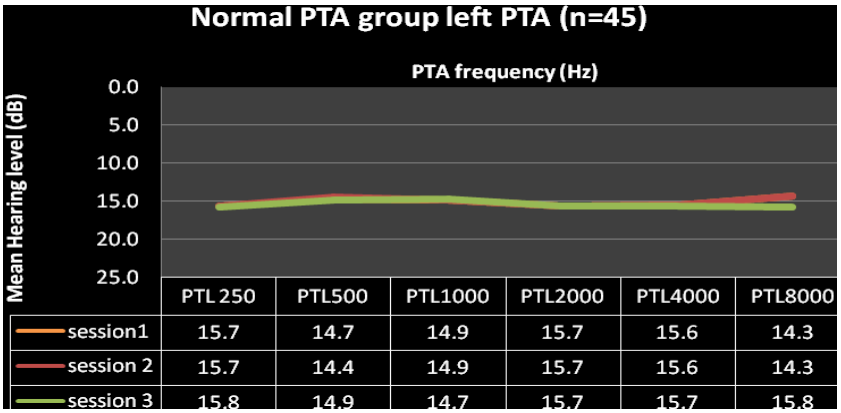
Table 29: Table depicting comparison of results for the control and experimental group

CONTROL GROUP	EXPERIMENTAL GROUP
Description 46 participants at baseline Total number of participants after attrition = 16 65% attrition rate	**Description** 104 participants at baseline Total number of participants after attrition = 54 **48%** attrition rate
Immune function Significant decline in CD4 count over 3 sessions (from 182 to 58 cells/mm^3)	**Immune function** Significant improvement in CD4 count over 3 sessions (from 101 to 216 cells/mm^3)
Occurrence of hearing loss 22% prevalence rate of hearing loss 50% of hearing loss presented at session 3	**Occurrence of hearing loss** 31% prevalence rate of hearing loss 66% of hearing loss presented after ARV use (44% at session 3)
Description of hearing • 90% of hearing loss was SNHL and 10% MHL • 40% mild-moderate hearing loss followed by 30% moderate to severe (the degree of the hearing loss tended to be more sereve in the control group when compared to the experimental group) • 80% flat/irregular configuration and 20% sloping/high frequency (less tendency of high frequency hearing loss when compared to experimental group) • 70% bilateral hearing loss and 30% unilateral	**Description of hearing** • 91% of hearing loss was SNHL and 9% CHL • 41% mild hearing loss followed by 32% mild-moderate (the degree of the hearing loss tended to be mild in the experimental group when compared to the control group) • 53% flat/irregular configuration and 47% sloping/high frequency (higher tendency of high frequency hearing loss when compared to control group) • 62% bilateral hearing loss and 38% unilateral
Type of onset Gradual/progressive onset	**Type of onset** Gradual/progressive onset
Possible causes Meningitis 10% Oto/syphilis 40% Otitis media 10% TB treatment 10% Unknown 40%	**Possible causes** Meningitis 3% Oto/syphilis 16% Otitis media 9% Previous ARV use 6% Possible interaction with previous TB treatment 31% Unknown 3% Current ARV use 41% Other (noise exposure, diabetes) 13%
Ototoxicity monitoring Pure tone audiometry: no statistically significant changes and no clinically significant changes DPOAEs: no statistically significant changes and no clinically significant changes	**Ototoxicity monitoring** Pure tone audiometry: statistically significant changes at 8000Hz in Left ear and no clinically significant changes DPOAEs: statistically significant changes and clinically significant changes at 6 and 8kHz at session 3

9.5. ANALYSIS OF THE GROUP WITH NORMAL PURE TONE AUDIOMETRY (SUBCLINICAL HEARING LOSS GROUP) (n=45)

Those participants in the experimental group who presented with normal pure tone audiometry results at all three sessions were closely analysed since DPOAEs are reported to be more sensitive to cochlea damage than pure tone audiometry. Changes in DPOAE results have been reported in the absence of changes in pure tone audiometry as a sign of damage to the cochlea. Those participants that presented with clinical hearing loss were eliminated from the study sample in order to ascertain whether the changes found in DPOAE results were not due to clinical hearing loss.

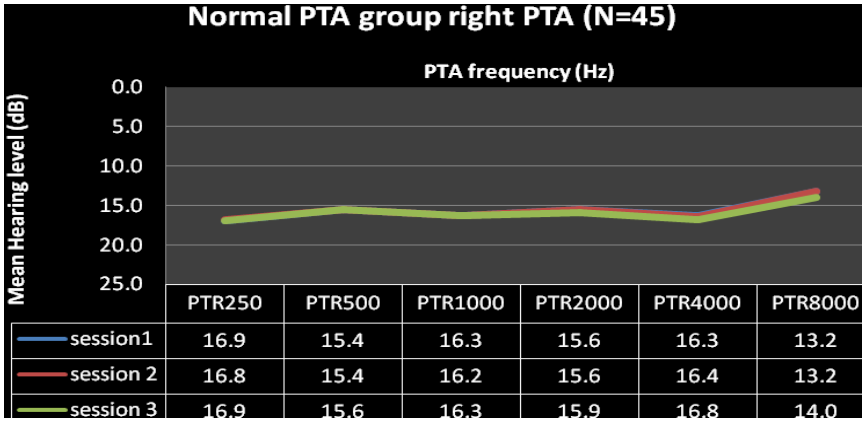
Analysis of the results for the subgroup of the experimental group with normal pure tone audiometry (n=45) involved comparing the results of all measures at all three assessment sessions in order to determine if any changes occurred during the period when the patients were receiving ARVs. All participants in this group had normal middle ear functioning. They also all had normal hearing as measured by pure tone audiometry at all three sessions of evaluation. The results are depicted in Figures 34, 35 and 36.



SD	PTL250	PTL500	PTL1000	PTL2000	PTL4000	PTL8000
Session1	5.2	5.5	5.3	4.8	6.6	5.8
Session2	5.2	5.6	5.3	4.8	6.6	5.9
Session3	5.2	5.3	5.4	4.8	6.5	9.9

Key: PTL = pure tone left ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

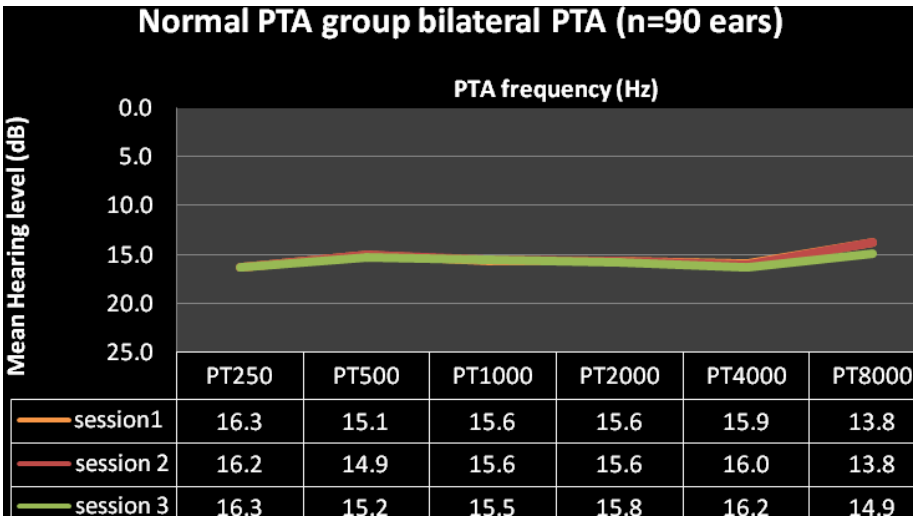
Figure 34: Mean Left Pure Tone audiometry results (in dBHL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=45)



SD	PTR250	PTR500	PTR1000	PTR2000	PTR4000	PTR8000
Session1	4.7	5.2	4.8	4.6	6.1	7.2
Session2	4.8	5.2	4.9	4.6	5.9	7.5
Session3	5.0	5.5	4.8	5.4	6.4	8.6

Key: PTR = pure tone right ear; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 35: Mean Right Pure Tone audiometry results (in dBHL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=45)



SD	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Session1	4.9	5.3	5.1	4.7	6.3	6.5
Session2	4.9	5.4	5.1	4.7	6.2	6.7
Session3	5.1	5.3	5.1	5.1	6.5	9.3

Key: PT = pure tone; dB = decibel; PTA = pure tone audiometry; SD = standard deviation

Figure 36: Mean bilateral Pure Tone audiometry results (in dBHL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=90 ears)

Close inspection of the results either unilaterally (Figures 34 and 35) or bilaterally (Figure 36) for pure tone audiometry revealed hearing within normal limits with average PTA being above the level regarded as indicative of normal hearing across all frequencies evaluated.

Statistically (Table 30), repeated measures ANOVA revealed no statistically significant changes except at 8000Hz in the Right ear (p=0.03).

Table 30: Results of repeated measures ANOVA for pure tone audiometry results for the group with normal PTA indicating levels of significance

Frequency	P	F	α	Frequency	P	F	α
PTL250	**0.372021**	**1.00**	**>0.05**	PTR250	**0.782606**	**0.25**	**>0.05**
PTL500	**0.089675**	**2.48**	**>0.05**	PTR500	**0.372021**	**1.00**	**>0.05**
PTL1000	**0.135289**	**2.05**	**>0.05**	PTR1000	**0.372021**	**1.00**	**>0.05**
PTL2000	**0.633241**	**2.15**	**>0.05**	PTR2000	**0.372021**	**1.00**	**>0.05**
PTL4000	**0.372021**	**1.00**	**>0.05**	PTR4000	**0.114039**	**2.23**	**>0.05**
PTL8000	**0.179187**	**1.75**	**>0.05**	PTR8000	**0.028364**	**3.71**	**<0.05**

Key: PTL = pure tone left; PTR = pure tone right; P = P value; F = F ratio; Statistical significance = alpha (α) less than 0.05; *df* = 2(time); *df* = 44(participants)

Because only one frequency presented statistically significant changes, no Tukey-Kramer test was run for this analysis.

Again, although the 8000 Hz frequency change was statistically significant, it was not clinically significant according to audiological protocols as it was not greater than 10dB (Table 31).

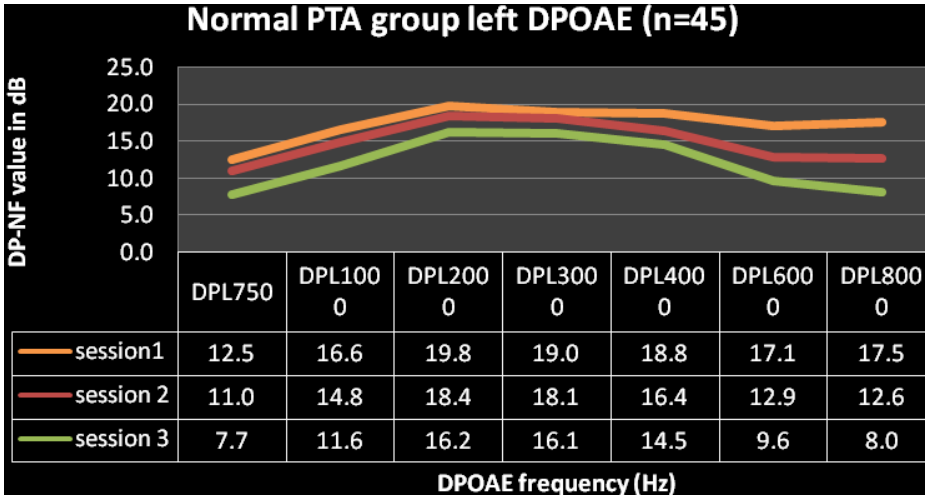
Table 31: Mean changes in bilateral pure tone audiometry (in dBHL) indicating clinically significant changes over session 1 and 3 for the group with normal PTA (n=90 ears)

Frequency	PT250	PT500	PT1000	PT2000	PT4000	PT8000
Mean change	0.1	0.2	-0.1	0.2	0.2	1.1

Key: PT = pure tone in dBHL; Clinical significance = 10dB or more

Similarly, close inspection of the DPOAE results either unilaterally (Figures 37 and 38) or bilaterally (Figure 39) for distortion product otoacoustic emissions revealed cochlea functioning to be within normal limits with average DPOAE emission size being above the level regarded as indicative of a normally functioning cochlea across all frequencies evaluated only for

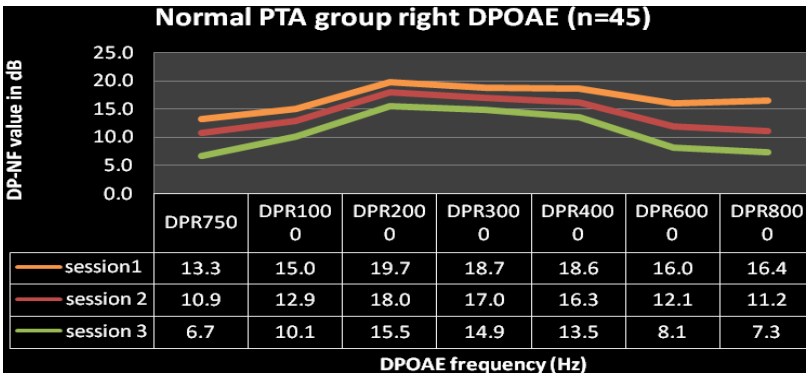
sessions one and two (the DP amplitude exceeded the noise floor by at least 7dB across all frequencies measured) (Hall, 2000). These results for mean DPOAE amplitudes were seen to be declining in size from session to session with severe declines at session 3 (when standard deviations were taken into consideration). Frequencies significantly affected at session 3 were 750Hz, and again, 6000Hz and 8000Hz.



SD	DPL750	DPL1000	DPL2000	DPL3000	DPL4000	DPL6000	DPL8000
Session1	5.9	6.4	6.4	5.6	5.3	5.3	4.8
Session2	5.4	6.5	7.1	5.5	4.9	6.1	5.6
Session3	7.9	8.3	8.4	5.7	6.9	8.0	7.8

Key: DPL = distortion product left ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

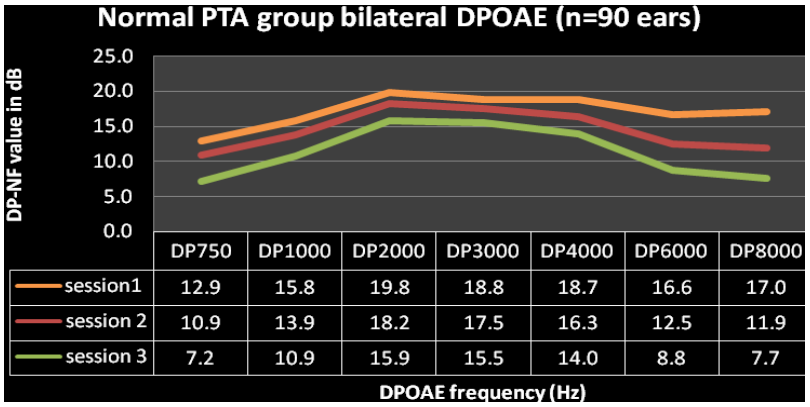
Figure 37: Mean Left DPOAE results (in dBSPL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=45)



SD	DPR750	DPR1000	DPR2000	DPR3000	DPR4000	DPR6000	DPR8000
Session1	5.8	6.8	5.3	4.9	5.1	4.4	5.0
Session2	5.5	7.0	5.9	5.7	5.1	4.5	5.5
Session3	8.0	9.2	8.6	6.9	6.9	6.4	6.9

Key: DPR = distortion product right ear; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 38: Mean Right DPOAE results (in dBSPL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=45)



SD	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Session1	5.9	6.6	5.8	5.2	5.2	4.8	4.9
Session2	5.4	6.8	6.5	5.6	5.0	5.4	5.6
Session3	7.9	8.7	8.5	6.4	6.9	7.3	7.4

Key: DP = distortion product; dB = decibel; DPOAE = distortion product otoacoustic emissions; SD = standard deviation

Figure 39: Mean bilateral DPOAE results (in dBSL) and their standard deviations for the group with normal PTA at the 3 different sessions (n=90 ears)

Repeated measures ANOVA of DPOAE results between measures at baseline and at six months after initiation of ARVs in the experimental group with normal pure tone audiometry revealed extremely statistically significant changes ($p < .001$) at all frequencies (Table 32).

Table 32: Results of repeated measures ANOVA for DPOAEs results for the group with normal PTA indicating levels of significance and Tukey-Kramer test indicating time when significant changes occurred

Frequency	P	F	α	Tukey	Frequency	P	F	α	Tukey
DPL750	**0.000001**	**16.35**	**<0.05**	**0>3**	DPR750	**0.000000**	**29.78**	**<0.05**	**0>3 0>6 3>6**
DPL1000	**0.000000**	**18.43**	**<0.05**	**0>3**	DPR1000	**0.000001**	**15.69**	**<0.05**	**0>3 0>6 3>6**
DPL2000	**0.000001**	**17.04**	**<0.05**	**0>3**	DPR2000	**0.000000**	**17.28**	**<0.05**	**0>3**
DPL3000	**0.000006**	**13.81**	**<0.05**	**0>3**	DPR3000	**0.000000**	**20.54**	**<0.05**	**0>3 0>6 3>6**
DPL4000	**0.000000**	**17.46**	**<0.05**	**0>3 0>6 3>6**	DPR4000	**0.000000**	**20.64**	**<0.05**	**0>3 0>6 3>6**
DPL6000	**0.000000**	**40.60**	**<0.05**	**0>3 0>6 3>6**	DPR6000	**0.000000**	**41.70**	**<0.05**	**0>3 0>6 3>6**
DPL8000	**0.000000**	**50.44**	**<0.05**	**0>3 0>6 3>6**	DPR8000	**0.000000**	**59.35**	**<0.05**	**0>3 0>6 3>6**

Key: DPL = distortion product left ear; DPR = distortion product right ear; P = P value; F = F ratio; Statistical significance = alpha (α) less than 0.05; *df* = 2(time); *df* = 44(participants)

Based on the results of the Tukey-Kramer post-test, the aforementioned statistically significant changes were found to be generally occurring between the baseline measures and session 2 for the lower frequencies in the participants' left ears, with the higher frequencies experiencing significant changes throughout the testing protocol (Table 32). Participants' right ears seemed to be experiencing changes throughout the test protocol for all frequencies tested.

Mean changes in DPOAE results were similar to those in the total experimental group in that they were clinically significant at 6 and 8 kHz bilaterally (Table 33). At these two frequencies the mean changes in DPOAE results were greater than 6dB.

Table 33: Mean changes in bilateral DPOAEs (in dBSPL) indicating clinically significant changes over session 1 and 3 for the group with normal PTA (n=90 ears)

Frequency	DP750	DP1000	DP2000	DP3000	DP4000	DP6000	DP8000
Mean change	5.7	4.9	3.9	3.3	4.7	7.7	9.3

Key: DP = Distortion Product OAE in dBSPL; Clinical significance = 6 to 9dB change or more

CHAPTER TEN

DISCUSSION OF RESULTS

According to the research literature, auditory abnormalities associated with HIV/AIDS and its treatments have been reported in persons with varying degrees of HIV infection, in both symptomatic and asymptomatic patients (Bankaitis & Keith, 1995; Bankaitis, 1996; Birchall et al., 1992; Chandrasekhar et al., 2000; Gold & Tami, 1998; Hausler et al., 1991; Khoza & Ross, 2002; Lalwani & Sooy, 1992; Marra et al., 1997; Soucek & Michaels, 1996; Welkoborsky & Lowitzsch, 1992) as well as in patients on antiretroviral treatment (Christensen et al., 1998; Martinez & French, 1993; Monte, Fenwick & Monteiro, 1997; Powderly et al., 1990; Schouten et al., 2006; Simdon et al., 2001; Vogeser et al., 1998). Findings from the current study have particular relevance to the field of audiology as well as to the field of pharmacology. The possible increase in the scope of practice of audiologists during the drug development and drug approval process is highlighted with the importance of utilization of sensitive ototoxicity monitoring tools such as DPOAEs demonstrated. The results arising from the investigation and monitoring of the auditory status of a group of adults with AIDS on ART and other therapies attending a hospital outpatient clinic are discussed in this chapter.

The study at baseline comprised 150 participants (104 in the experimental group and 46 in the control group). The sample included 53 (35%) males and 97 (65%) females between the ages of 20 and 46 years with a mean age of 33.9 years. All the participants had been diagnosed

with HIV/AIDS and were all at the AIDS stage of the disease. The average CD4+ count at baseline was 124 cells/mm^3, and this was consistent with the CD4+ requirement that persons need to have before they can be enrolled in an ARV programme in South Africa (CD4+ has to be below 200 cells/mm^3). It is acknowledged that the unequal number of participants in the control group and the experimental group represented a threat to generalization of the results – however this could not be controlled for since at the time of the study it was extremely difficult to find participants who were not enrolling into an ARV treatment programme at the research site.

Close inspection of the demographic profile of the participants who participated in the current study reveals similarities between the sample evaluated and the general South African population infected with HIV/AIDS with regard to age, gender and race. This therefore implies a strong similarity to the South African population infected with HIV/AIDS, suggesting that the current study was performed on a sample that was fairly representative of the South African situation, particularly persons attending public health clinics. Dorrington et al. (2006) assert that women continue to have the highest HIV prevalence rates in the country. Most recent antenatal clinic data show that the prevalence rates amongst women exceeds 30% and that of men just over 25% (Dorrington et al., 2006). As in the rest of sub-Saharan Africa, HIV has been noted to disproportionately affect more women than men (Shisana & Simbayi, 2005). This gender bias in the prevalence rates of the disease was also evident in the sample recruited for the present study, with a much higher number of participants in the study being female.

Furthermore, analysis of demographic information in terms of ethnic group also indicates similarities in features of the current study sample to the general South African population of

HIV infected patients attending hospitals in the public health sector. Tshabalala-Msimang (2000) reports that ethnic extrapolations in terms of HIV by population group are impossible to reliably obtain because women attending public health clinics are predominantly African. She further states that the sample sizes of Indian, Coloured and White women are too small for any reliable conclusions to be drawn on HIV in these population groups. According to the Henry J. Kaiser Family Foundation (2001), 80% of the South African population attends clinics in the public health sector with the private sector covering only around 20% of the total population. Due to the fact that the study was performed in a public health sector hospital, which provides health care services to the majority of the South African population, it is believed that the sample may have been more representative of the South Africa situation than a sample recruited from the private sector. Furthermore, the fact that South African statistics on HIV/AIDS are mostly compiled in the public sector strengthens the argument for the current study sample being fairly representative of the South African situation, particularly persons attending public health clinics. It is acknowledged though that even though these similarities exist, the fact that the sample was drawn from one hospital in Johannesburg, Gauteng, limits the generalizability of the results to the broader South African adult population with AIDS.

