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Vestibular functioning and pathology in adults with HIV/AIDS: A comparative study

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Abstract

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The human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is a worldwide pandemic that affects the lives of millions of people across all ages. Its devastating effects are far-reaching and affect all aspects of an individual's daily life. HIV/AIDS is responsible for widespread clinical manifestations involving the head and neck. Disorders of the auditory and vestibular systems are often associated with HIV/AIDS, however the extent and nature of these vestibular manifestations is still largely unknown.

The main aim of this research study was to investigate vestibular functioning and pathology in adults with HIV/AIDS. This was achieved through three main research steps: a systematic literature review of the body of peer-reviewed literature on HIV/AIDS related vestibular manifestations and pathology, a description and comparison of vestibular involvement in adults with and without HIV/AIDS and an investigation to determine if HIV/AIDS influence the vestibulocollic reflex (VCR) pathways.

For the first study a systematic literature review related to vestibular findings in individuals with HIV infection and AIDS was conducted. A varied search strategy was used across several electronic databases to identify relevant peer-reviewed reports in English. Several databases (Medline, Scopus and PubMed) and search strategies were employed. Where abstracts were not available, the full paper was reviewed, and excluded if not directly relevant to the study's aims. Articles were reviewed for any HIV/AIDS associated vestibular symptoms and pathologies reported.

For the second and third study, a cross-sectional, quasi-experimental comparative research design was employed. A convenience sampling method was used to recruit subjects. The sample consisted of 53 adults (29 male, 24 female, aged 23-49 years, mean = 38.5, SD = 4.4) infected with HIV, compared to a control

group of 38 HIV negative adults (18 male, 20 female, aged 20-49 years, mean = 36.9, SD = 8.2). A structured interview probed the subjective perception of vestibular complaints and symptoms. Medical records were reviewed for cluster of differentiation 4+ (CD4+) cell counts and the use of antiretroviral (ARV) medication. An otologic assessment and a comprehensive vestibular assessment (bedside assessments, vestibular evoked myogenic potentials, ocular motor and positional tests and bithermal caloric irrigation) were conducted on all subjects.

The systematic literature review identified 442 records, reduced to 210 after excluding duplicates, reviews, editorials, notes, letters and short surveys. These were reviewed for relevance to the scope of the study. There were only 13 reports investigating vestibular functioning and pathology in individuals affected by HIV/AIDS. This condition can affect both the peripheral and central vestibular system, irrespective of age and viral disease stage. Post-mortem studies suggest direct involvement of the entire vestibular system, while opportunistic infections such as oto- and neurosyphilis and encephalitis cause secondary vestibular dysfunction resulting in vertigo, dizziness and imbalance.

The second study showed an overall vestibular involvement in 79.2% of subjects with HIV in all categories of disease progression, compared to 18.4% in those without HIV. Vestibular involvement increased from 18.9% in the Centers for Disease Control and Prevention (CDC) category 1 to 30.2% in category 2. Vestibular involvement was 30.1% in category 3. There was vestibular involvement in 35.9% of symptomatic HIV positive subjects and 41.5% in asymptomatic HIV positive subjects. Individuals with HIV were 16.6 times more likely to develop vestibular involvement during their lifetime, than among individuals without this disease. Vestibular involvement may occur despite being asymptomatic.

The third study showed that abnormal cervical vestibular evoked myogenic potentials and caloric results were significantly higher in the HIV positive group (p=.001), with an odds ratio of 10.2. Vestibulocollic reflex and vestibulo-ocular reflex involvement increased with progression of the disease. There were more abnormal test results in subjects using ARV therapies (66.7%) compared to those not using ARV therapies (63.6%), but this difference was not statistically significant.

Vestibular involvement was significantly more common in subjects with HIV than among those without this disease. This disease and its associated risk profile include direct effects of the virus on the vestibular system as demonstrated by post-mortem studies. Opportunistic infections may compromise the functioning of the sensory and neural structures of hearing and the vestibular system indirectly, causing vertigo, dizziness or disequilibrium. Ototoxicity may also be related to vestibular dysfunction, due to the ototoxic nature of certain ARV medications. HIV/AIDS influence not only the vestibulo-ocular reflex, but also the vestibulocollic reflex pathways. Primary health care providers could screen HIV positive patients to ascertain if there are symptoms of vestibular involvement. If there are any, then they may consider further vestibular assessments and subsequent vestibular rehabilitation therapy, to minimize functional limitations of quality of life.

Key words

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Acquired immunodeficiency syndrome

Antiretroviral therapy

Disease progression

Disequilibrium

Dizziness

Human immunodeficiency virus

Opportunistic infections

Ototoxicity

Quality of life

Vertigo

Vestibular involvement

Vestibulocollic reflex

Vestibulo-ocular reflex

Vestibulospinal reflex

List of abbreviations and acronyms

_____

3TC	Lamivudine
ABR	Auditory Brainstem Response
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of Variance
ARC	AIDS Related Complex
ARV	Antiretroviral
AZT	Zidovudine
BPPV	Benign Paroxysmal Positional Vertigo
CD4+	Cluster of Differentiation 4+
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CN III	Third Cranial Nerve
CN VI	Sixth Cranial Nerve
CN VIII	Eighth Cranial Nerve
cVEMP	cervical Vestibular Evoked Myogenic Potential
d4T	Stavudine
dBnHL	decibel normal Hearing Level
DP	Directional Preponderance
DPOAEs	Distortion Product Otoacoustic Emissions
DVA	Dynamic Visual Acuity
EFV	Efavirenz
EMG	Electromyography

ENT	Ear-Nose-Throat
EO	Extra-ocular
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HVIN	Hyperventilation Induced Nystagmus
Hz	Hertz
ICF	International Classification of Functioning, Disability, and Health
ID	Infectious Disease
LC	Left Cool
LPV/r	Lopinavir/ritonavir
LW	Left Warm
MEP	Middle Ear Pathology
MeSH	Medical Subject Heading
MLF	Medial Longitudinal Fasciculus
ms	milliseconds
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
oVEMP	ocular Vestibular Evoked Myogenic Potential
PM	Postmortem
PTA	Pure Tone Audiometry
RC	Right Cool
RW	Right Warm
SCC	Semicircular Canals

SCM	Sternocleidomastoid
SD	Standard Deviation
SNHL	Sensorineural Hearing Loss
SPV	Slow Phase Velocity
SVV	Subjective Visual Vertical
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	Joint United Nations Programme on HIV/AIDS
VCR	Vestibulocollic Reflex
VEMP	Vestibular Evoked Myogenic Potential
vHIT	video Head Impulse Test
VNG	Videonystagmography
VOR	Vestibulo-ocular Reflex
VSR	Vestibulospinal Reflex
VST	Vestibulospinal Tract
WHO	World Health Organization

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PART I

INTRODUCTION

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Chapter 1

HIV/AIDS and auditory-vestibular functioning

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"The extent of its global reach and its pervasive and devastating nature has ensured that HIV/AIDS is the health care challenge of our time. Its affects are far reaching and impact not only those affected, but also the wider family, community, and societal structures." (Swanepoel & Louw, 2010:1)

1.1   Introduction

The human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) is a worldwide pandemic that affects the lives of millions of people of all ages (Swanepoel & Louw, 2010). Its devastating effects are far-reaching and affect all aspects of an individual's daily life. HIV/AIDS is at this stage a non-curable disease and can be regarded as a long-term health problem, which ultimately affects how an individual performs activities of daily living. If the individual, because of health related aspects, experiences difficulty in functioning independently and in contributing to society and living life, his/her quality of life is compromised.

In countries and regions where the incidence of HIV/AIDS is very high, there are additional health challenges that contribute to an increase in mortality and morbidity among children and adults. These include — but are not limited to — maternal and child health, tuberculosis, chronic communicable (contagious diseases such as HIV and tuberculosis) and non-communicable diseases (non-contagious such as cancer and diabetes), mental health, violence and injury (Chopra et al., 2009). Health care systems often experience tremendous financial difficulties since such countries are often plagued by poverty that affects countless communities. Issues such as poverty result in inadequate access to medical services, inappropriate nutrition and lack of community support, all of which exacerbates the consequences of the disease (Majumdar & Mazaleni, 2010). Developing countries,

especially those in the sub-Saharan region, where the incidence is very high, are suffering with the ability to cope with the increased demands posed by HIV/AIDS.

A recent study (Majumdar & Mazaleni, 2010) reported that, in addition to the physical difficulties surrounding the medical health status of those living with HIV/AIDS, these individuals are confronted with emotional issues such as fear, distress and despair regarding their own and their family's future and with isolation as well. Health care systems in developing countries experience financial difficulties due to poverty, which affects countless communities. Furthermore, poverty results in inadequate access to medical services, inappropriate nutrition and lack of community support, all of which exacerbates the consequences of the HIV/AIDS pandemic (Majumdar & Mazaleni, 2010).

Despite the fact that there is currently no cure for HIV/AIDS, the advent of antiretroviral therapies (ARVs) has significantly improved the life expectancy of those living with this disease. This, in turn, has shifted the focus from a life threatening, acute disease to a more manageable disease with an emphasis on quality of life (Swanepoel & Louw, 2010). Antiretroviral therapies are administered to suppress the virus and help to prevent progression of the disease by preserving immunity and reducing viral loads (Walker, Sarah & Gibb, 2011). Typically, three to four drugs are administered in order to improve immunity optimally and this is referred to as highly active antiretroviral therapy (HAART). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) there have been improvements in access to treatments. An estimated 6.6 million people in low- and middle-income countries were receiving ARVs at the end of 2010, which is 1.4 million more than a year earlier (UNAIDS, 2011). Although this may seem like an impressive milestone, about 9 million people eligible for treatment were not receiving it, despite strategies on the way to achieve global access (UNAIDS, 2011).

1.2   Epidemiology of HIV/AIDS

Recent reports estimate the global incidence of adults and children living with HIV/AIDS to be 34 million (UNAIDS, 2011). With just over 10% of the world's

population living in sub-Saharan Africa, it is home to more than two-thirds (68%) of all individuals living with HIV/AIDS (UNAIDS, 2010). In 22 countries situated in sub-Saharan Africa, significant changes in incidence rates of HIV/AIDS have been documented. Reports indicate a decrease in incidence rates by more than 25%, while in other countries it is stabilizing (UNAIDS, 2011). Despite the number of new infections and AIDS related deaths decreasing between 2001 and 2010, the overall number of individuals living with the disease is still very high. It is estimated that in 2001 there were 20.3 million (18.9-21.7 million) children and adults living with HIV/AIDS in sub-Saharan Africa, while in 2010 there were an estimated 22.9 million (20.9-24.2 million) children and adults living with HIV/AIDS in this region (UNAIDS, 2011).

HIV/AIDS affects millions of people worldwide, and for this reason it can now be regarded as a pandemic. The Joint United Nations Programme on HIV/AIDS (2011) estimated that in 2001 the global number of children and adults living with HIV/AIDS were 28.6 million (27.1-30.3 million), while this increased to 34 million (31.4-35.5 million) in 2010. Globally, the highest prevalence rate of HIV/AIDS among children and adults occur in South Africa, with an estimated 5.6 million individuals (5.4-5.8 million) in 2010 (UNAIDS, 2011). Increased life expectancy and periods of survival of those living with HIV/AIDS can, among other factors (such as public health education and awareness programmes), be attributed to HAART and improvements in accessibility to health care facilities. This reduction in morbidity and mortality has changed the face of HIV/AIDS from a life-threatening disease to a chronic illness.

1.3   The immune response to HIV

The human immunodeficiency virus enters the host through various body fluids. It is a retrovirus that attacks and slowly damages the body's immune system as it enters the cells that are responsible for controlling immunity against foreign pathogens (Evian, 2000). It therefore belongs to the subgroup of retroviruses called lentivirus, which means it takes a long time from initial infection to causing a disease (Williamson & Martin, 2005). The immune system contains many types of white

blood cells that are responsible for fighting off infections, diseases and malignancies, of which one of them are known as helper T cells or helper T lymphocytes (Webber, 2010). The human immunodeficiency virus binds to the CD4+ surface protein that is present on these helper T lymphocytes and macrophages. Most other cells in the body do not contain this protein (Fan, Conner, & Villarreal, 2004), but these specific cells become a target for HIV. After binding and penetrating into the CD4+ cell, it will destroy the immune cells leading to the body's inability to fight off infections (Evian, 2000). Gradually, the body becomes more and more predisposed to opportunistic infections, which are caused by organisms that take advantage of a weakened immune system and result in distressing infections that would usually not occur (Fan et al., 2004).

Some of the world's most common HIV/AIDS-related opportunistic infections and diseases are caused by (Evian, 2000):

- Bacteria such as tuberculosis, mycobacterium avium complex (MAC) and bacterial pneumonia
- Viruses such as cytomegalovirus (CMV), herpes simplex and herpes zoster
- Protozoa such as toxoplasmosis, microsporidiosis and cryptosporidiosis
- Fungi such as candidiasis, pneumocyctis pneumonia (PCP) and cryptococcosis
- Other malignancies such as Kaposi's sarcoma and lymphoma.

Individuals without HIV may also suffer from these disease processes; however, when the immune system is very weak, individuals infected with HIV are more susceptible to contracting these diseases and recovery may be prolonged. Highly active antiretroviral therapy has reduced the occurrence of these opportunistic infections; however it is not yet accessible to every individual living with HIV/AIDS.

1 4   Head and neck manifestations in HIV/AIDS

Diseases involving the head and neck area are often the first signs of an immune compromised body, and may occur in between 40% and 90% of individuals with HIV/AIDS (Barzan, Tavio, Tirelli, & Comoretto, 1993; Lubbe, 2004; Marsot-

Dupuch, Quillard, & Meyohas, 2004; Salzer, 1994; Somefun et al., 2001). In most cases HIV/AIDS-related head and neck manifestations can be attributed to opportunistic infections as a result of a suppressed immune system (Moayedi, 2010). Some commonly occurring head and neck pathologies that are associated with HIV/AIDS are listed in Table 1.1.

Table 1.1

HIV/AIDS-related head and neck manifestations

Site of lesion	Diseases involved at this site
Central nervous system	Toxoplasmosis; cryptococcus; progressive multifocal leukoencephalopathy
Oropharynx	Oral candidiasis; oral ulcerations; oral hairy leukoplakia
Larynx	Laryngeal candidiasis; histoplasmosis; lymphomas; Kaposi's sarcoma
Nose and sinus	Sinusitis; allergic rhinitis; nasopharyngeal lymphoid hypertrophy
Ear	Diseases that affect the external auditory canal and otitis media, causing conductive or mixed hearing loss; infections or ototoxicity causing sensorineural hearing loss; vestibular disorders causing vertigo, dizziness or disequilibrium.

Note: Adapted from Cohen and Berger (2007), Gurney and Murr (2003) and Moayedi (2010).

Many infections, diseases and/or malignancies involving the head and neck are deadly, necessitating early detection and prompt treatment in order to prevent morbidity and mortality. More often than not, the existence of these diseases may indicate the presence of HIV or, in some cases, progression to AIDS. Individuals can now survive these diseases and have a better quality of life, since the disease processes are now better controlled through treatment and strategies that protect immunity (Gurney & Murr, 2003).

1.5   Auditory and vestibular manifestations

An individual infected with HIV/AIDS often presents with abnormalities of the ear, which may result in hearing and/or vestibular problems which contributes to a poor quality of life for the individual infected with this disease (Chandrasekhar et al., 2000). HIV/AIDS-related auditory dysfunction is estimated to occur between 21 and 49% (Lalwani & Sooy, 1992). This correlates with the results of more recent studies (Prasad, Bhojwani, Shenoy, & Prasad, 2006) that reported auditory manifestations of the disease among 20% of individuals with HIV/AIDS and with the study by (Chandrasekhar et al., 2000) that indicated a prevalence rate of 33%. However, auditory dysfunction may occur in as many as 75% of adults with HIV/AIDS (Zuniga, 1999), which may be attributed to either HIV/AIDS as the primary direct cause, or indirectly to opportunistic infections and ototoxic therapies.

There is ample evidence that HIV/AIDS could either directly or indirectly have an adverse effect on the delicate structures of the ear, causing a conductive, mixed or sensorineural hearing loss (Chan et al., 2008; Devaleenal, Ahilasamy, Solomon, & Kumarasamy, 2008; Matas, Sansone, Iorio, & Succi, 2000; Palacios et al., 2008; Vincenti et al., 2005). However, only a limited number of studies have reported on vestibular symptoms of individuals infected with HIV/AIDS or on the functioning of the vestibular system despite the cochlea and vestibular system constituting part of the same structure, namely the membranous labyrinth (Teggi, Giordano, Pistorio, & Bussi, 2006). Common complaints of individuals with some form of vestibular disorder are dizziness or vertigo and disturbance in balance (hence referred to as disequilibrium). Vertigo is the subjective sensation of rotating movement of oneself or of the surroundings, and it can be a result of peripheral or central vestibular impairments (Bennet, 2008).

The life expectation of individuals infected with HIV/AIDS has improved as a result of access to medication as well as advances in medical technology, although in many developing countries this is not the case. Vestibular symptoms such as dizziness, vertigo and/or disequilibrium were most probably merely masked by other illnesses and disorders associated with HIV/AIDS (Teggi et al., 2006); therefore the

nature of vestibular symptoms and possible mechanisms of pathology in these individuals were probably overlooked. Another possible explanation might be that, currently, little is known about the precise nature and extent of the effects of HIV/AIDS on the vestibular system, given its close anatomical proximity to the auditory system. However, what is known is that HIV/AIDS commonly involves the neurological system at numerous levels, which include, but are not limited to, the vestibular system (Hofmeyr & Baker, 2010). Disruption in vestibular functioning has a serious and negative impact on an individual's quality of life. The WHO has developed and endorsed the International Classification of Functioning, Disability, and Health (ICF) in 2001 to describe and measure health and disability (WHO, 2012). It is further used to describe restrictions and limitations of functioning and health of auditory, vestibular and other related disorders. One of the components of the ICF relates to how deviation or loss of a body function or structure results in activity limitations and participation restrictions, for example disequilibrium may result in an individual having difficulties executing activities of daily living (activity limitations), and problems being involved in life situations (participation restrictions). These effects may be seen in an individual's social, occupational and recreational environments.

1.6 Auditory and vestibular manifestations throughout disease progression

HIV/AIDS is a progressive disease and occurs in stages of severity. In order to understand how auditory and vestibular manifestations are presented throughout the HIV/AIDS disease progression, an overview of the various classification and staging systems will be descirbed. There are two classification and staging systems used worldwide as tracking and monitoring tools that provide important information about disease progression and clinical management: (1) the World Health Organization (WHO, 2007), and (2) the 1993 Centers for Disease Control and Prevention for adolescents and adults (CDC, 1992).

1.6.1 The WHO classification system

Once the individual has been diagnosed with HIV/AIDS, the clinical staging is useful at the time of diagnosis of the disease, as well as in the follow-up of treatment regimes. It also serves as a guideline for when to start administering ARVs or other HIV/AIDS-related treatments and is particularly useful in settings where testing of CD4+ cell counts are not available. Table 1.2 lists the WHO stages of HIV/AIDS in adolescents and adults with confirmed HIV infection and each stage is defined by specific clinical conditions or symptoms.

1.6.2 The CDC classification system

The Centers for Disease Control and Prevention (CDC, 1992) use a revised system to classify HIV/AIDS disease and infection. This system is based on the CD4+ cell counts and presence of HIV/AIDS-related conditions and symptoms to categorize the severity of the disease and determine clinical management. It is known that the CD4+ cell count determines the health of the immune system and therefore reduced numbers indicate an increase in the degree of immunosuppression (Bekker, 2010) which places the individual at-risk for various infections or diseases.

Table 1.2

WHO clinical staging of HIV/AIDS

Clinical stage 1: Asymptomatic
Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2: Mild symptoms
Moderate unexplained weight loss
(<10% of presumed or measured body weight)
Recurrent respiratory tract infections: sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

Clinical stage 3: Advanced symptoms
Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6°C—intermittent or constant—
for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis,
bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre)
or chronic thrombocytopaenia (<50 × 109 per litre)

Clinical stage 4: Advanced symptoms
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (oro-labial, genital or anorectal
of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

Note: From WHO (2007)

The CDC categorization is firstly based on the lowest CD4+ T-lymphocyte cell count (Table 1.3). The CD4+ count among HIV seronegative adults are approximately 800 cells per microliter (µL) (Wilson et al., 2008). HIV/AIDS-related infections and diseases are likely to occur with CD4+ counts between 350 and 500 cells/µL (Bekker, 2010), while individuals with CD4+ counts less than 200 cells/µL are highly susceptible to infections and diseases due to a severely injured immune system (Holmes, Wood, & Badri, 2006).

Table 1.3

CD4+ T-lymphocyte categories

Category	CD4+ T-lymphocyte counts
Category 1	Greater than or equal to 500 cells/ µL
Category 2	200-499 cells/ µL
Category 3	Less than or equal to 199 cells/ µL

Note: Adapted from CDC (1992)*;* CD4+ = cluster of differentiation 4+; µL = micro Liter.

Secondly, categorization is also based on HIV/AIDS-related symptoms, diseases and/or conditions (Table 1.4). There are three clinical categories, namely A, B and C with category A being the earlier, least severe stage and category C being the advanced most severe stage. Individuals in category A may be asymptomatic or present with mild symptoms. Individuals in category B may have various symptomatic conditions, while those in category C have AIDS-indicator conditions.

Lalwani and Sooy (1992) and Chandrasekhar and colleagues. (2000) reported a relationship between auditory manifestations and disease progression. They revealed a higher prevalence of hearing loss and worsening of hearing thresholds as the disease progresses. Two later studies (De Lange, 2007; Van der Westhuizen, 2011) also reported a significantly higher prevalence and more severe degrees of hearing loss in the advanced stages of HIV/AIDS.

Table 1.4

CDC clinical categories of HIV/AIDS infection

Category A
Asymptomatic HIV infection
Persistent generalized lymphadenopathy
Acute (primary) HIV infection with accompanying illness or history of acute HIV infection
Category 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°C) or diarrhea lasting longer than 1 month
Oral hairy leukoplakia
Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
Idiopathic thrombocytopenic purpura
Listeriosis
Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
Peripheral neuropathy
Category C
Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (longer than 1 month in duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (longer than 1 month in duration); bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (greater than 1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of the brain
Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

Note: From CDC (1992)

To date, five studies have described vestibular disorders in adults with HIV/AIDS throughout progression of the disease (Castello, Baroni, & Pallestrini, 1998; Dellepiane, Medicina, Mora, & Salami, 2005; Hausler, Vibert, Koralnik, &

Hirschel, 1991; Teggi et al., 2006; Teggi, Ceserani, Luce, Lazzarin, & Bussi, 2008). The studies mentioned above used the CDC classification system and therefore the present study employed the same system to compare findings with the literature. All these studies revealed progressive vestibular damage. There was a higher occurrence of vestibular disorders, particularly central vestibular disorders, among individuals in advanced stages of HIV/AIDS compared to those in earlier stages of the disease, although vestibular disorders occurred even in the early stages.