Even though the current study started at baseline with 150 participants (104 in the experimental and 46 in the control group), because of the repeated measures design nature of the study, some participants did not complete all three assessment sessions, and 9 participants were on different ARV regimen to that taken by the majority of the sample. Hence, the numbers significantly declined to a total of 54 in the experimental group (on regimen 1) and 16 in the control group who attended all 3 sessions of evaluations for monitoring. Attrition factors in the

experimental group included defaulting and stopping antiretroviral treatment over and above other general factors such as failure to attend or inconsistency in attending follow up appointments, death, and clinical hearing loss that was due to other diagnosed causes. Unlike in the control group where some participants dropped out because they commenced ARV treatment, in the experimental group, some participants were excluded when they defaulted from their treatment, with poor adherence to treatment contributing to the attrition rate in the experimental group. Dybul et al. (2002) believe that situations will always arise where interruption of ART is necessary in a given patient. These authors list factors such as toxicity, severe illness, and other circumstances as contributors to poor adherence.

The attrition rate was found to have been significantly higher in the control group than in the experimental group (only 35% of the participants comprised the analysis at the end of the study in the control group, as opposed to 52% of the participants in the experimental group). This finding demonstrates that 65% of participants in the control group were lost while 48% of participants in the experimental group were excluded from the final analysis of the study. This attrition further impacted on the small and unequal sample sizes of the control and experimental groups. It is acknowledged that the unequal number of participants in the control group and the experimental group represented a limitation of the study, and makes comparing the results of the two groups difficult.

All participants in the current study were at the end stage of HIV (AIDS) with CD4 counts at below 200 cells/mm^3 (182 cells/mm^3 for the control group and 102 cells/mm^3 for the experimental group) at baseline assessment. These levels significantly declined for the control

group over the 6 months follow up period, while they improved for the experimental group after initiation of ARVs. The mean CD4+ count of the control group declined significantly from 182 cells/mm^3 to 58 cells/mm^3 – representing a decrease of approximately 70% in immunologic function as measured by CD4+ count in 6 months without ART. Contrary to this finding, the mean CD4+ count of the experimental group significantly improved from 102 cells/mm^3 to 219 cells/mm^3 – doubling to approximately 50% increase in immunologic function as measured by CD4+ count in six months of taking ART. These results should be interpreted with caution though, because not all participants had had their CD 4 counts done at each testing session.

The aforementioned mentioned striking improvement in CD4+ counts found in the experimental group from baseline to 6 months is consistent with literature on expected objective clinical improvement that is common in patients with clinically significant HIV disease once they enrol in an appropriate HAART regimen, adhere successfully to it, and do not experience significant adverse side effects of medication. In the experimental group, unlike in the control group, subjective improvements were also noted and these included increased appetite, increased energy, improved sleep, and a general feeling of improved well being.

Objective clinical improvement from the use of HAART in patients with AIDS has been noted with CD4+ counts that are said to commonly rise dramatically, often by several hundred cells per microliter – to levels characteristic of clinically quiescent middle stage of HIV disease. The length of time for the current retrospective study (six months) did not allow for this quiescent stage to be observed, however the dramatic increase in CD4+ counts was evidenced. Use of combination antiretroviral therapy has been reported to correlate with decreases in HIV-

related deaths, reported AIDS cases, and hospitalisations due to opportunistic infections in centres where such therapy is widely available (CDC, 1997; Palella et al., 1998). This finding has significant implications for a country like South Africa where a large proportion of the workforce is reportedly infected by HIV/AIDS, where state resources such as hospitals do not seem to be coping with the numbers of patients that need to be admitted due to HIV/AIDS related illnesses, and where socioeconomic support from the government is required by a large proportion of its people.

It is acknowledged that a positive response to ARV treatment should also be determined by measurements of viral loads (Pakker et al., 1998). Literature shows that the first indication of successful treatment is a decline in viral load (Perelson et al., 1997). This decline is reported by these authors to occur as early as during the first two weeks of treatment for most patients. As viral load declines, the number of circulating CD4+ cells are reported to increase – the initial increases in CD4 count during the first 1-3 month/s of therapy are believed to be caused primarily by a redistribution of cells trapped from lymphoid tissue (Pakker et al., 1998). This monitoring of viral load could not be undertaken in the current study as many of the participants did not have this measure taken at the time of the current study. However, the CD4 count monitoring data were felt to have provided a fair indication of the participants' adherence to the antiretroviral therapy (for the experimental group), and continuing decline in immune status due to lack of ARV treatment (for the control group) – even though CD4 count measurement was also not conducted on all participants.

On the examination of the prevalence of hearing loss in the sample evaluated, the results implied a high prevalence of hearing loss in this population. At baseline, the prevalence of hearing loss was 10%, with a significantly higher prevalence rate after 6 months of follow up. After session 3 (assessment at 6 months) of the evaluations, the total prevalence rate of 28% of the participants presented with hearing loss with tinnitus and vertigo in varying degrees and combinations. This prevalence rate of hearing loss in adults with AIDS is significantly higher than the general South African population statistics of people with hearing loss which was last reported to be at 20% (Statistics South Africa, 2005). The general South African statistic may be different currently since this was based on the 2001 Census when conditions such as HIV and TB were not as rife as they are currently. The prevalence rate of hearing loss in the current study was higher than the general South African population even when examined separately for the control group (22%) and the experimental group (31%). Therefore, this higher occurrence of hearing loss in the sample assessed underscores the need for more research into this population to enhance generalizability of results so that vital decisions can be made regarding the anticipated burden of disease. Given the prevalence and disease burden of undetected hearing impairment and the availability of effective treatments, it is important for audiologists to engage in assessment and management of this population. The difference in prevalence rate between findings when only session 1 was considered to that after six months of follow up raises an important issue in prevalence studies where results may be inaccurate if only the cross-sectional and not longitudinal data are analyzed.

With regard to prevalence of hearing loss in HIV/AIDS in the international literature, results from the current study appear to be inconsistent with some internationally published

studies on clinical auditory system abnormalities in AIDS. Flower (1991) reported prevalence rates as high as 75%. However, current findings seem consistent with those which suggest that the prevalence of otologic manifestations of HIV/AIDS is not as high (Birchall et al, 1992; Abemayor & Calcaterra, 1983; Kohan et al., 1988; Sooy, 1987). For example, Sooy (1987) described abnormal audiologic findings greater than 25dB HL on pure tone testing in 49% of the total sample tested in his study while Birchall et al. (1992) noted a common presence of hearing loss on pure tone testing in 39% of a small sample of patients who were HIV-positive and syphilis-negative with no neurological symptoms. Although these international studies are based on samples that are vastly different to a sample from a developing world that may be treatment naive – comparing current results to these results from industrialised countries may highlight the existing gaps in the literature and practice, and may also contribute towards setting up and implementation of treatment protocols that may improve the quality of life of patients with AIDS in developing countries.

Consistent with the aforementioned studies on prevalence of hearing loss, the current study confirmed the presence of otologic disease in some patients with HIV/AIDS who presented with head and neck symptoms. This finding however differs from some studies that report a total absence of otologic signs in this population. These studies have concluded that there is an extremely low incidence or no incidence of otologic disease in adults, with a much higher incidence in paediatric patients. The high incidence of conductive hearing loss in paediatric patients is attributed in part to the high incidence of serous otitis media which may occur in up to 80% of cases (Smith & Canalis, 1989). Rosenberg, Schneider and Cohen (1985) reviewed medical records of 102 adult patients with AIDS and found that although 71% of the patients had

symptoms localised in the head and neck, none had otologic signs and symptoms. Similar results were reported by Marcusen and Sooy (1985) who also could not find any otologic findings in 165 AIDS infected patients they evaluated. Lalwani and Sooy (1992) report that otologic manifestations associated with HIV/AIDS do occur but are less prevalent than other head and neck complaints. Of note though in these studies is the fact that they employed cross sectional designs which may have limited their ability to identify hearing loss that may have developed over time as was seen in the current study (prevalence was 10% at baseline, but this increased to 28% after six months of follow up). The high prevalence of hearing loss in the current sample provides strong support for the views and beliefs held by several authors, that audiologists should be involved in the assessment and management of patients with HIV/AIDS (Gold & Tami, 1998; Khoza & Ross, 2002; Larsen, 1998). Furthermore, on a practical level, these results can be utilised to negotiate with hospital management and to motivate for budgets to be set aside for purchasing of hearing aids for patients who may be referred from the HIV/AIDS clinics to Hearing Clinics at Government hospitals in South Africa.

Further analysis of the data with regard to associated signs and symptoms of hearing loss indicated the prevalence of these signs and symptoms in the form of tinnitus and dizziness with a significantly higher prevalence of tinnitus in comparison to dizziness. The lower occurrence of dizziness is reassuring since this sign is believed to be more debilitating to the patient and can significantly affect the patients' quality of life (Katz, 2002). Balance disorders and dizziness have been linked to an increased incidence of injurious falls (Katz, 2002). Furthermore, the lower occurrence of dizziness can be viewed as a positive factor as it may imply that otologic

disease in HIV/AIDS at least may not have as significant an effect on the balance system of the ear as on the sensory system.

With regard to the description of the hearing status in the current study, firstly, participants that presented with hearing loss did so at different sessions of testing for both the control group and the experimental group. Half (50%) of the participants with hearing loss in the control group presented with onset at session 3, while 66% of those in the experimental group presented after initiation of ARVs (44% at session 3). However, the presentation of hearing loss at session 3 for the control group was expected as hearing loss has been associated with declining immune status in HIV/AIDS (Khoza & Ross, 2002) – and the declining immune function was evident in the control group's monitoring of CD4+ count – as discussed earlier. This presentation of hearing loss at session 3 was, however unexpected and surprising for the experimental group. Although the declining immune status was seen in the control group, the same was not evidenced in the experimental group since the monitoring of CD4+ counts demonstrated improving rather than deteriorating immune status. This finding raised some questions about the possibility of another contributing factor to the presentation of hearing loss in the two groups other than compromised immune function. Moreover, the fact that the percentage of occurrence of clinical hearing loss in the experimental group was higher than in the control group of the current study lead the researcher to suspect possible contribution of ARVs (in the form of 3TC and D4T with Stocrin) or at least the interaction of these ARVs with other factors (other therapies and/or supplements, and so forth) to the hearing loss found in the experimental group. This difference in the percentage occurrence of hearing loss in the two samples could potentially be attributed to the one factor that differentiated the two groups – the use of antiretroviral drugs. Although it is

acknowledged that other significant factors could have explained this difference – the one factor that was different in the two groups that could be identified was that of ART use. On their own, the other medications used in the current study have no documented ototoxic effects, however; in combination with other medications, the audiological effects are unknown.

Although a variety of adverse effects have been attributed to treatment with ARVs for HIV/AIDS, ototoxicity has rarely been reported. While hearing loss in HIV-infected people after beginning nucleoside reverse transcriptase inhibitors (NRTIs) has been described (Kakuda, 2000), there still needs to be extensive investigations to confirm this relationship. Some cross-sectional studies and case reports have shown an association between hearing loss and NRTI therapy (Marra et al., 1997; McNaghten et al., 2001; Rey et al., 2002; Simdon et al., 2001; Williams, 2001), however, findings from these studies have recently been disputed by a prospective study by Schouten et al (2006) which did not find clinical ototoxicity in patients following initiation of regimens containing NRTIs (zidovudine and didanosine).

Secondly, in describing the hearing loss in the participants presenting with clinical hearing loss in the current study, the type of hearing loss tended to be mainly sensorineural in nature for both the control group and the experimental group. As many as 90% of participants with hearing loss presented with SNHL with 10% presenting with mixed hearing loss (MHL) in the control group, while 91% presented with SNHL and 9% with conductive hearing loss (CHL) in the experimental group. In reviewing the literature, the current findings provide support for the reports that claim the hearing loss seen in HIV/AIDS to be of any type (Chandrasekhar et al. 2000; Friedmann & Noffsinger, 1998; Khoza & Ross, 2002; Timon & Walsh, 1989). The limited

occurrence of conductive hearing loss was not a surprising finding particularly since this was consistent with previous findings (Khoza & Ross, 2002), of less occurrence of conductive hearing loss in the AIDS stage even though otitis media has been reported to be most common in this population (Friedmann & Noffsinger, 1993; Gold & Tami, 1998; Lalwani & Sooy, 1992). These authors report that the most common otologic problems documented in this population are serous otitis media and recurrent acute otitis media, which are predominantly due to Eustachian tube dysfunction – implying that one would expect the conductive type of hearing loss to be the most common. Contrary to the reported literature, in the current study, the most common type of hearing loss seen in both the control group and the experimental group was the SNHL, further confirming earlier findings of a higher occurrence of SNHL in AIDS due to various opportunistic infections and treatments in this population group (Khoza & Ross, 2002).

The rate of occurrence of SNHL is reported by Gold and Tami (1998) to range between 20% and 50% based on reviews of studies by Bankaitis and Keith (1995); Lalwani and Sooy (1992); and Tami and Lee (1994). Findings from the current study showed a slightly higher occurrence rate of SNHL in the sample studied. This higher incidence of SNHL in the control group can possibly be attributed to the fact that the participants in the control group were not on ARV treatment and had declining immune functioning – which possibly increased their vulnerability to opportunistic infections. The increase in the occurrence of SNHL with advanced stages of the disease, as previously stated, may be attributed to the progressive decline in patients' immunologic status which potentially places the patients at risk for being susceptible to the neurotrophic nature of the disease and to opportunistic infections, which have been found to cause hearing loss (Friedmann & Arnold, 1993; Real et al., 1987; Schuknecht, 1993; Stephens,

1997). This finding possibly suggests that ARVs (in the form of 3TC and D4T with Stocrin) can potentially slow down the rate of occurrence of SNHL since they retard the deterioration of immune function. On the other hand, it is difficult to attribute the higher incidence of SNHL in the experimental group to declining immune function since this group showed improvement in their CD4 counts in the presence of ART, even though opportunistic infections were still found to be occurring in the experimental group. This again raises the possibility of a different causal factor in this group of participants – that which was not present in the control group. Mata et al. (2000) reported sensorineural hearing loss to be the most common finding in their study of patients on ART, and they associated this with the administration of antiretroviral drugs in their study. This possibility is raised in the current study, although it cannot be confirmed since there were confounding variables such as concurrent use of other medications – most of which have unknown interaction effects with ARVs. Nevertheless, whether or not there were interactions, there seemed to be some role that regimen 1 of ARVs used in the current study was playing in the presentation of SNHL in the experimental group.

Thirdly, in further describing the hearing loss in the participants presenting with clinical hearing loss in the current study, results revealed that the hearing loss could occur in any degree of severity. These results were consistent with those reported in the literature where severity of hearing loss has been described as ranging from mild to severe with little mention of profound hearing loss – as was found in the current study. Despite the absence of the profound degree of hearing impairment in this sample, the implications for the patients' quality of life are still significant – and the role of the audiologist with regard to early and prompt effective services to this population is highlighted. Although the severity of the hearing loss varied, there seemed to

be a distinct pattern observed. The severity tended to be less severe in the experimental group when compared to that of the control group. While the majority of the participants' hearing loss in the control group ranged in severity from mild to severe (40% presented with mild to moderate and 30% presented with moderate to severe hearing loss), this severity range was lower for the experimental group (41% presented with mild hearing loss and 32% with mild to moderate degree of hearing loss). This difference in severity presentation between the two groups raises the possible notion that ARVs may have some influence on the degree of the opportunistic infections and their consequences for hearing function. A tentative explanation is put forward in that it is possible that even if regimen 1 of ARVs used in the current study may be associated with hearing impairment in terms of ototoxicity – the degree of that hearing loss may be mild when compared to the scenario when ARVs are not being used – as was evident in the current study. The milder degree of hearing loss found in the experimental group highlights the need for early detection of hearing impairment in patients on ART since multiple management options may be available where there is still reasonable residual hearing to either amplify or conserve hearing function. This is particularly crucial where the patients' general health and immune function is improving and their need for communication should not be compromised.

Findings with regard to the degree of hearing loss have implications in terms of the timing when audiologic management of patients with AIDS should commence. It is recommended that early intervention be implemented. In view of the high prevalence of mild hearing loss found in the current sample, audiologists may need to assess these patients very early on so that in the event of the hearing loss being due to treatable opportunistic infections, appropriate referrals for medical management could be made, thereby preventing further

deterioration of hearing thresholds over time or reversing hearing loss is cases of treatable infections such as otitis media. This is particularly important at this stage of the disease (AIDS stage) where quality of life may be adversely affected by various other conditions due to severely compromised immune function, hence highlighting the importance of promptly and efficaciously managing those conditions that can be positively managed – hearing impairment being one of these conditions. Prioritization of management of these conditions that can be more easily remediated has the potential to significantly improve the patients' quality of life and their ability to remain productive members of society.

Furthermore, in the description of hearing loss as far as the configuration of the hearing loss, the experimental group and the control group presented with some differences. Although, no typical pattern of configuration of hearing loss could be established in the control group, 80% of the participants presented with flat and/or irregular audiograms and only 2 (20%) participants presented with a sloping/high frequency hearing loss. These results are consistent with findings documented by Khoza and Ross (2002) on patients who were also not taking ARVs, where they found that all frequencies were affected equally or to varying degrees, depending on the possible cause of the hearing loss, and the hearing loss was not necessarily confined to high frequencies as previously reported. Several authors have reported a tendency towards sloping/high frequency hearing loss, and this finding was not the general trend observed in the current study for the control group (Chandrasekhar et al., 2000; Gold & Tami, 1998; Lalwani & Sooy, 1992; Marcusen & Sooy, 1985).This finding was significantly different to that in the experimental group.

Unlike in the control group where no typical pattern of configuration of hearing loss could be established, in the experimental group almost half (47%) of the participants presented with a sloping/high frequency hearing loss (some with just a hearing loss at only 8 kHz). The remaining 53% presented with flat and/or irregular audiograms with an equal chance of involvement of all frequencies. These results were consistent with data commonly documented in respect to configuration of the hearing loss in patients with HIV/AIDS taking ART. For example, Marcusen and Sooy (1985) reported that in their sample some of their participants presented with a hearing loss, on pure tone testing, involving 8000 Hz, which was very similar to the current study. Mata et al. (2000) reported that in their study of 30 patients, the most common findings included high frequency sensorineural hearing loss. Chandrasekhar et al. (2000), Gold and Tami (1998), and Lalwani and Sooy (1992) state that the hearing loss steadily worsens with an increase in frequency, with high frequencies at a moderate degree of severity. These authors' reports seem to indicate a sloping/high frequency hearing loss, and this finding was the general trend observed in the experimental group when compared to the control group in the current study. The conclusion drawn from the present study regarding configuration of the hearing loss in participants on ART was that all frequencies may be affected equally or to varying degrees, but the configuration does tend to have more high frequencies affected than lower and middle frequencies.

If ARVs (in the form of 3TC and D4T with Stocrin), either singly or in interaction with other factors, have any effect on hearing function, the current results, with regard to configuration of the loss, were consistent with reports that the initial stages of auditory toxicity involve selective destruction of the outer hair cells of the organ of Corti (Singer et al., 1996) -

where in the early stages of toxicity, the damage is usually limited to the higher frequency levels (4000 to 8000Hz), with the frequencies utilized in conversational hearing reported to be commonly unaffected at this stage (Garrison, Zaske & Rotschafer, 1990). The progression to involvement of the lower frequencies has not been widely reported with ARVs and this could be due to the length of time that patients on ARVs have been audiologically monitored – as in the current study where the participants were only monitored for six months.

Lastly, in relation to the description of hearing loss, as far as the symmetry of the hearing loss, both the experimental group and the control group participants with clinical hearing loss presented with bilateral hearing loss as the main presentation (70% in the control group and 68% in the experimental group presented with bilateral hearing loss). A review of literature on the symmetry of hearing loss in HIV/AIDS yielded limited results, however there are reports in the literature about hearing loss in HIV/AIDS being either unilateral or bilateral (Khoza & Ross, 2002; Sooy, 1987). The current study confirmed these findings; however, a higher occurrence of bilateral rather than unilateral hearing loss was found. Although the degree of hearing impairment in the experimental group (post ART initiation) seemed to be milder than in the control group (if ART was not used), the symmetry of the hearing loss did not seem to be any different. These findings highlight the crucial need for communication rehabilitation services by audiologists to minimise or eliminate the impact that the hearing impairment may have on the individual's communicative skills (Hodgson, 1985; Stephens, 1997).

The high prevalence of bilateral hearing loss in the sample evaluated suggests that hearing impairment probably occurs more frequently in the general population of patients with

AIDS than is realized. Bilateral hearing loss is reported to impact more severely on communication than unilateral hearing loss, and therefore requires prompt diagnosis and management (Hodgson, 1985; Stephens, 1997). The higher prevalence of bilateral hearing loss is of grave concern as it is also known that binaural hearing is important in detecting the direction of a sound source, solving the problem of echoes as well as extracting wanted information from multiple sound sources (Kidd, 2002). Early intervention in terms of medical management and/or amplification would enhance patients' communication abilities, allowing them an improved chance of correctly following their required medical treatment. Therefore, enhanced communication in this case could potentially not only improve the patients' quality of life socially, academically, and vocationally; but also in terms of their general health.

Similarly to the symmetry of hearing loss, no difference in the type of onset of the hearing loss was found between the control group and experimental group. All participants presenting with clinical hearing loss in both groups presented with gradual/progressive hearing loss (no participant presented with sudden onset). Results on the type of onset of hearing loss in the current study are inconsistent with earlier reports by Khoza and Ross (2002) which revealed that sudden onset was mostly experienced by participants who presented with severe to profound SNHL, while gradual onset was mostly found in participants who presented with conductive and/or mixed hearing losses. In the current study, regardless of the type or degree of hearing loss, all participants presented with gradual onset of hearing loss. The tendency towards gradual/progressive bilateral hearing loss was similar in the experimental and control groups – again highlighting the need for the audiologists' increased involvement in assessment and management of the HIV/AIDS population, on and off ART.

The involvement of audiologists in the assessment and management of the HIV/AIDS population is further highlighted by the possible causes of hearing loss that were found in the current study. Again, some trend differences were observed between the control group and experimental groups in terms of aetiological factors. Major possible causes in the control group were oto/syphilis (40%) and unknown causes (40%), with meningitis, otitis media and TB treatment being the other possible causes found. These findings were not surprising as these conditions are commonly seen in persons living with HIV/AIDS where immunological status has been severely compromised (Khoza & Ross, 2002; Larsen, 1998), and in up to 50% of HIV-infected people with hearing loss, no cause can be identified (Lalwani & Sooy, 1992). Findings of the control group were consistent with those of the total sample at baseline (before initiation of ARVs) – with opportunistic infections being the major causes of hearing loss. This was contrary to the findings from the experimental group where major possible causes were current ARV use (41%), possible ARV interaction with previous TB treatment (31%) and oto/syphilis (16%), with meningitis, otitis media and other factors (diabetes, noise exposure after ART) being the additional possible aetiological factors. Opportunistic infections were found to occur less often in the experimental group than in the control group, and this was consistent with reports in the literature about ARVs improving immune status and reducing the occurrence of opportunistic infections. Syphilis (as an opportunistic infection) occurred as a possible cause of hearing loss in both groups regardless of whether the patients were on ARVs or not, and this finding echoes Schuknecht's (1993) claim that acquired syphilis may erupt as otosyphilis at any stage of HIV disease even after successful therapy. Of significance in the current study is the finding that 41% of the participants in the experimental group with clinical hearing loss had hearing loss that

could have possibly been due to the use of ARVs (in the form of 3TC and D4T with Stocrin), either singly or in interaction with other medications, with 31% presenting with a cause that was thought to be an association of ARVs with previous use of ototoxic drugs (that of previous TB treatment).

To further scrutinize the possible ototoxic effects of regimen 1 of ARVs used in the current study, repeated measures statistics were conducted. This ototoxicity monitoring aim of the study yielded interesting results for both the control and the experimental group. Because DPOAEs were also used as part of the ototoxicity monitoring battery, it should be noted that all participants in this group had normal middle ear functioning, based on otoscopic and tympanometric results, to enable them to be evaluated through the use of DPOAEs. Moreover, only participants without any evidence of newly acquired noise exposure, TB, radiotherapy, syphilis and/or middle ear pathology after the baseline testing were included in this ototoxicity monitoring phase of the study. Because the researcher looked at both statistical significance and clinical significance, the findings highlight the importance of including both these means of establishing significance in any longitudinal audiological study.

Statistically significant change may have more power in the academic and scientific literature – however, the current researcher believes that clinically significant changes may have more relevance in the clinical population of patients being studied. This view is supported by other authors including Campbell (2005) and Kazdin (1999) who believe that clinical significance focuses on the importance or applied value or importance of the change in everyday life - that is, whether the intervention makes a real (e.g. palpable, practical, noticeable) difference

in everyday life to the clients. In the current study, most changes found with both pure tone audiometry and DPOAEs were statistically significant ($p < .05$) in both the control group and experimental group (over three testing sessions), which provided support for rejecting the null hypothesis. The presence of statistically significant changes in the absence of clinically significant changes highlights the need for more stringent analysis methodologies in researching this population. It also raises questions regarding which of the two methods has more merit in clinical research. It would seem though that the presence of both statistically significant and clinically significant changes in any sample would have more weighting than other possible scenarios of the same situation (e.g. statically significant changes with no clinically significant changes; no statistically significant changes but clinically significant changes; and no statistically significant and no clinically significant changes).

Specifically, pure tone audiometry results in the control group revealed hearing within normal limits with average PTAs being above the level regarded as indicative of normal hearing across all frequencies evaluated. These mean results were normal for all 3 sessions. However, when the standard deviations were taken into consideration, the results were normal only for sessions 1 and 2 with slight hearing changes at session 3 at all frequencies tested. This explains the variance in the results as 80% of participants with clinical hearing loss in the control group presented with irregular and/or flat configuration of hearing loss. With regard to MANOVA tables, all changes were found not to be statistically significant over the 3 testing sessions. Moreover, these changes were also not audiologically clinically significant changes. Most often a change of 10dB at one or more frequencies is commonly taken to be indicative of clinically significant change (Ludman & Wright, 1998). In that way short term reliability changes due to

factors such as fatigue, concentration levels, time of day, and so forth are accounted for. None of the mean changes in pure tone results of the control group in the current study were greater than 10dB; suggesting that they were not clinically significant changes.

Furthermore, DPOAE measures for the control group revealed cochlea functioning to be within normal limits with average DPOAE emission size being above the level regarded as indicative of normally functioning cochleas across all frequencies evaluated for all 3 sessions, however, when standard deviations were taken into consideration, these results were below the norm for 500Hz, 6000Hz, and 8000Hz for bilateral DPOAE results at session 3. MANOVA tables indicated that, statistically, all 'within group' repeated measures analysis results provided support for the acceptance of the null hypothesis [i.e. changes were not statistically significant ($p>.05$) – according to Motulsky (1999). Furthermore, these changes were also not clinically significant. Change is only regarded as clinically significant in DPOAE measures if there is a change of at least 6 to 9dB in DPOAE level between consecutive measures (Dreisbach et al., 2006; Roede et al., 1993). In that way short and long term reliability effects due to factors such as subject noise, probe tip placement/position, equipment, changes in middle ear pressure, and so forth (Franklin et al., 1992; Marshall & Heller, 1996; Roede et al., 1993; Zhao & Stephens, 1999) are accounted for. In the control group, none of the mean changes in DPOAE results were greater than 6dB – indicating that no clinical changes occurred in the cochlear function.

The absence of clinically significant changes in pure tone audiometry and DPOAEs in the control group in the 3 different sessions over a period of 6 months confirmed intact hearing functioning and the absence of evidence of cochlea damage, even microcochlear pathology –

which is often evident in OAEs long before being depicted on the pure tone audiogram (Hall, 2000). It is now well established that OAE measures are more sensitive to inner ear dysfunction than conventional pure tone audiometry or auditory brainstem responses. Dreisbach et al. (2006) and Ress et al. (1999) reported that DPOAEs were more sensitive and superior to pure tone audiometry (even ultrahigh frequency audiometry) as an ototoxic assessment tool, hence it would seem reasonable to conclude that based on the objective nature of DPOAE measures, no clinically significant auditory changes were found in the current study after a 6 month period in the control group of AIDS infected adults who were not on ARVs (having excluded participants with other established causes of hearing loss).

The lack of changes in hearing status possibly excludes hearing loss due to medications used by participants in this control group. This finding is consistent with reports by Chandrasekhar et al. (2000) which maintain that routine medications used in outpatient management of HIV in their study did not cause hearing loss. The general medications that were used in various combinations by participants in the control group included antibiotics, antidepressants, antifungals, antivirals, analgesics, as well as traditional medicine. The control group was not on ARVs but were on treatment for various opportunistic infections as well as being treated for general health management. "*Ubhejane"* is a form of African traditional medicine that some of the participants reported using either as a form of complimentary medicine (as in the experimental group) or as an alternative (as in control group) to antiretroviral medications. These medications do not seem to have had any clinically significant effect on hearing function in the current study, nor have they been reported to exert an ototoxic effect.

However the statistically significant changes that were found in the control group may require further research to determine exactly what they mean.

The risk of ototoxicity has been reported to increase and be associated with factors such as large or prolonged doses of antibiotics (Konrad-Martin et al., 2005). Those participants that did present with a hearing loss in the control group (discussed separately as the group with clinical hearing loss) had configurations that were not consistent with what is known to be associated with ototoxic hearing loss, and also had histories that have been documented to be the possible causal factors of hearing loss in this population. Otologic symptoms consistent with ototoxicity include high frequency hearing loss (ranging from 4 kHz up) (Bergstrom et al., 1985; Fausti et al., 1999; Schwade, 2000) particularly at the initial stages of the hearing loss (Konrad-Martin et al., 2005) – and this was not the case with the control group. In fact, only 20% of participants in the control group presented with high frequency hearing loss.

For the experimental group, the ototoxicity monitoring phase of the current study yielded different results to those of the control group in that some results indicated the presence of both statistically and clinically significant changes in the sample analysed. For pure tone audiometry data, criteria for clinically significant change were not met - none of the mean changes in pure tone results were greater than 10dB. MANOVA tables for repeated measures analysis of variance (within group) revealed no statistically significant changes (alpha was greater than 0.05), with the exception of significant changes 8000Hz [left ear ($p=0.04$)]. However, results of the DPOAE analysis revealed cochlea function to be normal at sessions 1 and 2 at all frequencies evaluated with changes indicating declining DPOAE values at repeated measures. These changes were

found to occur at all frequencies evaluated but were more clinically significant at 6 and 8 kHz bilaterally in session 3. When comparing DPOAE results for the experimental group at session 1 to those at session 3, some clinically significant changes were noted across all frequencies (with the exception of 3000Hz) with a particularly significant change at 6000 and 8000Hz. The DPOAE results at these two frequencies at session 3 were in fact below the norm in that the DPOAE value did not exceed the noise floor by at least 7 dB as expected in a normally functioning cochlea. Statistically, MANOVA [within group (time)] results indicated extremely significant ($p<.001$) for all frequencies assessed – implying that cochlear function changed after ARV initiation.

The presence of significant changes on DPOAEs in the three different sessions over a period of six months indicated possible microcochlear pathology that was not necessarily indicated on pure tone audiometry. The changes at these frequencies were found to be greater than 6dB bilaterally. Hence, it would seem to be a possibility that based on the objective nature of DPOAE measures, subclinical auditory changes were found in the current study after a six month period. These results imply subclinical hearing loss which is particularly significant at high frequencies and, these subclinical changes seem consistent with reports that state that DPOAEs can detect microcochlear pathology before it is reflected on pure tone audiometry. This finding again supports reports that claim that DPOAE testing can detect early cochlea damage a long time before this is seen on an audiogram (Hall, 2000). This finding also highlights the crucial need for the use of such sensitive measures (DPOAE) in monitoring the possible effects of toxins on the ear since DPOAE have been shown to be superior to pure tone audiometry in this regard.

The high sensitivity of DPOAEs to microcochlea changes was further illustrated by the interesting findings from the analysis of the group of participants from the experimental group with normal pure tone audiometry (subclinical hearing loss group). Pure tone audiometry results for this group were within normal limits with average PTA being above the level regarded as indicative of normal hearing across all frequencies evaluated at all 3 testing sessions. None of the mean changes in pure tone results were greater than 10dB; therefore no clinically significant changes were present. The changes were also not statistically significant ($p > .05$) except for 8000Hz in the Right ear ($p=0.03$). Although this frequency change was statistically significant, it was not clinically significant.

For DPOAEs, results in this group with normal PTA revealed cochlear functioning to be within normal limits with average DPOAE emission size being above the norm (the DP amplitude exceeded the noise floor by at least 7dB across all frequencies measured) only for sessions one and two. These results for mean DPOAE amplitudes were seen to be declining in size from session to session with severe changes at session 3 (when standard deviations were taken into consideration) - as the time on ARVs progressed. Frequencies significantly affected at session 3 were 750Hz, 6000Hz and 8000Hz. The ANOVA table results revealed statistically significant changes that were also found to be clinically significant at 6 and 8 kHz bilaterally – as seen in the total experimental group. At these two frequencies the mean changes in DPOAE results were greater than 6dB indicating clinical significance of the findings. These findings clearly illustrate how DPOAEs can forecast ototoxicity before it becomes clinical.

For the statistically significant results for DPOAEs in the 'within group' analysis, the Tukey-Kramer test indicated that, generally, the significant changes occurred between baseline measures and session 2 (at 3 months) for the lower frequencies, with the higher frequencies being significantly affected throughout the 3 sessions of testing. This early onset of symptoms (though subclinical) again highlights the need for early involvement of the audiologist in the assessment and management of patients with AIDS.

The presence of DPOAE changes indicating subclinical changes in hearing status suggested hearing loss that could have possibly been due to medications used by participants in the experimental group – antiretroviral drugs (with or without interactions with other factors). These results were consistent with the reports that have associated iatrogenic hearing loss with many of the drugs used to treat HIV/AIDS (Bankaitis & Keith, 1995; Kohan et al., 1990). The participants in the experimental group were on regimen 1 which comprised 3TC, D4T, and Stocrin; with supplements, general health medications and traditional medicine used in various combinations. These medications seem to have possibly had an effect on hearing function. Although the other medications used by the experimental group have no documented ototoxic effects, their interactional effects with ARVs have not been established and so their use in the current study make it difficult to draw conclusions about the ototoxic effects of ARVs.

Participants in the experimental group presented with both clinical and subclinical hearing impairment. Those participants that presented with clinical hearing loss in the experimental group (discussed separately as the group with clinical hearing loss) had configurations that seemed to be consistent with ototoxic hearing loss. Otologic symptoms

consistent with ototoxicity include high frequency hearing loss particularly at the initial stages of the hearing loss. Those participants with subclinical hearing symptoms also showed a high frequency configuration as indicated by significant changes in DPOAEs at 6 and 8 kHz bilaterally.

Although the current study may not be able to draw the definitive conclusion that ARVs (in the form of 3TC and D4T with Stocrin) had a direct effect on hearing – because of the difficulty in controlling for other interacting factors, an index of suspicion is raised by the fact that the results of the participants in the experimental group seem more consistent with ototoxic hearing loss than in the control group, and the fact that the only identifiable difference between the two groups was that of ARVs use. The fact that the participants in the study were taking various other medications, and were exposed to other potentially contributing factors, prevents the researcher from reaching a definitive conclusion about the ARV regimen used in the current study – however the need for future research in this area is highlighted. The current researcher is of the opinion though that isolating all these possibly contributing factors may provide a more accurate answer, but may not necessarily provide a more practical, relevant, and context-sensitive answer. Within this population (South African AIDS population), it may be impossible to find participants who are only exposed to just one strict ARV regimen without any of the other medications coming into play. The results of the current study therefore are felt to be valuable and applicable to the South African context, and may provide more realistic and context specific implications.

As is clear from the results of the group with clinical hearing loss, clinical hearing loss in the patients taking ARVs seemed to also be closely associated with a history of use of other ototoxic medications such as was seen in the current study with 31% of the cases having had TB treatment in their medical history. Therefore the implication may be that the regimen of ARVs used in the current study may have ototoxic potential and this may be exacerbated by a concomitant history of factors that have an influence on hearing (such as a history of ototoxic drug use, noise exposure at the same time as ARVs; and so forth) – as seen in the current study. For example, as early as 1971, an increased risk of ototoxicity was reported to be related to previous or concurrent use of other ototoxic medications (Jackson & Arcieri, 1971).

The results presented and discussed in this chapter are not without limitations; however they do have important implications. These implications may be context specific to the population studied. Regardless of the fact that they may not be generalizable to other contexts, they can however spur much debate in other contexts and encourage more research to further clarify some of the findings from the current study. These implications are discussed in the following chapter with conclusions drawn from the current study also brought forward.

PART V - EPILOGUE

Chapter 11

CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

CHAPTER ELEVEN

CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

HIV/AIDS remains the most important public health problem facing the country. It also remains one of the most difficult and challenging problems confronting the South African government and Department of Health. HIV/AIDS therefore remains an area where continued research could improve patients' quality of life not only in South Africa but throughout the world. Opie (2005) believes that South Africa should be leading the world in AIDS research, a sentiment which the current researcher echoes. The role of the audiologist in the research, assessment and treatment of HIV/AIDS has been limited; and this needs to change if comprehensive as well as efficacious management programmes are to be successfully implemented. This chapter summarizes the key points discussed in the thesis, delineates the main results that emerged from the study, and offers conclusions drawn from the findings while acknowledging the limitations that surfaced during the process of the study. This chapter also highlights recommendations for clinical assessment and management of patients with HIV/AIDS on and off ARVs; training and education of team members; policy formulation; and future research.

11.1. THEORETICAL FRAMEWORK AND CONTEXT OF THE STUDY:

Research into any aspect of HIV/AIDS requires a thorough understanding of the disease, the disease process, as well as its effects on the human body. Focusing as it did, on the effects of HIV/AIDS and its treatment on auditory function, a clear discernment of the disease itself in terms of symptomatology, classification and staging, testing, transmission and risk factors, as well as disease progression, the current thesis covered these aspects deemed crucial as part of the theoretical backdrop to the current study. Furthermore, comprehensive insight into the treatment of HIV/AIDS with the known toxicities and side effects of ART also seemed an essential component in establishing a sound theoretical background to the study. Lastly, since the study also aimed at monitoring for possible ototoxicity of ART; an in-depth discussion of ototoxicity and its monitoring methods was also considered as an important part of the theoretical framework of this study. This theoretical framework provided an imperative backdrop to the study within the South African context.

Worldwide, no country is immune from HIV and AIDS and its debilitating impact on health, productivity and economic growth. Although the impact of HIV/AIDS is experienced by every sector of the South African society, including commerce and industry, agriculture, education, transport, and so on (in both public and private departments); it would seem the public sector has been most affected. For the public sector in South Africa, what is at stake is its ability to render essential services (especially to the poor) in order to sustain democracy and social progress. HIV and AIDS impact severely on the capacity of the state, its skills base, and the efficient use of public funds to render high quality services to the broad populace. Public sector organizations are under immense pressure to implement policies and programmes to mitigate the

impact of HIV and AIDS in the country. In the case of the South African Public Service, many HIV and AIDS policies and programmes have been implemented with varying levels of success. The same can be said for the provision of health care services to those infected by HIV/AIDS, including provision of ART to the infected.

Research on the demographic, economic, and institutional impact in the Sub-Saharan region shows that HIV and AIDS have already had a wide scale impact on the populations of these countries, as well as the ability of their Public Services to address such impact. The bulk of the population in Sub-Saharan countries infected and affected by HIV and AIDS are impoverished rural and urban populations who do not have access to private healthcare and are accordingly highly dependent on public services for their well-being. To ensure effective service provision to the broad population infected and affected by HIV and AIDS, productive and effective public services are of vital importance. South Africa has by no means been immune from this imperative.

Some aspects of the South African framework for managing HIV and AIDS in the country have been introduced, some more comprehensively and successfully than others. One of the main reasons for the lack of wide scale introduction of the aspects contained in the framework is a need for senior management's commitment and the necessary skills to implement the policy framework for managing HIV and AIDS in the general population. Other reasons include, but are not limited to, the complexity of the treatment plans recommended. For example, combination HIV therapies are complex as well as costly. Regimens may involve multiple doses of different medications with precise scheduling and nutritional requirements. Side effects,

patient responsiveness to treatment, disease progression, and drug interactions all mandate frequent and comprehensive clinical monitoring (Hammer, Saag, Schechter et al., 2006), including ototoxicity monitoring. Medical benefits are highly dependent on strict maintenance of treatment regimens for which most patients need substantial and continual education.

Studies of HIV/AIDS and ARV toxicity face a challenging and interesting future. On the clinical side, confirmation of ototoxicity of ARVs followed by early detection of clinical hearing loss and prevention of toxicity remains a critical need. This need for the clinical focus is partly because of the current increase of HIV/AIDS and concomitant TB and the associated use of aminoglycosides (and traditional medicine in South Africa). Hence, taking heed of the following results from the current study is recommended:

11.2. SUMMARY OF MAIN FINDINGS

- Hearing loss with tinnitus and dizziness in various combinations was found in both the treatment (experimental) and non-treatment (control) group - with a prevalence rate that increased from 10% to 28% over a six month period of monitoring. The prevalence of 28% was significantly higher than that of the general South African population (that of 20%).
- A significantly higher percentage of SNHL (90% of clinical hearing loss was SNHL) was found in both the control and experimental groups with the degree of hearing loss tending to be more severe in the control group when compared to that in the experimental group.
- A tendency for sloping/high frequency configuration was observed in the experimental group with the control group having no distinctive pattern of configuration. 80% of

clinical hearing loss in the control group had a flat/irregular configuration, while 47% of clinical hearing loss in experimental group had a distinctive sloping/high frequency configuration. The sensorineural and high frequency nature of the hearing loss in the experimental group seemed to be consistent with features typical of ototoxic hearing loss.

- The symmetry of hearing loss was mainly bilateral in both groups with more than 60% of the participants with clinical hearing loss presenting with bilateral hearing loss.
- The type of onset of hearing loss was gradual/progressive for all participants in both the control and experimental groups.
- The possible causes of hearing loss seemed to be similar in the experimental and control groups with opportunistic infections (meningitis, otosyphilis, otitis media) contributing significantly, even in the experimental group where ARVs were being used. However, another significant possible cause of hearing loss in the experimental group was that of ARVs in the form of 3TC, D4T and Stocrin (41% of participants with clinical hearing loss) – although this could not be confirmed because of unidentified interactions with other treatments, and/or other factors. However, the fact that the control group was also exposed to similar interactions raises an index of suspicion about the possible effects of ARVs used in the current study on hearing.
- ARVs (in the form of 3TC, D4T and Stocrin) appeared to have an ototoxic potential that was possibly aggravated to clinical hearing loss by the presence of risk factors that were thought to contribute to the changes on audiograms. These risk factors included previous use of ototoxic medications such as history of previous TB treatment (31% of participants), previous use of ARVs (6% of participants), and noise exposure at the same time as ARV use.

- On audiological monitoring, no statistically significant changes were found for both pure tone audiometry and DPOAEs for the control group – with absent clinically significant changes. However, clinically significant changes with statistically significant changes were found for DPOAEs in the experimental group, particularly at the high frequencies (6 and 8kHz) – implying possible sub-clinical hearing changes (cochlea function changes detected before the hearing loss is seen on an audiogram). This possibility of subclinical hearing changes was also seen in findings of the subclinical hearing loss group who had normal pure tone function with clinical changes on DPOAEs at 6 and 8 kHz.

11.3. LIMITATIONS OF THE STUDY

Although results from the present study have the potential to contribute toward enhancing management of adults on antiretroviral medications as far as audiological assessment and management are concerned, particularly with regard to early detection and monitoring of the toxic effects of the drugs and prompt management, these results need to be considered in relation to methodological weaknesses identified in the project's research design and analysis. Critical analysis of the study revealed the following limitations:

- The nature of the disease and the population being studied precluded complete control over confounding variables that could have had an influence on the results, such as interactions of ARVs with other therapies. Although this is acknowledged as a limitation that prevents definitive conclusions about the effects of ARVs – it would seem more worthwhile to conduct drug trials under realistic conditions that are likely to be present when the medication is being taken than to create ideal conditions that may not yield reliable results.