1.7   Mechanisms of HIV/AIDS-related auditory-vestibular dysfunction

Figure 1.1 illustrates the various mechanisms of pathology of HIV-related auditory and vestibular dysfunction. Each mechanism of pathology will be discussed next.
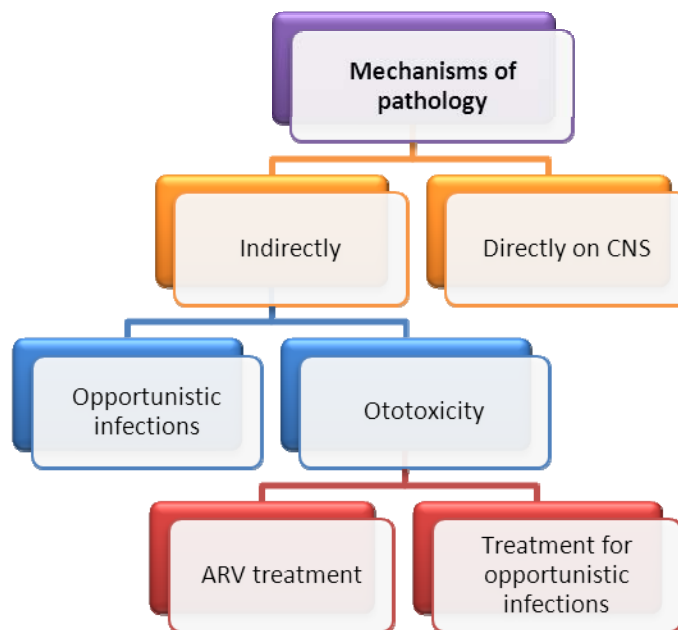
Figure 1.1. Mechanisms of HIV/AIDS-related auditory-vestibular dysfunction (adapted from Stearn & Swanepoel, 2010)

1.7.1 Direct effects of HIV/AIDS

Several reports have indicated that HIV/AIDS affects the auditory and vestibular systems *directly*. Abnormalities recorded by auditory brainstem responses (ABR) suggested involvement of the peripheral and central auditory nervous system (Matas et al., 2000; Matas, Leite, Magliaro, & Gonçalves, 2006; Reyes-Contreras et al., 2002). These abnormalities may be due to demyelination because of direct infection of the glial and neurological cells (Reyes-Contreras et al., 2002). Abnormalities of the peripheral and central vestibular systems have also been reported. Postmortem studies (Chandrasekhar, Siverls, & Chandra Sekhar, 1992; Pappas Jr., Roland Jr., Lim, Lai, & Hillman, 1995) demonstrated micro structural changes as well as viral-like particles, characteristic of HIV, within the epithelium and endolymphatic spaces of the end-organs. In addition, the majority of these studies showed structural abnormalities within the central nervous system (CNS). Studies of vestibular dysfunction in individuals infected with HIV/AIDS (Palacios et al., 2008; Teggi et al., 2006; Teggi et al., 2008) found a high occurrence of central vestibular abnormalities as demonstrated by the ocular motor tests and the characteristics of positioning/positional, head shake, caloric and rotatory testing induced nystagmus. These findings also suggested direct involvement of the virus.

1.7.2 Indirect effects of HIV/AIDS

Certain opportunistic infections may compromise the functioning of the sensory and neural structures of hearing and the vestibular system, causing hearing loss and vertigo/dizziness or disequilibrium respectively. Common opportunistic infections include cytomegalovirus, otosyphilis, toxoplasmosis, meningitis and herpes zoster virus (Hofmeyr & Baker, 2010; Stearn & Swanepoel, 2010).

Ototoxicity may also be related to auditory and vestibular dysfunction, due to the ototoxic nature of certain ARVs, or due to the treatment for opportunistic infections. Firstly, a wide variety of ARVs has been reported to have side effects on the auditory and/or vestibular systems. Although the exact mechanisms are not clear, it is thought that it causes damage to the mitochondrial DNA (Bektas 2008; Newton 2006; Shibuyama 2006). Nucleoside reverse transcriptase inhibitors

(NRTIs) and combinations of drugs have been reported to show evidence of ototoxicity in children and adults (Rey, L'Héritier, & Lang, 2002). However, the ototoxic effects of these drugs are influenced by drug type, combinations, dosages and age of the individual. Secondly, ototoxic medication for opportunistic infections include antibiotics, antifungal and antiviral agents. Tuberculosis (TB), a very common and deadly disease affects up to a third of individuals infected with HIV and is often treated with antibiotics such as aminoglycosides, including amikacin and streptomycin, both established ototoxic agents.

1.8   The role of the audiologist in HIV/AIDS care

Chandrasekhar and colleagues (2000) argued that the prevalence of auditory manifestations could increase with HIV/AIDS progression and therefore these findings indicate that the audiologist has a very important role in the management of individuals infected with HIV/AIDS and ear-related disorders. According to the American Speech-Language-Hearing Association (ASHA, 2004:1) "Audiologists are professionals engaged in autonomous practice to promote healthy hearing, communication competency, and quality of life for persons of all ages through the prevention, identification, assessment, and rehabilitation of hearing, auditory function, balance, and other related systems. The audiologist is the professional responsible for the identification of impairments and dysfunction of the auditory, balance, and other related systems". The role of the audiologist therefore includes the assessment and rehabilitation of ear-related disorders within multi- and interdisciplinary teams, which aims to provide the individual infected with HIV/AIDS with prompt and appropriate treatment to improve overall quality of life (HPCSA, 2005). The high incidence of HIV/AIDS in South Africa and the high prevalence rate of ear-related disorders in individuals infected with this disease, necessitates that the audiologist be well acquainted with the possible effects of HIV/AIDS on hearing and vestibular function. The audiologist should therefore be familiar with the types and nature of auditory-vestibular disorders that may be expected due to the direct or indirect effect of HIV/AIDS, in order to manage this chronic condition optimally.

Chapter 2

Diagnostic techniques in vestibular testing

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2.1   Introduction

Abnormalities in the peripheral and/or central vestibular pathways can cause vertigo, dizziness or disequilibrium. The vestibular system is responsible for postural stability, sensing of head and body positions in space and for providing stability of images on the fovea of the retina during head movements (Schubert & Shepard, 2008).   Other systems that contribute to these functions are the visual, somatosensory and auditory systems (Harsha, Phillips, & Backous, 2008).   The three dominant inputs that sense the environment are the vestibular, visual and somatosensory (proprioceptive) inputs (Figure 2.1). The cerebellum and vestibular nuclei in the brainstem process and integrate all these sensory inputs and create motor commands (Figure 2.1). Finally, execution of these motor commands, namely postural stability of the head (vestibulocollic reflex) and the body (vestibulospinal reflex) and eye stabilization (vestibulo-ocular reflex) serve as the output system (Goebel, 2008a).
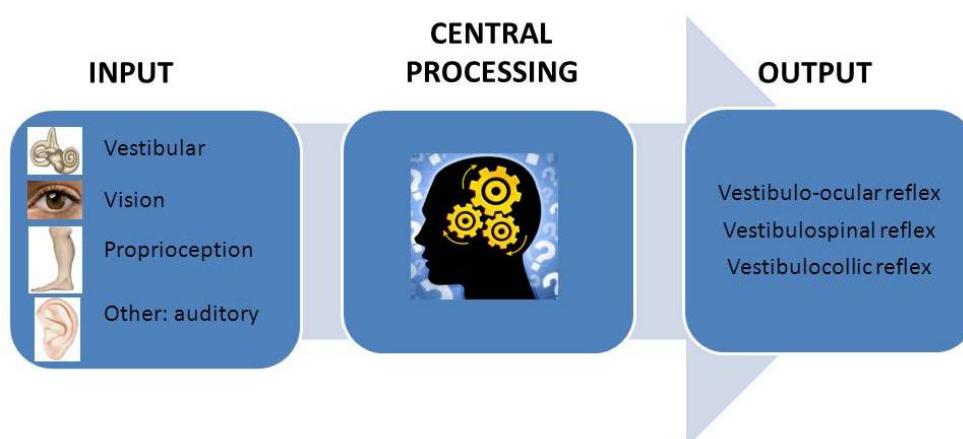
Figure 2.1. Balance control: central processing of inputs and motor outputs (adapted from Goebel, 2008a)

The vestibular system is a complex system that involves many structures (Sakka & Vitte, 2004). The peripheral vestibular inputs comprise 5 different sensors. Angular movements of the head are detected by means of three fluid-filled semicircular canals (SCCs) in each ear that are located within an outer bony labyrinth in the petrous portion of the temporal bone (Figure 2.2).
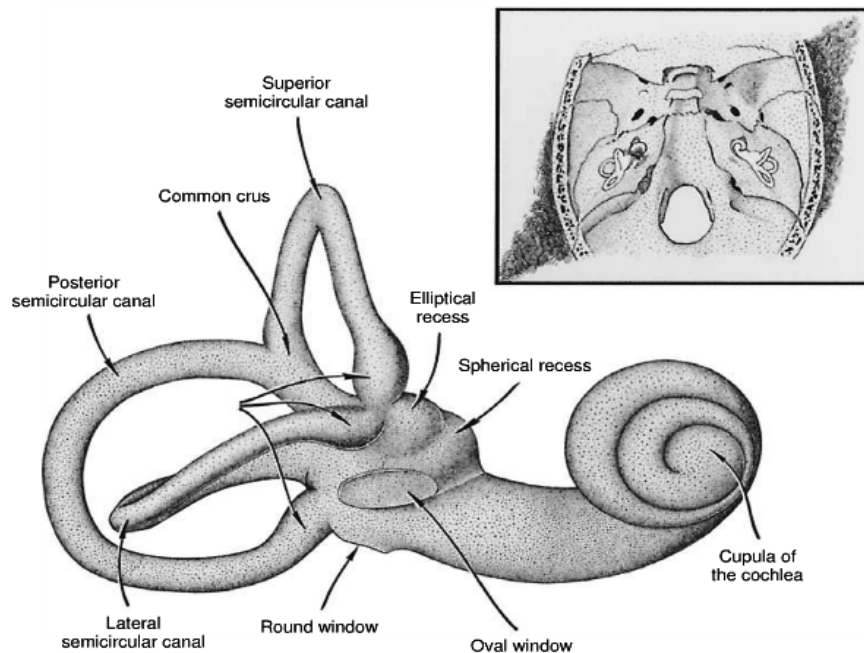
Figure 2.2. Anatomy of the vestibular end organ in the temporal bone, depicting the three semicircular canals (source: Schuknecht, 1974)

Figure 2.3 shows the orientation of the three SCCs in the temporal bone: the two horizontal canals are co-planar as are the posterior canals on one side and the superior canals on the other side. This means that the left posterior canal is coplanar with the right superior canal and the right posterior canal is coplanar with left superior canal. The horizontal (lateral) canals are at an angle of 30 degrees with respect to the horizontal plane. The superior (anterior) and posterior (inferior) canals are almost perpendicular to each other (Harsha et al., 2008).
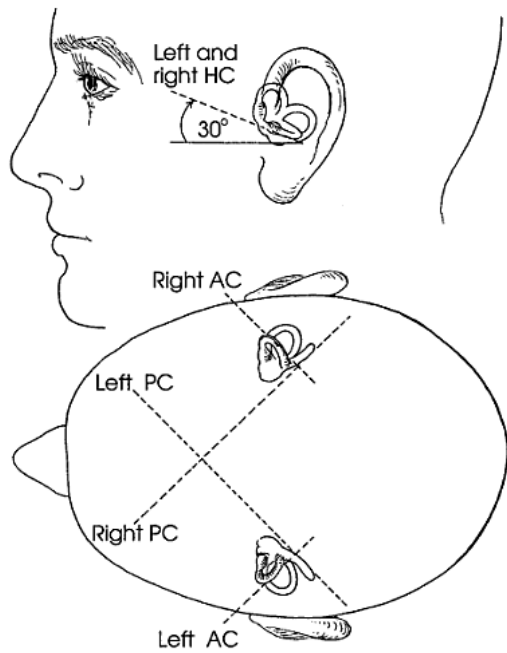
Figure 2.3. Orientation of the semicircular canals. AC = anterior (superior) canal; HC = horizontal; PC = posterior canal (source: Baloh & Honrubia, 2001)

The SCCs are primarily responsible for detecting angular accelerations of the head in the pitch (around y-axis), yaw (around z-axis) and roll (around x-axis) planes (Figure 2.4).
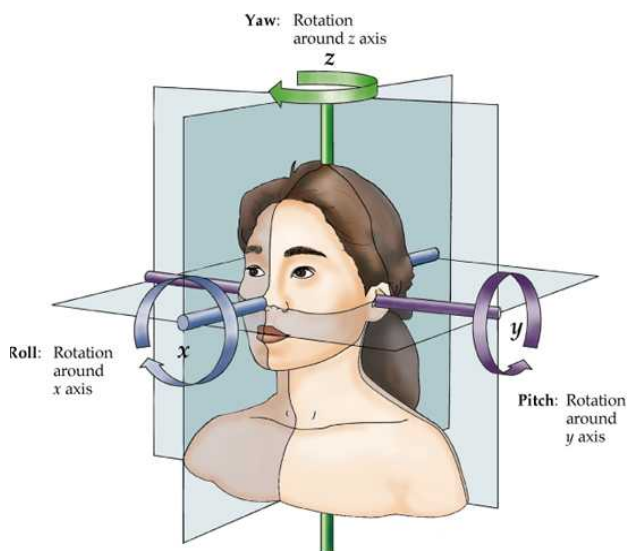
Figure 2.4. The three semicircular canals are responsible for angular acceleration (source: Purves et al., 2004)

The peripheral vestibular inputs furthermore comprise two otolithic organs, namely the saccule and utricle (Figure 2.5). The saccule is orientated in a nearly vertical plane and is sensitive to vertical (linear) accelerations and gravity, while the utricle is oriented in a nearly horizontal plane and hence is sensitive to horizontal accelerations, head tilt and sideways movement (Harsha et al., 2008; Tascioglu, 2005). The utricles and saccules are also paired across the head, similar to the semicircular canals.
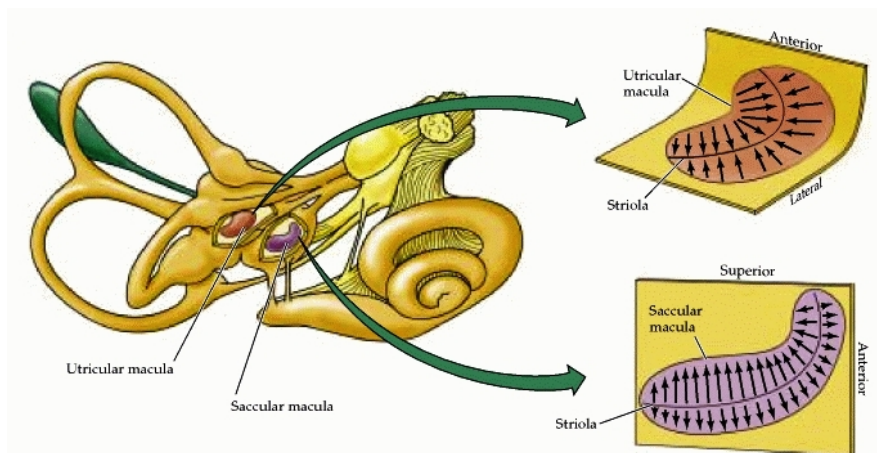
Figure 2.5. Orientation of the saccule and utricle (source: Purves, 2004)

The eighth cranial nerve has a cochlear portion and a vestibular portion (Figure 2.6). Two divisions or branches constitute the vestibular portion, namely the superior and inferior branches. The superior branch innervates the utricle, the horizontal semicircular canal, the superior semicircular canal and the anterior-superior part of the saccule. The inferior branch innervates the posterior semicircular canal and the main portion of the saccule (Baloh & Kerber, 2011; Goebel, 2008a). The vestibular nerves converge in Scarpa's ganglion, which is located within the internal auditory meatus. Scarpa's ganglion consists of cell bodies of bipolar neurons (Harsha et al., 2008).
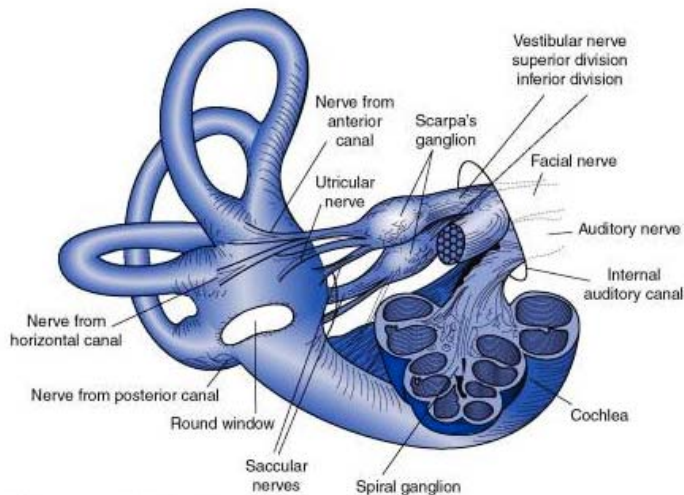
Figure 2.6. Vestibular nerve innervations (source: Baloh & Honrubia, 2011)

Processes that predominantly occur in the vestibular nuclei within the brainstem control the vestibular reflexes, namely the vestibulo-ocular reflex (VOR), the vestibulocollic reflex (VCR) and the vestibulospinal reflex (VSR). However, there are several connections between the vestibular nuclei and other structures such as the reticular formation, thalamus and cerebellum (Schubert & Shepard, 2008). These central vestibular pathways end in the vestibular cortex which is located in the parietal and insular regions (Brandt et al., 2002). Central vestibular dysfunction implicates dysfunction of not only the central pathways, but also of the ocular motor pathways (Bennet, 2008).

It is important to employ a comprehensive vestibular test battery, since there is no single test or device that can adequately test all areas of the vestibular system (Kiderman, 2010). This chapter will review and describe all the test procedures performed on the subjects that participated in this research study. It does not describe all the existing vestibular test procedures, but only those that the researcher included (and had access to) in the present study. Furthermore, this chapter describes the anatomical and physiological principles of each test in order to understand which area/s of the vestibular system is/are being tested. The identification of peripheral and central vestibular signs by utilizing these test procedures is described in Chapter 5. The methods and procedures that were followed for each vestibular test are described and illustrated in Chapter 3.

2.2 Bedside/clinical assessments

2.2.1 Fukuda stepping test

The Fukuda stepping test was developed and described by Fukuda in 1959 (Fukuda, 1959) as a test to determine the presence of a peripheral vestibular weakness. The presence of a peripheral vestibular lesion will result in an asymmetry in the lower extremity VSR pathways, which causes a rotation of the body in the direction of the affected side (McCaslin, Dundas, & Jacobson, 2008). The goal of the VSR is to maintain postural stability and equilibrium in order to keep the body in its centre of gravity by producing appropriate contractions of spinal, hip, knee and ankle muscles (Goebel, 2008a; Schubert & Shepard, 2008). Figure 2.7 shows that neurons travel from the vestibular end organs to the vestibular nuclei (mainly the lateral vestibular nucleus) and through the lateral vestibulospinal tract (LVST) to innervate the extensor motor neurons that terminate in the axial and proximal limb muscles responsible for the VSR (Purves et al., 2004).
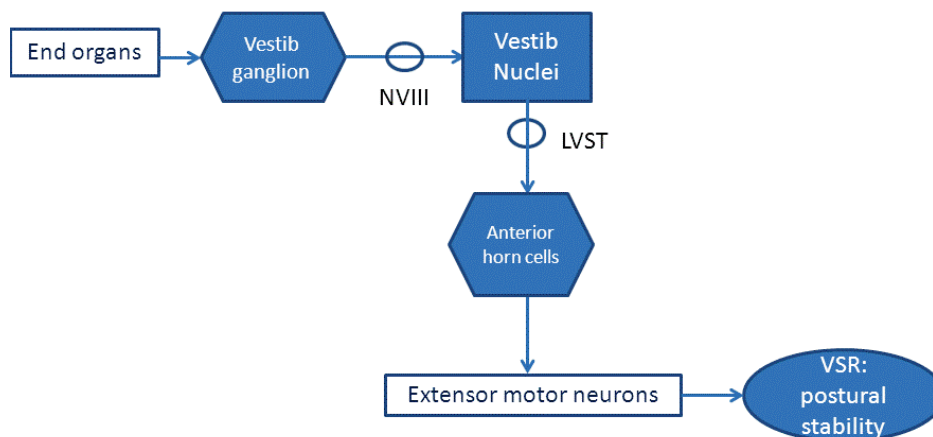
Figure 2.7. Anatomical pathway of the vestibulospinal reflex (adapted from Purves et al., 2004)

The Fukuda stepping test has a 70% sensitivity and a 59% specificity in identifying peripheral vestibular weakness and can therefore be considered a useful test to screen for vestibular disorders (McCaslin et al., 2008). It should be used in conjunction with other clinical tests of vestibular function to identify and localize

peripheral vestibular dysfunction (Honaker, Boismier, Shepard, & Shepard, 2009). Not only does this test provide information of the functioning of the VSR, but also of proprioceptive functioning, since it contributes to ensure that the subject does not rotate while the test is performed (Honaker et al., 2009). A deviation of 30 degrees or less in any direction was originally suggested by Fukuda (Fukuda, 1959) to be considered normal. A deviation of 45 degrees or more was considered abnormal (Fukuda, 1959; Furman & Cass, 2003) and probably predictive of the presence of asymmetrical vestibular function and VSR dysfunction.

2.2.2 Subjective visual vertical test

The otolith organs sense linear acceleration and act as gravito-inertial force sensors that play a role in the perception of spatial orientation (Akin, Murnane, Pearson, Byrd & Kelly, 2011). The subjective visual vertical (SVV) test is regarded as a sensitive test for assessing the functioning of the otolith organs, particularly the utricle, and graviceptive pathways (Fetter, 2000). The perception of true gravitational vertical (0 degrees) will be altered toward the side of the lesion in cases of acute utricular dysfunction (Janky & Shepard, 2011). It may also be altered in cases of brainstem lesions and uncompensated peripheral vestibular lesions (Bömmer & Mast, 1999; Zwergal et al., 2009). A normal result can be regarded as two to three degrees off real vertical, while any offsets greater than this are regarded as abnormal (Zwergal et al., 2009). Abnormalities may indicate a peripheral or central vestibular disorder and interpretation of results should be coupled with other tests in order to make this distinction.