- Due to the limited access to patients who were not on ARVs at the time of the study, the researcher was unable to recruit a larger sample for the control group to be able to match the two groups with regard to sample size, age and gender.
- The small size of the control group was further reduced by attrition factors such as death, commencement of ART, and so forth.
- The nature of the disease, coupled with other reasons such as financial factors, failure to adhere to treatment, death, and so forth impacted on the total number of participants who attended all three sessions of evaluation; however, the final sample appeared sufficiently large and sufficiently representative for cautious generalizability of the results to similar contexts.
- The participants that presented with clinical hearing loss were referred to Ear, Nose, and Throat Specialists for assessment and management. These participants were not followed up as part of the study, and this could have represented a weakness of the study. The researcher excluded these participants in an attempt to control for extraneous variables that could have impacted on the results of the study, such as the effects of treatment modalities that the ENTs could have instituted.
- The length of time for which the monitoring occurred (maximum of 6 months) may have been too short to allow for clinical hearing loss possibly caused by ART to manifest and therefore be detected. However, the researcher had valid reasons for not further extending the longitudinal nature of the study. The main reasons included avoidance of attrition due to poor adherence, death, and any other factors that influence patient attendance at outpatient clinics.

- The researcher collected details from patient medical records and from the case history interview of all the medications that the participants were taking or had taken in the past. However, the researcher had no control over the use of other medications that were not documented in the medical record or that the participants admitted to having used or were using. The researcher was most concerned about the use of complimentary/alternative treatments in the form of traditional medicines such as *"Ubhejane"* which participants may not have felt comfortable in divulging to the researcher as a member of the western health care team.
- Dosing schedules of the medication for all other therapies to determine the amount, frequency, and length of time that the participants were on the medications could not be compiled. Besides the dosing schedules of ARVs which were consistent and uniform, the dosing schedules for all other medications taken were so varied and inconsistent that this information proved impossible to collate, and this is an acknowledged limitation of the current study.
- Extended or ultrahigh frequency testing was not performed as part of the test protocol due to unavailability of appropriate equipment, and this could have exerted an effect on the results of the study. Clinical high frequency hearing loss could have been identified and depicted on the audiogram had extended high frequency formed part of the test battery.
- Although the protocol employed in this research appeared to be adequate and of internationally recommended study design, the inclusion of acoustic reflexes and ABR could have added another dimension to the study.
- The final limitation to the current study was the fact that there were no strict participant exclusion criteria, other than patients who were not diagnosed as HIV/AIDS positive.

However, case history information that has been documented to exert an effect on auditory function was collected for every participant and recorded. This information was then used during the interpretation of the results with the aim of discovering relationships between case history reports and hearing function in the sample studied. Controlling for factors such as previous history of treatment for syphilis and/or TB was thought to be inappropriate to the South African circumstances and context, and therefore to the sample tested at the Johannesburg hospital. The South African Department of Health (2000) states that TB occurs in as many as 50% of patients with HIV/AIDS in the South African context, and so research in this population should take cognisance of this reality, and characterization of the burden of the disease should be true to this reality. The same applies for concomitant use of other medications such as traditional medicine.

11.4. CONCLUSIONS

Since the first quarter of the year 2004, the use of combination therapies has proven to be a dramatic advance in the treatment of HIV/AIDS, allowing longer and healthier lives for many people in this country - a reality which has been in existence in developed countries for over 10 years (Hammer et al., 2006; Noring et al., 2001). These scientific advances, together with substantially increased public-sector funding for HIV/AIDS treatment, clearer standards of HIV care, and greater HIV expertise among health care providers in the country, should be expected to substantially improve the quality of clinical care for the large majority of people with HIV/AIDS in South Africa. However, the information on clinical benefits as well as pitfalls of the treatment modalities still require characterization and dissemination to the patients who are sometimes still deprived of adequate information as well as adequate access. The problem of

inadequate and unequal access to HIV therapies can only be improved if the three critical issues that are believed in many health care arenas to be contributing factors to poor success of treatment plans are addressed. The three critical issues are firstly, the difficulties in designing treatment regimens for patients with complex socioeconomic and medical needs; secondly, barriers to appropriate care that stem from organizational structures such as staff training and policy; and lastly, the pervasive problems of treatment maintenance or adherence - all of which are applicable to the South African situation (Noring et al., 2001). Research into the impact of HIV/AIDS on sensory, cognitive as well as motor aspects of human functioning as well as the impact of ARVs on quality of life needs to be intensified to ensure that benefits gained from the comprehensive HIV/AIDS treatment programmes are not negated by poor adherence due to toxicities of the treatments.

The need for audiometric testing to identify early changes in hearing thresholds resulting from drug therapy is widely recognized. Life-threatening conditions may require treatment with highly ototoxic agents, and the risk of hearing loss may well be unavoidable. In many cases, however, alternative drugs, reduced dosages, or altered treatment regimens are options if ototoxicity is detected early in the treatment period. Prospective monitoring of high-frequency auditory function can enable the physician and the audiologist to weigh the merits of alternative treatment before the loss of hearing sensitivity progresses into the speech communication range. This monitoring can also allow for preventative measures and counselling to be instituted ensuring that progression of hearing loss to speech frequencies is either halted or retarded. Conversely, the absence of evidence of ototoxicity can justify continued or more aggressive treatment. Monitoring hearing threshold changes can also alert the family and the patient to be

aware of the potential for hearing loss and, if needed, early amplification assistance. Thus far, data from the current prospective study suggest that identifying and testing for ototoxicity that includes distortion product otoacoustic emissions as one of the measures for each patient, could provide much more sensitive early detection capability than pure tone audiometry alone. The current study indicates that changes in cochlear function can be detected far earlier in its development through the use of DPOAEs than with pure tone audiometry. Use of DPOAEs has been shown to provide increased sensitivity for early detection of ototoxicity than pure tone audiometry, and therefore should form part of the ototoxicity monitoring protocol for ARVs.

Although in therapy for AIDS, iatrogenically induced hearing loss may be tolerated in pursuit of cure or palliation, identification of this toxicity still requires characterization. This is particularly critical since unexplained hearing loss during treatment, particularly in the absence of adequate audiologic monitoring and conservation safeguards might pose severe problems that could hamper the development of a promising therapeutic agent. Regularly scheduled, on-site audiologic monitoring would allow an opportunity to detect early ototoxic side effects with increased sensitivity so they may be arrested or reversed (Anteunis et al., 1994; Grau et al., 1991; Hadley & Herr, 1979; Sataloff & Rosen, 1994; Schweitzer, 1993; Walsh et al., 1982). Because the optimal duration of treatment with antiretroviral agents may be open-ended, there is potential for cumulative toxicity and the need for ongoing vigilance – making audiologic monitoring a necessary safeguard.

Early recognition of an agent's ototoxic potential, along with sensitive mechanisms for quantifying the magnitude of impairment, may afford clinicians the opportunity to reduce the

dose or substitute the toxic agent with less toxic substances before the onset of significant hearing loss. Monitoring in order to limit, and even forestall, ototoxicity as early as possible in the course of clinical treatment is clearly in the best interests of patients. Naturally, as clinical experience accrues for a particular drug, the magnitude of ototoxic risk will become better defined. If the preponderance of data shows minimal risk for hearing loss – as in the current study, then screening and monitoring recommendations can be relaxed accordingly. Conversely, in populations at increased ototoxic risk, more intense scrutiny (shorter intervals between audiometric testing) may be warranted, as in the South African population infected with HIV/AIDS where TB treatment is an added risk for ototoxicity. In the case of long term interventions, one must also bear in mind that even minimal risks for ototoxicity can be magnified over time. The fact that the current study showed more evidence of subclinical hearing impairment than clinical hearing loss measurable on a conventional audiogram highlights the critical need for long-term monitoring, as one does not know when clinical hearing loss will manifest or the rate of progression of the hearing loss. Moreover, the interaction of the medications used with other factors has not been clearly established.

The protocols generally followed for ototoxicity monitoring are intentionally limited to conventional audiometry (0.25 to 8 kHz) which is the generally accepted standard of care. High-frequency audiometry, formerly a research tool, is increasingly used to detect ototoxic changes above 8 kHz, which correspond to early cochlear insults (Campbell & Durrant, 1993; Dreschler et al., 1989; Fausti et al., 1984; Fausti, Rapapport et al., 1984; Huang & Schacht, 1989; Jacobson, Down & Fletcher, 1969; van der Hulst, Dreschler & Urbanus, 1988). High frequency audiometry clearly detects preclinical ototoxicity with greater sensitivity than conventional

audiometry (Dreschler et al., 1989; Fausti et al., 1984; Fausti, Rapapport et al., 1984; Jacobson, Down & Fletcher, 1969), and may be used to detect early cochlear insults (Huang & Schacht, 1989; van der Hulst, Dreschler & Urbanus, 1988). Although such instrumentation is commercially available, it is not universally used. Consequently, high frequency testing for ototoxicity monitoring is encouraged. Though the same may be said for OAEs, their availability and their increased use in clinical settings far outweigh ultrahigh frequency audiometry. Furthermore, OAEs allow for testing of difficult to test populations since they are objective and do not rely on the patient's response. Testing chronically ill patients or terminally ill persons who may be unwell during the testing session through the use of ultra-high frequency audiometry may not yield as reliable and as accurate results as through the use of DPOAEs. The current study highlighted this sensitivity of DPOAEs.

It is acknowledged that for life-threatening illnesses such as cancer or HIV/AIDS, toxicity may be tolerated in the absence of viable alternatives. However, when promising agents first advance into clinical trials, toxicities need to be identified or well-defined, particularly for drugs intended for prolonged administration, such as ARVs.

11.5. RECOMMENDATIONS IN TERMS OF FUTURE DIRECTIONS

Despite limitations of the current study, the results obtained from this study have significant implications. Over and above an attempt to extensively describe the auditory status in a group of adult patients with AIDS receiving ART and other therapies, this study afforded an opportunity to tentatively display and highlight an expanded role for the audiologist in Food and Drug Administration processes of drug development, drug approval, and drug monitoring.

Furthermore, this research also demonstrated the important role that the audiologist may have in both the assessment and treatment of patients with HIV/AIDS. Finally, the study was conducted within the South African context – which is considered to be the epicentre of the African HIV/AIDS pandemic, a context that is acknowledged to present with unique challenges of which political, social, economic, health, equipment, and personnel challenges are deemed non-exhaustive. Hence implications raised by the current study can be translated into recommendations for the clinical assessment and management of patients with HIV/AIDS who are taking ARVs; education of team members; policy formulation; as well as further research.

11.5.1. Recommendations for the clinical assessment and management of patients with HIV/AIDS:

- Results from the present study have the potential to contribute toward enhancing audiological assessment and management of patients infected with this virus, thereby impacting positively on their quality of life. This type of intervention is particularly important in the current era of financial constraints across services in provincial hospitals. On the identification and prioritization of patients' needs, the current study can potentially assist in the design of appropriate audiologic services for AIDS patients on and off ARVs. The results also potentially allow for improved caregiver/patient communication and can alert caregivers to the possible need for appropriate referral of the patient to in-house speech and hearing therapy when patients respond inappropriately to speech and other sounds. Appropriate management would include factors such as regular monitoring of hearing to determine the progression of hearing loss, as well as counselling regarding hearing conservation practice where the use of hearing protection is emphasized as persons with ototoxicity are more

susceptible to noise induced hearing loss. Should clinical hearing loss start presenting, other management input from which the patients could benefit would include correct hearing aid fittings where progression of the hearing loss is known or suspected, regular rechecks of hearing status for possible adjustment of hearing aid settings to ensure maximum benefit from amplification, and visual training where hearing aids are of no or minimal benefit to patients. Furthermore, appropriate referrals to Ear, Nose and Throat specialists for management of potentially treatable causes could also contribute to direct benefit of patients from audiological services.

- Moreover, the results of the current study suggest that ARVs (in the form of 3TC, D4T and Stocrin) may have the potential to cause hearing impairment (singly or in interaction with other factors) which requires constant monitoring to ensure that prompt management is provided as soon as the speech frequencies are involved. Prolonged monitoring of patients on ARVs could potentially enable researchers to discover when clinical hearing loss commences, which could guide management protocols. This strategy would also allow researchers to explore factors such as drug changes, dosing alterations, and provision of protective agents along with ARVs – since termination of drug use is not an option in these cases.
- Audiological changes attributable to HIV/AIDS and the antiretroviral medications used to treat the condition and its associated opportunistic infections is likely to increase the demand for audiologists to work with patients with HIV/AIDS. Results from the current study highlight the need for ototoxicity monitoring of patients on ARVs (particularly of those persons at risk of ototoxicity) including the use of sensitive measures such as DPOAEs since

these detect subclinical changes to cochlear function prior to being depicted on the conventional audiogram.

- Finally, in as far as expanding the ear care services provided to patients with HIV/AIDS, the following specific recommendations could be noted:
  - Audiologists should form part of the drug development, testing and approval process.
  - Physicians should ensure that all patients with or who are at higher risk for hearing loss or vestibular problems are identified at baseline and closely monitored.
  - A feasible schedule for audiologic monitoring is suggested for each patient at risk.
  - Drug-related hearing loss needs to be distinguished from hearing loss due to other causes.
  - Appropriate steps for evaluating ototoxicity encountered in clinical trials should be suggested; and
  - An awareness of an under-recognized problem with newer drugs should be raised – particularly the interaction of these drugs with other factors which will often be present in clinical populations requiring these drugs (e.g. use of supplements, use of TB treatment, noise exposure, and so forth).

11.5.2. Recommendations for education of team members:

- It is recommended that the results from the current study be used to educate the various team members involved in the management of patients with HIV/AIDS in health care settings in South Africa. Results regarding the prevalence of hearing loss in this population and the possible causes in the sample evaluated can potentially alert the medical team to the possible communication impairment that the patients could present with. The possibility of drug induced hearing loss in this population could highlight the importance of audiological

monitoring for early detection and early management of those patients prone to ototoxicity. By enhancing knowledge and awareness of health care professionals regarding hearing problems in patients with HIV/AIDS, audiologists can potentially contribute towards better total management of patients, thereby impacting positively on patients' quality of life.

- Results from the current study could also be used to educate investigators involved in drug trials, of the importance of utilizing sensitive measures to determine ototoxicity of drugs, and to recommend protocols that are appropriate for this purpose.

11.5.3. Recommendations for policy formulation:

- One of the reasons for performing the current study was to gather information that could be used practically at the Johannesburg Hospital's Audiology Clinic in terms of budget planning and resource management. Results from this study could therefore be utilised to motivate and apply for funds to be made available for hearing aid purchasing for patients with HIV/AIDS. In this way, findings from the present study could potentially impact on South African health care policy and resource allocation for patients with HIV/AIDS, attending public sector clinics throughout the country. Furthermore, when budgets are allocated for comprehensive HIV/AIDS management, audiological services could be included in these programmes. Recommendations need to be made for audiological services in terms of the provision of sensitive and objective equipment such as OAE measures as well as the appointment of audiologists at all HIV/AIDS clinics in government institutions.
- Policy frameworks that are developed and put forward for comprehensive HIV/AIDS treatment need to include monitoring for side effects of medications including ototoxicity – and not only focus on adverse life threatening events. Side effects of medications may not

increase mortality, but may significantly increase morbidity which has negative impact on quality of life.

11.5.4. Recommendations for Future Research

Finally, in view of the paucity of research literature on auditory function in patients with HIV/AIDS in the South African context, and the dearth of international research on the effects of ARVs on hearing, it is hoped that these findings may provide the springboard for further research in this area, thereby enhancing knowledge and understanding of a vital but neglected domain. Specific recommendations for future research include the following:

- Future research should be conducted on an extended time frame for monitoring to determine the time when onset of clinical hearing loss occurs, if it does eventually – and the progression of this hearing loss.
- Ultrahigh frequency testing should form part of future test protocols.
- Since the virus is said to manifest differently in adults and in children, and since susceptibility to ototoxicity is believed to be different in the different age groups – replication of the current study on the paediatric population would be a fruitful extension of findings obtained in this study. This would be particularly interesting since TB is not as prevalent in paediatric HIV/AIDS as in adults, although middle ear infections may be a huge confounding variable in this population. Determination of ototoxicity in paediatric patients with HIV/AIDS would also appear to be of critical importance because of its impact on speech-language development, as well as social and academic development of that population.

- The effect of traditional medicines on hearing function in HIV/AIDS needs to be explored, particularly the concomitant use of this medication with ARVs and the interaction effects of these different agents.
- Individual case studies that allow for detailed analysis and scrutiny of all audiological function and close correlation with medical reports are recommended as part of future studies. It is possible that this methodology may lead to better control over the confounding variables found in the current study (even though generalization of the results may be even more compromised in a case study).
- Further attempts should be made at replicating the current study on matched groups, even if sample sizes are smaller.
- A longer time frame for the longitudinal study of the participants who participated in the study in terms of monitoring testing would probably have yielded a clearer picture in response to the question regarding the progression of the subclinical hearing loss with the continued use of antiretroviral drugs. The participants who presented with a clinical hearing loss could also have been followed up as part of the study to determine whether the hearing loss was stable, progressive or fluctuating in nature. Understanding the nature of hearing loss with the long term use of the drugs is likely to facilitate better and more accurate management in terms of when amplification is provided, the type of amplification that is chosen, and/or the kind of aural rehabilitation that is selected.

Focusing as it does, on HAART the most widely used and singularly challenging treatment for HIV/AIDS and its ability to sustain life and improve its quality, results detailed in this thesis would appear to be of critical importance to the context within which the study was conducted.

Given the potential impact of HIV and AIDS as well as its treatment on the auditory function, recommendations made in this thesis deserve serious consideration. Of specific importance, is the need for audiologists to become more involved in both the assessment and management of the infected patient and to forge their role in the drug development process. The coordinated efforts of all health care workers, including audiologists, and combined resources as well as the commitment of all health care workers in engaging with the critical challenge of providing efficacious care to patients with HIV/AIDS, may potentially ensure that quality of life of those infected and affected by this pandemic is enhanced and that lack of adherence to medications due to side effects is greatly reduced.

In conclusion, the results from the present study strongly suggest a high prevalence of hearing loss in a group of adults with AIDS on ART and other therapies – higher than that of the general South African population. A potential effect of ARVs (in the form of 3TC and D4T with Stocrin) on hearing was raised even though this effect was not conclusively established, and this ototoxicity potential was particularly evident when the patients fell within the group at risk for ototoxicity. However, the benefits in reduction of opportunistic infections that lead to more severe degree of hearing loss than the high frequency subclinical hearing loss due to ototoxicity seemed to cancel out the potential ototoxic effects of ARVs used in the current study. Current findings suggest that evoked DPOAEs are a sensitive and a reliable indicator of subtle inner ear dysfunction and should therefore form a crucial aspect of all ototoxicity monitoring test batteries. Because, the recording of DPOAEs is time efficient and can be performed at bedside, they are particularly crucial in assessing the population of HIV/AIDS patients who are often too tired and not well enough to concentrate and attend to ultrahigh frequency pure tone audiometry testing.

The current researcher believes that DPOAE measurement should be routinely used in monitoring of cochlea function in the presence of potentially toxic factors. Furthermore, the current researcher is of the firm belief that the role of the audiologist in pharmacology – ranging from the drug development stage to the clinical trial and approval stage – needs to be expanded. This expanded role is likely to enhance the management of patients with HIV/AIDS (over and above identifying hearing loss due to opportunistic infections) and ensure that their quality of life is improved and their contribution in the society is sustained – allowing for the words of Nelson Mandela "*This is not just a disease anymore - it is a human rights issue*" (Madiba, 2007) to be echoed in all efforts aimed at intensifying research in this field.

"*Know HIV/AIDS in all its manifestations and relations, and all other things clinical will be added unto you*"

Adapted from Sir William Osler (1950, cited in Zapor, et al., 2004)

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Sir/Madam

RE: PERMISSON TO CONDUCT AUDIOLOGY RESEARCH ON HIV/AIDS PATIENTS ON ANTIRETROVIRAL TREATMENT

I am an Audiologist working within the hospital who has previously performed research at the HIV/AIDS clinic as part of her Master's degree. Results obtained from that study led to establishment of audiology services at this clinic and the results were also presented at several conferences and published in an academic journal. One of the recommendations from the previous study was to assess patients on antiretroviral drugs so as to determine if these drugs have any effect on hearing. This letter is therefore an application for permission to perform such a study at the Adult HIV/AIDS clinic. Permission to perform audiological measures in the form of basic audiology testing and Otoacoustic emissions on a sample of adult patients attending the HIV/AIDS clinic is sought. Patients will be tested before they start antiretroviral treatment and twice after a period of 3 and 6 months as an attempt to establish possible ototoxicity of ARVs.

Should you have any queries, please do not hesitate to contact me.

Sincerely

KATIJAH KHOZA
(Senior Audiologist)

Appendix B

Private bag X39, Johannesburg 2000, South Africa
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Gauteng Department of Health

Enq : Dr D.Wojciechowska
Tel : (011) 488 –3754 / 3710
Fax : (011) 488 –4751
E-mail dana01@mweb.co.za

Date : 04/11/2004

Attention: Ms Katijah Khoza
AUDIOLOGIST

RE: PERMISSION TO CONDUCT AUDIOLOGY RESEACH ON HIV/AIDS PATIENTS ON ANTIRETROVIRAL TRATMENT.

Dear Ms. Katijah Khoza

Permission to perform audiological measures in the form of basic audiology testing and Otoacoustic emission on a sample of adult patients attending the HIV/AIDS clinic,as research towards your Phd is granted to you, subject to the following conditions.

1. Approval must be obtained from the Academic and Clinical Head of the HIV/AIDS CLINIC (in writing).
2. Approval has to be granted for the commencement of your research by the Wits Human Research Ethics Committee.

Yours sincerely

DR D. WOJCIECHOWSKA
SENIOR CLINICAL EXECUTIVE

Appendix C

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Sir

RE: PERMISSION TO CONDUCT AUDIOLOGY RESEARCH ON HIV/AIDS ADULTS ON ANTIRETROVIRAL TREATMENT

I am an Audiologist working in AREA 357C who has previously performed research at the HIV/AIDS clinic as part of her Master's degree. Results obtained from that study led to establishment of audiology services at this clinic and the results were also presented at several conferences and published in an academic journal. One of the recommendations from the previous study was to assess patients on antiretroviral drugs so as to determine if these drugs have any effect on hearing. This letter is therefore an application for permission to perform such a study at your clinic. Audiological measures in the form of basic audiology testing and otoacoustic emissions will be done on 100 patients. Patients will be tested before they start ARV treatment and 3 months after commencement of therapy, and lastly at 6 months.

THE COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS requires written permission from all relevant authorities before consideration of the research proposal. Pending, your permission, this has been obtained (attached) from:
(Senior Clinical Executive Officer (Dr D. Wojciechowska)
Head of Audiology Department (Ms T. Jogianna)
My proposal will be discussed at the November Ethics meeting.
Thanking you in advance for your help.
Should you have any queries please do not hesitate to contact me.

Supported but
Suggest: await Ethics approval.

Dr Jwili
Per Dr M Molekwa

Katijah Khoza
(Senior Audiologist)
Tel: 683 8011 **Cell:** 082 339 0605

Appendix D

Department of Speech Therapy and
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KATIJAH KHOZA

RE: PERMISSON TO CONDUCT AUDIOLOGY RESEARCH ON HIV/AIDS PATIENTS ON ANTIRETROVIRAL TREATMENT

Permission to perform audiologycal measures in the form of basic audiology testing and Otoacoustic emissions on a sample of adult patients attending the HIV/AIDS clinic, as research towards your Phd is granted to you. Patients will be tested before they start antiretroviral treatment and twice after a period of 3 and 6 months as an attempt to establish possible ototoxicity of ARVs.

Should you have any queries, please do not hesitate to contact me.

Sincerely

T.JOGIANNA
(Head of Department)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Khoza

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M041131**
PROJECT	Audiologic Monitoring for Ototoxicity in Adult Patients on Anti-Retroviral Drugs attending a Provincial Hospital HIV/AIDS...
INVESTIGATORS	Ms K Khoza
DEPARTMENT	SHCD/Speech Pathology & Audio
DATE CONSIDERED	04.11.26
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.11.29 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof E Ross

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

FACULTY OF HUMANITIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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MS K KHOZA
P O BOX 57
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2050

APPLICATION NUMBER 9301186M
STATUS (DEG 11) (AD002) BAD

2005-01-15

Dear Ms Khoza

FULL CANDIDATURE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (part time)

I am pleased to be able to advise you that readers of the Graduate Studies Committee have approved your proposal entitled " Audiologic monitiring for Ototoxicity in adult patients on antiretroviral drugs attending a provincial hospital HIV/AIDS clinic in Johannesburg, Gauteng" and you have now been admitted to full candidature. I confirm that Prof E Ross has/have been appointed your supervisor/s, in the Department of Speech Pathology And Audiology

The normal period of registration for a full-time candidate for the degree of Doctor of Philosophy (part time) is four years minimum and six years maximum. The thesis is normally submitted to the Faculty Office on or before 31 December. There is a period of grace to 15 February, whereby the student REGISTERS, but DOES NOT PAY FEES.

You are required to submit 3 bound copies and 2 unbound copies (loose pages) of your thesis to the Faculty Office. (The 3 bound copies go to the examiners and are retained by them and the 2 unbound copies are eventually sent to Archives and to the Library.)

I should be glad if you would keep us informed of any changes of address during the year.

Yours sincerely

M SENAMELA (Ms)
Faculty Officer
FACULTY OF HUMANITIES

cc Head of Department
Supervisor
Agenda file

Appendix G

KK

PARTICIPANT INFORMATION LETTER

Good day
My name is Katijah Khoza. I am an Audiologist working at the Hearing clinic (Area 357C), orange block in the hospital. I am currently studying for my postgraduate degree through the University of the Witwatersrand. As part of my research work, I am investigating the possible effects that antiretroviral treatment may have on hearing function in South African patients.

I would like to invite you to take part in my study. Should you decide to take part in the study, I will need about half an hour of your time at three different appointments. I will need to test you once before you start taking the antiretroviral medication, and again at 3 months after you started using the drugs, and the last time at 6 months. During these times, you will be asked a few questions, about your health and hearing, and your hearing will be tested. The hearing test will consist of otoscopy, tympanometry, audiometry, and otoacoustic emissions testing. These tests involve the following:

- Otoscopy: I will look into your ear using an otoscope (ear torch)
- Tympanometry: a probe will be placed in your ear and this will introduce pressure into your ear. This will last for approximately 10 seconds and will not cause you any pain
- Audiometry: this involves listening and responding to beep sounds that you will hear through headphones. These sounds will move from loud to very soft, and to indicate that you can hear them, all you will need to do is press a button that will be provided to you. If you have difficulties with pressing the button, you may have to respond by saying “yes” or raising your hand
- Otoacoustic emissions: Like in tympanometry, a probe will be placed in your ear and this will introduce a beeping sound into your ear, and this lasts for about one minute. This time you will not need to respond to indicate whether you can hear the sound or not. All that will be required of you is to sit still and relax. The test will not be painful and will not cause you any harm.

Your participation in this study is voluntary. You may stop taking part in it at any time without penalty or loss of benefits that are due to you.

I hope that by you taking part in this study, you will be helping the Audiologists in gaining knowledge about how antiretroviral treatment affects hearing. We may also be able to assist you with your hearing problem should you happen to have one by providing you with hearing aids or therapy. With this knowledge, the Audiologists will be able to provide better and improved care to patients with HIV/AIDS. Please note that your name will not be used in the study, instead a number will be used. This is to ensure that nobody gets to know that you were part of this study. If you would like to be part of this study, please fill in the consent form at the bottom of this page. If you wish to be informed of the results of the study, please feel free to request for these and they will be provided to you. I can be reached in Area 357C (Phone no. 488 4303/3044)

Thank you very much for your help.
Sincerely,
Katijah Khoza

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CONSENT FORM

This is to certify that I_____ hereby agree to volunteer to be part of this study authorized by the University of the Witwatersrand and the Superintendent of the hospital. The study and my participation in it have been explained in full to me by Ms Khoza and I understand her explanation. Questions that I asked were answered to my satisfaction, and I understand that I can stop participating in the study at any time I wish to.

_____ _____
Participant’s signature Date

I, the undersigned, have defined and fully explained the study to the above participant. I have also answered all questions raised by the participant.

_____ _____
Audiologist Date

QUESTIONNAIRE ON HEARING AND HIV/AIDS

Demographic Information
Test session:…….....
Patient no.:…… Age:……Gender:…….
Where do you live?……

Medical History:

Health at	CD4+
Session 1	
Session 2	
Session 3	

Viral load at	
Session 1	
Session 2	
Session 3	

Have you ever suffered from any medical problems associated with hearing loss?

Medical Problem	Treatment Given	When
Ear discharge		
Earache		
Trauma to ear		

Have you ever been or are you on treatment for any of the following?

Disease	Was on treatment	Am on treatment	Type of treatment	Length of time
TB				
Cancer				
Syphilis				

Noise Exposure:
Have you ever been exposed to excessive noise?

Environment	Type of noise	Period (months/ Yrs)
Workplace		
Home		
Other (specify)		

Tinnitus:
Do you experience any ringing/buzzing/other noises in your ears? (Y/N)

Ear	Session 1	Session 2	Session 3
Right			
Left			
Both			

Vertigo:
Do you experience dizziness/ spinning of the house around you? (Y/N)

Session 1	Session 2	Session 3

Please explain:……..

Hearing Status:

Does anyone in your family have hearing problems?

Yes	
No	

If yes, please explain…….

How was your hearing before you were diagnosed with HIV/AIDS?

Good	
Fair	
Bad/Poor	

Has your hearing changed since you were diagnosed?	Session1	Session2	Session3
Yes			
No			

How (please explain)……

How was the change in your hearing?

Sudden	
Gradual/Progressive	

How is your hearing at present?	Session1	Session2	Session3
Good			
Fair			
Bad/Poor			

Is your hearing:	Session1	Session2	Session3
Stable (remaining the same)			
Deteriorating (getting worse)			
Fluctuating (sometimes good/sometimes bad)			

Which ear/s give you problems?	Session1	Session2	Session3
Right			
Left			
Both			
Neither			

Antiretroviral drugs you are taking:

Name	Dosage	Period (wks/months/ Yrs)

Other drugs taken:

Name	Dosage	Period (wks/months/ Yrs)

Additional Comments:
Is there any other information you would like to add about your hearing?
……..
……..
……..
……..

Thank you for your co-operation

OTOTOXICITY MONITORING

KATIJAH KHOZA
JHB HOSPITAL AUDIOLOGY

Name: **Sticker:**

Referral source:

OTOSCOPY:

OTOSCOPY	SESSION 1	SESSION 2	SESSION 3
RIGHT			
LEFT			

ACOUSTIC IMMITTANCE

EAR	Type			Canal volume			Compliance			Pressure			Gradient		
SESSION	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
RIGHT															
LEFT															

AUDIOMETRY – AC

HERTZ	250HZ			500HZ			1000HZ			2000HZ			3000HZ			4000HZ			6000HZ			8000HZ		
SESSION	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
RIGHT																								
LEFT																								

AUDIOMETRY – BC

HERTZ	250HZ			500HZ			1000HZ			2000HZ			3000HZ			4000HZ			6000HZ			8000HZ		
SESSION	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
RIGHT																								
LEFT																								

OTOACOUSTIC EMMISSIONS RESULTS (DPOAE) (DP-NF)

HERTZ	750HZ			1000HZ			2000HZ			3000HZ			4000HZ			6000HZ			8000HZ		
SESSION	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
RIGHT																					
LEFT																					

APPENDIX J - Control group

SUBJECT	AGE	GENDER	RACE	CD4	VL	VOL L	VOL R	COMPL L	COMPL R	GRAD L	GRAD R	PRESS L	PRESS R	PTL 250	PTR250	PTL500	PTR500	PTL1000	PTR1000	PTL2000	PTR2000	PTL4000	PTR4000	PTL8000	PTR8000	DPL750	DPR750	DPL1000	DPR1000	DPL2000	DPR2000	DPL3000	DPR3000	DPL4000	DPR4000	DPL6000	DPR6000	DPL8000	DPR8000	TINNITUS	VERTIGO
SUBJ1A	28	F	B	204		0.85	0.86	0.4	0.54	0.23	0.33	-31	-16	15	15	10	15	15	20	15	10	10	5	15	15	10	11	14	16	15	15	12	15	24	25	24	19	22	20	N	N
SUBJ1B														15	10	15	15	15	20	15	10	10	10	10	10	12	13	14	17	18	16	14	14	24	27	23	19	22	21	N	N
SUBJ1C				26										15	10	15	15	10	20	15	10	10	10	10	10	10	12	14	17	16	16	13	15	23	25	23	18	23	20	N	N
SUBJ2A	29	F	B	188		0.75	1.38	0.54	0.79	0.34	0.52	-14	-18	25	25	30	40	35	30	40	45	40	45	55	55	-3	0	0	0	0	0	-1	0	0	0	0	0	0	0	Y	N
SUBJ2B				ENT												ENT																		ENT						
SUBJ2C				ENT												ENT																		ENT						
SUBJ3A	37	M	B	156		1.21	1.26	0.99	0.54	0.7	0.29	-13	-21	10	15	15	10	20	20	20	10	10	10	15	10	17	17	18	15	24	20	23	25	11	21	6	23	7	7	N	N
SUBJ3B				85										15	15	15	10	20	20	20	10	10	10	15	10	16	18	18	15	25	20	24	24	11	20	5	23	6	7	N	N
SUBJ3C									DNA								DNA								DNA								DNA					DNA		
SUBJ4A	29	M	B	198		1.08	1.18	0.63	0.79	0.35	0.6	-83	-110	15	10	10	15	15	10	10	15	10	15	10	5	10	7	12	8	14	16	19	12	14	15	16	16	12	13	N	N
SUBJ4B														15	10	10	15	15	10	10	15	10	15	10	5	10	6	12	8	13	16	17	12	13	16	16	17	10	11	N	N
SUBJ4C				56										20	15	10	15	15	10	10	15	10	15	10	5	11	7	13	10	14	15	18	11	13	14	15	15	11	12	N	N
SUBJ5A	33	F	C	101		1.01	0.88	1.06	0.97	0.86	0.76	-22	-32	15	20	10	10	15	20	20	20	15	10	10	10	18	21	28	28	24	21	14	16	19	14	9	12	14	15	N	N
SUBJ5B														15	20	10	10	15	20	20	20	15	10	10	10	15	19	27	28	26	20	12	18	18	14	11	13	12	13	N	N
SUBJ5C				14										15	20	10	10	15	20	20	20	15	10	10	10	17	20	28	28	25	20	13	17	19	14	8	13	13	15	N	N
SUBJ6A	32	F	B	205		1.03	1.02	0.69	0.68	0.25	0.25	-27	-27	10	15	20	15	15	20	15	10	10	5	5	10	19	19	17	17	19	19	11	22	18	21	14	22	16	11	N	N
SUBJ6B														10	15	20	15	15	20	15	10	10	5	5	10	19	19	15	18	18	21	9	24	17	23	9	14	8	5	N	N
SUBJ6C				101										40	15	50	15	40	20	45	10	40	5	50	10	18	18	16	16	19	20	11	23	18	22	7	4	6	2	Y	N
SUBJ7A	30	M	B	55		1.11	1.13	0.98	0.98	0.5	0.5	-12	-10	20	10	10	15	15	15	5	5	10	10	5	10	9	7	12	9	12	7	15	9	21	16	22	14	9	11	N	N
SUBJ7B				12										15	10	10	15	15	15	10	10	10	10	5	10	3	6	12	9	12	7	15	9	21	16	22	11	9	10	N	N
SUBJ7C									DNA								DNA								DNA								DNA					DNA		
SUBJ8A	26	F	C	48		1.21	1.21	0.99	0.99	0.7	0.7	-13	-13	20	10	10	10	20	15	10	5	10	15	15	10	19	14	22	19	16	7	21	25	27	25	22	23	19	21	N	N
SUBJ8B				25										15	10	10	10	15	15	10	5	10	15	15	10	13	12	22	19	15	7	21	25	27	25	22	23	19	21	N	N
SUBJ8C									DNA								DNA								DNA								DNA					DNA		
SUBJ9A	33	M	B	202		1.35	1.29	0.4	0.37	0.15	0.19	-28	-24	15	10	15	15	10	15	10	10	10	10	15	15	18	21	28	28	24	21	14	16	19	14	9	12	14	15	N	N
SUBJ9B														15	10	15	15	10	15	10	10	10	10	15	15	21	21	29	30	22	21	13	16	19	14	11	14	17	16	N	N
SUBJ9C				33										15	10	15	15	10	15	10	10	10	10	15	15	19	20	27	29	23	22	15	16	20	13	10	13	14	14	N	N
SUBJ10A	38	F	B	198		0.99	0.87	0.27	0.17	0.1	0.05	-36	-28	10	5	10	10	15	10	10	15	10	15	10	5	4	6	7	7	15	7	16	19	19	14	34	32	24	27	N	N
SUBJ10B														10	5	10	5	10	10	10	10	10	15	10	5	3	8	8	9	15	9	17	20	21	13	32	34	26	29	N	N
SUBJ10C				93										10	5	10	10	10	10	10	15	10	15	10	5	-3	6	7	6	15	7	16	19	20	13	33	33	23	27	N	N
SUBJ11A	37	F	B	200		1.29	1.21	0.51	0.53	0.25	0.25	-32	-28	10	15	5	10	15	15	5	10	10	10	10	10	14	9	17	15	16	11	17	7	26	12	25	22	20	18	N	N
SUBJ11B														10	15	5	10	15	15	10	10	10	10	10	10	16	8	15	17	18	12	19	9	27	13	23	23	22	19	N	N
SUBJ11C				55		1.29	2.74	0.51	0	0.25	0	-32	0	10	60	5	75	15	70	10	65	10	70	10	65	14	0	16	0	15	0	18	0	26	0	24	0	21	0	Y	N
SUBJ12A	26	F	B	106		1.32	1.12	0.52	0.36	0.27	0.14	-24	-28	15	10	10	15	10	20	10	15	15	15	10	15	22	19	26	22	21	16	16	17	21	24	16	16	17	14	17	N	N
SUBJ12B				23										40	35	45	30	40	40	45	40	50	40	35	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Y	Y
SUBJ12C									ENT								ENT								ENT								ENT					ENT		
SUBJ13A	27	M	B	198		1.91	1.95	0.93	1.03	0.52	0.71	-48	-64	15	10	10	20	15	10	5	5	10	10	15	10	10	18	21	28	28	24	21	14	16	19	14	9	12	14	N	N
SUBJ13B														15	10	10	20	15	10	5	5	10	10	15	10	10	20	22	31	30	26	22	13	14	17	17	11	13	16	N	N
SUBJ13C				34										15	10	10	20	15	10	5	5	10	10	15	10	11	19	21	29	28	25	21	14	15	18	15	9	11	15	N	N
SUBJ14A	30	F	B	103		0.28	0.29	0.11	0.11	0.05	0.07	4	4	20	10	15	10	10	15	10	10	10	15	15	15	8	15	17	21	17	20	17	23	18	20	6	9	7	9	N	N
SUBJ14B														20	10	10	10	10	10	10	10	10	15	15	15	11	16	19	19	17	23	20	25	16	21	8	11	8	11	N	N
SUBJ14C				56										20	10	10	10	10	10	10	15	10	15	15	15	9	16	17	20	15	19	18	22	17	20	7	10	7	10	N	N
SUBJ15A	31	M	B	203		1.28	1.28	0.35	0.36	0.19	0.19	-20	-24	20	10	10	20	15	10	15	10	10	15	15	10	10	11	22	19	29	26	18	27	13	17	14	14	18	19	N	N
SUBJ15B														20	10	10	20	15	10	15	10	10	15	15	10	13	11	24	21	31	27	19	25	15	15	6	8	8	12	N	N
SUBJ15C				33										15	10	10	20	15	10	15	10	10	15	15	10	11	10	22	21	30	25	16	26	14	16	0	7	0	8	N	N
SUBJ16A	30	M	B	196		1.14	1.15	0.8	0.8	0.42	0.43	-44	-28	10	15	10	15	10	10	15	5	5	5	5	10	14	11	20	19	7	18	8	10	7	10	6	6	7	14	N	N
SUBJ16B				98										10	15	10	15	10	10	15	15	5	5	5	10	15	13	18	17	9	21	10	9	5	9	7	8	8	12	N	N
SUBJ16C									DNA								DNA								DNA								DNA					DNA		
SUBJ17A	28	F	B	179		1.5	1.1	0.95	0.45	0.55	0.22	-32	-20	5	10	10	15	15	15	20	10	10	10	15	15	14	7	20	22	11	11	10	14	19	14	21	21	15	7	N	N
SUBJ17B				54										5	10	10	15	15	15	20	10	10	10	15	15	15	8	20	23	10	9	13	12	20	13	20	21	13	6	N	N
SUBJ17C									DNA								DNA								DNA								DNA					DNA		
SUBJ18A	42	F	B	195		1.08	1.14	1.21	1.77	0.7	1.12	-36	-24	10	10	5	10	20	15	10	15	20	15	20	10	15	16	26	28	28	29	26	22	24	14	6	15	10	15	N	N
SUBJ18B														15	10	10	10	20	15	10	15	20	15	15	10	18	14	28	26	31	27	26	20	23	11	9	18	12	13	N	N
SUBJ18C				21										10	10	5	10	20	15	15	10	15	20	15	15	10	16	16	25	28	29	28	25	21	24	13	6	16	13	N	N
SUBJ19A	40	F	C	143		1.52	1.17	0.78	0.86	0.35	0.49	-20	-28	5	15	10	10	10	20	10	10	20	15	10	10	10	14	17	19	31	33	32	30	30	28	20	19	20	10	N	N
SUBJ19B														5	15	10	10	10	20	10	10	20	15	10	10	13	12	15	22	30	32	34	32	31	26	23	19	19	9	N	N
SUBJ19C				23										5	15	10	10	10	15	10	10	20	15	10	10	11	13	17	21	30	32	33	32	29	27	21	20	21	10	N	N
SUBJ20A	29	M	B	195		1.72	1.43	0.6	0.57	0.25	0.23	-28	-32	5	10	15	15	15	15	10	15	10	10	15	5	14	6	22	12	12	9	17	8	21	14	17	10	10	13	N	N
SUBJ20B														10	10	15	15	15	15	10	15	10	10	10	10	15	9	25	13	12	11	19	11	23	12	18	9	11	15	N	N
SUBJ20C				56										10	10	15	15	15	15	10	15	10	10	10	10	13	7	23	11	10	10	18	9	22	13	16	8	11	12	N	N
SUBJ21A	41	M	B	189		1.8	1.81	0.8	0.79	0.26	0.25	-12	-10	10	10	15	15	10	15	10	10	10	20	10	10	10	9	16	7	17	6	8	17	12	21	8	20	10	14	N	N
SUBJ21B				31										10	10	15	15	10	15	10	10	10	20	10	10	10	8	15	5	15	6	9	19	11	20	8	21	8	16	N	N
SUBJ21C									CTR								CTR								CTR								CTR					CTR		
SUBJ22A	36	F	B	193		1.79	1.68	1.3	2.12	0.8	1.54	-56	-44	15	20	15	10	15	15	5	10	20	20	20	20	9	9	11	8	10	8	18	8	17	14	13	10	7	21	N	N
SUBJ22B				98										10	15	10	10	15	15	5	10	20	20	20	20	8	8	11	10	11	10	15	9	18	12	11	11	8	21	N	N
SUBJ22C									DNA								DNA								DNA								DNA					DNA		
SUBJ23A	33	F	B	203		0.9	0.92	0.31	0.34	0.12	0.17	-32	-28	10	10	15	10	10	15	5	10	10	15	15	15	10	7	7	16	13	7	11	19	15	23	14	20	8	7	N	N
SUBJ23B				140										10	10	10	10	10	10	5	10	10	15	15	15	11	9	5	19	14	8	13	18	15	24	11	18	10	8	N	N
SUBJ23C									CTR								CTR								CTR								CTR					CTR		
SUBJ24A	29	F	B	167		1.39	1.37	0.59	0.61	0.28	0.29	-32	-28	10	5	10	15	10	10	10	15	10	10	10	10	8	9	8	8	7	12	8	14	13	17	8	19	6	15	N	N
SUBJ24B				95										10	5	10	15	10	10	10	15	10	10	10	10	9	11	9	9	5	11	9	11	12	15	8	17	8	14	N	N
SUBJ24C									DNA								DNA								DNA								DNA					DNA		
SUBJ25A	43	F	B	200		1.42	1.04	0.67	0.63	0.33	0.4	-12	-28	5	10	10	15	10	10	15	10	15	10	10	10	13	9	21	8	15	12	21	15	18	17	17	19	13	15	N	N
SUBJ25B				42										5	10	10	15	10	10	15	10	15	10	10	10	12	8	20	7	16	12	20	13	19	17	13	15	9	9	N	N
SUBJ25C									DNA								DNA								DNA								DNA					DNA		
SUBJ26A	40	M	B	196		1.72	1.43	0.6	0.57	0.25	0.23	-28	-28	5	10	10	15	15	15	10	10	15	15	15	15	13	14	12	16	25	23	26	26	24	25	17	19	22	26	N	N
SUBJ26B				133										5	10	10	15	15	15	10	10	15	15	15	15	12	14	12	15	22	22	24	26	23	25	10	19	21	25	N	N
SUBJ26C				37										5	10	10	15	15	15	10	10	15	15	15	15	-8	8	9	10	17	11	11	22	11	25	7	8	2	20	N	N
SUBJ27A	46	M	B	187		2.11	2.28	1.72	1.36	1.02	0.83	-20	-24	0	5	10	10	15	10	10	10	5	5	0	5	9	9	19	15	8	18	12	13	14	12	25	11	23	26	N	N
SUBJ27B														0	5	10	10	15	10	10	10	5	5	0	5	11	9	17	13	8	17	14	14	12	11	23	12	21	27	N	N
SUBJ27C				89										40	35	45	30	40	40	45	40	50	40	35	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Y	Y
SUBJ28A	28	F	B	179		1.19	1.1	0.89	0.65	0.36	0.3	-64	-44	5	10	20	15	15	10	15	20	10	5	5	5	8	9	14	17	18	18	18	9	16	17	24	24	17	15	N	N
SUBJ28B									DNA								DNA								DNA								DNA					DNA		
SUBJ28C									DNA								DNA								DNA								DNA					DNA		
SUBJ29A	36	M	B	156		1.8	1.82	0.8	0.81	0.25	0.25	-8	-10	5	10	10	15	10	10	10	15	10	10	10	10	18	16	19	9	13	17	12	22	15	15	20	19	18	25	N	N
SUBJ29B				32										5	10	10	15	10	10	10	15	10	10	10	10	15	15	17	11	15	16	11	22	17	14	22	19	19	24	N	N
SUBJ29C									CTR								CTR								CTR								CTR					CTR		
SUBJ30A	33	M	B	198		1.24	1.09	0.47	0.42	0.19	0.15	-20	-44	20	10	10	15	10	10	20	15	15	15	10	10	12	19	21	18	16	18	18	19	22	17	21	24	17	10	N	N
SUBJ30B				12										20	10	10	15	10	10	20	15	15	15	10	10	11	18	23	19	15	16	19	19	23	15	22	22	18	8	N	N
SUBJ30C					CTR										CTR				CTR				CTR						CTR										CTR		
SUBJ31A	32	F	B	189		1.12	1.11	0.48	0.52	0.2	0.2	-20	-20	25	15	10	10	20	15	10	10	5	5	5	10	10	17	18	10	19	19	17	15	13	12	15	18	19	18	15	N	N
SUBJ31B				45										25	15	10	10	20	15	10	10	5	5	5	10	10	15	16	10	18	18	19	14	12	11	15	18	21	17	17	N	N
SUBJ31C			B		CTR										CTR				CTR				CTR						CTR										CTR		
SUBJ32A	33	F		201		2.08	1.84	2.11	1.84	1.49	1.26	-44	-44	20	10	5	10	20	15	15	10	20	15	10	10	17	10	20	9	12	9	15	13	13	15	14	13	15	14	N	N
SUBJ32B				67										20	10	5	10	20	15	15	10	20	15	10	10	18	11	23	11	10	9	13	11	12	15	14	13	14	14	N	N
SUBJ32C					CTR										CTR				CTR				CTR						CTR										CTR		
SUBJ33A	29	F	B	190		1.18	1.41	0.74	0.71	0.46	0.4	-28	-16	10	10	5	10	15	10	10	15	10	10	15	10	13	11	18	8	8	10	19	17	19	18	19	18	19	18	N	N
SUBJ33B				55										10	10	5	10	15	10	10	15	10	10	15	10	13	10	17	10	9	9	19	19	18	16	18	18	17	20	N	N
SUBJ33C					CTR										CTR				CTR				CTR						CTR										CTR		
SUBJ34A	30	F	B	100		1.09	1	0.52	0.67	0.29	0.38	-28	-28	10	5	10	10	15	10	10	20	10	10	10	15	14	13	18	9	9	13	21	22	22	21	22	20	19	21	N	N
SUBJ34B				98										10	5	10	10	15	10	10	20	10	10	10	15	12	13	16	11	8	12	22	22	24	21	20	19	19	20	N	N
SUBJ34C					CTR										CTR				CTR				CTR						CTR										CTR		
SUBJ35A	26	F	B	198		1.47	1.47	0.24	0.23	0.13	0.13	20	18	10	10	5	10	10	10	15	10	10	15	10	10	10	13	18	8	21	13	18	12	13	14	13	13	15	14	N	N
SUBJ35B				56										10	10	5	10	10	10	15	15	10	15	10	10	12	13	17	9	23	14	21	12	12	13	12	13	13	12	N	N
SUBJ35C					DNA										DNA				DNA				DNA						DNA										DNA		
SUBJ36A	29	F	B	201		1.7	1.81	1.94	1.61	1.33	1.01	-24	-28	10	10	5	15	10	10	5	5	10	10	5	5	11	13	13	9	13	12	15	10	12	12	13	15	14	11	N	N
SUBJ36B				86										10	10	5	15	10	10	5	5	10	10	5	5	10	15	13	11	11	11	16	12	10	11	13	15	12	9	N	N
SUBJ36C					DNA										DNA				DNA				DNA						DNA										DNA		
SUBJ37A	29	F	B	87		1.51	1.41	0.83	0.93	0.47	0.53	-24	-24	15	10	15	10	20	10	10	5	15	15	10	10	14	17	8	9	12	12	19	18	18	18	19	17	19	19	N	N
SUBJ37B				33										15	10	15	10	20	10	10	5	15	15	10	10	15	15	8	9	10	10	20	16	19	19	21	16	16	15	N	N