2.2.3 Head impulse test

The head impulse test is a simple bedside test that aims to identify the presence of a severe unilateral weakness in the semicircular canal. It is also used to lateralise the side of a unilateral vestibular weakness (Jorns-Häderli, Straumann, & Palla, 2007). It was first described by Halmagyi and Curthoys (Halmagyi & Curthoys, 1988) as a test of the VOR, and is also known as the Halmagyi head thrust test. The VOR is a reflexive eye movement that stabilizes images on the fovea of the retina during brief rotational movements of the head (Harsha et al., 2008). Without the

VOR there would be a loss of visual acuity. The VOR produces eye movements of the same speed in the direction opposite to head movement, therefore maintaining clear vision of the image in the centre of the visual field. For example, a horizontal head movement to the left will produce a horizontal eye movement to the right and vice versa. The horizontal VOR will be used to explain the mechanisms of this reflex arc (Jones, Jones, Mills, & Gaines, 2009). These pathways are depicted in Figure 2.8: when the head is turned to the left, sensory hair cells in the left horizontal semicircular canal are depolarized, resulting in increased neural discharge rates. The left side therefore becomes excited. Since the left and right sides work in 'push-pull' pairs, the right side simultaneously becomes inhibited. Primary afferents of the vestibular nerve send their signals to the vestibular nuclei complex, which receives increased input from the left horizontal semicircular canal and decreased input from the right horizontal semicircular canal. This increased input in the left vestibular nuclei activates second-order neurons that activate extra-ocular motor nucleus III (oculomotor) ipsilaterally and VI (abducens) contralaterally. At the same time, reduced input in the right vestibular nuclei deactivates neural activity of extra-ocular motor nucleus III on the right and extra-ocular motor nucleus VI on the left. Subsequently, motor neurons from the right abducens nucleus activate the right lateral rectus eye muscle which will contract and pull the right eye to the right. Motor neurons from the left oculomotor nucleus activate the left medial rectus eye muscle, resulting in the left eye being pulled to the right (Jones et al., 2009).
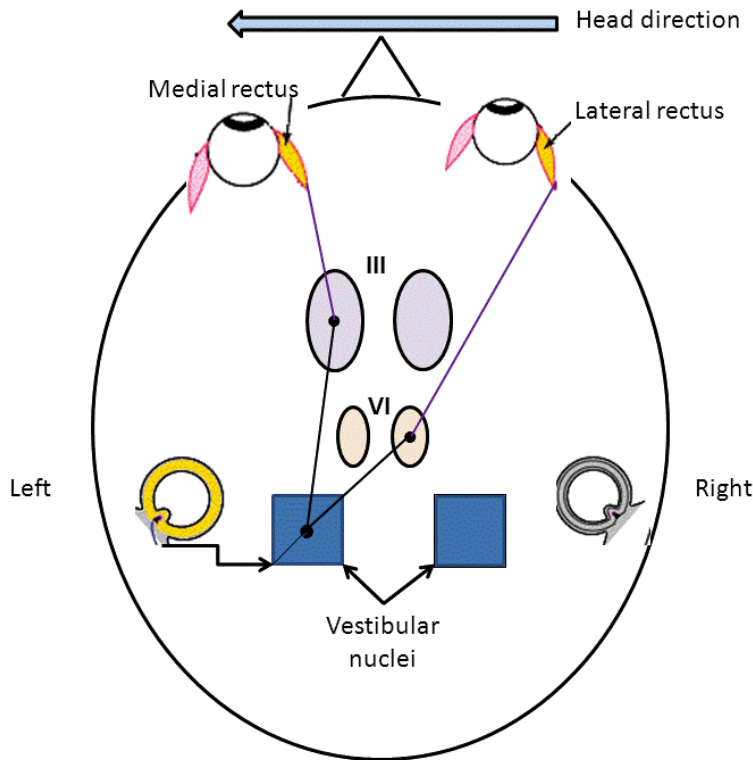
Figure 2.8. The vestibulo-ocular reflex pathways for horizontal eye movements (adapted from Jones et al., 2009)

The head impulse test provides insight into the integrity of the peripheral vestibular system, particularly the horizontal semicircular canal when it is performed in a horizontal manner (Curthoys, 2012). When there is a unilateral vestibular lesion, there is an asymmetry between excitatory and inhibitory neural responses from each horizontal semicircular canal and when the head is quickly turned to the side of the lesion, "…the VOR will be deficient and the eyes will move with the head so that they no longer fix on the point in the distance. The patient therefore needs a refixation saccade just after the thrust. When the head impulse is in the direction of the healthy side, the VOR will maintain the target on the fovea and no refixation saccade will be needed." (Wuyts, 2008:24). A lesion in the peripheral vestibular system, particularly the horizontal semicircular canal, will result in a catch-up saccade after head impulses toward the damaged side.

2.2.4 Dynamic visual acuity test

The dynamic visual acuity (DVA) test aims to evaluate the ability to perceive objects accurately during head movements. The VOR improves visual acuity during head movements by holding gaze steady during head movement. Damage to the VOR would result in poorer visual acuity during head movements than without (McCaslin et al., 2008). When there is a peripheral vestibular system dysfunction, a common complaint is blurry or bouncing vision during head movements, called oscillopsia. Oscillopsia is therefore a result of a dysfunctional VOR, implying damage to the peripheral vestibular end organs (Honaker & Janky, 2011). The DVA test is able to identify an underlying vestibular disorder, particularly in the horizontal semicircular canals when performing the test in the horizontal or yaw plane (McCaslin et al., 2008). When there is damage to the peripheral vestibular system, either unilateral of bilateral, there is a reduction in visual acuity during head movement. This will cause slippage of the target from the retina, resulting in the DVA test to be abnormal (Brickner, 1936). The DVA test should be used in conjunction with other tests to draw a conclusion about the functioning of the VOR.

2.3   Videonystagmography (VNG)

2.3.1. Spontaneous nystagmus

Spontaneous nystagmus is caused by an asymmetry of tonic activity in the vestibular nucleus reaching the oculomotor neurons (Baloh & Kerber, 2011). Often, this asymmetry originates from the vestibular system (Hain, 2009b). Damage to the vestibular hair cells or vestibular nerve creates an asymmetry that mimics head movement, resulting in a slow eye movement toward the weaker or damaged side, followed by a quick corrective eye movement toward the side of the increased activity (McCaslin et al., 2008). Therefore, nystagmus occurs with the fast phase in the direction of perceived head rotation. It most commonly has a dominant horizontal component, because tonic activity from the superior and posterior semicircular canals cancels out (Baloh & Kerber, 2011). The characteristics of spontaneous nystagmus that differentiate peripheral from central vestibular lesions as well as its site of lesion are summarized in Table 2.1.

Table 2.1

Differentiation of spontaneous nystagmus from peripheral vs. central vestibular origin (adapted from Baloh & Kerber, 2011)

	Nystagmus characteristics	Inhibition	Direction	Site of lesion
Peripheral	Horizontal AND torsional	Nystagmus inhibited by fixation	- Direction of nystagmus is fixed - Follows Alexander's law*	Vestibular end-organs or vestibular nerve
Central	Purely horizontal, OR vertical, OR torsional	Nystagmus not inhibited by fixation	Nystagmus changes direction	Brainstem or cerebellum

Note: * = Alexander's law refers to the phenomenon in which the velocity of spontaneous increases when the subject looks in the fast-phase direction. Therefore, right beating spontaneous nystagmus will be stronger when the subject looks to the right than to the left.

2.3.2 Gaze evoked nystagmus

Holding the eyes steady in eccentric positions requires continuous extraocular muscle contraction. This gaze holding system, that keeps the eyes in place, is modulated by a neural ocular motor integrator (Fukushima & Kaneko, 1995; Moschovakis, 1997). There are two neural intergrators (Leigh & Zee, 2006; Büttner-Ennever, 1988): the horizontal neural integrator is located in the nucleus prepositus hypoglossi and connects to CN III nucleus, CN VI nucleus and the superior colliculus. The vertical and torsional neural integrator is located in the interstitial nucleus of Cajal in the midbrain. The flocculus and paraflocculus in the cerebellum also contributes to the neural integrator.

The presence of gaze evoked nystagmus indicates a central lesion, particularly of the cerebellar flocculus or medial vestibular nucleus in the brainstem (Isaacson, Ort, & Rubin, 2008).

2.3.3 Random saccades and pursuit tracking

Lesions in the central vestibular pathways can also result in symptoms of dizziness and the eyes can be useful in testing the central nervous system (CNS) that controls the structures for eye movements (Shepard & Schubert, 2008). In contrast to the VOR that provides clear vision of a target during head movement, the visual tracking (ocular motor) systems interact with the vestibular system to provide clear vision of moving images as well as to maintain stability in gaze (Baloh & Kerber, 2011). There are three visual tracking systems, namely the saccade, smooth pursuit and optokinetic system. Their nuclei can be found in various regions in the brainstem and include the superior colliculus, interstitial nucleus of Cajal, nucleus of the optic tract, accessory optic nuclei, inferior olivary nucleus and prepositus hypoglossi (Jones et al., 2009). The cerebellum also plays an important role in the visual-vestibular action, particularly in areas such as the flocculus, paraflocculus, nodulus (Goebel, 2008a) and vermis (Jones et al., 2009). Lesions to and dysfunction of these areas in the cerebellum could result in poor ocular motor responses.

Two ocular motor systems were tested during this study, namely saccade and pursuit eye movements. Saccades are fast, reflexive eye movements that bring moving objects onto the fovea of the retina in a fast, single movement (Hain & Rudisill, 2008; Shepard & Schubert, 2008). There are four characteristics of saccadic eye movements, namely accuracies (controlled by the midline cerebellum and fastigial nuclei), latencies, velocities and conjugate deviation (controlled by the brainstem and frontal eye fields) (Goebel, 2008a). The smooth pursuit system allows fixation on slow moving objects, thereby generating smooth and conjugate eye movements in phase with the moving object and at the same velocity (Baloh & Kerber, 2011). Smooth pursuit is affected by many factors such as age, attention and medication and therefore some authors are of the opinion that it has limited clinical significance (Hain & Rudisill, 2008); however, abnormalities may indicate lesions in various areas of the cerebellum, cortex and brainstem (Goebel, 2008a). The anatomy and physiology of the ocular motor systems are presented in this section, which is adapted from Hain and Rudisill (2008), and Leigh and Zee (2006).

The primary role of the ocular motor system is to position the eyes so that moving images are on the fovea of the retina, in order to allow good vision. Figure 2.9 shows the order of structures and systems in the CNS involved in ocular motor control.

Cerebral centres
- Frontal eye fields
- Parieto-occipital eye fields

Higher order premotor system
- Superior colliculus
- Cerebellum: flocculus, paraflocculus

Lower order premotor system
- Paramedian pontine reticular formation
- Rostral interstitial nucleus of the median longitudinal fasciculus
- Median longitudinal fasciculus

Motor system
- Ocular motor nuclei and nerves (III, IV, VI)
- Extra-ocular muscles

Figure 2.9. Order of ocular motor control

In the *cerebral centres*, the frontal eye field in the frontal lobe is an executive centre that is involved in controlling and producing voluntary rapid eye movements (saccades). In addition, it is also involved in generating predictive smooth pursuit. The middle temporal visual area and medial superior temporal area in the parieto-occipital lobe are mainly responsible for generating unpredictable smooth pursuit as well as accurate pursuit.

Projections from the cerebral centres to the *higher order premotor system* include the superior colliculus and cerebellum. The superior colliculus in the roof of the midbrain carries motor commands to the paramedian pontine reticular formation (PPRF) and to the rostral interstitial nucleus of the median longitudinal fasciculus (riMLF); these serve to move the eyes quickly and accurately to the target. The cerebellum, particularly the flocculus and paraflocculus, contributes to the neural integrator, which is a gaze holding system that keeps the eyes in place in order to

counteract passive forces that want to pull the eyes to the centre. Damage to the cerebellum affects this neural integration and may result in inaccuracies of saccadic eye movements, thereby causing overshoots (hypermetria) or undershoots (hypometria) of eye movements. It may also cause gaze evoked nystagmus. Cerebellar damage may also cause diploplia or double vision due to misalignment of the eyes. An important function of the cerebellum is that it monitors and repairs ocular motor performance by adjusting premotor neural circuitry to compensate for mismatches.

The *lower order premotor system* is under control of the brainstem. The PPRF in the pons is mainly a horizontal saccade centre, while the riMLF in the midbrain is mainly a vertical saccade centre. Damage to neurons in these centres is associated with slow saccades. The median longitudinal fasciculus (MLF) is a long tract that runs along the midline of the brainstem from the pons to the midbrain. This vulnerable location of the MLF places it at risk for brainstem diseases that result in disconjugate eye movements. Neurons in the midbrain and pretectal region are responsible for vergence of eye movements (in other words, the ability to move both eyes inwards simultaneously).

The *motor system* or ocular motor output system is the final common pathway. There are six extra-ocular muscles that are innervated by three cranial nerves namely, the oculomotor nerve (III), the trochlear nerve (IV) and the abducens nerve (VI). The oculomotor nerve innervates the medial rectus, inferior rectus, superior rectus and the inferior oblique. The trochlear nerve innervates only the superior oblique and the abducens nerve innervates the lateral rectus only. The oculomotor and trochlear nerves originate from the midbrain, while the abducens nerve originates from the pons. The extra-ocular eye muscles are arranged in pairs that are aligned with the three semicircular canals. For example, horizontal head movements will result in horizontal eye movements, indicating that the horizontal semicircular canals are aligned with the lateral and medial rectus muscles of both eyes.

The results from the random saccade testing are analysed according to the following parameters: (1) velocity – the speed at which the eye moves; (2) latency –

the delay of the eye movement after the target has moved; and (3) accuracy of the eye movement. Table 2.2 indicates the abnormalities of random saccade test findings and the site of lesion (Goebel, 2008a); therefore, all recorded abnormalities indicated a central lesion.

Table 2.2

Abnormalities of random saccades and site of lesion (adapted from Goebel, 2008a)

Abnormalities	Site of lesion
Overshoots or undershoots	Cerebellum
Slow saccades	Brainstem
Late saccades	Brainstem, frontal lobe
Disconjugate saccades	Brainstem, medial longitudinal fasciculus

The results of the pursuit tracking test are analysed according to the following parameters: (1) gain – the accuracy of the eye movement on the target; (2) symmetry – the difference in performance between the leftward and rightward movement of each eye respectively; and (3) phase – the ability of the subject to follow the target in phase, without lagging eye movements or leading the target.

Table 2.3 indicates the abnormalities of pursuit tracking test findings and its site of lesion (Goebel, 2008a); therefore all recorded abnormalities indicated a central lesion.

Table 2.3

Abnormalities of pursuit and site of lesion (adapted from Goebel, 2008a)

Abnormalities	Site of lesion
Saccadic pursuit	Cerebellum, brainstem
Asymmetric pursuit	Ipsilateral parieto-occipital cortex
Absent pursuit	Visual acuity, cerebellum, brainstem

2.3.4　Position tests

There are two components of position testing, namely static and dynamic position tests. Nystagmus elicited in a static head position is called positional nystagmus, while nystagmus elicited by changes in head position is called positioning nystagmus (Barber & Stockwell, 1980). Positioning tests include the Dix-Hallpike and other provocative maneuvers. VOR activity is induced during changes in head position due to an imbalance in neural activity from the vestibular end organs to the vestibular nucleus. When there is nystagmus in a static position, it could indicate an imbalance in neural activity in either the peripheral or the central vestibular pathways (Roberts & Gans, 2008). Baloh and Kerber (2011:162) provided a further explanation of position induced nystagmus: "If a semicircular canal cupula is altered so that its specific gravity no longer equals that of the surrounding endolymph or if debris inappropriately enters a semicircular canal, the canal becomes sensitive to changes in the direction of gravity and can produce positional nystagmus."

Positioning and/or positional tests can be useful to distinguish between peripheral and central vestibular lesions (Gianoli & Smullen, 2008). The characteristics of positioning nystagmus that differentiate peripheral from central vestibular lesions as well as its site of lesion are summarized in Table 2.4. Benign paroxysmal positional vertigo (BPPV) is a common finding observed during positioning tests. This is associated with transient nystagmus and coincides with a subjective perception of vertigo. Reversal of nystagmus during a change of head or body position is regarded as a peripheral sign, while reversal of nystagmus is not expected in the case of central lesion (Roberts & Gans, 2008).

Table 2.4

Differentiation of positioning nystagmus from peripheral vs. central vestibular origin (adapted from Baloh & Kerber, 2011; Gianoli & Smullen, 2008; Roberts & Gans, 2008).

	Nystagmus characteristic	Latency	Duration	Symptoms
Peripheral	Rotatory UB (PC BPPV), rotatory DB (SC BPPV), geotropic or ageotropic horizontal nystagmus*	Short	Less than 60 sec	Subject experiences severe vertigo
Central	Pure rotatory, horizontal or vertical (often downbeats)	Absent	More than 60 sec, may persist	Often no symptoms of vertigo

Note: UB = up beating nystagmus; DB = down beating nystagmus; HC BPPV = horizontal canal benign paroxysmal positional vertigo; PC BPPV = posterior canal BPPV; SC BPPV = superior canal BPPV; * = geotropic horizontal nystagmus associated with canalithiasis and ageotropic associated with cupulolithiasis.

Nystagmus induced during positional testing is a result of a decrease in suppression of asymmetric semicircular canal function. This is thought to be due to otolith dysfunction or a lesion in the central vestibular pathway (Roberts & Gans, 2008). Positional testing includes head/body to the right and head/body to the left. Table 2.5 describes characteristics of positional nystagmus that differentiate peripheral from central vestibular lesions.

Table 2.5

Differentiation of positional nystagmus from peripheral vs. central vestibular origin (adapted from Roberts & Gans, 2008).

	Nystagmus characteristic	Fixation suppression	Nystagmus direction	Symptoms
Peripheral	Rotatory or horizontal	Yes*	Geotropic	Yes
Central	Vertical	No	Ageotropic[#]	No

Note: * = fixation suppresses positional nystagmus, except for horizontal canal benign paroxysmal positional vertigo (HC BPPV); # = must exclude HC BPPV.

2.3.5 Head shake test

The head shake test is, like the head impulse test, a method of measuring asymmetries in vestibular gain. These asymmetries may be due to a variety of factors such as lesions in the vestibular nerve, root entry zone or loss of vestibular hair cells (Hain & Cherchi, 2012). Cass (2008:82) describes how an asymmetrical discharge of the velocity storage results in post head shaking nystagmus: "During head shaking, the vestibular labyrinths send neural activity into the brainstem, which 'charge up' central vestibular circuits. This phenomenon is called velocity storage. If the inputs from the two vestibular labyrinths during head shaking are symmetric, the discharge of stored vestibular neural activity within the bilateral vestibular circuits will cancel and no nystagmus will occur. However, if the inputs are asymmetric after head shaking, the central circuits will discharge asymmetrically, causing a burst of nystagmus."

No nystagmus is expected when both vestibular labyrinths function equally well (normal) or equally poor as in bilateral vestibular loss (Hain & Cherchi, 2012). The presence of horizontal nystagmus after the horizontal head shake test indicates a unilateral peripheral vestibular lesion due to an imbalance between the ears. The direction of the fast phase of the nystagmus will be towards the normal or better side. The presence of vertical or torsional nystagmus after the horizontal head shake test could indicate a central lesion (Cass, 2008).

2.3.6 Hyperventilation induced nystagmus test

The hyperventilation induced nystagmus (HVIN) test is useful for detecting disorders of the vestibular nerve (Hain, 2011). It is also a useful bedside test to reveal latent cerebellar or peripheral vestibular diseases (Califano, Melillo, Vassallo, & Mazzone, 2011). The process of hyperventilation induced metabolic changes is illustrated in Figure 2.10.
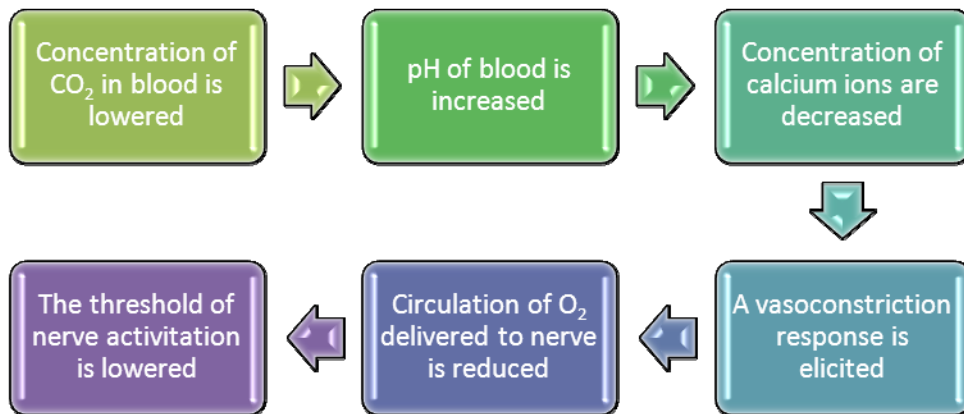
Figure 2.10. Hyperventilation induced metabolic changes (Bance, 1998; Califano et al., 2011; McCaslin et al., 2008)

In disorders of the vestibular nerve that cause focal demyelination and therefore blockage to neural conduction, hyperventilation increases metabolic activity, allowing the nerve to overcome this blockage in conduction. This results in stronger neural activity, causing the fast phase of nystagmus to beat towards the side of the lesion (Califano et al., 2011; McCaslin et al., 2008). The presence of horizontal nystagmus indicates a peripheral vestibular lesion, since normal subjects should not exhibit nystagmus. The nystagmus beats towards the side of the lesion (Cass, 2008). Vertical nystagmus, particularly down-beating nystagmus, indicates a central lesion, most probably of the cerebellum (Walker & Zee, 1999).

2.3.7 Bithermal caloric testing

During caloric testing, the external ear canal is irrigated with either water or air as stimulus at a temperature above (warm) and below (cool) body temperature; the process is referred to as bithermal caloric testing. It allows ipsilateral testing of each labyrinth separately, thereby making it possible to lateralize the site of lesion (Baloh & Kerber, 2011). The stimulus, which is nonphysiologic, generates a temperature gradient from one side of the canal to the other and changes the density of the endolymph in the canal (Baloh & Kerber, 2011). Because of the head positioned at an angle of 30 degrees with the body in the supine position, the horizontal semicircular canal develops the largest temperature gradient due to its close

proximity to the stimulus (Baloh & Kerber, 2011). A warm stimulus causes the endolymph to become lighter and move upwards, resulting in an ampullopetal (towards the ampulla) flow (Figure 2.11). This induces horizontal nystagmus beating toward the stimulated ear. Conversely, a cool stimulus causes the endolymph to become heavier and move downwards, resulting in an ampullofugal (away from the ampulla) flow and horizontal nystagmus away from the stimulated ear (Baloh & Kerber, 2011; Barin, 2008a). This is known as the "COWS" rule, i.e. **c**ool **o**pposite, **w**arm **s**ame.
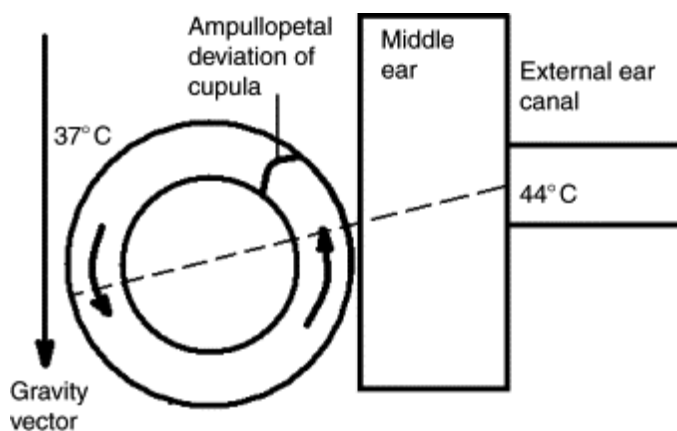
Figure 2.11. Caloric stimulation of the horizontal semicircular canal (source: Fetter, 2010)

Caloric stimulation evaluates the functioning of the VOR arc, a reflex arc that generates nystagmus (Gonçalves, Felipe, & Lima, 2008). The role and physiology of the VOR was discussed and illustrated earlier in this chapter, therefore Figure 2.12 illustrates how horizontal nystagmus is evoked during caloric stimulation. The horizontal semicircular canal becomes excited during warm and cool stimulation. This increased neural input from the horizontal semicircular canal sends its signals via the superior vestibular nerve to the vestibular nuclei in the brainstem. This activates the oculomotor nucleus (III) ipsilaterally and the abducens nucleus (VI) contralaterally, which innervate the medial rectus and lateral rectus eye muscles respectively. These eye muscles pull the eye horizontally and therefore this action results in the generation of horizontal nystagmus.
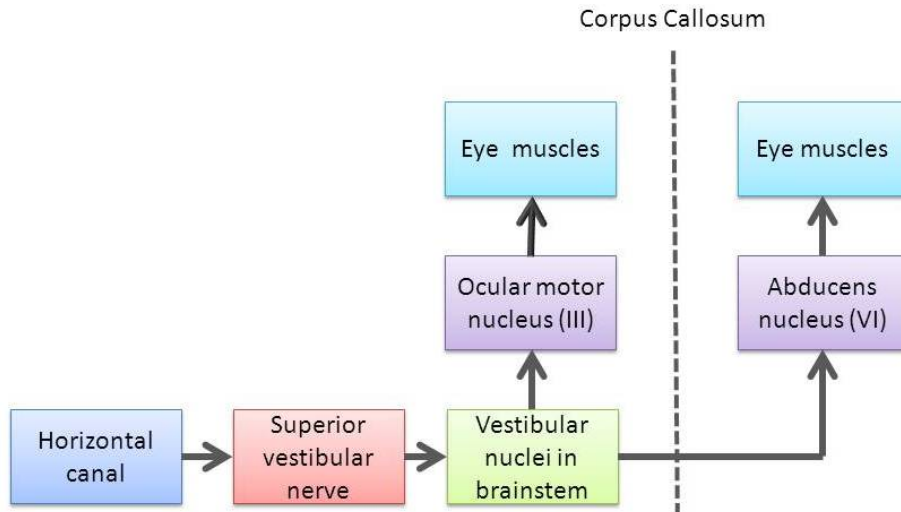
Figure 2.12. Simplified schematic representation of the pathways responsible for caloric induced nystagmus (adapted from Jones et al., 2009)

Normal labyrinths should respond symmetrically upon stimulation. When there is a unilateral weakness due to a lesion or pathology of the peripheral vestibular system, namely the horizontal semicircular canal, the superior vestibular nerve or the root entry zone of the vestibular nerve, the vestibular nucleus in the brainstem that drives the VOR arc receives an asymmetrical magnitude of information (Jacobson & Newman, 1997). An asymmetrical caloric response of 20% or greater is considered pathological and indicates a unilateral weakness, with the weaker ear demonstrating the pathology (Barin, 2008b; Jacobson, Newman, & Peterson, 1997).

A common pathology that affects the end organ (horizontal semicircular canal) and causes a unilateral weakness is Ménière's disease (Jacobson et al., 1997). HIV/AIDS related opportunistic infections such as syphilis (Jae, Lee, Sung, & Soon, 2005; Kobayashi et al., 1991; Wilson & Zoller, 1981) and meningitis (Wiener-Vacher, Obeid, & Abou-Elew, 2012) have also been documented to cause abnormalities in caloric test results. Diseases such as syphilis cause injury to the membraneous labyrinth, osteitic changes in the otic capsule and loss of function of the sensory structures (Belal Jr. & Linthicum Jr., 1980). Another cause of unilateral weakness may be demyelinating diseases such as multiple sclerosis (Jacobson et al., 1997). The human immunodeficiency virus may cause subcortical demyelination as seen in

abnormalities found in the auditory brainstem responses (Bankaitis & Keith, 1995; Reyes-Contreras et al., 2002). Demyelination may occur in the vestibular nerve and/or the vestibular nuclei and reduce the speed of neural conduction (Jacobson et al., 1997) and may therefore affect the caloric response.

Cerebellar degeneration/leukoencephalopathy has been described in the context of HIV infection (Ganos et al., 2012). Hyperactive caloric responses, also known as hyperreflexia, may be observed in injuries to the central vestibular system. This is due to the inability of the cerebellar flocculus to inhibit vestibular nucleus neurons, thereby failing to inhibit the VOR (Baloh & Kerber, 2011; Gonçalves et al., 2008). In this context, hyperactive caloric responses may therefore be observed in patients infected with HIV/AIDS, possibly indicating a central vestibular disorder. Hyperactivity is defined as total cool greater or equal to 99 degrees/sec, total warm greater or equal to 146 degrees/sec, or a total caloric response greater or equal to 221 degrees/sec (Jacobson et al., 1997).

In contrast to hyperactive caloric responses is the occurrence of hypoactive caloric responses or hyporeflexia. A well-documented cause of hypoactive caloric responses is substances that depress labyrinthine function and ototoxicity (Ishiyama, Ishiyama, Kerber, & Baloh, 2006). HIV/AIDS may affect the peripheral vestibular pathways (and therefore the caloric responses) indirectly through ototoxic treatments. These ototoxic treatments may be highly active antiretroviral therapy combinations or some treatments for opportunistic infections such as aminoglycosides (Hofmeyr & Baker, 2010). Hypoactivity is defined as total warm equal or less than 11 degrees/sec and total cool equal or less than 6 degrees/sec (Jacobson et al., 1997).

The caloric test is a very low frequency stimulus, namely 0.003 Hz, which is one cycle for every five and a half minutes. Because peripheral disorders first affect the low frequencies and the higher frequencies are affected later (McCaslin et al., 2008), the caloric test is very sensitive for detecting peripheral vestibular damage.

2.4 Cervical vestibular evoked myogenic potentials

Cervical or collic vestibular evoked myogenic potentials (cVEMPs) have been utilized since 1994 (Colebatch, Halmagyi, & Skuse, 1994) as part of the vestibular test battery. Test procedures such as the rotatory chair and caloric irrigation evaluate the functioning of the horizontal semicircular canal, the superior vestibular nerve and the VOR pathways, which constitute only a portion of the vestibular system. The cVEMP provides extra information about the functioning and integrity of the saccule and inferior vestibular nerve (Akin & Murnane, 2008) and VCR pathways. The goal of the VCR is to assist in maintaining head stability during movement and keeping the head in an upright position by acting on the neck muscles (Schubert & Shepard, 2008).

The cVEMP can be evoked by using three different stimuli, namely air conducted acoustic sound, bone conducted vibration or electrical/galvanic stimulation which is recorded using surface electrodes placed on a muscle (Rosengren, Welgampola, & Colebatch, 2010). Tone bursts between 500Hz and 1000 Hz elicit larger amplitudes than in higher frequencies (McCue & Guinan Jr., 1994). Bone conduction stimuli stimulate both the saccule and the utricle (Brantberg, Tribukait, & Fransson, 2003), whereas air conduction stimuli stimulate the saccule predominantly (Colebatch et al., 1994; Murofushi & Curthoys, 1997; Todd, Cody, & Banks, 2000; Welgampola & Colebatch, 2001). Air conduction tone bursts between 500Hz and 1000 Hz are clinically widely used (Rosengren et al., 2010).

Colebatch and colleagues (Colebatch et al., 1994) described the recording of VEMP responses from electrodes placed on the ipsilateral sternocleidomastoid (SCM) muscle, and hence the reference to the term cVEMP. It can also be referred to as collic VEMP. Because the cVEMP amplitude is dependent on the level of tonic SCM muscle activation it may be absent when the SCM muscle is at rest (Akin et al., 2004). VEMPs can also be elicited from other muscles, namely the extra-ocular muscles from the infra-orbital region and therefore this technique has been named ocular VEMPs, also known as oVEMPs (Todd, Rosengren, Aw, & Colebatch, 2007). Recent findings suggest that oVEMPs measure a part of the vestibular system that

differs from that measured by cVEMPs, namely the utricle and superior vestibular nerve (Curthoys & Vulovic, 2011; Jacobson et al., 2011). It was earlier unknown whether the utricle responds only through bone-conducted vibration, but these recent findings showed that air conducted sounds can also activate utricular afferents (Curthoys & Vulovic, 2011). This pathway, a manifestation of the VOR and similar to that measured by caloric testing, is tested by oVEMPs with inverting and non-inverting electrodes placed infra-orbitally.

The cVEMP is a biphasic potential that occurs at short latencies and its specific components have been shown to be of vestibular origin (Colebatch et al., 1994). Brief, high intensity acoustic stimuli give rise to an initial positivity around 13 ms, labelled as p13 or P1. This is followed by negativity around 23 ms, labelled as n23 or N1, during tonic activation of the SCM muscle. Figure 2.13 depicts a typical cVEMP tracing obtained with air conduction tone bursts, showing the P1-N1 waveform complex. The initial positive component is presented as a downward deflection, due to the active or non-inverting electrode that is positioned on the mid or upper third SCM muscle. The negative component is presented as an upward deflection, due to the inverting electrode placed on an electrically indifferent non-cephalic site. These sites may include the sternum, sterno-clavicular junction, nape of neck, forehead or hand (Hall, 2007; Jacobson & McCaslin, 2007; Zapala & Brey, 2004). The ground electrode is usually placed on the forehead.
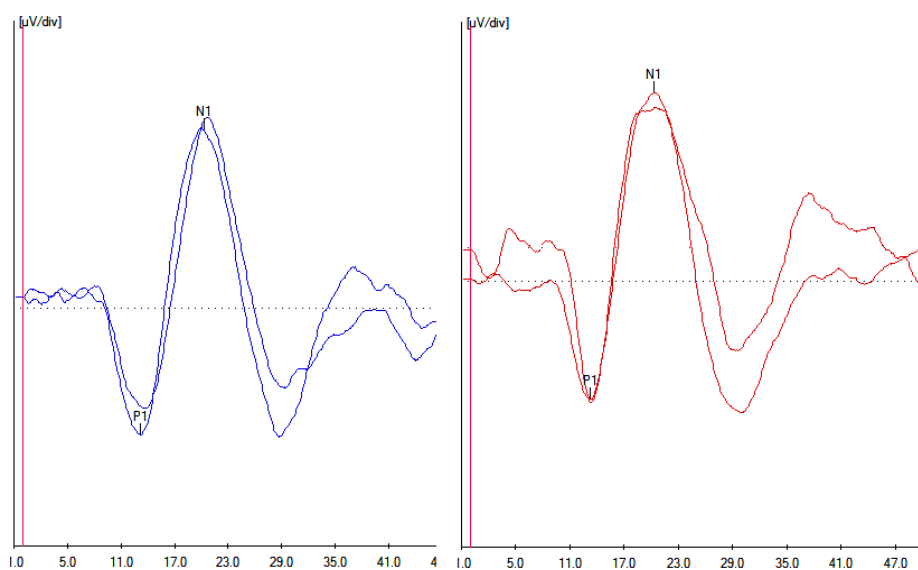
Figure 2.13. Biphasic cVEMP waveforms depicting the P1-N1 complex

The cVEMP is a manifestation arising from the VCR, also known as the sacculocollic reflex of the vestibulospinal tract (Rosengren et al., 2010) and is mediated ipsilaterally by a three-neuron arc. This anatomic pathway is illustrated in Figure 2.14. A loud acoustic stimulus, which may be a click or a tone burst, is conducted through the middle ear and activates the saccule (McCue & Guinan Jr., 1994; Murofushi, Curthoys, & Gilchrist, 1996). This acoustic stimulus has to be loud; between 90-95 dBnHL or 125-130 dB(pe)SPL in order to adequately trigger the saccular hair cells and thereby effecting the amplitude of the response (Wang & Young, 2004; Welgampola & Colebatch, 2005). Primary vestibular neurons that travel via the inferior vestibular nerve project into second order vestibular neurons in the lateral vestibular nucleus in the brainstem. From there, neurons descend in the medial vestibulospinal tracts (MVST) and connect to the motor nuclei of the accessory nerve (N XI). Third order vestibular neurons descend to the flexor and extensor neck muscles via the MVST. This pathway can be either excitatory or inhibitory as depicted in Figure 2.15.
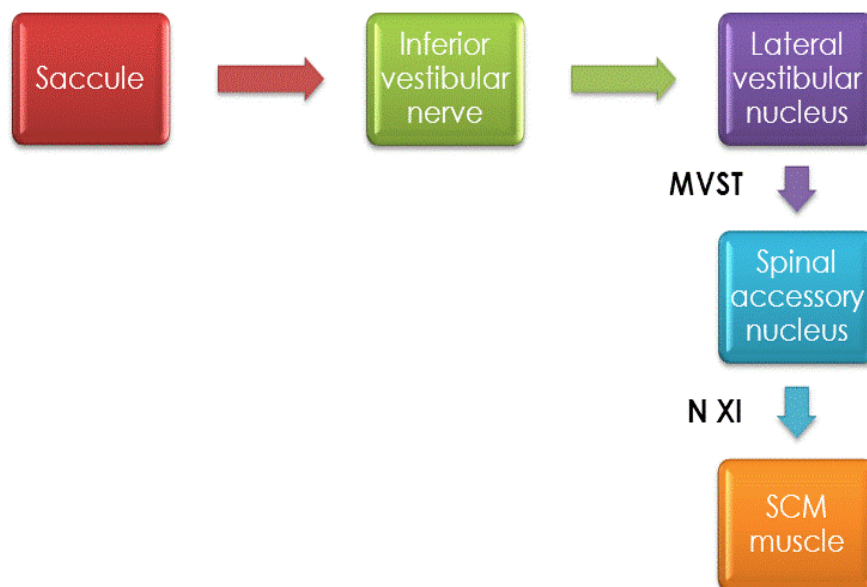
Figure 2.14. The anatomic pathway of the cVEMP response (adapted from Akin & Murnane, 2008; Stoody & Inverso, 2012)

SACCULOCOLLIC REFLEX PATHWAYS
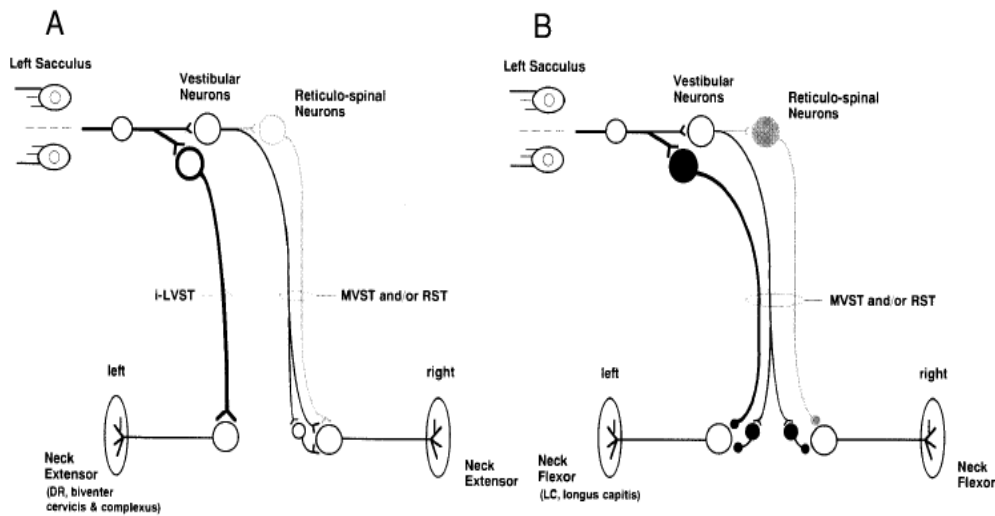
Figure 2.15. The vestibulocollic reflex pathway: A depicts the excitatory pathway and B the inhibitory pathway (Uchino et al., 1997)

From an evolutionary point of view, the saccule has retained its sound sensitivity, but it is not a primary organ of hearing. It may be, of the five vestibular end organs, the most sensitive to sound and is stimulated by loud sounds (Carey & Amin, 2006). This will cause a brief pressure gradient over the saccule, as a result of displacement of the stapes footplate due to the close anatomic proximity to each other. This, in turn, stimulates the hair cell bed, which activates the vestibulospinal reflex (VSR) pathway (Rosengren et al., 2010; Welgampola & Colebatch, 2005). Additionally, recent findings indicated that the utricular afferents coursing through the superior vestibular nerve also respond to acoustic stimulation (Curthoys & Vulovic, 2011) Therefore, the saccule and the utricle is sensitive not only to linear accelerations, but also to loud sounds.

When the cVEMP is recorded, there is active, sustained contraction of the SCM muscle, which generates background electromyographic activity that is briefly interrupted due to a short period of inhibition (Rosengren et al., 2010; Welgampola & Colebatch, 2005). The central vestibular system interprets this period of inhibition as a temporary loss of postural tone and, consequently, reacts reflexively to increase the extensor muscle activity and decrease the flexor muscle activity in the SCM muscle (Carey & Amin, 2006).

The cVEMPs offer essential diagnostic information pertaining to vestibular function and as well as information for detecting vestibular abnormalities (Maes et al., 2011). It may be offered as a useful clinical tool to identify the site of lesion of vestibular disorders associated with HIV/AIDS-related opportunistic infections such as the herpes zoster virus, Ramsay Hunt syndrome (Young, 2002), otosyphilis, toxoplasmosis and meningitis (Sazgar, Akrami, Akrami, & Karimi Yazdi, 2006), perhaps even before symptoms are clinically significant. Abnormalities of the cVEMP may indicate a lesion at any point along the VCR pathways (Figure 2.14 and 2.15) (Rosengren et al., 2010). Cervical vestibular evoked myogenic potential recordings with delayed latencies may indicate a central lesion such as demyelination diseases and brainstem pathologies (Welgampola & Colebatch, 2005), while absent responses could indicate a peripheral lesion of the saccule and/or inferior vestibular nerve (Rosengren et al., 2010). Unilateral absent cVEMP responses have been documented for vestibular diseases such as Meniére's disease, vestibular neuritis and vestibular schwannomas, while bilateral absent cVEMP responses have been documented in ototoxicity (Welgampola & Colebatch, 2005).

Cervical vestibular evoked myogenic potentials are observed in subjects with varying degrees of sensorineural hearing loss or abnormal cochleae, and/or abnormal semicircular canals (Sheykholeslami & Kaga, 2002), thereby indicating that the cVEMP originates from the otolith organ. However, an intact outer and middle ear is required for cVEMP responses. This requirement limits the clinical use of cVEMPs, particularly since a study has shown reduced or absent responses in subjects with air-bone gaps smaller than 10 dBHL (Bath, Harris, McEwan, & Yardley, 1999). In such cases, the use of a bone conduction stimulus may be a useful alternative (Seo et al., 2008). However, bone conduction stimulates both the saccule and the utricle (Brantberg et al., 2003), and the SCM receives both saccular and utricular projections. Bone conduction cVEMPs are less helpful in discerning saccule versus utricle dysfunction.

2.5   Summary

The vestibular system comprises many anatomical structures; it is divided into a peripheral and central system. The aim of vestibular testing is to distinguish between peripheral and central lesions. No single test that can fulfil this role exists currently; therefore, it is imperative to follow a comprehensive test battery. In order to understand the principles and anatomical structures of the vestibular system that is tested, it is important to have knowledge of the anatomical and physiological principles underlying each vestibular test.

Chapter 3

Research aims and methods

_____

3.1   Research aims

The main aim of this research study was to investigate vestibular functioning and pathology in adults with HIV/AIDS. This was achieved through three main research steps:

1. to systematically review the body of peer-reviewed literature on HIV/AIDS related vestibular manifestations and pathology

2. to describe the vestibular involvement in adults with HIV/AIDS

3. to determine if HIV/AIDS influence the vestibulocollic reflex (VCR) pathways.

These research aims are outlined in the following chapters:

Chapter 4 describes the systematic literature review of the current body of peer-reviewed publications on reported HIV/AIDS related vestibular manifestations and pathology. It includes the review procedures and search strategies used to identify relevant records. It describes and discusses the various reports related to vestibular findings in HIV/AIDS.

Chapter 5 describes the vestibular involvement in adults with HIV/AIDS. The peripheral and central vestibular functioning in HIV positive adults were compared with a control group that consisted of HIV negative adults. This chapter also describes and compares the occurrence and nature of vestibular involvement in these two study groups. In addition, it describes and compares the vestibular function of (1) symptomatic and asymptomatic HIV positive adults and (2) antiretroviral (ARV) therapy and non-ARV therapy users.

Finally, ***Chapter 6*** determines if HIV/AIDS influence the VCR pathways. This chapter also describes test results throughout progression of the disease and compares it in HIV positive subjects with and without ARV therapies.

Note: Articles one to three (Chapters 4-6) were edited in compliance with the editorial specifications of the various targeted international journals and they therefore differ in editorial style from the rest of this thesis.

3.2   Research methods

The following section describes the various research methods employed for the three main research steps.

3.2.1. Study 1: Systematic literature review of vestibular disorders related to HIV/AIDS

The research design was a systematic review of peer-reviewed literature. A varied search strategy was used across several electronic databases to identify relevant research reports. Reviews, editorials, notes, letters and short surveys were excluded, in order to determine relevant articles related to vestibular findings in patients with HIV/AIDS, and the possible pathologies of these findings. The design incorporated a multifaceted approach. Several databases were used, namely Medline, Scopus and PubMed, together with different search strategies. This allowed for comprehensive coverage and cross-checking of search findings (White & Schmidt, 2005). Table 4.1 in Chapter 4 indicates the databases and search strategies employed.

All available English language abstracts were reviewed. Where abstracts were not available, the full paper was reviewed and excluded if not directly relevant to the study's aims. After all duplicates and unrelated papers had been excluded, the remaining articles were reviewed according to the HIV/AIDS-associated

vestibular findings reported. Figure 4.1 in Chapter 4 illustrates the procedural steps in the systematic review to identify reports for inclusion.

3.2.2. Study 2: Peripheral and central vestibular involvement in adults with HIV/AIDS and Study 3: The influence of HIV/AIDS on the VCR pathways

3.2.2.1. Study design

A cross-sectional, quasi-experimental comparative research design was employed. A convenience sampling method was used to recruit subjects.

3.2.2.2. Ethical clearance and informed consent

When humans are participating in research their treatment and benefit from the research process must always be considered (Salkind, 2006). Individuals infected with HIV/AIDS should be specially considered as they are regarded a vulnerable population due to the physical and emotional effects the disease may have on their lives. The researcher has therefore been highly sensitive towards all subjects and strived towards maintaining their dignities.

The institutional review boards of the University of Pretoria and 1 Military Hospital (a tertiary referral hospital in Thaba Tswane, Pretoria), reviewed and approved the study before any data collection commenced (Appendix A).

In order to ensure the privacy and confidentiality of all the subjects (Huysamen, 1994; Hegde, 2003), no individuals were named in the research report. A code was allocated to each subject; therefore the names of each subject were neither used during the analysis of the data nor during reporting. The covering letter of informed consent clearly explained this to all subjects as indicated in Appendix B. The researcher regarded all information, which includes the identity of the subjects and results of the assessment as highly private and confidential.

Informed consent is an important ethical principle that consists of three parts (Hegde, 2003). Firstly, the research procedure should be explained in order for the

participant to fully understand all relevant aspects of the procedures. Secondly, the participants should give free and willing consent to participate in the research, and finally the participants are allowed to withdraw from the research at any point in time. Thus, each subject received and read a covering letter on informed consent (Appendix B) explaining the aims of the study and what will be expected from them. There has been adequate opportunity for the subjects to ask questions before the study commenced as well as during the collection of data. The letter of the informed consent form furthermore clearly stated that participation is voluntary and that subjects were allowed to withdraw at any point in time without any consequences. Confidentiality was also be ensured by this letter. By signing a form (Appendix C) each subject provided the researcher with written informed consent.

The letter of informed consent form also explained that the duration of the vestibular examination should be approximately one and half to two hours in duration. No inconvenience was caused to the subjects, other than their time participating in the study, by coordinating their participation with other health care visits to the Infectious Disease clinic. This letter furthermore explained that the results obtained from the study should provide useful information regarding the effect of HIV/AIDS on the functioning of the vestibular system and how to effectively manage vestibular disorders, and that the results will be published upon completion of the study.

3.2.2.3. Subjects

The subjects for study 2 and study 3 were the same. Table 5.1 (Chapter 5) and Table 6.1 (Chapter 6) summarizes the description of participating subjects from both the experimental and control groups. These chapters furthermore provide a detailed description of subjects from both groups.

3.2.2.4. Data collection procedures

Table 5.2 in Chapter 5 summarizes the data collection protocol and sequence for study 2, which included the following procedures:

1. Medical record review - to document subjects' CD4+ cell counts and use of ARV therapies;

2. Structured interview - to enquire about subjective perception of any vestibular complaints and symptoms. The questionnaire from Goebel (2008b) was used;

3. Otologic and audiologic examination – otoscopy, tympanometry and pure tone audiometry;

4. Vestibular bedside/clinical assessments – Fukuda stepping test, subjective visual vertical test, head impulse test, dynamic visual acuity test;

5. Videonystagmography – evaluation for spontaneous nystagmus and gaze evoked nystagmus, random saccades, pursuit tracking, positioning and positional tests, head shake test, hyperventilation test, bithermal caloric irrigation;

6. Evoked potentials – cervical vestibular evoked myogenic potentials (cVEMPs).

The data collection protocol for study 3 only included the following procedures:

1. Medical record review - to document subjects' CD4+ cell counts and use of ARV therapies;

2. Otologic and audiologic examination – otoscopy, tympanometry and pure tone audiometry;

3. Videonystagmography – evaluation for spontaneous nystagmus, bithermal caloric irrigation;

4. Evoked potentials – cVEMPs.

Prior to data collection, subjects were provided with a written list of pre-test instructions (Appendix D). The list of pre-test instructions explained that subjects were not permitted to take medication that may suppress vestibular symptoms or agents such as alcohol and/or sedatives that may suppress peripheral and/or central vestibular function and influence the results and their interpretation.