Key: A=session 1; B=sessin 2; C=sessin 3; F=female; M=male; B=black; C=coloured; DTR=deferred treatment; DNA=did not arrive; ENT=ear, nose throat referral; CTR=commenced treatment

SUBJECT	AGE	GENDER	RACE	CD4	VL	VOL L	VOL R	COMPL L	COMPL R	GRAD L	GRAD R	PRESS L	PRESS R	PTL 250	PTR250	PTL500	PTR500	PTL1000	PTR1000	PTL2000	PTR2000	PTL4000	PTR4000	PTL8000	PTR8000	DPL750	DPR750	DPL1000	DPR1000	DPL2000	DPR2000	DPL3000	DPR3000	DPL4000	DPR4000	DPL6000	DPR6000	DPL8000	DPR8000	TINNITUS	VERTIGO
SUBJ37C						DNA									DNA									DNA															DNA			
SUBJ38A	27	F	B		156	1.52	1.49	0.83	0.84	0.46	0.46	12	10	15	10	5	10	10	15	15	5	10	15	15	15	19	19	13	10	12	16	17	16	15	15	16	16	17	18	N	N
SUBJ38B					95									15	10	5	10	10	15	15	5	10	15	15	15	17	18	15	12	10	16	17	18	13	13	17	18	15	18	N	N
SUBJ38C						DNA									DNA									DNA															DNA			
SUBJ39A	33	M	B		101	1.68	1.69	0.43	0.64	0.15	0.36	-20	-28	5	10	20	15	15	10	10	10	10	15	15	10	8	6	11	15	19	19	21	19	19	19	18	17	18	18	N	N
SUBJ39B					33									5	10	20	15	15	10	10	10	10	15	15	10	7	8	10	14	20	21	20	17	18	13	10	8	11	6	N	N
SUBJ39C						DNA									DNA									DNA															DNA			
SUBJ40A	37	M	B		189	1.34	1.42	1.14	1.29	0.69	0.9	-12	-20	20	10	15	15	10	10	5	10	5	5	10	10	7	8	11	18	13	20	23	18	17	17	22	20	21	20	N	N
SUBJ40B					90									40	35	45	30	40	40	45	40	50	40	35	40	-3	0	0	0	0	0	0	0	0	0	0	0	0	0	Y	Y
SUBJ40C						ENT									ENT									ENT									ENT						ENT			
SUBJ41A	23	F	B		198	1.46	1.47	0.79	0.65	0.39	0.26	-40	-40	5	15	10	15	15	20	5	15	10	15	0	20	5	11	6	15	25	21	19	19	18	16	16	17	17	16	N	N
SUBJ41B				DNA				DNA			DNA				DNA				DNA				DNA						DNA						DNA						
SUBJ41C					241									5	15	10	15	15	20	5	15	10	15	0	20	3	13	7	13	26	22	19	17	17	15	17	16	15	15	N	N
SUBJ42A	46	M	B		11	2.95	2.49	1.97	2.21	1.08	1.43	-24	-40	25	25	20	25	25	25	25	25	25	25	25	25	10	12	19	15	23	19	13	17	25	27	21	20	22	21	Y	N
SUBJ42B					52									55	70	65	55	70	35	80	40	90	45	100	65	-7	-6	-14	1	7	7	0	9	5	-3	0	0	3	0	Y	Y
SUBJ42C									ENT				ENT				ENT						ENT						ENT				ENT					ENT			
SUBJ43A	30	F	B		183	2	1.73	1.41	1.61	0.76	0.89	-28	-68	15	20	20	25	25	25	25	25	5	20	10	20	20	18	15	7	18	15	14	16	9	17	18	19	18	18	N	N
SUBJ43B					201									15	20	20	25	25	25	25	25	5	20	10	20	22	17	15	6	17	15	15	14	11	17	16	7	9	8	N	N
SUBJ43C					201									15	20	20	25	25	25	40	40	5	20	10	20	21	-1	9	7	11	8	8	8	9	6	5	0	3	1	N	N
SUBJ44A	30	F	B		13									90	85	85	80	75	70	55	60	80	70	65	65	-3	0	0	-1	0	0	-4	-1	0	0	0	0	0	0	Y	N
SUBJ44B				ENT				ENT					ENT				ENT				ENT						ENT					ENT						ENT			
SUBJ44C				ENT				ENT					ENT				ENT				ENT						ENT					ENT						ENT			
SUBJ45A	41	M	B		111	2.28	2.12	2.28	0.27	1.65	0.16	-28	-12	25	20	35	25	40	25	45	25	45	10	70	20	2	3	-5	-8	-4	4	-8	3	2	11	0	6	0	0	Y	N
SUBJ45B					ENT								ENT								ENT						ENT					ENT						ENT			
SUBJ45C					ENT								ENT								ENT						ENT					ENT						ENT			
SUBJ46A	43	M	B		37	1.11	1.46	0.32	0.41	0.15	0.23	-45	-20	20	25	20	25	15	20	15	15	25	25	25	20	26	13	17	22	22	29	11	18	15	18	5	9	5	7	N	N
SUBJ46B				DNA							DNA								DNA						DNA							DNA						DNA			
SUBJ46C					129									30	40	30	35	20	25	15	15	45	40	50	40	13	12	17	17	17	26	7	6	2	0	0	0	0	0	N	N

Key: A=session 1; B=sessin 2; C=sessin 3; F=female; M=male; B=black; C=coloured; DTR=deferred treatment; DNA=did not arrive; ENT=ear, nose throat referral; CTR=commenced treatment

APPENDIX J - Study group

SUBJECT	AGE	GENDER	RACE	CD4	VL	VOL L	VOL R	COMPL L	COMPL R	GRAD L	GRAD R	PRESS L	PRESS R	PTL 250	PTR250	PTL500	PTR500	PTL1000	PTR1000	PTL2000	PTR2000	PTL4000	PTR4000	PTL8000	PTR8000	DPL750	DPR750	DPL1000	DPR1000	DPL2000	DPR2000	DPL3000	DPR3000	DPL4000	DPR4000	DPL6000	DPR6000	DPL8000	DPR8000	TINNITUS	VERTIGO	MEDS
SUBJ1A	27	F	B	23		0.85	0.86	0.4	0.54	0.23	0.33	-31	-16	10	10	15	10	5	10	15	10	10	15	15	15	10	7	12	8	14	16	19	12	14	15	16	16	12	13	N	N	1
SUBJ1B														10	10	10	10	5	10	15	10	10	15	15	15	10	6	14	9	15	15	21	12	15	14	17	17	10	9	N	Y	
SUBJ1C														10	10	15	10	5	10	15	10	10	15	15	15	11	7	13	8	14	15	18	10	12	12	15	15	5	0	N	N	
SUBJ2A	40	F	B	4		0.75	1.38	0.54	0.79	0.34	0.52	-14	-18	10	15	10	5	5	10	10	10	15	15	5	5	7	7	15	13	12	11	14	19	18	12	12	11	7	9	N	N	1
SUBJ2B														10	15	10	5	5	10	10	10	15	15	5	5	9	7	14	12	12	13	15	19	18	13	11	9	7	11	N	Y	
SUBJ2C														10	15	10	5	5	10	10	10	15	15	5	5	7	7	14	13	12	12	14	19	18	12	12	10	7	9	N	N	
SUBJ3A	30	M	B	20		1.21	1.26	0.99	0.54	0.7	0.29	-13	-21	20	20	15	15	10	10	10	10	10	10	5	5	19	18	20	20	24	11	14	19	19	10	10	10	14	14	N	N	1
SUBJ3B												DTR						DTR								DTR										DTR			N	N	
SUBJ3C												DTR						DTR								DTR										DTR			N	N	
SUBJ4A	36	M	B	73		1.08	1.18	0.63	0.79	0.35	0.6	-83	-110	15	15	10	10	10	10	10	5	15	15	10	10	15	13	12	12	24	23	20	19	10	11	10	10	7	8	N	N	1
SUBJ4B												DTR														DTR										DTR					
SUBJ4C												DTR														DTR										DTR					
SUBJ5A	29	F	B	36		1.01	0.88	1.06	0.97	0.86	0.76	-22	-32	10	10	5	5	10	10	15	10	15	15	10	5	19	19	17	17	19	19	11	22	18	21	14	22	16	11	N	N	1
SUBJ5B														10	10	5	5	10	10	15	10	15	15	10	5	18	19	17	18	19	19	12	21	17	22	9	14	8	5	N	Y	
SUBJ5C														10	10	5	5	10	10	15	10	15	15	10	10	18	18	16	17	18	18	11	22	17	21	7	4	6	2	Y	N	
SUBJ6A	27	F	B	23		0.85	0.86	0.4	0.54	0.23	0.33	-31	-16	10	10	15	10	5	10	15	10	10	15	15	15	10	7	12	8	14	16	19	12	14	15	16	16	12	13	N	N	1
SUBJ6B														10	10	10	10	5	10	15	10	10	15	15	15	10	6	11	7	13	16	19	12	13	15	16	16	10	9	N	Y	
SUBJ6C														10	10	15	10	5	10	15	10	10	15	15	15	11	7	12	8	13	15	18	10	12	12	15	15	5	0	N	N	
SUBJ7A	37	F	B	84		0.92	0.92	0.5	0.51	0.33	0.33	-10	-8	25	25	25	20	25	20	15	20	15	20	20	20	20	18	15	7	18	15	14	16	9	17	18	19	18	18	N	N	1
SUBJ7B														25	25	25	20	25	20	15	20	15	20	20	20	18	11	10	7	20	14	13	17	8	16	10	12	13	11			
SUBJ7C														25	25	25	20	25	20	15	20	15	20	25	25	19	2	9	5	18	15	14	16	9	16	0	0	0	4	Y	N	
SUBJ8A	26	F	B	46		0.99	0.87	0.27	0.17	0.1	0.05	-36	-28	10	15	10	15	5	20	15	15	5	5	10	10	7	-4	0	9	28	23	21	23	17	19	14	16	11	10	N	N	1
SUBJ8B														10	15	10	15	5	20	15	15	5	5	10	10	8	-4	0	8	26	22	19	24	15	18	8	7	5	4	N	N	
SUBJ8C														10	15	10	15	5	20	15	15	5	5	10	10	8	-5	0	9	27	22	20	23	16	19	4	6	1	0	N	N	
SUBJ9A	41	M	B	49		1.35	1.29	0.4	0.37	0.15	0.19	-28	-24	10	15	10	10	15	15	25	15	15	20	5	0	18	21	28	28	24	21	14	16	19	14	9	12	14	15	N	N	1
SUBJ9B														10	15	10	10	15	15	25	15	15	20	5	0	17	19	27	26	22	22	13	15	17	16	8	11	13	14	N	N	
SUBJ9C														10	15	10	10	15	15	25	15	15	20	5	0	17	20	28	27	23	21	13	15	18	14	9	12	13	15	N	N	
SUBJ10A	46	F	B	139		1.29	1.21	0.51	0.53	0.25	0.25	-32	-28	15	20	15	15	20	20	20	20	20	20	15	20	17	13	15	10	15	12	13	14	9	16	10	12	17	16	N	N	1
SUBJ10B														15	20	15	15	20	20	20	20	20	20	15	20	10	8	7	10	13	6	13	8	9	16	6	9	7	5	N	N	
SUBJ10C														15	20	15	15	20	20	20	35	20	30	15	30	-7	-13	5	10	5	-2	13	4	9	16	0	0	3	0	N	N	
SUBJ11A	22	F	B	104		1.32	1.12	0.52	0.36	0.27	0.14	-24	-28	10	15	10	10	10	10	15	15	15	15	15	15	10	11	22	19	29	26	18	27	13	17	14	14	18	19	N	N	1
SUBJ11B														10	15	10	10	10	10	15	15	15	15	20	15	11	10	20	17	30	28	18	25	11	18	6	8	8	12	N	N	
SUBJ11C														10	15	10	10	10	10	15	15	15	15	65	15	9	10	21	18	29	27	17	26	12	17	0	7	0	8	N	N	
SUBJ12A	32	F	B	84		0.28	0.29	0.11	0.11	0.05	0.05	4	4	5	10	5	5	10	10	15	20	10	5	15	5	8	14	15	14	12	10	19	11	15	15	18	10	18	18	N	N	2
SUBJ12B														5	10	5	5	10	10	15	20	10	5	15	5	9	14	13	16	14	10	17	9	16	8	19	9	19	12	Y	Y	
SUBJ12C														5	10	5	5	10	10	15	20	10	5	15	5	8	4	14	14	13	0	18	10	15	5	19	9	18	8	Y	N	
SUBJ13A	30	F	B	124		1.5	1.1	0.95	0.45	0.55	0.22	-32	-20	10	20	5	15	10	15	10	20	25	15	10	25	15	16	26	28	28	29	26	22	24	14	6	15	13	15	N	N	1
SUBJ13B														10	20	5	15	10	15	10	20	25	15	10	25	16	18	24	26	27	27	26	20	23	14	8	13	15	16	N	N	
SUBJ13C														10	20	5	15	10	15	10	20	25	15	10	25	15	16	25	27	28	28	25	21	23	13	7	14	13	14	N	N	
SUBJ14A	31	F	B	127		1.08	1.14	1.21	1.77	0.7	1.12	-36	-24	20	20	20	20	15	25	25	25	15	25	10	25	10	-1	20	5	12	13	26	10	27	13	18	10	15	17	N	N	1
SUBJ14B														20	20	20	20	15	25	25	25	15	25	10	25	12	-2	22	7	13	11	24	8	15	12	20	6	16	9	N	N	
SUBJ14C														20	20	20	20	15	25	25	25	15	25	10	25	11	-1	21	6	12	12	26	9	26	12	19	0	15	7	N	N	
SUBJ15A	22	F	B	32		1.52	1.17	0.78	0.86	0.35	0.49	-20	-28	20	20	20	15	15	15	20	20	25	25	25	25	12	11	24	16	24	26	22	22	23	16	18	15	15	13	N	N	1
SUBJ15B														30	25	25	25	20	15	25	25	35	35	45	55	8	8	22	12	22	23	18	16	20	10	14	5	8	8	N	N	
SUBJ15C														30	25	25	25	20	15	25	25	35	35	45	55	2	8	20	12	21	22	18	15	21	11	12	5	0	0	N	N	
SUBJ16A	27	F	B	80		1.79	1.68	1.3	2.12	0.8	1.54	-56	-44	20	20	10	10	10	20	15	20	25	25	20	20	16	9	21	13	28	11	26	16	15	15	20	15	20	15	N	N	2
SUBJ16B														20	20	10	10	10	20	15	20	25	25	20	20	15	11	19	11	29	9	27	10	11	7	6	9	8	7	N	Y	
SUBJ16C														20	20	10	10	10	20	15	20	25	25	20	20	16	9	20	12	28	10	25	6	9	5	0	5	2	0	N	N	
SUBJ17A	46	F	B	119		0.9	0.92	0.31	0.34	0.12	0.17	-32	-28	25	20	20	20	15	15	15	15	15	15	20	20	9	16	10	16	16	24	17	19	9	20	10	12	12	14	N	N	1
SUBJ17B														25	20	20	20	15	15	15	15	15	15	20	20	11	14	10	15	15	26	15	17	11	21	6	14	5	6	N	N	
SUBJ17C														25	20	20	20	15	15	15	15	15	15	20	20	9	15	-1	16	6	24	16	18	10	20	0	13	-2	4	N	N	
SUBJ18A	23	F	B	111		1.39	1.37	0.59	0.61	0.28	0.29	-32	-28	10	15	5	10	15	10	10	15	20	15	25	5	7	14	8	10	14	17	17	22	10	23	10	20	22	24	N	N	1
SUBJ18B														10	15	5	10	15	10	10	15	20	15	25	5	5	11	8	9	11	15	15	23	10	21	8	19	22	23	N	N	
SUBJ18C														10	15	10	10	10	10	10	15	20	15	25	5	-3	6	2	-1	5	5	6	12	6	8	0	0	0	0	N	N	
SUBJ19A	33	F	B	143		1.42	1.04	0.67	0.63	0.33	0.4	-12	-28	15	15	10	15	15	20	20	20	25	25	15	20	16	20	19	18	32	25	15	22	16	17	16	14	16	12	N	N	1
SUBJ19B														15	15	10	15	15	20	20	20	25	25	15	20	19	21	21	20	32	27	14	21	17	13	9	8	6	6	N	N	
SUBJ19C														15	15	10	15	15	20	20	20	25	25	15	20	17	20	20	18	30	26	14	21	15	7	1	4	1	2	Y	Y	
SUBJ20A	39	F	B	63		1.4	1.5	0.8	0.8	0.13	0.12	-18	-10	20	20	15	10	10	10	25	25	10	25	15	25	17	21	25	23	13	13	21	9	24	8	30	12	24	14	N	N	1
SUBJ20B														20	20	15	10	10	10	25	25	10	25	15	25	19	20	26	25	13	12	22	11	25	10	29	13	18	10	N	Y	
SUBJ20C														20	20	15	10	10	10	25	25	10	25	15	25	18	21	25	24	12	12	21	9	23	9	29	12	8	6	N	N	
SUBJ21A	34	M	B	133		1.91	1.95	0.93	1.03	0.52	0.71	-48	-64	5	5	10	10	10	15	10	10	20	10	10	15	10	11	14	16	15	15	12	15	24	25	24	19	22	20	N	N	1
SUBJ21B														DNA		DNA				DNA				DNA																		
SUBJ21C														5	5	10	10	10	15	10	10	20	10	10	15	-6	1	4	6	-5	14	10	15	4	15	4	9	12	0	N	N	
SUBJ22A	42	F	B	153		1.19	1.1	0.89	0.65	0.36	0.3	-64	-44	15	15	10	10	10	15	20	20	25	20	20	20	12	12	27	24	16	16	18	15	17	18	15	10	10	9	N	N	1
SUBJ22B														15	15	10	10	10	15	20	20	25	20	20	20	11	10	18	8	18	14	20	13	15	15	6	6	5	5	N	Y	
SUBJ22C														15	15	10	10	10	15	20	20	25	20	20	20	8	-2	7	-4	16	15	18	11	12	10	5	0	2	-2	N	N	
SUBJ23A	46	F	B	52		1.12	0.85	0.48	0.3	0.2	0.11	-20	0	20	20	20	20	20	20	20	25	25	25	25	25	18	20	25	22	28	18	21	15	15	16	16	14	16	13	N	N	1
SUBJ23B				77										25	25	20	20	20	20	25	25	30	30	25	25	15	16	20	9	23	10	15	9	8	10	8	13	7	5	Y	Y	
SUBJ23C														30	30	25	25	20	25	35	40	50	50	55	55	12	10	19	-1	20	0	13	-10	4	7	5	10	5	-4	Y	N	
SUBJ24A	38	F	B	156		2.08	1.84	2.11	1.84	1.49	1.26	-44	-44	15	20	15	15	10	10	25	20	20	20	20	25	10	12	13	13	16	16	15	14	16	16	15	16	18	16	N	N	1
SUBJ24B														15	20	15	15	10	10	25	20	20	20	20	25	8	6	9	9	9	16	12	12	16	14	11	12	11	13	N	N	
SUBJ24C														15	20	15	15	10	10	25	20	20	20	20	30	-13	-1	2	7	9	16	11	12	14	11	10	11	11	7	Y	N	
SUBJ25A	39	M	B	11		1.28	1.28	0.35	0.36	0.19	0.19	-20	-24	15	15	10	10	10	20	20	20	20	20	20	15	8	20	14	13	28	22	18	16	21	18	21	22	22	20	N	N	1
SUBJ25B														15	15	10	10	10	20	20	20	20	20	20	15	5	7	14	7	23	20	18	10	19	10	13	12	14	9	N	N	
SUBJ25C														15	15	10	10	10	20	20	20	20	20	20	15	1	3	4	-1	20	6	15	6	19	1	10	7	12	7	N	N	
SUBJ26A	25	M	B	126		1.14	1.14	0.8	0.82	0.42	0.42	-44	-28	10	15	10	15	10	10	15	25	20	15	10	0	10	5	19	12	26	18	19	23	16	22	10	18	9	22	N	N	1
SUBJ26B																					DNA	DNA			DNA		DNA			DNA				DNA				DNA				
SUBJ26C														10	15	10	15	10	10	15	25	20	15	10	0	11	6	17	10	24	18	20	22	16	21	10	17	10	21	N	N	
SUBJ27A	36	F	C	103		1.18	1.14	0.74	0.71	0.46	0.4	-28	-16	15	15	15	15	10	15	15	20	10	10	15	10	14	15	25	22	25	22	22	25	25	27	20	18	18	20	N	N	1
SUBJ27B														15	15	15	15	10	15	15	20	10	10	15	10	6	9	13	8	15	17	22	20	22	24	14	7	13	9	N	N	
SUBJ27C														15	15	15	15	10	15	15	20	10	10	15	10	-3	4	9	4	12	13	19	15	22	20	10	0	11	5	N	N	
SUBJ28A	29	F	B	74		1.09	1	0.52	0.67	0.29	0.38	-28	-28	5	15	5	5	10	10	15	15	0	5	10	5	-6	10	1	5	14	22	14	17	14	23	11	10	17	20	N	N	1
SUBJ28B				173						DNA				DNA		DNA				DNA				DNA							DNA				DNA						
SUBJ28C														5	15	5	5	10	10	15	15	0	5	10	5	-6	10	1	6	13	22	12	16	12	21	11	9	16	18	N	N	
SUBJ29A	32	M	B	174		1.24	1.09	0.47	0.42	0.19	0.15	-20	-44	10	10	15	15	15	10	10	20	25	20	10	5	10	14	17	19	31	33	32	30	30	28	20	19	20	10	N	N	1
SUBJ29B														10	10	15	15	15	10	10	20	25	20	10	5	13	12	19	17	30	31	33	31	30	26	22	17	19	9	N	N	
SUBJ29C														10	10	15	15	15	10	10	20	25	20	10	5	11	13	17	18	30	32	31	29	28	27	21	18	19	10	N	N	
SUBJ30A	28	M	B	136		1.7	1.81	1.94	1.61	1.33	1.01	-24	-28	10	5	5	15	10	10	15	5	10	15	10	0	13	11	10	13	23	24	17	20	22	21	16	19	24	28	N	N	1
SUBJ30B														10	5	5	15	10	10	15	5	10	15	10	0	15	11	9	15	25	23	19	21	21	22	14	18	23	28	N	Y	
SUBJ30C														10	5	5	15	10	10	15	5	10	15	10	0	13	10	10	14	24	23	16	21	21	21	15	18	24	27	N	N	
SUBJ31A	32	F	B	64		1.51	1.41	0.83	0.93	0.47	0.53	-24	-24	10	15	15	15	15	15	15	15	10	15	10	10	8	9	13	19	19	24	28	26	22	26	25	18	20	22	N	N	1
SUBJ31B				118																						10	7	14	21	18	21	21	16	14	22	17	16	9	18	N	N	
SUBJ31C																										8	4	13	20	19	20	19	13	10	19	10	14	7	3	N	N	
SUBJ32A	44	F	C	35		1.72	1.43	0.6	0.57	0.25	0.23	-28	-32	20	25	25	20	25	25	25	25	25	25	20	25	10	12	12	15	22	26	22	21	19	19	22	19	15	26	N	N	3
SUBJ32B				111										20	25	25	20	25	25	25	25	25	25	20	25	6	5	7	12	15	11	13	18	10	17	8	15	7	16	N	Y	
SUBJ32C				153										20	25	25	20	25	25	25	25	25	25	30	30	-2	-13	4	6	6	1	9	15	6	15	6	14	1	11	Y	N	
SUBJ33A	38	M	C	72		2.11	2.21	1.72	1.36	1.02	0.83	-20	-24	25	20	25	20	25	20	20	15	25	25	25	25	13	14	12	16	25	23	26	26	24	25	17	19	22	26	N	N	1
SUBJ33B														25	20	25	20	25	20	20	15	25	25	25	25	12	15	11	15	22	22	24	25	23	26	10	19	21	25	N	N	
SUBJ33C														25	20	25	20	25	20	20	15	25	25	30	30	-8	8	9	10	17	11	11	22	11	25	7	8	2	20	N	N	
SUBJ34A	24	F	B	181		1.68	1.69	0.43	0.63	0.15	0.36	-20	-28	15	20	5	15	10	10	20	0	5	15	0	15	-2	-15	16	10	11	26	13	21	12	19	11	16	13	11	N	N	1
SUBJ34B							DNA									DNA				DTR									DTR						DTR					
SUBJ34C							DNA									DNA				DTR									DTR						DTR					
SUBJ35A	44	M	B	181		1.34	1.42	1.14	1.29	0.69	0.9	-12	-20	25	20	20	20	25	25	25	25	25	25	25	25	1	1	-7	-3	11	13	11	13	13	12	12	14	17	19	N	N	1
SUBJ35B							DNA									DNA				DTR									DTR						DTR					
SUBJ35C							DNA									DNA				DTR									DTR						DTR					
SUBJ36A	40	F	B	92		1.68	1.72	1.36	0.72	0.83	0.36	-24	-12	10	10	15	10	15	25	20	25	15	25	20	25	9	14	24	23	38	28	18	13	15	26	23	26	24	24	N	N	1
SUBJ36B														10	10	15	10	15	25	20	25	15	25	25	30	9	13	24	23	38	28	18	7	4	12	9	11	13	6	Y	N	
SUBJ36C				153										10	10	15	10	15	25	20	25	15	25	30	35	-10	-4	17	15	36	16	13	6	2	1	0	6	0	-4	Y	N	
SUBJ37A	36	F	B	53		1.85	1.82	0.9	1.06	0.46	0.64	-24	-8	5	5	10	10	15	20	20	20	25	25	20	20	10	12	19	15	23	19	13	17	25	27	21	20	26	24	N	N	1
SUBJ37B				123										5	5	10	10	15	20	20	20	25	25	20	20	10	10	20	15	22	18	12	12	11	12	4	13	7	11	N	N	