3.2.2.5. Methods and procedures of vestibular testing

This section provides a detailed description of the methods and procedures of vestibular testing employed during data collection.

i.   *Fukuda stepping test*

The subjects were asked to extend the arms at a 90 degree angle in front of the body and keep eyes closed while they had to march in place for 50 steps. Figure 3.1 illustrates the Fukuda stepping test procedure. Literature results evaluating the Fukuda stepping test (Honaker et al., 2009) didn't provide significant findings that would support the use of this test as a reliable screening tool for peripheral vestibular asymmetry in chronic dizzy patients. Their results agree with previous reports (Bonanni & Newton, 1998) stating that the Fukuda stepping test shouldn't be used alone as a screening method. However, Bonanni and Newton (1998) have suggested and proven a more efficient use of the Fukuda stepping test with it is used in combination with other clinical vestibular tests in the assessment of vestibular pathologies. Since the Fukuda stepping test was part of a complete test protocol, this present study didn't base conclusions only on this one test.

Figure 3.1. Fukuda stepping test (source: McConnell, 2013)

ii.   *Subjective visual vertical test*

Zwergal and colleagues (2009) developed the "bucket method" as an inexpensive and reliable tool to evaluate the subjective verticality. Figure 3.2 illustrates an example of the bucket used to evaluate the subjects' perception of true vertical.

Figure 3.2. The bucket method used to determine visual vertical (source: Zwergal et al., 2009)

As can be seen from Figure 3.2 the subjects were seated upright while looking inside the bucket. They had no outside visual clues as the rim of the bucket covered their faces. There was a dark line on the inside of the bucket (picture on the right) that they had to rotate until where they perceived it to be truly vertical. The examiner read off the degrees on a protractor on the outside of the bucket (picture on the left).

iii.   Head impulse test

The subjects were seated and the examiner stood in front of the subject and held his/her head. The subjects were asked to fixate on the examiner's nose or look at a target straight ahead during the rapid head turn. The head was rotated unexpectedly to both the left and right side using small amplitude head movements of around 20 degrees, a velocity of up to 180 deg/s and a high acceleration of more than 2000 deg/s^2 (Figure 3.3).
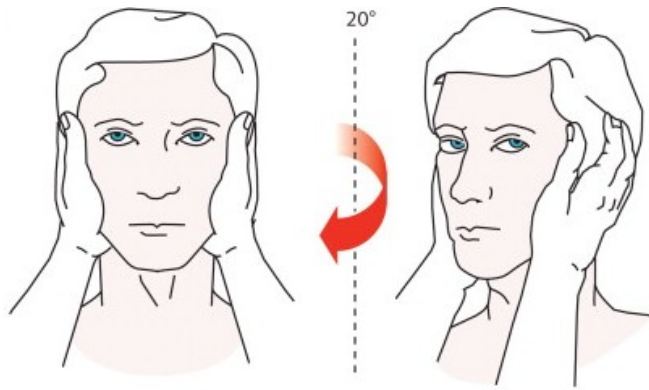
Figure 3.3. Procedure of performing the head impulse test (source: Edlow, Newman-Toker, & Savitz, 2008)

iv.   *Dynamic visual acuity*

Firstly, visual acuity was measured with the head still (static visual acuity), and secondly with the head in motion (dynamic visual acuity) at a frequency of 2 Hz. During head motion, the subjects were required to identify the direction of the optotype displayed on the computer screen. The optotype was a "Π" shape and they had to indicate whether the open legs were pointing up, down, left or right. The subject's head deviated 20-30 degrees to the left and right from centre. Figure 3.4 illustrates how the DVA test was performed. The subjects wore a sensor that measured head motion and velocity, and the optotype appeared during head motion and disappeared when head motion was ceased or when the head moved below the prescribed velocity. To prevent the subject from predicting the direction of the optotype, various directions were randomly intermixed.

Figure 3.4. Procedure of the DVA test: the subject was seated in front of a computer screen which displayed the optotype (source: Honaker & Janky, 2011)

v.   *Evaluation for spontaneous nystagmus*

The subjects were seated upright and binocular infrared video goggles were positioned over the eyes. Firstly, the presence of spontaneous nystagmus was determined with vision by allowing the subjects to fixate on a target on the lightbar for 30 seconds. Secondly, the presence of spontaneous nystagmus was determined with vision denied where the video goggles were covered and the subjects were in complete darkness. They were asked to keep their eyes open and eye movements were recorded for 60 seconds while they subjects were mentally alerted. The subjects with spontaneous nystagmus were asked to look in the direction of the fast phase of the nystagmus, in order to determine if the spontaneous nystagmus followed Alexander's law.

vi.   *Evaluation for gaze evoked nystagmus*

The subjects were seated upright and binocular infrared video goggles were positioned over the eyes. The subjects were asked to visually fixate on an eccentrically placed target on the lightbar for 15-20 seconds, which were stationary at an angle of 30 degrees off the centre to the horizontal positions left and right. Thereafter, the same procedure was performed in to the vertical positions up and down, also for 15-20 seconds in each of these eccentric positions.

vii.   *Random saccade test*

Random saccade testing is the choice of preference over fixed saccade testing, as random saccade testing is more sensitive for subtle central vestibular lesions than fixed random saccade testing (Goebel, 2008b). The binocular infrared video goggles were positioned over the eyes. The subjects were instructed to follow the target on the lightbar, while keeping the head in the primary position, as quickly and accurately as possible. The subjects were informed that the target will randomly appear on several locations on the lightbar and that it will continue doing so for one minute. The subjects were also instructed to follow the randomly appearing target and quickly and accurate as possible.

viii.   *Pursuit tracking test*

As with the previous ocular motor test, the binocular infrared video goggles were positioned over the eyes. The subjects were instructed to visually follow the moving target on the lightbar, while keeping the head stationary in the primary position, as smooth and continuously as possible. The subjects were furthermore informed that the target will at first slowly then gradually faster move like a pendulum (sinusoidal trajectory) on the lightbar. The target frequencies were 0.1 Hz, 0.2 Hz and 0.4 Hz.

ix.   *Position tests*

Infrared video goggles were positioned over the subjects' eyes and vision was denied (without fixation). For the positional tests, the subjects were supine with their heads firstly turned to the left for 60 seconds then to the right for 60 seconds. They were instructed to keep their eyes open and eye movements were recorded while they were mentally alerted. Next, the subjects were instructed to lie on their left and right sides respectively also for 60 seconds in each position. Eye movements were once again recorded. The test was repeated with fixation for those subjects with nystagmus, in order to differentiate if their nystagmus was of peripheral or central vestibular origin.

The Dix-Hallpike and roll test was performed as the positioning test. Infrared video goggles were positioned over the eyes and vision was denied. Figure 3.5 illustrates the procedure of the Dix-Hallpike positioning test.
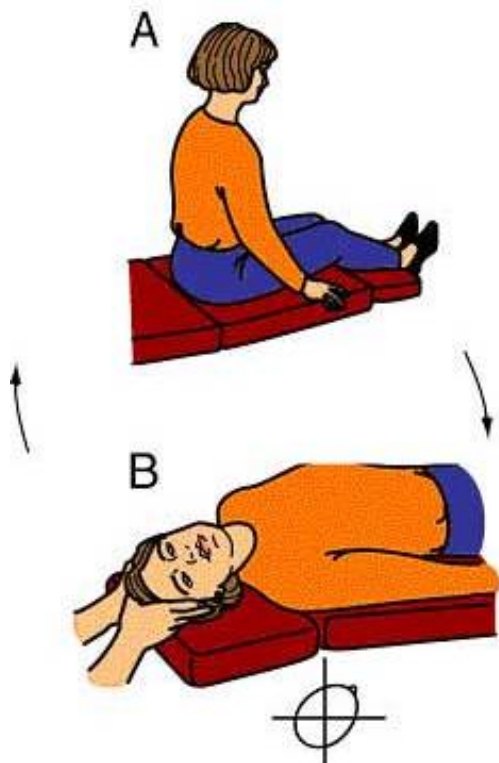
Figure 3.5. Procedure for performing the Dix-Hallpike positioning test. a) the subject is taken from seated to b) supine with head extended. Although not shown in this illustration but indicated with arrows, the test ends with positioning the subject from the supine back to a seated position (source: Hain, 2009a)

x.   Head shake test

The protocol for performing the head shake test is summarized in Table 3.1.

Table 3.1

Protocol for performing the head shake test

Parameters	Protocol
Head position	Tilted 30 degrees forward
Frequency	2 Hz
Cycles	20-25
Head deviation	30 degrees to left and right from centre
Eyes post head shake	Open

The subjects were seated upright and infrared video goggles were positioned over the eyes. Their heads were firmly grasped and shaken in the horizontal plane at a frequency of about 2 Hz for 20-25 cycles (Table 3.1) and then stopped abruptly. The subjects' vision was denied in order not to visually fixate and inhibit the nystagmus, and they were instructed to keep their eyes open during the recording.

xi.   *Hyperventilation induced nystagmus test*

The subjects were seated comfortably upright and infrared video goggles were positioned over the eyes. Vision was denied to prevent visual fixation and inhibition of nystagmus. The subjects were asked to take fast and deep breaths, about one breath per second for 60 seconds while keeping their eyes open.

xii.   *Bithermal caloric test*

Videonystagmography was used to record caloric induced nystagmus. Bithermal (cool 24°C, warm 47°C) air caloric testing was used to irrigate the external auditory canal. The AirFX from Micromedical Technologies Inc. (Chatham, Illinois, U.S.A.) allowed visualization of the tympanic membrane, ensuring appropriate air flow into the ear canal to induce a caloric response. Figure 3.6 illustrates the equipment and set up used during data collection.
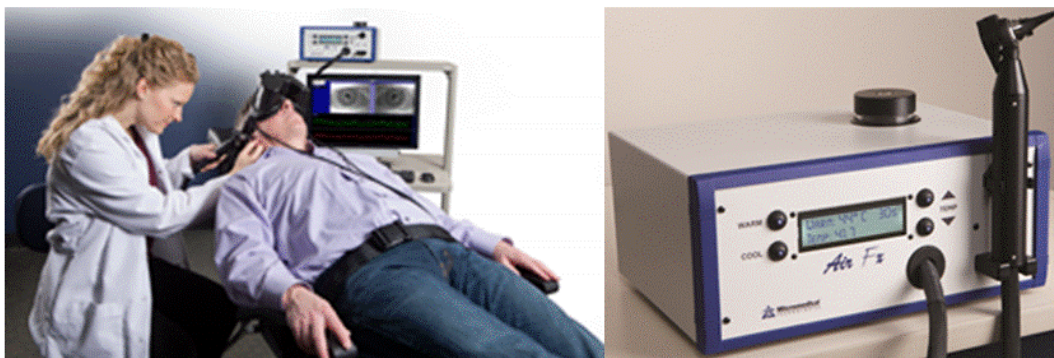
Figure 3.6. Caloric irrigation set up (source: Micromedical technologies)

Air caloric was chosen over water irrigation, because water irrigation of the external ear canal may result in damage to the delicate skin lining of the outer ear,

which in turn places it at risk for invasive external otitis due to bacterial invasion (Zikk, Rapoport, & Himelfarb, 1991). This frequently occurs in those who are immunocompromised, such as persons with HIV/AIDS. Subjects were placed in a supine position with the head tilted forward at an angle of 30 degrees from the horizontal plane for correct positioning of the horizontal semicircular canals. Air was irrigated for 60 seconds and the time elapsing between stimuli was five minutes. The peak of the slow phase eye velocity (SPV) of caloric nystagmus post-irrigation was used as a parameter of superior vestibular nerve and horizontal canal function. Jongkees' formula (Jongkees, Maas, & Philipszoon, 1962) was used to calculate unilateral weakness or asymmetry and directional preponderance. Subjects were mentally alerted during all four irrigations.

xiii.   Cervical vestibular evoked myogenic potentials

The cVEMP procedure was performed using an auditory evoked potential system (Bio-logic Navigator Pro, Natus Medical Inc., San Carlos, California, U.S.A.). Table 3.2 summarizes the stimulus and recording parameters used to record cVEMPs.

Table 3.2

Stimulus and recording parameters used to record cVEMPs

Stimulus parameters		Recording parameters	
Stimulus	Tone bursts	Amplifier gain	1000µV
Stimulus frequency	750 Hz	High pass filter	1500 Hz
Polarity	Alternating	Low pass filter	30 Hz
Level	95 dBnHL	Time window	100ms
Stimulus rate	3.9/sec	Maximum average	100µsec
Rise-Fall	2 cycles	Artifact rejection	2375µV
Plateau	0 cycles	Number of channels	2
Gating	Blackman	Non-inverting electrode	Mid SCM muscle
Earphones	Insert	Inverting electrode	Fpz*
		Ground electrode	Fz

Note: * = Wester (2012) described this electrode montage; SCM = sternocleidomastoid.

Subjects were comfortably seated with the head rotated approximately 45 degrees to the opposite side of the ear being tested ear. A blood pressure manometer with a rolled up inflatable cuff positioned between the subject's hand and jaw was used as feedback method of the contracted sternocleidomastoid (SCM) muscle during the recording of the cVEMP. The subjects pushed with their heads against the rolled up inflatable cuff and were asked to sustain a pressure of 40mmHg. This allowed control of the SCM contractions and ensured comparable muscle contractions between the left and right side (Maes et al., 2009). Both the subjects and the investigator monitored this sustained pressure. Insert-type earphones (Etymotic-ER-3, Elk Grove Village, Illinois, U.S.A) with disposable foam tips were used. Every measurement, including absent responses, was repeated twice to test for wave reproducibility and to eliminate potential artifacts. The average of the two recordings was used for analysis. The first peak on the waveforms was marked as P1, while the second was marked as N1 within a period of 30 milliseconds (ms).

The researchers recorded and measured the latencies of P1 and N1 in ms, inter-peak amplitude in microvolt (µV), and amplitude asymmetry in percentage (%). The asymmetry ratio was determined by calculating the interaural amplitude difference according to the following formula where A_L indicated the amplitude for the left ear and A_R the amplitude for the right ear: $[(A_L - A_R) / (A_L + A_R)] \times 100$. Responses were interpreted as follows: (1) the absence of unilateral or bilateral waveforms were considered abnormal (absence of an identifiable P1 and N1); (2) two standard deviations above the mean of the HIV negative group were used to calculate the upper limits for P1 and N1 latencies (17.0ms and 26.3ms respectively). Latencies above these upper limits were regarded as present yet delayed, and considered abnormal; and (3) the presence of an amplitude asymmetry ratio of ≥40% was considered abnormal, since it indicated side-to-side differences in amplitude.(Akin & Murnane, 2008).

3.3 Data analyses

Study 1 identified a total of 442 records from the three databases. After excluding duplicates, letters, reviews, short surveys, notes and four non-English language articles, only 210 records remained. These remaining articles were reviewed by reading their abstracts, to determine their relevance to our study. The studies had to relate to HIV positive patients with otologic disease, vestibular symptoms such as vertigo, dizziness or disequilibrium, or vestibular test procedures that were performed on these patients. A total of 197 records were not directly relevant to the scope of the review, being unrelated to vestibular findings in individuals infected by HIV. The majority of excluded reports considered pharmacological side effects; others reported HIV-negative patients. Only 13 articles reported vestibular functioning and pathology in individuals infected with HIV.

All analyses of data for study 2 were performed using the statistical software package SPSS for Windows version 21. Mean, standard deviation (±) and percentages (%) were used to describe the data. One-way analysis of variance (ANOVA) was used to compare the distribution of HIV positive subjects between the three CDC categories. The One-Sample Kolmogorov-Smirnov Test was used to demonstrate normality of data. The independent samples t-test was used to compare mean values between the experimental and control groups. P values <0.05 were accepted as statistically significant. Effect sizes were determined using Cramer's V; and odds ratios were calculated. The chi-square non-parametric test was used to compare the findings between the two study groups and the three CDC categories.

Data analyses for study 3 were also performed using the statistical software package SPSS for Windows version 21. Means, standard deviations (±) and percentages (%) were used to describe the data. One-way analysis of variance (ANOVA) was used to compare the distribution of HIV positive subjects between the three CDC categories. The One-Sample Kolmogorov-Smirnov Test was used to demonstrate normality of data. The Independent Samples t-Test was used to compare mean values between the experimental and control groups. P values <0.05

were accepted as statistically significant. Odds ratios were calculated. The chi-square non-parametric test was used to compare the findings between the two study groups and the three CDC categories.

PART II

PUBLICATIONS

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Chapter 4

Systematic review of vestibular disorders related to human immunodeficiency virus and acquired immunodeficiency syndrome

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Abstract

Introduction: Disorders of the auditory and vestibular system are often associated with HIV/AIDS. However, the extent and nature of these vestibular manifestations are unclear.

Objective: To systematically review the current peer-reviewed literature on vestibular vestibular manifestations and pathology related to HIV/AIDS.

Method: Systematic review of peer-reviewed articles, related to vestibular findings in individuals with HIV/AIDS. Several electronic databases were searched.

Results: We identified 442 records reduced to 210 after excluding duplicates and reviews. These were reviewed for relevance to the scope of the study.

Discussion: We identified only 13 reports investigating the vestibular functioning and pathology in individuals infected with HIV/AIDS. This condition can affect both the peripheral and central vestibular system, irrespective of age and viral disease stage. Peripheral vestibular involvement may affect up to 50% of patients and central vestibular involvement may be even more prevalent. Postmortem studies suggest direct involvement of the entire vestibular system, while opportunistic infections such as oto- and neurosyphilis and encephalitis cause secondary vestibular dysfunction resulting in vertigo/dizziness and disquilibrium.

Conclusion: Patients with HIV/AIDS should routinely be monitored for vestibular involvement to minimize functional limitations on quality of life.

4.1. Introduction

The global pandemic of HIV/AIDS affects millions of people directly and countless more indirectly. It is a multifaceted condition resulting in widespread clinical manifestations, including those in the head and neck area (Nwaorgu, Kokong, Onakoya, Adoga, & Ibekwe, 2007). Head and neck disease is amongst the most commonly reported manifestation of HIV/AIDS and has been documented since the discovery of HIV in the early 1980's (Marcusen & Sooy, 1985; Singh et al., 1999). The incidence of head and neck related symptoms in HIV/AIDS has been reported to vary between 40 to 90% (Barzan et al., 1993; Lubbe, 2004; Salzer, 1994; Somefun et al., 2001). Many of these symptoms are characterized by involvement of the auditory system, as a result of the direct effect of HIV infection, or indirectly due to a combination of opportunistic infections or associated ototoxic treatments (Rey et al., 2002; Rinaldo, Brandwein, Devaney, & Ferlito, 2003).

Auditory pathology associated with HIV/AIDS involves structures including the outer and middle ear, cochlea, neural pathways and central nervous system (CNS). The diease may involve one or many of these structures. Opportunistic infections related to the outer and middle ear may include acute otitis externa (Beers & Abramo, 2004), and otitis media with effusion (Gurney & Murr, 2003). Highly active antiretroviral therapy (HAART) combinations may be ototoxic, as may some treatments for opportunistic infections, resulting in hearing loss, tinnitus and hyperacusis (Jastreboff & Hazell, 2004; Newton, 2006; Stearn & Swanepoel, 2010). A direct effect of HIV/AIDS on the neural pathways, resulting in neural auditory disorders, has also been reported (Bankaitis & Keith, 1995; Reyes-Contreras et al., 2002; Stearn & Swanepoel, 2010). Although the exact incidence and prevalence of auditory disorders are unknown, as many as 75% of adults with HIV/AIDS may present with auditory pathologies and aetiologies associated with HIV/AIDS (Zuniga, 1999).

In addition to the auditory manifestations of HIV/AIDS, vestibular dysfunction has also been documented (Teggi et al., 2008). The cochlea and vestibular organ, situated in the temporal bone, are interconnected and constitute the membraneous

labyrinth; they also share the same fluids, namely endolymph and perilymph. Their nerve fibres together constitute the eighth cranial (cochleovestibular) nerve (Kevetter & Correia, 1997). Considering this shared anatomy and physiology and the known effects of HIV/AIDS on the auditory system, it is not surprising that vestibular symptoms occur. Individuals with vestibular involvement may present with symptoms such as vertigo or a sensation of spinning (Bennet, 2008), and in some cases there may be subclinical vestibular damage. Despite being a common symptom of vestibular involvement, only a limited number of reports have investigated the prevalence of vertigo in patients with HIV/AIDS. One study (Khoza & Ross, 2002) reported that 9% of individuals with HIV/AIDS complained of vertigo, while another reported the same complaint in 30% of HIV/AIDS affected adults (Hofmeyr & Baker, 2010; Marra et al., 1997). Such symptoms have probably been underreported in individuals with HIV/AIDS due to the emphasis on the life-threatening aspects of the disease, as opposed to more chronic non-communicable disease processes.

The advent of HAART and improvements in treatment accessibility are changing the face of HIV/AIDS, from an acute, life-threatening disease to a chronic condition. Thus, there is now a greater emphasis on quality of life concerns, as life expectancy increases for those living with the disease (Zapor, Cozza, Wynn, Wortmann, & Armstrong, 2004). Although a cure for HIV/AIDS may not yet exist, enhanced management of HIV/AIDS related diseases and symptoms could facilitate improved well being. Just as hearing loss affects communication and human interaction, other sensory deficits, such as vestibular disorders, may also negatively affect quality of life (Mira, 2008). Living with vestibular symptoms, such as vertigo or dizziness, may potentially restrict patients' activities of daily living, since such symptoms are often accompanied by anxiety, stress and fear of falling. In fact, the general health status of such patients is significantly affected by a perceived reduction in physical and socio-emotional functioning, associated with vertigo and dizziness (Fielder, Denholm, Lyons, & Fielder, 1996). However, to date there has been little consensus on the extent and nature of the vestibular manifestations of HIV/AIDS.

The present study aimed to systematically review the current body of peer-reviewed publications on reported HIV/AIDS related vestibular manifestations and pathology.

4.2. Methods and materials

A varied search strategy was employed, searching several electronic databases, to identify relevant research articles and conference proceedings (excluding reviews, editorials, notes, letters and short surveys) from the peer-reviewed literature. To merit inclusions, relevant articles had to relate to vestibular findings in patients with HIV/AIDS and to the possible pathology of these findings. Articles relating to vestibulotoxicity aetiology were excluded from this systematic review, since the vestibulotoxic effects of aminoglycosides (commonly used to treat HIV/AIDS related opportunistic infections) and other potentially ototoxic medications has been reviewed elsewhere (Da Silva et al., 2007; Hofmeyr & Baker, 2010; Selimoglu, 2007). Many drugs may have vertigo/dizziness as side-effects, thus complicating the diagnosis of vestibulotoxicity.

All relevant articles and conference proceedings published before 1 February 2010 were included. Table 4.1 indicates the databases and search strategies employed. The Medline database was searched using two strategies: (1) searching for HIV/AIDS related articles reporting vertigo in patients, and (2) searching for HIV/AIDS related articles reporting any vestibular finding in patients. The second database search was conducted on SCOPUS. The search strategy aimed to identify HIV/AIDS related articles reporting vestibular findings or vertigo in patients. The third database search was conducted on Pubmed, utilizing Medical Subject Heading (MeSH) terms to locate articles reporting vestibular diseases with HIV/AIDS, as well as vestibular function tests with HIV/AIDS. The search term "dizziness" was omitted in all the database searches, since it is considered an imprecise MeSH term used to describe various sensations and symptoms, each with a different pathophysiological mechanism and significance. In contrast, the terms "vestibular" and "vertigo" are strongly associated with involvement of the inner ear, vestibular nerve, brainstem and cerebral cortex; furthermore the MeSH term "vestibular disease" includes the

term vertigo, while the MeSH term "vestibular function tests" include caloric tests and electronystagmography. Thus, these terms were used in database searches.

Table 4.1

Database and search strategy details

Database	Search strategy	Identifiers	Results
Medline	HIV related articles reporting vertigo in subjects. The terms occurred in title, keywords and/or abstract of articles	"HIV and vertigo"	28
Medline	HIV related articles reporting on vestibular findings in subjects. The terms occurred in title, keywords and/or abstracts of articles	"HIV and vestibular"	24
Scopus	HIV related articles reporting on vestibular findings or vertigo in subjects. The terms occurred in title, keywords and/or abstracts of articles	"HIV AND vestibular OR vertigo"	367
Pubmed	MeSH terms related to vestibular diseases in subjects with HIV occurring in all fields	"hiv"[All Fields] AND "vestibular diseases"[MeSH Terms]	16
Pubmed	MeSH terms related to vestibular function tests in subjects with HIV occurring in all fields	"hiv"[All Fields] AND "vestibular function tests"[MeSH Terms]	7
		TOTAL NUMBER OF RECORDS:	**442**

Note: HIV = human immunodeficiency virus; MeSH =Medical Subject Heading

By using a multifaceted approach, covering several databases and employing different search strategies, we aimed to ensure comprehensive coverage and to enable crosschecking of results. All available English language abstracts were reviewed. Where abstracts were not available, the full paper was reviewed, and excluded if not directly relevant to our study objectives. After all duplicates and unrelated papers had been excluded, the remaining articles were reviewed according to the HIV/AIDS associated vestibular findings reported.

4.3. Results

Figure 4.1 summarises the different phases of our systematic review procedure used to identify reports for inclusion. A total of 442 records were identified from the three databases. After excluding duplicates, letters, reviews, short surveys,

notes and four non-English language articles, only 210 records remained. These remaining articles were reviewed by reading their abstracts, to determine their relevance to our study. One-hundred-and-ninety-seven (197) records were not directly relevant to the scope of our review, being unrelated to vestibular findings in individuals infected by HIV. The majority of excluded reports considered pharmacological side effects; others reported HIV-negative patients. Only 13 articles reported vestibular functioning and pathology in individuals infected with HIV. Appendix E provides a brief summary of these articles.
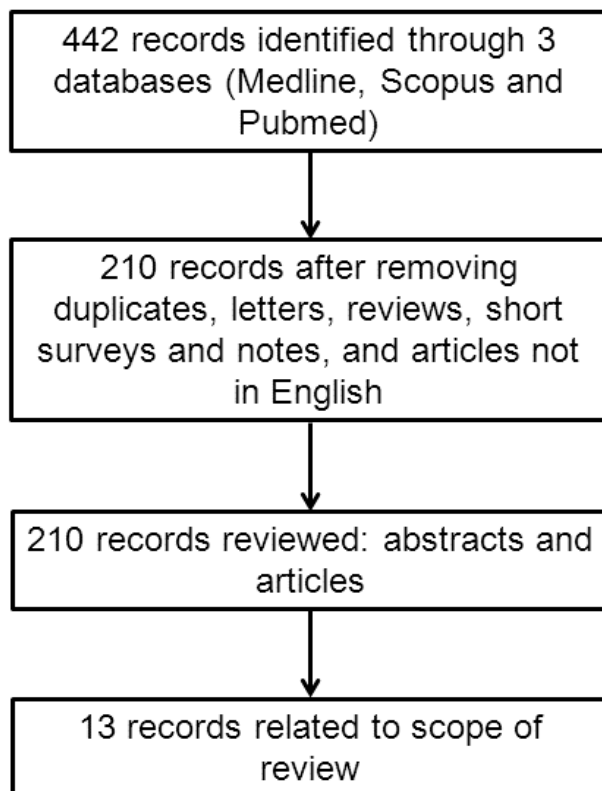
Figure 4.1. Procedural steps in the systematic review to identify reports for inclusion

Of these 13 articles, four were case presentations reporting the results of auditory and vestibular examination of adults presenting with vestibular symptoms (Grimaldi et al., 1993; Hart, Geltman Cokely, Schupbach, Dal Canto, & Warwick Coppleson, 1989; Jae et al., 2005; Macher, 2008). Seven group studies were identified, of which two were descriptive (Palacios et al., 2008; Teggi et al., 2006) and five were quasi-experimental in nature (Castello et al., 1998; Dellepiane et al., 2005; Hausler et al., 1991; Johnston, Miller, & Nath, 1996; Teggi et al., 2008).

These group studies aimed to investigate the nature of vestibular disorders and types of vestibular manifestations associated with HIV/AIDS. All patients were adults, except for one study investigating HIV/AIDS related vestibular function in children aged 16 years and below (Palacios et al., 2008).

Figure 4.2 illustrates the various vestibular tests described in the seven group studies. The most common test used was the smooth pursuit tracking test (a test for CNS functioning), followed by caloric irrigation (a peripheral vestibular test). Saccade testing (also a test for CNS functioning) was used in four studies, along with positional or positioning nystagmus tests. Three studies used spontaneous nystagmus testing, and two used rotatory tests. A single study utilised posturography, Dynamic Gait Index, head shake and thrust, and gaze stability testing.
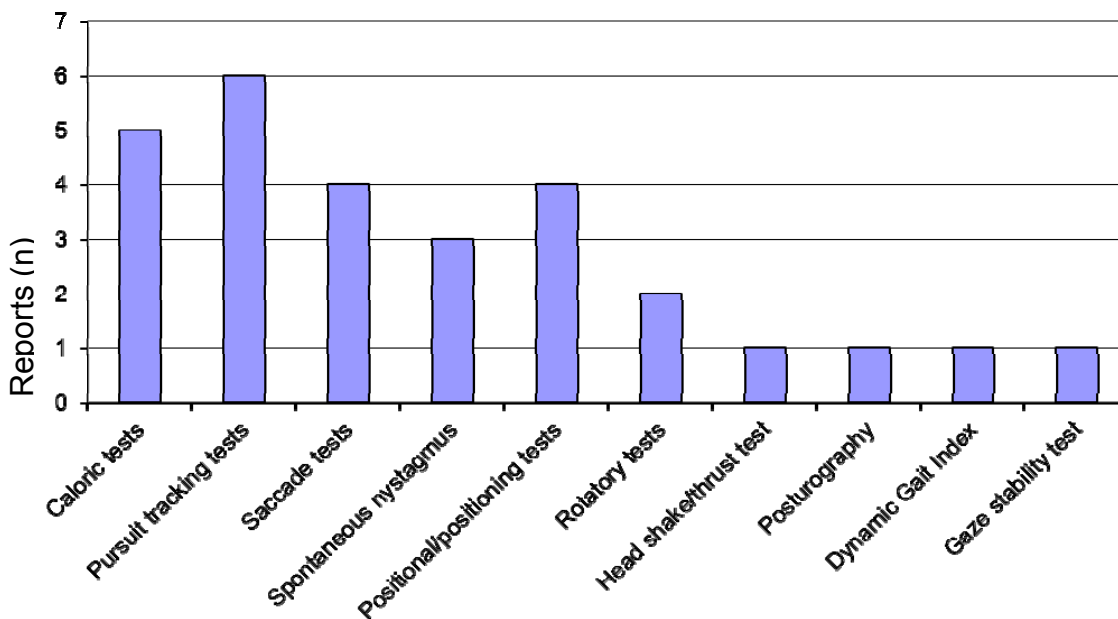
Figure 4.2. Vestibular tests used in the reports retrieved

Postmortem studies accounted for three of the 13 articles. Two of these used electron microscopy to investigate the mechanism of vestibular pathology in the vestibular end-organs of 10 and 12 autopsy cases, variously, in confirmed patients with AIDS (Chandrasekhar et al., 1992; Pappas Jr. et al., 1995). The third report was a single case presentation that also included a postmortem study of a patient with HIV (Hart et al., 1989).

4.4. Discussion

4.4.1. Vestibular system involvement in HIV/AIDS

There are many more reports of the auditory manifestations of HIV/AIDS than the vestibular manifestations. The present review only identified seven reports of vestibular assessment in a group of HIV/AIDS patients. Although it has been reported that vestibular disorders occur in 15 per cent of individuals infected with HIV (Kohan, Hammerschlag, & Holliday, 1990), we could find only four reports identifying the prevalence of various types of vestibular involvement in infected adults.

Two reports (Castello et al., 1998; Hausler et al., 1991) employed a quasi-experimental research design comparing their patients' results with those of a control group of HIV-negative adults. Both these studies categorised their HIV-positive participants using the Centers for Disease Control criteria, as either stage II, III or IV. Participants in both studies were asymptomatic, with no neurological or vestibular symptoms, apart from a subgroup of 14 participants in Hausler and colleagues' study (Hausler et al., 1991). These were, however, classified as stage IV and suffered from AIDS, opportunistic infections and AIDS related complex (ARC).

Both these studies found that the CNS was involved even in early stages of the disease. Results indicated poor ocular motor test performance and poor fixation suppression, suggesting abnormalities in CNS and central vestibular functioning respectively. These test results were evident at all disease stages, even in asymptomatic individuals with no reported neurological or vestibular symptoms. Castello and colleagues (Castello et al., 1998) reported a 52% prevalence of such central vestibular involvement in asymptomatic HIV positive adults. Such involvement implicated the pons-cerebellar pathways, supratentorial areas and pretectal and paramedical pontine regions, as demonstrated by abnormalities in the saccade and pursuit tracking tests. The cerebellar-vestibular pathways were affected in 82% of asymptomatic HIV positive adults, as indicated by nystagmic alterations observed during the caloric tests. This CNS involvement occurred

regardless of disease stage. Although the caloric test results were quantitatively within normal limits and suggested normal labyrinth functioning, the lack of a more comprehensive testing meant that peripheral vestibular involvement could not be excluded. Although Castello and colleagues (Castello et al., 1998) classified their patients according to the Centers for Disease Control criteria, the vestibular findings for each stage were not compared or discussed.

Three studies (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008) aimed to compare the prevalence of vestibular involvement at various stages of HIV infection (see Table 4.2). One of these studies (Hausler et al., 1991) reported abnormal central vestibular functioning as the presenting feature in 22% of asymptomatic stage II patients, 50% of stage III patients and 57% of stage IV patients (all stage IV patients complained of vestibular symptoms). Although only two patients (14%) from the latter group had both abnormal peripheral and central vestibular functioning, it was not clear from the report what criteria had been used to distinguish abnormal peripheral versus central vestibular functioning. Teggi and colleagues (Teggi et al., 2006) reported a higher prevalence of peripheral and central vestibular involvement. Results indicated that, among symptomatic HIV positive adults in the advanced stages of HIV/AIDS, up to 40% had both abnormal peripheral and central vestibular findings. However, these findings may have been influenced by the fact that, although all procedures were essentially identical to other, similar studies Teggi and colleagues' test battery included the Dynamic Gait Index (a sensitive tool to identify vestibular disorders and to assess risk of falling). Also of note, Hausler and colleagues (Hausler et al., 1991) defined abnormal caloric irrigation as a unilateral weakness of 40% or more, although other authors have recommended setting normal limits for gain symmetry from as low as 22% (Kohan et al., 1990) to as high as 30% (Halmagyi, Cremer, Anderson, Murofushi, & Curthoys, 2000). Teggi and colleagues (Teggi et al., 2006) considered a difference of more than 15% to consider a labyrinthine preponderance. Given this variance in recommended normal limits, the incidence of peripheral vestibular involvement reported by Hausler and collagues (Hausler et al., 1991) may have been higher if more conservative limits of normality were employed.

Castello and colleagues (Castello et al., 1998) utilized bithermal caloric irrigation, but quantitative caloric response parameters were within normal limits for the peripheral vestibular system (i.e. the labyrinth and vestibular nerve pathways). Thus, these authors identified the CNS as the causal area affected. Both Hausler et al. (1991) and Castello et al. (1998) concluded that neurological complications are likely to occur in HIV infected individuals, which may result in vestibular manifestations. Abnormalities in ocular motor test results (i.e. saccade and smooth pursuit tracking) of HIV positive adults with cluster of differentiation (CD4+) glycoprotein cell counts lower than 500 cells/mm^3 also indicated neurological insults (Johnston et al., 1996). Results for static and dynamic posturography (Dellepiane et al., 2005) indicate that the CNS and vestibular system is involved in all stages of HIV/AIDS, including in asymptomatic individuals.   This implies that balance problems, postural instability and/or disequilibrium may be found in all individuals with HIV/AIDS irrespective of disease stage. Thus, patients' quality of life and daily functioning may already be negatively affected by vestibular disorders early on in the disease process.

In contrast to earlier studies (Castello et al., 1998; Hausler et al., 1991) which included only asymptomatic, early stage participants, the most extensive study thus far has been by Teggi and colleagues (Teggi et al., 2008). These authors assessed 60 HIV positive adults with vestibular symptoms, who reported a history of balance disorders and chronic dizziness. Participants' disease stage ranged across three CDC categories. Their reported prevalence of vestibular involvement is presented in Table 4.2.   Unsurprisingly, the prevalence of central vestibular involvement increased from 3.3% in the early stages of the disease to 100% in the advanced stage. Peripheral vestibular disorders occurred in one third of patients in the early stages of the disease, rising to one half of patients in the advanced stages.

Table 4.2

Vestibular involvement at various HIV/AIDS disease stages: three studies' findings

Stage	Hausler et al. (1991)						Teggi et al. (2006)*			Teggi et al. (2008)*		
	Asymptomatic			Symptomatic								
	Periph	Central	Both	Periph	Central	Both	Periph	Central	Both	Periph	Central	Both
II	-	22%	-	-	-	-	36%	0%	0%	33%	3%	NI
III	-	50%	-	-	-	-	0%	27%	27%	50%	35%	NI
IV	-	-	-	NI	43%	14%	0%	60%	40%	50%	NI	100%

Note: NI = test results not indicated in study; Periph = Peripheral; * = all subjects in study were symptomatic

The only report on vestibular manifestations associated with HIV/AIDS in the paediatric population indicated a high prevalence of abnormal auditory and vestibular function (Palacios et al., 2008). However, the exact prevalence and nature of vestibular involvement (whether peripheral or central) was not indicated.

4.4.2. Aetiology of HIV/AIDS related vestibular involvement

Vestibular involvement occurs in HIV positive children and adults irrespective of disease stage. The exact pathological mechanisms are still unclear. However, the four case case report studies and three postmortem studies (one of which was also a case report) identified by the present review provide some information on possible contributing factors. Dizziness, vertigo, disequilibrium or imbalance may result when there is a lesion in the vestibular, visual and/or proprioceptive system (Bennet, 2008). HIV/AIDS associated dysfunction in any of these systems may potentially result in balance disturbance, especially if affecting the vestibular and neurological systems (Hofmeyr & Baker, 2010). Opportunistic infections and ototoxic medications associated with HIV/AIDS may also cause (or contribute to) vestibular symptoms. In the present review, the four identified case report studies of HIV infected adults complaining of dizziness and imbalance demonstrate the causal role of opportunistic infections.

4.4.3. Case reports

Macher's study (Macher, 2008) reported a number of HIV positive adults with conditions such as syphilitic meningitis, secondary syphilis, a syphilitic mass in the internal auditory canal, and oto- and neurosyphilis, in whom symptoms indicated vestibular involvement. Only two of the cases received a partial vestibular examination. In one case (with secondary syphilis), caloric test results indicated bilateral vestibular function loss, resulting in dizziness and persistent imbalance. In the other case, a vestibular examination utilized the Romberg test; a positive result confirmed the presence of a syphilitic mass in the left internal auditory canal.

Jae and colleagues (Jae et al., 2005) reported the case of an adult diagnosed with otosyphilis who presented with auditory and vestibular symptoms, including a

sensorineural hearing loss, dizziness and imbalance. Caloric testing revealed progressive involvement of the peripheral vestibular system. Initial caloric test results indicated unilateral vestibular dysfunction; two months later, total bilateral vestibular dysfunction was evident. The authors concluded that the incidence of syphilis is increasing in patients with HIV/AIDS, and that otosyphilis (diagnosed from auditory and vestibular symptoms and serological testing) is a commonly associated disease with severe sequelae.

Grimaldi and colleagues (Grimaldi et al., 1993) described bilateral cochleovestibular nerve neuropathy in an HIV positive adult with sudden bilateral hearing impairment, high fever and vomiting. There were no reported vestibular symptoms such as vertigo, dizziness or imbalance. However, brainstem auditory evoked potentials and bithermal caloric testing suggested bilateral involvement of both the cochlear and vestibular nerves. Vestibular nerve involvement was diagnosed solely on the results of the caloric test, as no other vestibular assessment procedures were performed. The authors called for research into eighth cranial nerve (CN VIII) neuropathy associated with HIV/AIDS, since the pathogenesis is still unknown.

Hart and colleagues (Hart et al., 1989) reported an adult AIDS patient with complaints of vestibular symptoms such as dizziness, lightheadedness and imbalance, as well as cognitive changes. Vestibular examination revealed abnormal results for pursuit tracking and optokinetic testing. Caloric testing also revealed central vestibular involvement, suggesting a brainstem lesion. The patient was subsequently diagnosed with sub-acute encephalitis (commonly associated with HIV/AIDS), which was the probable cause of vestibular changes. The authors suggested that auditory and vestibular assessment tests could be useful tools to monitor the progression of sub-acute encephalitis (characterized by subtle cognitive changes even in early stages of the disease).

4.4.4. Postmortem studies

Two group studies were conducted postmortem (Chandrasekhar et al., 1992; Pappas Jr. et al., 1995). A third study comprised a case presentation, with auditory and vestibular test results, together with subsequent postmortem findings (Hart et al.,

1989). Postmortem studies of microstructural changes may help elucidate the possible mechanisms of HIV/AIDS related vestibular involvement (Chandrasekhar et al., 1992; Pappas Jr. et al., 1995).

Pappas and colleagues' findings (1995) indicated not only that the CNS is vulnerable to direct viral infections, but that their patients' peripheral vestibular labyrinth neuroepithelium contained viral-like particles characteristic of the human immunodeficiency virus. Specifically, pathology was observed within the cristae ampullares as well as in both the otolith organs (i.e. the utricle and saccule). Chandrasekhar and colleagues (1992) reported similar abnormalities within the utricle and saccule, together with precipitations in the fluid filled semicircular canals. This suggests that HIV/AIDS affects the peripheral vestibular system directly, and could explain the presence of peripheral vestibular dysfunction and symptoms of chronic imbalance and dizziness reported by participants of a recent study (Teggi et al., 2008). The semicircular canals and otolith organs are the receptor organs for balance; their function is primarily to maintain postural stability and to aid spatial orientation, as well as keeping the eyes focused on a target of interest while the head is moving (Hofmeyr & Baker, 2010).

Hart and colleagues' (Hart et al., 1989) case presentation, of a deceased HIV positive adult with vertigo attacks and imbalance, also reported autopsy findings which indicated neuronal loss in the area of the vestibular-cerebellar projections, with inflamed sells in the vestibular nuclei. The vestibular assessment performed premortem suggested central vestibular involvement, and the subsequent autopsy confirmed these findings.

4.5. Conclusion

Individuals living with HIV/AIDS now have improved life expectancy due to improvements in treatment. However, their overall quality of life may be limited by persistent vestibular symptoms such as vertigo, dizziness and/or imbalance. Peripheral and central vestibular functioning may be affected, irrespective of age or disease stage. However, the prevalence of central vestibular disorders seems to be greater, compared with peripheral disorders, especially at more advanced stages of the disease. The aetiology of HIV/AIDS-associated vestibular dysfunction is

complex, and may include direct effects of the virus on the peripheral and central vestibular system, together with the effects of a variety of HIV/AIDS-associated opportunistic infections (e.g. otosyphilis, encephalitis and cochleovestibular nerve neuropathy).

Chapter 5

Vestibular involvement in adults with HIV/AIDS

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Abstract

Objectives: HIV/AIDS is responsible for widespread clinical manifestations involving the head and neck. The prevalence and nature of vestibular involvement is still largely unknown. This study aimed to describe and compare the occurrence and nature of vestibular involvement among a group of adults infected with HIV compared to a control group. It also aimed to compare the vestibular function of symptomatic and asymptomatic HIV positive adults who receive antiretroviral (ARV) therapies to subjects not receiving ARV.

Methods: A cross-sectional study was conducted on 53 adults (29 male, 24 female, aged 23-49 years, mean=38.5, SD=4.4) infected with HIV, compared to a control group of 38 HIV negative adults (18 male, 20 female, aged 20-49 years, mean=36.9, SD=8.2). A structured interview probed the subjective perception of vestibular symptoms. Medical records were reviewed for CD4+ cell counts and the use of ARV medication. An otologic assessment and a comprehensive vestibular assessment (bedside/clinical assessments, vestibular evoked myogenic potentials, ocular motor and positional tests and bithermal caloric irrigation) were conducted.

Results: There was vestibular involvement in 79.2% of subjects with HIV/AIDS in all categories of disease progression, compared to 18.4% in those without HIV/AIDS. Vestibular involvement increased from 18.9% in CDC category 1 to 30.2% in category 2. Vestibular involvement was 30.1% in category 3. There were vestibular involvement in 35.9% of symptomatic HIV positive subjects, and 41.5% in

asymptomatic HIV positive subjects. There was no significant difference in the occurrence of vestibular involvement in subjects receiving ARV therapies compared to those not receiving ARV therapies (*p*=.914;chi-square test). The odds ratio indicates that individuals with HIV/AIDS have a 16.6 times higher risk of developing vestibular involvement during their lifetime of living with the disease and that it may occur despite being asymptomatic.

Conclusion: Vestibular involvement was significantly more common in subjects with HIV/AIDS, especially peripheral vestibular involvement and should be examined and monitored throughout progression of the disease.

5.1. Introduction

The human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is a world-wide pandemic affecting the lives of millions of people. Despite the number of new infections and AIDS related deaths decreasing between 2001 and 2009, the overall number of individuals living with the disease is still very high (UNAIDS, 2010). Increased life expectancy and duration of survival of those living with HIV/AIDS may, among other factors such as public health education and awareness programmes, be attributed to antiretroviral (ARV) therapy and improvements in access to health care services. The reduction in morbidity and mortality is changing HIV/AIDS from a life-threatening disease to a chronic illness with an increasing emphasis on quality of life issues (Heinze, Swanepoel, & Hofmeyr, 2011).

After HIV binds with and penetrates into the CD4+ cell, it compromises the body's immune response gradually and predisposes it to opportunistic infections (Evian, 2000; Fan et al., 2004). Diseases involving the head and neck area are often the first signs of an immune compromised body and may occur in as many as 40% to 90% of individuals with HIV/AIDS (Barzan et al., 1993; Lubbe, 2004; Marsot-Dupuch et al., 2004; Salzer, 1994; Somefun et al., 2001). Common HIV/AIDS-associated head and neck pathologies include manifestations in the central nervous system (CNS), the naso-, oro- and laryngopharynx and in the inner ear, that may result in hearing loss and/or vestibular disorders (Cohen & Berger, 2007; Gurney & Murr, 2003; Moayedi, 2010).