Key: A=session 1; B=sessin 2; C=sessin 3; F=female; M=male; B=black; C=coloured; DTR=deferred treatment; DNA=did not arrive; ENT=ear, nose throat referral; CTR=commenced treatment

APPENDIX J - Study group

SUBJECT	AGE	GENDER	RACE	CD4	VL	VOL L	VOL R	COMPL L	COMPL R	GRAD L	GRAD R	PRESS L	PRESS R	PTL 250	PTR250	PTL500	PTR500	PTL1000	PTR1000	PTL2000	PTR2000	PTL4000	PTR4000	PTL8000	PTR8000	DPL750	DPR750	DPL1000	DPR1000	DPL2000	DPR2000	DPL3000	DPR3000	DPL4000	DPR4000	DPL6000	DPR6000	DPL8000	DPR8000	TINNITUS	VERTIGO	MEDS
SUBJ37C				196										5	5	10	10	15	20	20	20	25	25	20	20	9	10	19	15	22	18	12	5	0	3	0	10	0	8 N	N		
SUBJ38A	40	F	B	12		1.86	1.55	0.82	1.49	0.44	1.05	-44	-32	15	20	15	20	15	15	20	20	25	25	25	25	25	25	10	12	19	15	23	19	13	17	25	27	21	20	26	24 N	N		1
SUBJ38B				66										15	20	15	20	15	15	20	20	25	25	25	30	11	10	17	13	22	18	12	12	11	12	4	13	7	11 N	N		
SUBJ38C				142										15	20	15	20	15	15	20	20	25	30	25	35	2	3	6	2	10	11	4	6	9	0	2	0	-7	2 N	N		
SUBJ39A	42	F	B	13		2.26	1.99	0.84	0.39	0.44	0.23	-20	-24	5	15	15	25	15	25	20	20	10	15	10	15	22	19	24	17	23	23	25	24	18	28	26	25	19	23 N	N		1
SUBJ39B				DNA					DNA				DNA				DNA				DNA				DNA				DNA				DNA		DNA		DNA				
SUBJ39C				197										5	15	15	25	15	25	20	20	10	15	10	15	7	-6	20	11	18	12	12	9	2	0	2	0	3	0 N	N		
SUBJ40A	39	M	B	191		2.29	1.47	0.61	0.6	0.24	0.32	-20	-28	20	20	25	25	25	25	25	15	25	25	25	25	9	14	24	23	38	33	18	23	15	26	23	26	24	24 N	N		1
SUBJ40B				210										20	20	25	25	25	25	25	15	25	25	25	25	6	13	17	11	22	29	11	18	15	18	5	9	5	7 N	N		
SUBJ40C				256										20	20	25	25	25	30	25	15	25	25	30	35	5	-2	-3	6	14	26	9	14	13	12	0	0	1	1 N	N		
SUBJ41A	23	F	B	198		1.46	1.47	0.79	0.65	0.39	0.26	-40	-40	5	15	10	15	15	20	5	15	10	15	0	20	5	11	6	15	25	21	19	19	18	16	16	17	17	16 N	N		1
SUBJ41B				DNA				DNA			DNA				DNA			DNA			DNA				DNA			DNA								DNA					
SUBJ41C				241										5	15	10	15	15	20	5	15	10	15	0	20	6	10	6	13	23	19	18	19	18	14	14	16	16	16 N	N		
SUBJ42A	46	M	B	11		2.95	2.49	1.97	2.21	1.09	1.43	-24	-40	25	25	20	25	25	25	25	25	25	25	25	25	10	12	19	15	23	19	13	17	25	27	21	20	22	21 Y	N		1
SUBJ42B				52										55	70	65	55	70	35	80	40	90	45	100	65	-7	-6	-14	1	7	7	0	9	5	-3	0	0	3	0 Y	Y		
SUBJ42C									ENT				ENT				ENT				ENT				ENT				ENT				ENT				ENT				
SUBJ43A	30	F	B	183		2	1.73	1.41	1.61	0.76	0.89	-28	-68	15	20	20	25	25	25	25	25	5	20	10	20	20	18	15	7	18	15	14	16	9	17	18	19	18	18 N	N		1
SUBJ43B				201										15	20	20	25	25	25	25	25	5	20	10	22	21	17	14	9	17	14	13	14	11	16	16	7	9	8 N	N		
SUBJ43C				201										15	20	20	25	25	25	40	40	5	20	10	21	20	-1	9	8	11	8	8	8	10	6	5	0	3	1 N	N		
SUBJ44A	30	F	B	13										90	85	85	80	75	70	55	60	80	70	65	65	-10	-3	0	0	0	0	-1	0	0	0	0	0	-1	-4 Y	N		1
SUBJ44B				ENT				ENT				ENT				ENT				ENT						ENT						ENT				ENT				
SUBJ44C				ENT				ENT				ENT				ENT				ENT						ENT						ENT				ENT				
SUBJ45A	41	M	B	111		2.28	2.12	2.28	0.27	1.65	0.16	-28	-12	25	20	35	25	40	25	45	25	45	10	70	20	2	3	-5	-8	-4	4	-8	3	2	11	0	6	0	0 Y	N		1
SUBJ45B				ENT								ENT								ENT						ENT						ENT				ENT				
SUBJ45C				ENT								ENT								ENT						ENT						ENT				ENT				
SUBJ46A	43	M	B	37		1.11	1.46	0.32	0.41	0.15	0.23	-45	-20	20	25	20	25	15	20	15	15	25	25	25	20	26	13	17	22	22	29	11	18	15	18	5	9	5	7 N	N		1
SUBJ46B				DNA							DNA							DNA								DNA						DNA				DNA				
SUBJ46C				129										30	40	30	35	20	25	15	15	45	40	50	40	13	12	17	17	17	26	7	6	2	0	0	0	0	0 N	N		
SUBJ47A	40	F	B	45		1.44	1.39	1.12	1.24	0.72	0.9	-11	-17	20	10	15	10	10	10	10	10	10	15	20	20	9	12	16	10	22	22	23	19	18	16	21	17	17	16 N	N		1
SUBJ47B				DNA								DNA				DNA				DNA								DNA				DNA								
SUBJ47C				74										20	10	15	10	10	10	10	10	10	15	25	25	5	8	12	2	19	13	16	14	7	13	15	6	5	2 N	N		
SUBJ48A	32	F	B	133		1.38	1.54	0.88	0.48	0.62	0.3	-40	-2	20	25	20	25	20	25	10	15	20	15	15	10	13	17	9	12	12	21	22	19	20	16	17	13	17	13 N	N		1
SUBJ48B														20	25	20	25	20	25	10	15	20	15	15	10	12	11	9	4	9	11	12	7	13	9	12	6	11	7 N	N		
SUBJ48C				418										20	30	20	30	20	25	10	15	20	15	15	10	3	1	5	-2	7	-1	7	3	0	7	4	0	3	0 N	N		
SUBJ49A	44	F	B	183		1.39	1.42	1.24	0.7	0.9	0.49	-17	-9	20	25	20	25	20	20	5	10	10	10	15	15	3	2	4	5	2	0	7	5	0	0	0	0	0	0 N	N		1
SUBJ49B									DNA						DNA				DTR				DTR				DTR					DTR						DTR			
SUBJ49C									DNA						DNA				DTR				DTR				DTR					DTR						DTR			
SUBJ50A	28	F	B	52		1.38	1.38	0.88	0.88	0.62	0.62	-40	-38	20	20	20	25	15	15	10	10	10	15	15	5	13	17	23	22	19	26	24	19	17	24	21	17	17	13 N	N		1
SUBJ50B														20	20	20	25	15	15	10	10	10	15	15	5	12	9	22	13	9	15	16	18	11	17	9	13	11	4 N	N		
SUBJ50C				304										20	20	20	25	15	15	10	10	10	15	15	5	4	3	17	1	3	11	14	18	7	16	0	0	0	0 N	N		
SUBJ51A	34	M	B	198		1.19	1.19	1.17	1.15	0.77	0.79	-6	-12	20	20	20	20	25	20	15	10	25	15	25	10	17	25	21	15	20	22	15	21	17	22	21	16	18	24 N	N		1
SUBJ51B														25	20	25	25	25	25	15	10	25	15	25	10	11	17	13	7	13	15	8	15	9	14	11	9	11	17 N	N		
SUBJ51C				454										25	25	25	25	30	25	15	10	30	15	30	10	-9	15	11	5	10	12	5	11	7	12	1	6	8	14 N	N		
SUBJ52A	27	F	B	54		1.12	1.7	2.03	2	1.58	1.12	-6	35	25	25	25	25	25	20	5	10	10	15	15	20	15	17	22	23	24	20	25	23	21	17	15	13	14	12 N	N		1
SUBJ52B				DNA											DNA																		DNA						DNA			
SUBJ52C				157										25	25	25	25	25	20	5	10	10	15	15	20	5	17	22	18	14	10	15	13	10	0	1	0	5	5 N	N		
SUBJ53A	24	F	B	186		1.08	1.21	0.86	0.3	0.59	0.1	-13	-236	20	30	25	35	20	30	25	40	15	25	20	30	1	3	-3	5	-4	12	6	12	6	13	0	9	5	4 Y	N		1
SUBJ53B				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ53C				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ54A	32	F	B	83		1.11	1.12	0.78	1.3	0.48	0.99	-18	-9	25	25	25	30	20	25	15	20	20	15	30	15	23	24	31	29	36	27	26	23	21	22	20	18	19	10 N	N		3
SUBJ54B														25	25	25	30	20	25	15	20	20	15	30	15	11	15	21	23	30	19	19	16	11	15	10	13	11	3 N	Y		
SUBJ54C				277										25	25	25	30	20	25	15	20	20	15	30	15	3	14	21	20	30	17	16	13	11	12	0	0	1	0 N	N		
SUBJ55A	37	F	B	111		1.21	1.08	0.68	0.69	0.45	0.42	-14	-13	20	25	20	25	15	25	15	15	15	20	25	20	9	11	11	15	17	17	23	25	21	25	12	20	7	17 N	N		1
SUBJ55B				DNA								DNA											DNA							DNA									DNA			
SUBJ55C				198										20	25	20	25	15	25	15	15	15	20	25	20	6	10	11	14	18	15	22	24	21	23	10	18	8	16 N	N		
SUBJ56A	30	F	B	54		0.92	0.92	0.64	0.59	0.41	0.31	-11	-50	20	20	20	20	20	20	20	15	10	15	10	10	21	17	19	19	19	25	27	20	24	19	29	16	25	21 N	N		1
SUBJ56B				DNA							DNA												DNA							DNA									DNA			
SUBJ56C				123										20	20	20	20	20	20	20	15	10	15	10	15	20	18	19	17	25	27	18	24	9	25	6	15	1 N	N		
SUBJ57A	40	F	B	125		1.12	0.89	1.02	1.16	0.71	0.88	-3	-3	20	20	20	20	25	20	15	10	25	15	25	10	17	25	21	15	20	22	15	21	17	22	21	16	18	24 N	N		3
SUBJ57B				158										25	20	25	25	25	25	15	10	25	15	25	10	11	17	13	7	13	15	8	15	9	14	11	9	11	17 N	N		
SUBJ57C				216										25	25	25	25	30	25	15	10	30	15	30	10	-9	15	11	5	10	12	5	11	7	12	1	6	8	14 N	N		
SUBJ58A	32	M	B	3		1.04	1.16	1.09	1.81	0.73	1.29	-16	-3	20	25	20	25	20	25	10	20	20	20	15	15	-6	5	9	10	14	20	14	10	15	13	16	8	22	9 N	N		1
SUBJ58B				DNA							DNA											DNA							DNA									DNA			
SUBJ58C				120										20	25	20	25	20	25	10	20	20	20	15	15	-9	3	8	11	15	19	15	9	13	12	15	9	21	9 N	N		
SUBJ59A	29	M	B	158		1.04	1.18	0.62	0.52	0.37	0.33	-8	-17	15	15	15	15	15	15	10	10	5	15	5	15	18	13	21	16	26	19	26	23	21	21	18	15	21	14 N	N		1
SUBJ59B														15	15	15	15	15	15	10	10	5	15	5	15	17	13	19	17	25	17	25	21	20	19	18	13	19	15 N	N		
SUBJ59C				250										15	15	15	15	15	15	10	10	5	15	5	15	17	12	19	16	25	18	25	22	21	19	17	14	19	12 N	N		
SUBJ60A	46	M	B	5		1.46	1.46	0.83	0.89	0.52	0.57	-12	-12	20	20	20	25	20	20	20	10	25	25	25	25	28	25	22	23	19	20	21	19	14	22	22	26	23	25 Y	N		1
SUBJ60B				47										20	25	20	25	20	20	20	10	30	30	35	30	8	15	12	11	9	10	13	11	6	13	11	9	9	11 Y	N		
SUBJ60C				156										20	25	20	25	20	20	20	10	30	30	60	45	-8	15	-2	-3	9	10	11	9	4	12	0	0	3	0 Y	N		
SUBJ61A	46	M	B	27		1.11	1.13	0.18	0.17	0.07	0.09	-7	-12	20	30	20	40	15	55	15	40	20	25	20	35	22	-5	23	2	18	13	15	6	18	7	22	1	19	0 N	N		1
SUBJ61B				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ61C				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ62A	46	F	B	146		0.82	0.81	0.44	0.51	0.22	0.34	-17	-18	20	20	15	25	25	20	5	10	20	20	25	25	22	23	20	24	29	24	37	25	28	26	20	28	21	30 N	N		1
SUBJ62B				203										20	20	15	25	25	20	5	10	25	25	30	30	15	15	20	20	19	22	35	24	20	18	11	9	7	5 N	N		
SUBJ62C				404										20	20	15	25	25	20	5	10	40	30	40	40	12	13	20	20	19	22	34	23	18	16	0	0	0	0 Y	N		
SUBJ63A	44	F	C	35		1.16	1.09	0.39	0.36	0.24	0.17	-37	-40	25	25	20	25	25	20	10	15	20	15	20	10	9	12	16	9	18	14	19	22	21	20	20	16	19	17 N	N		1
SUBJ63B				DNA							DNA		DNA				DNA						DNA							DNA									DNA			
SUBJ63C				103										30	25	20	25	30	25	10	15	20	15	25	10	1	-2	6	3	9	6	12	12	11	10	0	0	0	0 N	N		
SUBJ64A	41	F	C	48		0.82	1.11	0.44	0.41	0.24	0.22	-20	-21	20	20	20	20	20	20	10	15	5	15	0	10	2	2	1	-3	9	23	14	14	16	9	18	9	23	16 N	N		1
SUBJ64B														20	20	20	20	20	20	10	15	5	15	0	10	-2	0	0	-5	11	22	13	13	17	8	17	8	22	16 N	N		
SUBJ64C				151										20	20	20	20	20	20	10	15	5	15	0	10	-2	0	0	-2	9	22	14	13	16	8	17	8	22	15 N	N		
SUBJ65A	45	M	B	123		1.93	1.93	1.67	1.67	1.33	1.33	-13	-13	20	20	20	20	20	20	20	15	25	25	15	15	21	18	15	7	18	15	14	16	9	17	18	19	18	18 N	N		1
SUBJ65B				153										20	20	20	20	20	20	20	15	25	25	15	15	10	15	13	7	17	13	14	14	8	16	16	7	9	8 N	N		
SUBJ65C				180										20	20	20	20	20	20	20	15	25	25	15	15	7	2	2	-1	13	3	12	4	1	0	1	0	4	7 N	N		
SUBJ66A	33	M	B	98		1.46	1.46	0.83	0.89	0.52	0.57	-12	-12	15	20	20	20	20	20	10	10	10	10	20	5	-10	17	10	19	13	22	26	25	17	17	14	17	16	15 N	N		1
SUBJ66B														15	20	20	20	20	20	10	10	10	10	20	5	-8	18	10	18	11	20	24	21	14	15	9	10	8	6 N	N		
SUBJ66C				106										15	20	20	20	20	20	10	10	10	10	25	5	-10	16	8	18	11	15	24	20	10	15	6	6	2	3 N	N		
SUBJ67A	46	M	B	242		1.27	1.12	0.24	0.34	0.11	0.19	-31	-30	15	20	20	15	20	15	10	10	20	20	10	10	9	8	19	15	21	19	14	17	14	14	7	8	8	8 N	N		1
SUBJ67B				DNA						DNA						DNA						DNA							DNA									DNA			
SUBJ67C				DNA						DNA						DNA						DNA							DNA									DNA			
SUBJ68A	38	F	B	137		0.85	0.77	0.4	0.57	0.23	0.37	-40	-21	20	20	20	20	20	15	10	10	10	5	10	10	19	20	23	19	21	27	13	24	19	22	21	16	27	21 N	N		1
SUBJ68B														20	20	20	20	20	15	10	10	10	5	10	10	8	15	13	20	23	25	14	26	18	23	16	6	22	15 N	N		
SUBJ68C				176										20	20	20	20	20	15	10	10	10	5	10	10	4	14	3	20	21	26	13	25	18	22	13	6	17	11 N	N		
SUBJ69A	28	F	B	257		1.04	0.95	0.62	0.53	0.41	0.37	-11	-17	25	25	25	25	20	20	15	10	25	20	15	25	12	13	10	10	14	15	13	17	8	8	7	12	9	12 N	N		1
SUBJ69B				DNA						DNA			DNA									DNA							DNA									DNA			
SUBJ69C				514										25	25	25	25	20	20	15	10	25	20	15	25	14	12	10	10	13	14	11	17	7	7	7	10	8	11 N	N		
SUBJ70A	24	M	B	191		1.16	1.06	0.38	0.33	0.18	0.12	-18	-33	15	15	15	20	10	10	10	10	5	15	10	20	14	15	13	13	16	18	18	22	21	23	14	14	17	15 N	N		1
SUBJ70B				DNA						DNA						DNA						DNA							DNA									DNA			
SUBJ70C				216										15	15	15	20	10	10	10	10	5	15	10	20	2	-10	8	3	14	17	9	9	10	10	2	0	4	2 N	N		
SUBJ71A	32	F	B	135		1.57	1.55	0.62	0.58	0.46	0.39	-23	-23	20	20	20	20	20	15	5	5	10	15	20	20	22	23	20	24	29	24	37	25	28	26	20	28	21	30 N	N		3
SUBJ71B				194										20	20	20	20	20	15	5	5	10	15	25	20	15	15	20	20	19	22	35	24	20	18	11	9	7	5 Y	N		
SUBJ71C				428										20	20	20	20	20	15	5	5	10	15	30	20	4	-3	-11	3	-2	-7	9	12	14	11	0	6	0	1 Y	N		
SUBJ72A	35	F	B	134		1.08	0.96	0.53	0.55	0.35	0.36	-9	-8	20	20	20	20	20	20	15	15	10	10	10	25	22	23	20	24	29	24	37	25	28	26	20	28	21	30 N	N		1
SUBJ72B														20	20	20	20	20	20	15	15	10	10	10	30	15	15	20	20	19	22	35	24	20	18	11	19	17	5 N	N		
SUBJ72C				208										20	20	20	20	20	20	15	15	10	10	10	45	9	1	9	6	12	10	21	9	18	10	8	14	15	0 N	N		
SUBJ73A	44	F	B	179		1.26	1.05	1	0.4	0.76	0.19	2	-22	15	15	20	20	25	25	25	25	25	25	-3	4	6	9	7	9	14	18	16	17	0	0	0	0	0 Y	N		1
SUBJ73B				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ73C				ENT					ENT						ENT								ENT						ENT								ENT				
SUBJ74A	27	M	B	50		0.8	0.7	0.39	0.76	0.24	0.41	-18	17	20	20	20	20	20	20	10	20	10	15	5	25	9	14	24	23	38	33	18	23	20	26	23	26	24	24 N	N		1
SUBJ74B														20	20	20	25	20	20	10	20	10	15	5	40	6	13	17	11	22	29	15	18	20	23	15	19	5	7 N	N		