There is growing evidence that HIV/AIDS could either directly or indirectly, through opportunistic infections or ototoxic medication, have an adverse effect on the delicate structures of the ear, causing a conductive, mixed or sensorineural hearing loss (Chan et al., 2008; Devaleenal et al., 2008; Matas et al., 2000; Palacios et al., 2008; Teggi et al., 2006; Teggi et al., 2008; Vincenti et al., 2005). Auditory dysfunction has been reported to occur in between 20% to 75% of adults with HIV/AIDS (Chandrasekhar et al., 2000; Lalwani & Sooy, 1992; Prasad et al., 2006; Zuniga, 1999). The auditory and vestibular system is situated in the temporal bone and constitutes part of the same membranous labyrinth. It is not surprising that with auditory symptoms, which often accompany HIV/AIDS, vestibular dysfunction and

associated symptoms may also occur. Vestibular symptoms may include dizziness, vertigo, disequilibrium and/or nausea and vomiting.

However, only a limited number of studies have investigated vestibular dysfunction and pathology related to HIV/AIDS, despite the shared anatomy and physiology of the auditory system (Heinze et al., 2011). Teggi and colleagues (Teggi et al., 2008) suggested that vestibular symptoms are often masked by other more serious and life-threatening illnesses and disorders associated with HIV/AIDS. As a result, the nature of vestibular symptoms and the potential for manifestations of vestibular pathology resulting from HIV/AIDS have been largely neglected.

The most recent and extensive reports were group studies of adults (Castello et al., 1998; Dellepiane et al., 2005; Teggi et al., 2006; Teggi et al., 2008) and children (Palacios et al., 2008) infected with HIV who underwent auditory and vestibular assessments. The findings demonstrated vestibular dysfunction to be more frequent among subjects with HIV/AIDS than those without HIV/AIDS. Signs of both peripheral (involving the vestibular end-organs and eighth cranial nerve) and central (vestibular nuclei in the brainstem, cerebellum and ocular motor, vestibulospinal and proprioceptive pathways) vestibular dysfunction have been reported (Castello et al., 1998; Dellepiane et al., 2005; Palacios et al., 2008; Teggi et al., 2006; Teggi et al., 2008). Vestibular dysfunction occurred across all categories of the disease with a higher prevalence in more advanced categories, particularly regarding central vestibular involvement (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). These studies employed various tests of vestibular function, included spontaneous and positional/positioning nystagmus tests, ocular motor tests, caloric tests and posturography. Cervical vestibular evoked myogenic potentials (cVEMPs) have recently been introduced in the clinical evaluation of the saccule (vestibular end-organ) and inferior vestibular nerve. However, no study has yet utilized cVEMPs as part of a vestibular test battery in individuals with HIV/AIDS to determine peripheral involvement.

One study compared the vestibular functioning of 60 HIV positive adults suffering from vestibular symptoms with 30 HIV negative adults also with vestibular symptoms (Teggi et al., 2008). This study showed a higher number of abnormal peripheral and central vestibular findings among the HIV positive group than among

the HIV negative group. Another study compared vestibular functioning of HIV positive and HIV negative adults without any vestibular symptoms (Castello et al., 1998) and reported central vestibular involvement in the HIV positive group. No signs of peripheral vestibular involvement were however reported in the sample of asymptomatic subjects. Both of these studies utilised essentially the same test procedures, namely spontaneous and positional nystagmus tests, ocular motor tests and caloric tests, with the exception of the auditory brainstem response included in the latter. It is therefore not clear if HIV/AIDS affects the peripheral vestibular system in asymptomatic individuals. It is also not clear if the vestibular function of symptomatic HIV positive individuals would differ from asymptomatic HIV positive individuals. No studies to date have compared the peripheral and central vestibular functioning of HIV positive individuals with and without vestibular symptoms.

There are also no studies that described peripheral and central vestibular functioning in adults with HIV/AIDS receiving ARV therapies compared to those without this treatment. The present study aimed (1) to describe the occurrence and nature of vestibular involvement among a group of adults infected with HIV, compared to a control group without HIV by including cVEMPs in the vestibular test battery; (2) to describe and compare the vestibular function of symptomatic and asymptomatic HIV positive adults; (3) to describe and compare the vestibular function of a group of adults with HIV receiving ARV therapies to those not receiving ARV therapies.

5.2. Methods and materials

5.2.1. Ethical clearance and informed consent

The institutional review boards of the University of Pretoria and the tertiary referral hospital where subjects were registered reviewed and approved the study before any data collection commenced. Subjects provided written informed consent for the researcher to access their medical records, to have access to their HIV/AIDS status, to document the CD4+ cell count and the use of ARV therapies.

5.2.2. Study design

A cross-sectional comparative research design was employed. A convenience sampling method was used to recruit subjects.

5.2.3. Subjects

Table 5.1 summarizes the description of participating subjects. A total of 91 subjects participated, comprising 53 HIV positive and 38 HIV negative adults. There were no statistically significant differences in mean ages between the groups (p=0.26; t-test) and therefore there was not a difference in age groups. Since age only affects the vestibular system after 55 to 65 years (Maes et al., 2010), the age of the subjects were below 50 in order to minimize the likelihood of age affecting the results. Age distribution was the same across the two study groups (Mann-Whitney U test). In addition, gender distribution was similar between and within the groups. HIV positive subjects were evenly distributed between the three Centres for Disease Control and Prevention (CDC) classification categories (p>0.05; one-way ANOVA). Fifteen subjects were in category 1 (eight male, seven female), 20 subjects were in category 2 (eight male, 12 female) and 18 subjects were in category 3 (eight male, 10 female). Table 5.1 furthermore shows the ARV therapy regimes for the subjects with HIV/AIDS. There were 42 subjects with HIV/AIDS who used ARV therapies and 11 subjects with HIV/AIDS who did not use ARV therapies at the time of entry in the study.

Table 5.1

Description of subjects

Description	HIV negative group	HIV positive group
Number of subjects (n)	38	53
Mean age	36.9 (SD= 8.2)	38.5 (SD= 4.4)
Min-Max age	20-50 years	23-49 years
Gender distribution	Male = 47.4% (n=18) Female = 52.6% (n=20)	Male = 55% (n=29) Female = 45% (n=24)
CDC categories	Not applicable	CDC category 1: n=15 CDC category 2: n=20 CDC category 3: n=18
ARV therapies	Not applicable	TDF+ FTC+ NVP: n=11 d4T+3TC+NVP: n=4 TDF+3TC+EFV: n=13 TDF+3TC+LPV/r: n=3 AZT+3TC+EFV: n=2 AZT+3TC+LPV/r: n=1 Unknown/not documented: n=8 non-ARV therapy users: n=11

Note: 3TC = lamivudine; ARV = antiretroviral; AZT = zidovudine; CDC = Centres for Disease Control and Prevention; d4T = stavudine; EFV = efavirenz; FTC = emtricitabine; HIV = human immunodeficiency virus; LPV/r = lopinavir/ritonavir; NVP = nevirapine; SD = Standard Deviation; TDF = tenofovir.

5.2.3.1. Experimental group

Subjects in the experimental group were HIV positive patients from the Infectious Disease (ID) clinic of a tertiary referral hospital in South Africa. The majority of recruited patients were HIV positive. Those who were HIV negative (n=1) were assigned to the control group.

The inclusion criteria were a positive diagnosis of HIV/AIDS as determined by blood serological tests; aged between 18-50 years since this age group has the highest prevalence of HIV/AIDS (Dorrington & Bourne, 2008) and to minimize age as a contributing influence on results; and any ethnic group and gender. The following

conditions excluded participation by potential candidates: exposure to ototoxic agents prior to contracting HIV/AIDS; a history of vestibular involvement and/or complaints of dizziness, vertigo or disequilibrium prior to contracting HIV/AIDS, thus reducing the likelihood of other vestibular disorders affecting the results; blindness or other disorders of vision that would not allow videonystagmography (VNG), particularly for the evaluation of random saccades, pursuit tracking and fixation suppression.

The subjects with HIV/AIDS were further divided into categories according to their CD4+ cell counts at entry in the study. Subjects with counts higher than 500 cells/uL were assigned to CDC category 1, while those with counts of 200-499 cells/uL and less than 200 cells/uL were assigned to categories 2 and 3 respectively.

5.2.3.2.   Control group

Subjects in the control group were patients from the ID clinic confirmed not to have HIV/AIDS, acquaintances of the researcher and employees of the tertiary referral hospital. Individuals were required to agree to an HIV blood serological test before being included. Once the latter two groups agreed and gave written informed consent, medical staff at the tertiary referral hospital conducted an HIV blood serological test. These test incurred no costs to subjects and the medical staff documented and managed the results. The inclusion criteria were: (1) HIV negative; (2) aged between 18-50 years to account for normal aging of auditory and vestibular structures; (3) and any ethnic group and gender. Exclusion criteria were reported previous exposure to ototoxic agents and blindness or other disorders of vision.

5.2.4. Procedures

Table 5.2 summarizes the data collection protocol, its sequence and purpose. Prior to data collection, subjects were provided with a letter requesting of informed consent that also explained the procedures for the auditory and vestibular assessments as well as a written list of pre-test instructions. The list of pre-test instructions explained that subjects were not permitted to take medication that may suppress vestibular symptoms or agents such as alcohol and/or sedatives that may suppress peripheral and/or central vestibular function and influence the results and

their interpretation. The procedures for the first two points in Table 5.2 were a medical record review to document subjects' CD4+ cell counts at the time of participation in the study, use of antiretroviral agents and a structured interview. We used the questionnaire from Goebel (Goebel, 2008b) to probe for any subjective perception of vestibular symptoms. The remainder of the test procedures as indicated in Table 5.2 were performed in a single session lasting approximately two hours.

Table 5.2

Summarised data collection protocol according to test sequence

Category and sequence	Purpose / tests
1. Medical record review	Document CD4+ cell counts, use of antiretroviral therapies.
2. Structured interview	Subjective perception of any vestibular symptoms (questionnaire from Goebel (Goebel, 2008b).
3. Otologic and audiologic examination	Otoscopy, tympanometry, pure tone audiometry
4. Vestibular bedside/clinical assessments	Fukuda stepping test, subjective visual vertical, head impulse test, dynamic visual acuity
5. Videonystagmography	Spontaneous nystagmus, gaze evoked nystagmus, random saccades, pursuit tracking, positioning/positional tests, head shake test, hyperventilation test, bithermal caloric irrigation
6. Evoked potentials	Cervical Vestibular Evoked Myogenic Potentials (cVEMP)

Note: CD4+ = cluster of differentiation 4+.

5.2.4.1   Otologic and audiological examination

Outer ear functioning was assessed through an otoscopic examination. A physician managed the ear canals of subjects with impacted cerumen prior to the vestibular evaluation. Tympanometry was performed using a diagnostic Y-226 Hz probe tone (GSI Tympstar, Grason-Stadler, Eden Prairie, MN, USA). The following criteria (Jerger, 1970) were used for normal adult admittance profiling: ear canal volume (0.8 to 2.0 ml), compliance (0.3 to 1.8 ml) and middle ear pressure (-100

daPa to +50 daPa). Pure tone audiometry (air and bone conduction) was performed to determine the presence of air-bone gaps. VEMP data was not analysed if air-bone gaps were greater than 10 dB.

5.2.4.2   Vestibular bedside/clinical assessments

Vestibular clinical/bedside assessments that were conducted are listed in Table 5.2. During the Fukuda stepping test, subjects were asked to step or march 50 times with eyes closed and arms extended. A sideward rotation greater than 45 degrees was considered pathological. For the subjective visual vertical (SVV) test the bucket method was used, described and illustrated elsewhere (Zwergal et al., 2009), as bedside tool to detect abnormal subjective tilt. The subjects looked into the bucket without having gravitational orientation clues and had to vertically straighten a line on the bottom inside of the bucket. The average of five repetitions was taken. Offsets greater than three degrees were considered pathological. During the horizontal head impulse test the investigator stood in front of the subject and firmly held the head while rapidly rotating the head to both the left and right side by 20-30°. The subjects had to maintain visual fixation and corrective eye movements or failure of visual fixation during these rapid head movements were considered pathological. Dynamic visual acuity testing was performed using a computerized VNG/ENG system (Micromedical Technologies Inc., Chatham, Illinois, U.S.A.). A visual optotype appeared when the head velocity exceeded 100 degrees per second and blanked during periods of low head velocity. The head was oscillated horizontally and vertically at a frequency of 2 Hz. Subjects had to identify the direction of the visual optotype correctly. Incorrect identification of the visual optotype that increased two or more times from baseline visual acuity during head rotation was considered pathological.

5.2.4.3   Videonystagmography

Next, the four channel Visual Eyes infrared video-based system (Micromedical Technologies Inc., Chatham, Illinois, U.S.A.) was used to record eye movements. The presence of spontaneous nystagmus was evaluated with and without fixation, and such presence was considered pathological. Gaze evoked nystagmus evaluated the subject's abilities to maintain gaze in eccentric positions, both horizontally and

vertically. The presence of gaze evoked nystagmus was considered pathological.

For the ocular motor tests the same infrared video goggles were used, during which eye movements were recorded. A digital light bar was used to perform the ocular motor tests. Age and visual acuity may affect the outcomes of the ocular motor tests (Baloh, Enrietto, Jacobson, & Lin, 2001; Kerber, Ishiyama, & Baloh, 2006), therefore age was accounted for when selecting subjects, as well as their visual acuity. Random saccade testing was analysed according to the following parameters: velocity, latency and accuracy of the eye movements. Pursuit tracking was analysed for smooth eye movements, according to the following parameters: gain, symmetry and phase at the velocities of 0.1 Hz, 0.2 Hz and 0.4 Hz. Any abnormalities in saccades and pursuit were considered pathological. Optokinetic testing was not performed because a full visual field stimulus was unavailable at the time.

The Dix-Hallpike positioning test and various positional head and body nystagmus tests (also with vision denied) were performed using the infrared video goggles. The presence of nystagmus induced by position was considered pathological.

Subsequently, the subject's head was moved sinusoidally in the horizontal (yaw) plane at a cycle of 2 Hz for 25-30 seconds and the presence of post headshake induced nystagmus was noted with vision denied. Post headshake nystagmus was considered pathological.

Subjects were then asked to inhale and exhale deeply at a cycle of 1 Hz for 45 seconds during which nystagmus induced by hyperventilation was noted with vision denied. The presence of nystagmus induced by hyperventilation was considered pathological.

Finally, a bithermal, binaural air caloric test (AirFX, Micromedical Technologies Inc., Chatham, Illinois, U.S.A.) was performed to evaluate individual horizontal semi-circular canal responsiveness. This system allowed visualization of the entire ear canal and tympanic membrane, and was safe to use for subjects with outer and/or middle ear infections and/or tympanic membrane perforations, without risking further

infection in comparison to water caloric tests. The air currents were 47 and 24 degrees Celsius respectively and the stimulus was applied for 60 seconds, with an interval of five minutes between irrigation. Jongkees' formula (Jongkees et al., 1962) was used to calculate unilateral weakness or asymmetry and directional preponderance: (RW + RC) – (LW + LC) / (RW + RC + LW + LC) x 100. A unilateral weakness or asymmetry of ≥20% (Baloh & Kerber, 2011; Jacobson et al., 1997), directional preponderance of ≥30% (Baloh & Kerber, 2011), bilateral weakness (Barber & Stockwell, 1980) and hyperreflexia (total response more than 221 degrees per second) was considered abnormal (Jacobson et al., 1997).

5.2.4.4   Cervical vestibular evoked myogenic potentials

Cervical vestibular evoked myogenic potentials were measured with the non-inverting electrode placed on the medial portion of the sternocleidomastoid muscle (SCM), the inverting electrode on Fpz and ground on Fz (Bio-logic Navigator Pro, Natus Medical Inc., San Carlos, California, U.S.A.). Skin impedance was less than 5kΩ. Wester (Wester, 2012) described this electrode montage. Colebatch and colleagues (Colebatch et al., 1994) as well as Vanspauwen and colleagues (Vanspauwen, Wuyts, & Van De Heyning, 2006) described a similar electrode montage, with the exception of the inverting electrode on the upper sternum. In this study, cVEMPs from 24 normal ears without a history of vestibular dysfunction with the inverting electrode on Fpz (montage 1) were recorded and compared with the inverting electrode on the upper sternum (montage 2). The mean amplitude was 146.57 (±44.75) and 158.31 (±53.88) for montage 1 and 2 respectively, which was statistically insignificant (p=.09; t-test). The mean P1 latency was 13.47 (±0.84) and 13.63 (±0.95) for montage 1 and 2 respectively, which was statistically insignificant (p=.34; t-test). The mean N1 latencies were 21.88 (±1.34) and 21.82 (±1.42) for montage 1 and 2 respectively, which was statistically insignificant (p=.82; t-test). Alternating polarity tone burst (750 Hz) stimuli were presented at 95 dBnHL monaurally with insert earphones. A blood pressure manometer with rolled up inflatable cuff was positioned between the subjects' hand and jaw as feedback method of the contracted SCM muscle during recordings. A sustained pressure of 40mmHg was obtained to ensure comparable muscle contraction between both sides. This method was described by Vanspauwen and colleagues (Vanspauwen et al., 2006) as well as by Maes and colleagues (Maes et al., 2009) and was proved to

provide reliable VEMP amplitudes. All measurements both present and absent responses, were repeated to test for wave repeatability. The first positive peak on the waveforms was marked P1, while the first negative deflection was marked N1. The following VEMP asymmetry ratio formula was used (Akin & Murnane, 2008): $[(A_L - A_R) / (A_L + A_R)] \times 100$, where '$A_L$' indicated the amplitude for the left ear and 'A_R' the amplitude for the right ear. Responses were interpreted as follows: (1) the absence of unilateral or bilateral waveforms were considered abnormal (absence of an identifiable P1 and N1); (2) two standard deviations above the mean of the HIV negative group were used to calculate the upper limits for P1 and N1 latencies (17.0ms and 26.3ms respectively). Latencies above these upper limits were regarded as present yet delayed, and considered abnormal; and (3) the presence of an amplitude asymmetry ratio of ≥40% was considered abnormal, since it indicates side-to-side amplitude differences (Akin & Murnane, 2008).

5.2.4.5 Identification of peripheral signs

The presence of at least one of the following findings suggested signs of a peripheral vestibular involvement: (1) spontaneous nystagmus inhibited by fixation, fixed direction and that follows Alexander's law; (2) re-fixation or catch-up saccadic eye movement with the head impulse test; (3) horizontal post headshake nystagmus; (4) rotation greater than 45 degrees with the Fukuda stepping test; (5) vertical offsets ≥3 degrees without concomitant skew deviation and/or ocular tilt; (6) horizontal nystagmus induced by hyperventilation; (7) abnormal dynamic visual acuity; (8) positioning induced torsional upbeat, horizontal or torsional downbeat nystagmus with a short latency, a duration less than 60 seconds and fixation suppresses or reduces positional nystagmus; (9) caloric unilateral weakness of 20% or greater, bilateral weakness with a history of a vestibular disorder or exposure to ototoxic agents and fixation suppression response; (10) absent cVEMP recordings, asymmetry ratio ≥40% and delayed latencies.

5.2.4.6 Identification of central signs

The presence of at least one of the following findings suggested signs of central vestibular involvement: (1) spontaneous nystagmus not inhibited by fixation, direction changing nystagmus; (2) gaze evoked nystagmus in the horizontal or

vertical positions; (3) perverted (vertical or torsional) post head shake nystagmus; (4) vertical offsets ≥3 degrees with concomitant skew deviation and/or ocular tilt; (5) vertical hyperventilation induced nystagmus; (6) direction changing nystagmus, vertical nystagmus and nystagmus enhanced with fixation; (7) abnormalities in random saccade velocities, accuracies or latencies; (8) saccadic, asymmetric or absent pursuit; (9) position induced vertical nystagmus without a latency and duration longer than 60 seconds, persistent nystagmus while in position and fixation and that does not inhibit or suppress nystagmus; (10) bilateral caloric weakness without a history of a vestibular disorder or middle ear pathology, failure of fixation suppression, hyperreflexia, directional preponderance of 30% or greater without a unilateral weakness.

5.2.5. Data analysis

All analyses of data were performed using the statistical software package SPSS for Windows version 21. Mean, standard deviation (±) and percentages (%) were used to describe the data. One-way analysis of variance (ANOVA) was used to compare the distribution of HIV positive subjects between the three CDC categories. The One-Sample Kolmogorov-Smirnov Test was used to demonstrate normality of data. The independent samples t-test was used to compare mean values between the experimental and control groups. *P* values <0.05 were accepted as statistically significant. Effect sizes were determined using Cramer's V; and odds ratios were calculated. The chi-square non-parametric test was used to compare the findings between the two study groups and the three CDC categories.

5.3. Results

There was a significantly higher occurrence of vestibular involvement in subjects with HIV/AIDS (*p*=.001; chi-square). Peripheral and central vestibular involvement was measured in 79.2% of subjects with HIV/AIDS compared to 18.4% of subjects without HIV/AIDS (Figure 5.1). The effect size was large (Cramer's V value = .602), demonstrating a strong association between vestibular signs and HIV/AIDS. This association between vestibular signs and HIV/AIDS was further confirmed by the odds ratio. A ratio of 16.6 was obtained, showing a 16.6 times higher risk for developing vestibular signs in persons who are HIV positive.

Almost half (45.3%; n=24) of the HIV positive subjects with vestibular involvement had signs of peripheral vestibular involvement, while 22.6% (n=12) had peripheral with central vestibular involvement and 11.3% (n=6) had central vestibular involvement (Figure 5.1). Among the subjects without HIV/AIDS, only peripheral vestibular involvement occurred.
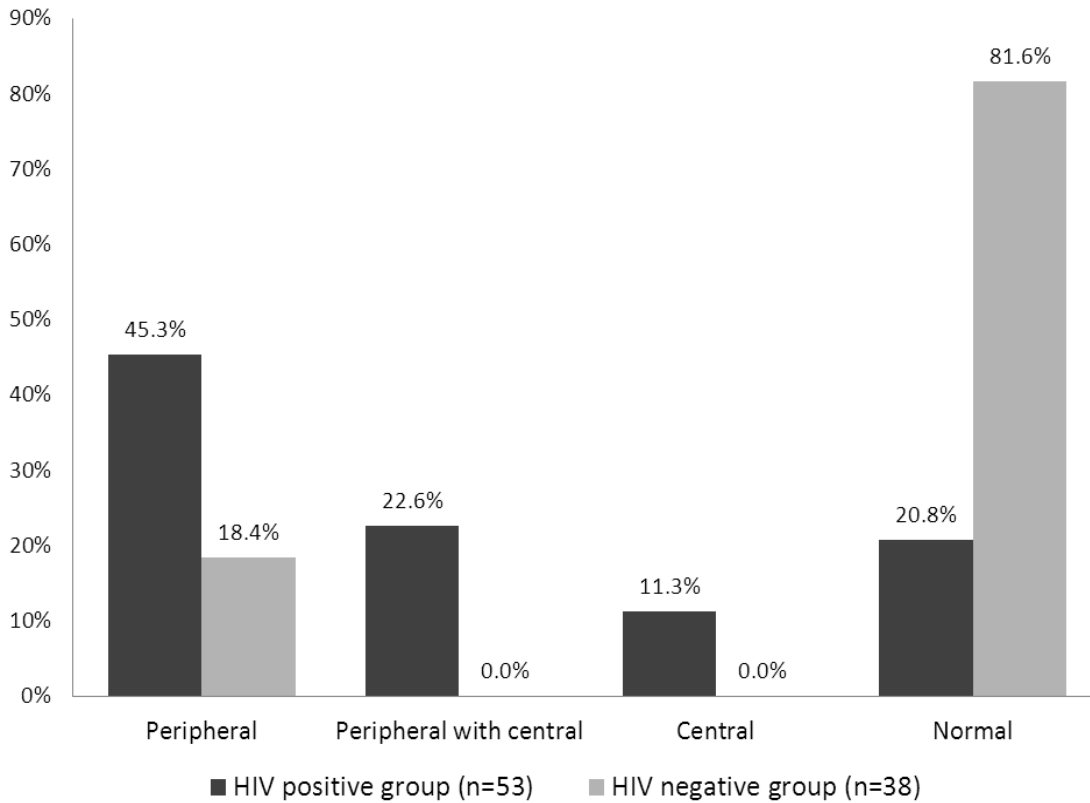
Figure 5.1. Vestibular involvement across HIV positive and HIV negative groups

The types of vestibular test abnormalities presented by the groups are included in Table 5.3. Means were supplied for caloric and cVEMP tests due to the objective nature of the tests.