Key: A=session 1; B=sessin 2; C=sessin 3; F=female; M=male; B=black; C=coloured; DTR=deferred treatment; DNA=did not arrive; ENT=ear, nose throat referral; CTR=commenced treatment

SUBJECT	AGE	GENDER	RACE	CD4	VL	VOL L	VOL R	COMPL L	COMPL R	GRAD L	GRAD R	PRESS L	PRESS R	PTL 250	PTR250	PTL500	PTR500	PTL1000	PTR1000	PTL2000	PTR2000	PTL4000	PTR4000	PTL8000	PTR8000	DPL750	DPR750	DPL1000	DPR1000	DPL2000	DPR2000	DPL3000	DPR3000	DPL4000	DPR4000	DPL6000	DPR6000	DPL8000	DPR8000	TINNITUS	VERTIGO	MEDS
SUBJ74C				156										20	25	20	30	20	20	10	20	10	15	5	60	-8	6	13	9	16	9	14	14	17	21	13	15	4	0	Y	N	
SUBJ75A	21	F	B	199		1.06	1.21	1.49	0.29	1.17	0.2	-9	-3	20	20	20	20	20	10	15	15	15	5	15	10	15	13	18	12	15	17	18	18	19	21	19	15	16	12	N	N	1
SUBJ75B														20	20	20	20	20	10	15	15	15	5	15	10	15	12	16	4	6	9	13	13	11	12	9	5	9	8	N	N	
SUBJ75C				303										20	20	20	20	20	10	15	15	15	5	15	10	10	-2	15	-3	-3	-9	9	-1	5	0	5	0	4	0	N	N	
SUBJ76A	26	F	B	34		0.77	0.75	0.64	0.45	0.38	0.23	-7	-12	20	20	20	20	20	20	20	15	20	25	25	25	17	25	21	15	20	22	15	21	17	22	21	16	18	24	N	N	1
SUBJ76B														20	20	20	20	20	20	20	15	20	25	25	25	11	17	13	11	13	15	8	15	9	14	11	9	11	17	N	N	
SUBJ76C				127										20	20	20	20	20	20	20	15	20	25	30	35	-4	9	11	10	6	11	0	0	0	4	5	1	0	10	N	N	
SUBJ77A	29	F	B	199		1.31	1.48	0.51	0.45	0.31	0.22	-18	-30	20	20	20	20	20	20	10	10	15	15	5	0	17	17	17	22	31	29	14	19	18	19	8	9	6	7	N	N	2
SUBJ77B														20	20	20	20	20	20	10	10	15	15	5	0	18	17	15	21	33	28	15	21	17	18	10	8	8	7	N	N	
SUBJ77C				393										20	20	20	20	20	20	10	10	15	15	5	0	16	16	16	21	32	28	14	19	17	18	9	8	6	6	N	N	
SUBJ78A	31	F	B	156		0.95	0.98	0.42	0.22	0.28	0.07	-13	-73	20	20	20	20	20	20	15	15	10	10	10	15	22	19	16	17	14	14	16	22	23	22	29	18	17	14	N	N	1
SUBJ78B														20	20	20	20	20	20	15	15	10	10	10	15	5	9	7	7	7	12	18	20	24	22	25	9	7	8	N	N	
SUBJ78C				285										20	20	20	20	20	20	15	15	10	10	10	15	-3	1	5	2	4	13	16	21	22	23	23	6	2	4	N	N	
SUBJ79A	43	F	B	77		0.9	0.91	0.36	0.34	0.14	0.14	-16	-25	20	20	20	20	20	20	15	15	10	15	25	20	11	-3	16	12	10	24	15	17	12	16	11	12	14	10	N	N	1
SUBJ79B				DNA						DNA						DNA						DNA								DNA							DNA				
SUBJ79C				125										20	20	20	20	20	20	15	15	10	15	25	20	10	-7	14	12	10	23	14	15	11	16	10	12	14	9	N	N	
SUBJ80A	39	M	B	192		PERF			PERF			PERF		35	20	30	25	35	25	20	10	30	15	45	40			DNT					DNT				DNT					1
SUBJ80B				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ80C				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ81A	34	F	B	143		0.6	1.29	0.54	1.11	0.4	0.7	-61	-13	20	20	20	20	20	20	10	10	20	20	20	16	15	15	15	15	18	19	19	22	21	26	23	26	19	18	N	N	1
SUBJ81B				271										20	20	20	20	20	20	20	10	10	20	20	20	11	7	6	5	15	12	19	22	16	25	9	16	11	11	N	N	
SUBJ81C				360										20	20	20	20	20	20	20	10	10	20	20	20	9	-10	5	-3	13	12	9	16	16	21	3	6	4	8	N	N	
SUBJ82A	41	F	B	2		0.89	0.9	0.57	0.57	0.36	0.36	-16	-12	20	20	20	20	20	20	15	10	15	5	10	10	-2	-3	-8	0	14	11	15	13	16	16	11	17	9	7	N	N	1
SUBJ82B				DNA						DNA						DNA						DNA								DNA							DNA				
SUBJ82C				150										20	20	20	20	20	20	15	10	15	5	10	10	-7	-3	-10	-3	12	11	14	11	16	15	10	16	8	7	N	N	
SUBJ83A	33	M	B	265		0.95	0.99	0.94	0.83	0.62	0.53	-40	-32	25	40	30	60	60	55	60	65	50	55	30	15	0	-5	6	12	0	0	0	1	1	0	5	8	5	0	Y	Y	1
SUBJ83B				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ83C				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ84A	38	M	B	154		1	1.49	1.03	0.71	0.78	0.46	-9	-22	20	20	20	20	20	10	15	15	20	10	15	10	3	3	15	9	9	15	12	13	12	15	4	5	0	2	N	N	1
SUBJ84B				DTR						DTR						DTR						DTR								DTR							DTR				
SUBJ84C				DTR						DTR						DTR						DTR								DTR							DTR				
SUBJ85A	44	M	B	246		0.79	1.02	0.9	0.48	0.42	0.28	-13	-25	15	20	15	20	15	20	15	15	10	25	10	25	18	20	24	23	26	26	33	32	33	27	22	21	16	14	N	N	1
SUBJ85B														15	20	15	20	15	20	15	15	10	25	10	25	10	14	17	13	15	19	26	25	25	20	7	9	10	7	N	N	
SUBJ85C				441										20	25	20	25	20	25	15	15	10	25	10	30	-1	10	11	9	11	16	22	25	25	20	1	6	8	0	N	N	
SUBJ86A	28	F	B	3		0.8	0.92	0.99	0.83	0.73	0.56	-14	-18	20	20	20	20	20	20	10	15	5	10	20	10	7	11	13	4	14	17	19	23	24	24	26	24	23	21	N	N	1
SUBJ86B				21										20	20	20	20	20	20	10	15	5	10	20	10	4	5	11	3	12	16	21	22	22	22	27	26	23	20	N	N	
SUBJ86C				74										20	20	20	20	20	20	10	15	5	10	20	10	4	1	12	3	12	16	20	22	22	23	26	25	22	20	N	N	
SUBJ87A	39	M	B	66		1.65	1.61	1.41	0.98	0.87	0.48	11	-6	20	20	20	20	25	25	15	15	25	20	25	15	22	23	20	24	29	24	37	25	28	26	20	28	21	30	N	N	1
SUBJ87B														20	20	20	20	25	25	15	15	25	20	25	15	15	15	20	20	19	22	35	24	20	18	11	19	17	5	N	N	
SUBJ87C				265										20	20	20	20	25	25	15	15	25	20	25	15	2	2	3	0	9	13	17	18	6	12	0	1	0	0	N	N	
SUBJ88A	46	F	B	130		1.12	1.13	1.8	1.79	1.39	1.29	-22	-18	40	50	50	50	50	40	60	50	60	50	60	40	0	-5	6	12	0	0	0	1	1	0	5	8	5	0	Y	Y	1
SUBJ88B				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ88C				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ89A	41	M	B	34		1.24	1.33	0.64	0.89	0.39	0.54	0	-22	35	30	45	30	85	35	110	15	110	20	110	20	8	12	2	14	0	4	0	0	0	0	0	5	0	3	Y	Y	1
SUBJ89B				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ89C				ENT						ENT						ENT						ENT								ENT							ENT				
SUBJ90A	22	F	B	38		0.79	1.02	0.9	0.48	0.42	0.28	-13	-25	25	20	20	20	20	20	25	15	20	20	20	20	8	8	22	12	22	23	18	16	20	10	14	15	18	18	N	N	1
SUBJ90B														25	20	20	20	20	20	25	15	20	20	20	20	9	10	22	10	23	23	18	15	21	10	14	14	18	17	N	N	
SUBJ90C				163										25	20	20	20	20	20	25	15	20	20	20	20	-2	-2	-6	3	19	20	9	16	12	11	11	11	3	15	N	N	
SUBJ91A	36	F	B	110		0.87	0.95	0.33	0.36	0.16	0.2	-21	-7	20	20	20	20	20	20	15	15	25	25	10	10	20	14	22	19	21	20	20	20	19	15	12	12	15	23	N	N	1
SUBJ91B														20	20	20	20	20	20	15	15	25	25	10	10	18	14	24	17	21	22	19	20	17	15	10	13	17	22	N	N	
SUBJ91C				152										20	20	20	20	20	20	15	15	25	25	10	10	19	11	22	18	20	22	21	19	18	15	12	12	16	23	N	N	
SUBJ92A	27	F	B	30		0.98	0.96	0.4	0.75	0.22	0.51	-9	-17	20	20	20	20	20	20	15	15	20	20	15	15	10	10	10	7	25	23	22	23	24	16	19	14	18	13	N	N	2
SUBJ92B														20	20	20	20	20	20	15	15	20	20	15	15	9	10	10	9	24	23	22	25	22	17	19	13	15	9	N	N	
SUBJ92C				144										20	20	20	20	20	20	15	15	20	20	15	15	12	9	10	6	25	23	22	24	23	16	17	14	17	12	N	N	
SUBJ93A	31	F	B	198		0.96	0.96	0.54	0.73	0.28	0.52	-10	-8	20	20	20	20	20	20	10	10	15	10	10	10	15	18	16	21	17	27	26	20	21	21	24	24	23	19	N	N	1
SUBJ93B				DNA												DNA														DNA							DNA				
SUBJ93C				DNA												DNA														DNA							DNA				
SUBJ94A	32	M	B	144		0.95	0.94	0.43	0.76	0.28	0.58	0	-14	20	20	20	20	20	20	10	10	15	10	10	10	13	16	19	21	16	27	24	24	22	22	24	23	22	22	N	N	1
SUBJ94B				DNA												DNA														DNA							DNA				
SUBJ94C				DNA												DNA														DNA							DNA				
SUBJ95A	31	F	B	34		0.77	0.75	0.64	0.45	0.38	0.23	-7	-12	20	20	20	20	20	20	10	10	15	10	10	10	15	18	16	21	17	27	26	20	21	21	24	24	23	19	N	N	1
SUBJ95B				DNA												DNA														DNA							DNA				
SUBJ95C				139										20	20	20	20	20	20	10	10	15	10	10	10	13	16	19	21	16	27	24	24	22	22	24	23	22	21	N	N	
SUBJ96A	28	F	B	204		0.85	0.86	0.4	0.54	0.23	0.33	-31	-16	15	15	10	15	15	20	15	10	10	5	15	15	10	11	14	16	15	15	12	15	24	25	24	19	22	20	N	N	4
SUBJ96B														15	10	15	15	15	20	15	10	10	10	10	10	12	13	14	17	18	16	14	14	24	27	23	19	22	21	N	N	
SUBJ96C				26										15	10	15	15	10	20	15	10	10	10	10	10	10	12	14	17	16	16	13	15	23	25	23	18	23	20	N	N	
SUBJ97A	29	F	B	188		0.75	1.38	0.54	0.79	0.34	0.52	-14	-18	25	25	30	40	35	30	40	45	40	45	55	55	-3	0	0	0	0	0	-1	0	0	0	0	0	0	0	Y	N	1
SUBJ97B				ENT												ENT																		ENT							
SUBJ97C				ENT												ENT																		ENT							
SUBJ98A	37	M	B	156		1.21	1.26	0.99	0.54	0.7	0.29	-13	-21	10	15	15	10	20	20	20	10	10	10	15	10	17	17	18	15	24	20	23	25	11	21	6	23	7	7	N	N	1
SUBJ98B				85										15	15	15	10	20	20	20	10	10	10	15	10	16	18	18	14	25	21	24	24	9	20	5	22	6	9	N	N	
SUBJ98C									DNA								DNA								DNA									DNA					DNA			
SUBJ99A	29	M	B	198		1.08	1.18	0.63	0.79	0.35	0.6	-83	-110	15	10	10	15	15	10	10	15	10	15	10	5	10	7	12	8	14	16	19	12	14	15	16	16	12	13	N	N	1
SUBJ99B														15	10	10	15	15	10	10	15	10	15	10	5	10	6	13	10	13	16	17	12	13	16	16	17	10	11	N	N	
SUBJ99C				56										20	15	10	15	15	10	10	15	10	15	10	5	11	7	12	8	14	15	18	11	13	14	15	15	11	12	N	N	
SUBJ100A	33	F	C	101		1.01	0.88	1.06	0.97	0.86	0.76	-22	-32	15	20	10	10	15	20	20	20	15	10	10	10	18	21	28	28	24	21	14	16	19	14	9	12	14	15	N	N	1
SUBJ100B														15	20	10	10	15	20	20	20	15	10	10	10	15	19	27	28	26	20	12	18	18	14	11	13	12	13	N	N	
SUBJ100C				14										15	20	10	10	15	20	20	20	15	10	10	10	17	20	28	28	25	20	13	17	19	14	8	12	12	14	N	N	
SUBJ101A	32	F	B	205		1.03	1.02	0.69	0.68	0.25	0.25	-27	-27	10	15	20	15	15	20	15	10	10	5	5	10	19	19	17	17	19	19	11	22	18	21	14	22	16	11	N	N	1
SUBJ101B														10	15	20	15	15	20	15	10	10	5	5	10	21	21	15	18	18	21	9	24	17	23	9	14	8	5	N	N	
SUBJ101C				101										40	15	50	15	40	20	45	10	40	5	50	10	18	18	16	16	19	20	11	23	18	22	7	4	6	2	Y	N	
SUBJ102A	20	M	B	198		1.4	1.1	0.5	0.5	0.4	0.7	-35	-25	80	15	85	25	95	25	100	25	70	5	85	15	-2	9	-1	-6	1	22	2	19	6	21	1	21	0	23	N	N	1
SUBJ102B				ENT												ENT																		ENT							
SUBJ102C				ENT												ENT																		ENT							
SUBJ103A	21	M	B	133		1.8	1.9	1	0.8	0.6	0.8	-10	-20	15	15	10	20	5	15	5	25	10	20	5	25	11	13	18	15	23	14	18	16	9	7	14	10	0	15	N	N	1
SUBJ103B				DNA								DNA						DNA																DNA							
SUBJ103C				CTR								CTR						CTR																CTR							
SUBJ104A	39	F	B	143		0.9	0.7	1	0.9	0.5	0.6	40	45	45	45	35	45	40	35	45	40	30	25	20	25	19	14	31	23	20	25	15	21	10	8	0	0	0	1	Y	Y	1
SUBJ104B				ENT												ENT																		ENT							
SUBJ104C				ENT												ENT																		ENT							

Key: A=session 1; B=sessin 2; C=sessin 3; F=female; M=male; B=black; C=coloured; DTR=deferred treatment; DNA=did not arrive; ENT=ear, nose throat referral; CTR=commenced treatment