Table 5.3

Distribution and number of abnormal vestibular tests results and its parameters in the HIV positive and negative groups

Vestibular tests and parameters	Subjects with abnormalities				p value
	HIV positive group		HIV negative group		
	N (%)	mean (SD)	N (%)	mean (SD)	
Bithermal caloric tests					
Unilateral weakness	15 (28.3)	18.6 (20.5)[a]	3 (7.9)	10.1 (16.4)[a]	.03[d]
Bilateral weakness[e]	1 (1.9)	-	1 (2.6)	-	.81[g]
Hyperreflexia[f]	2 (3.8)	233.5 (13.4)	-	-	-
DP	3 (5.7)	35.3 (4.0)	-	-	-
cVEMP					
Bilateral absent	5 (9.4)	-	1 (2.6)	-	-
Unilateral absent	6 (11.3)	-	1 (2.6)	-	-
Asymmetry ratio	10 (18.9)[b]	32.4 (30.9)[c]	3 (7.9)[b]	15.3 (17.2)[c]	.002[d]
Delayed latencies	9 (17)	-	-	-	-
Spontaneous nystagmus					
Without fixation	1 (1.9)	-	-	-	-
With fixation	-	-	-	-	-
Head impulse test					
Unilateral	10 (18.9)	-	3 (7.9)	-	.18[g]
Bilateral	1 (1.9)	-	1 (2.6)	-	.81[g]
Horizontal head shake test					
Horizontal nystagmus	13 (24.5)	-	2 (5.3)	-	.03[g]
Vertical/torsional nystagmus	-	-	-	-	-
Fukuda stepping test					
≥45 degrees deviation	15 (28.3)	-	2 (5.3)	-	.01[g]
Subjective visual vertical test					
≥3 degrees off vertical	2 (3.8)	-	-	-	-
Hyperventilation induced nystagmus					
Horizontal nystagmus	3 (5.7)	-	-	-	-
Vertical nystagmus	-	-	-	-	-
Dynamic Visual Acuity					
Unilateral	2 (3.8)	-	-	-	-
Bilateral	1 (1.9)	-	-	-	-
Gaze evoked nystagmus					
Horizontal gaze	-	-	-	-	-
Vertical gaze	-	-	-	-	-
Random saccades					
Velocity	2 (3.8)	-	-	-	-
Accuracy	-	-	-	-	-
Latency	-	-	-	-	-
Pursuit tracking					
Saccadic pursuit	9 (17)	-	-	-	-
Asymmetric pursuit	-	-	-	-	-
Absent pursuit	-	-	-	-	-
Positioning/Positional tests					
Torsional upbeat nystagmus	5 (9.4)	-	-	-	-
Torsional downbeat nystagmus	-	-	-	-	-
Horizontal nystagmus	8 (15.1)	-	-	-	-
Vertical nystagmus	4 (7.5)	-	-	-	-

Note: n = number of subjects; % = percentage; cVEMP = cervical vestibular evoked myogenic potential; DP = directional preponderance; SD = standard deviation;

[a] = the mean unilateral weakness was calculated from 50 HIV positive subjects (1 subject excluded due to bilateral weakness, 2 due to hyperreflexia) and 37 HIV negative subjects (1 excluded due to bilateral weakness).

[b] = subjects with an asymmetry ratio ≥40%.

[c] = the mean asymmetry ratio was calculated from 44 HIV positive subjects (4 subjects excluded due to conductive and mixed hearing loss, 5 due to bilateral absent responses) and 37 HIV negative subjects (1 subject excluded due to bilateral absent responses).

[d] = t-test for Equality of means (p<.05 was considered statistically significant).

[e] = bilateral weakness or hypoactive response was regarded as total warm response from both sides less than 11 degrees per second and total cool response from both sides less than 6 degrees per second (Barber & Stockwell, 1980).

[f] = hyperreflexia or hyperactive response was regarded as a total response more than 221 degrees per second

[g] = chi-square (p<.05 was considered statistically significant).

Table 5.3 shows that the majority of caloric test abnormalities were due to unilateral weaknesses. In addition to caloric tests, the Fukuda stepping test revealed the most abnormalities. The horizontal head shake test and head impulse test revealed the second and third most abnormalities respectively. The HIV positive group demonstrated more abnormalities in different vestibular test procedures than the HIV negative group (13 versus five).

Vestibular involvement was measured across all CDC categories of HIV/AIDS (Figure 5.2). Vestibular involvement was 18.9% in CDC category 1, 30.2% in category 2 and 30.1% in category 3. There were no statistically significant differences in the occurrence of vestibular involvement between category 1 and 2 (p=.65; chi-square) or between category 2 and 3 (p=.76; chi-square).
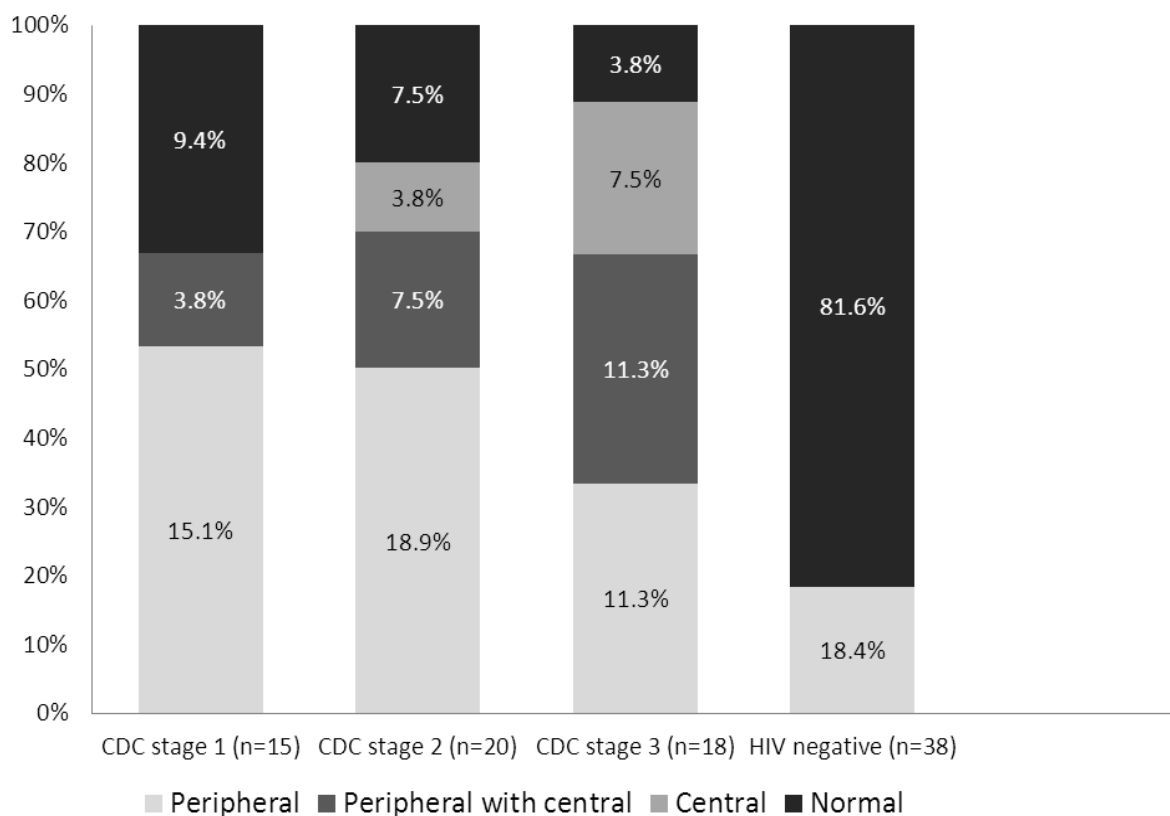
Figure 5.2. Distribution of peripheral and central vestibular involvement across the CDC categories of HIV/AIDS disease progression

Figure 5.2 illustrates that there were peripheral vestibular involvement and both peripheral and central involvement in category 1. Central signs (without peripheral signs) occurred in category 2 and category 3, and although there was a noticeable increase in its occurrence from earlier to more advanced stages of disease progression (3.8% to 7.5%), this was not statistically significant (p>.05; chi-square). In addition, the occurrence of peripheral with central vestibular involvement increased with disease progression as well, but this was also not statistically significant (p>.05; chi-square). Peripheral vestibular involvement increased from category 1 to category 2, but there was a slight decrease in its occurrence in category 3, which was not statistically significant (p=.43; chi-square).

Vestibular symptoms which included dizziness, vertigo, disequilibrium and/or nausea and vomiting were reported by 37.7% of HIV positive subjects (n=20), while 62.3% (n=33) had no self-reported symptoms. In category 1, six subjects were symptomatic and nine were asymptomatic. In category 2, nine subjects were symptomatic and 11 were asymptomatic. In category 3, five were symptomatic and 13 were asymptomatic. None of the HIV negative subjects reported having these symptoms. There was vestibular involvement in 35.9% (n=19) of symptomatic HIV positive subjects compared to only one symptomatic subject (1.9%) who had normal vestibular function (p=.001; chi-square). In addition, there was a statistically significant (p=.05; chi-square) higher occurrence of vestibular involvement among asymptomatic HIV positive subjects (43.3%; n=23) compared to normal vestibular function in 20.7% (n=11) of asymptomatic subjects.

Figure 5.3 compares the occurrence of vestibular involvement in HIV/AIDS subjects with and without ARV therapies. There was no statistically significant difference between the occurrence of vestibular involvement in these two groups (p>.05; chi-square).
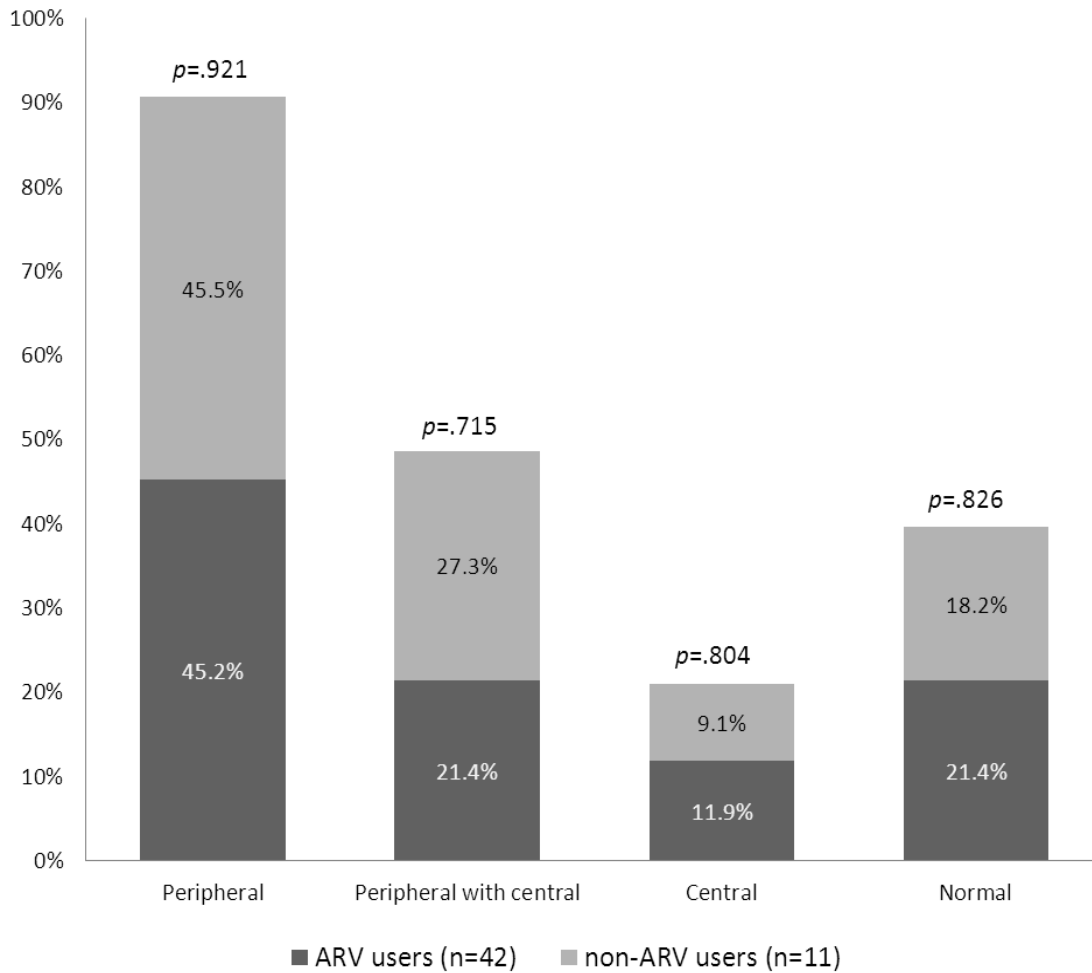
Figure 5.3. Occurrence of vestibular involvement in HIV positive subjects with and without ARV therapies

5.3. Discussion

The present study demonstrated a significantly higher occurrence of vestibular involvement among adults with HIV/AIDS than among those without HIV/AIDS infections. There is a high likelihood of vestibular involvement in individuals with this disease, as demonstrated by the odds ratio.   These findings correspond with previous studies that indicated a higher occurrence of vestibular dysfunction among adults with HIV/AIDS (Castello et al., 1998; Dellepiane et al., 2005; Hausler et al., 1991; Johnston et al., 1996; Teggi et al., 2008)

Vestibular involvement presented throughout all categories of HIV/AIDS disease progression. The occurrence of vestibular involvement increased from category 1 to category 2, but not from category 2 to category 3. Peripheral vestibular

involvement increased from 18.9% in category 1 to 26.4% in category 2, and then slightly decreased to 22.6% in category 3. This decrease, although not statistically significant was quite surprising, considering that three other studies showed a high occurrence of vestibular involvement in the advanced categories, particularly category 3 (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). A possible suggestion for this equal occurrence in vestibular involvement in category 2 (30.2%) and category 3 (30.1%) and the decrease in peripheral vestibular involvement from category 2 to category 3 might be related to ARV therapies. In category 2, 38.2% of subjects with HIV/AIDS used ARV therapies, while 40.5% of subjects in category 3 used ARV therapies. Administering ARV therapies and highly active antiretroviral therapy (HAART) has shown to prevent the progression of HIV/AIDS (Schneider et al., 2005). A recent study (Cohen et al., 2012) demonstrated no association between peripheral vestibular impairment among HIV positive subjects using HAART and HIV negative subjects. In this regard Cohen and colleagues (Cohen et al., 2012) suggested a therapeutic effect on immunity. Antiretroviral therapies aim to restore immune function and help protect the body against secondary opportunistic infections that are associated with vestibular dysfunction. This, in turn can reduce the occurrence of peripheral vestibular dysfunction in advanced stages of the disease. Another possible explanation for the decrease in peripheral vestibular involvement in the advanced category, where the majority of subjects (n=13/18) were asymptomatic, might be that vestibular function was possibly being compensated for centrally with increased disease duration. It is not possible to be very sure about central compensation, because of a lack of clear evidence for this. It is possible that they might have latent spontaneous nystagmus and rotatory testing would have provided the evidence for that, therefore central compensation could be a possibility. However, the subjects with HIV/AIDS did not know when they became infected with the virus and therefore the relationship between disease duration, disease category and compensated vestibular function is unclear. With such a multifactorial disease, a repeated measures within subjects design would have provided more conclusive evidence.

This study, together with two recent studies (Teggi et al., 2006; Teggi et al., 2008), showed that signs of central vestibular involvement increased throughout disease progression. These findings are in agreement with other studies (Castello et al., 1998; Johnston et al., 1996; Sacktor et al., 2001) that demonstrated an

association with centrally mediated ocular motor abnormalities, consistent with CNS dysfunction among HIV positive individuals. The occurrence of signs of central vestibular involvement in this study was smaller compared to those described by Teggi and colleagues (Teggi et al., 2006; Teggi et al., 2008). A possible explanation may be that the sample of subjects in this study consisted of both symptomatic and asymptomatic individuals and that almost two-thirds (62.3%) were asymptomatic. The studies by Teggi and colleagues only included symptomatic subjects, which could explain the higher occurrence of vestibular dysfunction, particularly central vestibular dysfunction, in their studies.

A higher occurrence of peripheral vestibular involvement compared to central vestibular involvement was evident in the current sample of HIV positive adult subjects. The occurrence of peripheral vestibular involvement in adult subjects with HIV/AIDS may be attributed to related opportunistic infections and malignancies. Opportunistic bacterial and viral infections have been implicated to involve the sensory structures of the inner as well as the eighth cranial nerve (CN VIII). Commonly occurring diseases that result in dysfunction of the vestibular end-organs and vestibular portion of CN VIII are, among others, vestibular neuritis and labyrinthitis, otosyphilis Ramsay Hunt syndrome and herpes simplex virus (Goldani, Ferreira Da Silva, & Dora, 2009; Gurney & Murr, 2003; Jae et al., 2005; Macher, 2008; Moayedi, 2010; Prasad et al., 2006; Pérez-Larraya & Riverol, 2009). According to Arbusow and colleagues (Arbusow, Theil, Strupp, Mascolo, & Brandt, 2001) the mechanisms of peripheral vestibular involvement caused by opportunistic infections such as the herpes simplex virus involves a migration of the virus from the vestibular ganglia to the labyrinth of the vestibular end-organ, which may eventually result in vestibular deafferentation. However, these diagnoses of opportunistic infections were not documented in any of the subjects' medical records when data was collected.

Another possible explanation for the significantly higher occurrence of peripheral vestibular involvement found in the subjects with HIV/AIDS compared to those without HIV/AIDS, is the direct effect of HIV/AIDS on the peripheral vestibular system. Abnormalities of the cVEMP suggested involvement of the saccule (otolith organ) and inferior vestibular nerve, while test procedures such as the head impulse, head shake, positional and caloric tests suggested involvement of the semi-circular

canals and superior vestibular nerve. Several reports have indicated that HIV/AIDS may directly affect the auditory system (Rey et al., 2002; Rinaldo et al., 2003) and because of the close anatomical proximity, shared nerve innervations and blood supply this may also affect the peripheral vestibular system. Mathews and colleagues (Mathews, Albert, & Job, 2012) recently showed that HIV/AIDS affects the auditory-vestibular pathway as demonstrated by the high incidence of sensorineural hearing loss and associated vestibular dysfunction in HIV positive compared to HIV negative subjects. However, the nature of this association in individuals with HIV/AIDS is not yet clear. A postmortem study (Pappas Jr. et al., 1995) suggested that not only is the CNS vulnerable to direct viral infections, but the peripheral vestibular labyrinth neuroepithelium displayed a presence of viral-like particles that seemed characteristic of the human immune-deficiency virus. Specifically, pathologies were observed within the semi-circular canals as well as in both the otolith organs. Another report (Chandrasekhar et al., 1992) indicated similar results of abnormalities within the otolith organs, together with precipitations in the fluid filled semi-circular canals.

Almost two thirds of the subjects with HIV/AIDS who presented with vestibular involvement did not report any vestibular symptoms since contracting the virus. Previous reports (Castello et al., 1998; Hausler et al., 1991) also indicated some vestibular involvement, even in asymptomatic individuals with no neurological or vestibular symptoms. The results of the present study indicated that vestibular involvement, particularly peripheral vestibular involvement, occurred among asymptomatic subjects with HIV/AIDS. A possible explanation for observing vestibular involvement in asymptomatic HIV/AIDS positive subjects might be the fact that cVEMP was included, making the test battery more sensitive for identifying peripheral vestibular disorders. Abnormal cVEMP occurred in 35.8% (n=19) of the subjects with HIV/AIDS, of which 15.1% (n=8) had only an abnormal cVEMP with no other signs of peripheral vestibular involvement. Including the cVEMP was the first of its kind in a study of this nature, and was able to detect involvement of not only the saccule in the vestibular end-organ, but also of the functioning and integrity of the inferior branch of the vestibular nerve (CN VIII). Nola and colleagues (Nola et al., 2011) showed the diagnostic value of the cVEMP in subjects with vestibular neuritis. They demonstrated abnormal caloric responses with normal cVEMP responses in subjects with superior vestibular neuritis, and normal caloric responses with

abnormal cVEMPs in subjects with inferior vestibular neuritis. Some subjects with abnormal cVEMPs reported rotatory vertigo while others reported disequilibrium. This data, together with findings of Aw and colleagues (Aw, Fetter, Cremer, Karlberg, & Halmagyi, 2001) indicate that a virus can not only affect the superior vestibular nerve, but also the inferior vestibular nerve. Eighth cranial nerve neuropathies have been identified through evoked potentials such as auditory brainstem responses (ABR) among individuals with HIV/AIDS, since ABR is adequately sensitive to detect early subclinical and clinical neural auditory pathologies (Larsen, 1998; Moazzez & Alvi, 1998; Vincenti et al., 2005). Cervical vestibular evoked myogenic potential testing might therefore be considered useful in identifying peripheral vestibular involvement in individuals with HIV/AIDS. Hausler and colleagues (Hausler et al., 1991) found only central vestibular involvement in their sample of asymptomatic subjects, while peripheral vestibular involvement was reported only in the symptomatic subjects during the advanced stages of disease progression. In a study by Castello and colleagues (Castello et al., 1998) The HIV infection seemed to have no effect on the vestibular labyrinth or eighth cranial nerve in the sample of asymptomatic subjects.

No other studies compared the occurrence of vestibular involvement in symptomatic and asymptomatic HIV positive subjects. The present findings therefore suggest that vestibular involvement, particularly peripheral vestibular involvement in HIV/AIDS, may be present, but sub-clinical in some patients. Primary health care providers should be aware that patients with HIV/AIDS have an increased prevalence of vestibular dysfunction. Once patients have symptoms, primary health care providers could consider referring them for vestibular assessments and vestibular rehabilitation therapy. Preventative measures could be taken to reduce the risk of serious, painful falls that can impede quality of life and activities of daily living. This may be especially important in light of recent evidence of a significant link between vestibular dysfunction and the risk of falling, even in asymptomatic subjects (Agrawal, Carey, Della Santina, Schubert, & Minor, 2009).

The occurrence of vestibular involvement was equal in subjects receiving ARV therapies compared to those not receiving ARV therapies. This lack of differences was a surprising finding, considering a recent report (Cohen et al., 2012) that demonstrated no significant difference in the prevalence of vestibular abnormalities in subjects with HIV/AIDS using HAART and subjects without HIV/AIDS. We therefore

expected less vestibular abnormalities in HIV positive subjects using ARV therapies. The findings indicated that the administration of ARV therapies does not reduce the risk of having vestibular abnormalities. A possible explanation for dissimilar results of this study and that of Cohen and colleagues (Cohen et al., 2012), may be attributed to the vestibular test procedures employed. The present study employed a test battery consisting of various tests of peripheral and central vestibular function. It included objective measurements, such as caloric tests and cVEMP recordings. This might have made the study more sensitive for identifying vestibular disorders, even sub-clinical ones. The occurrence of vestibular test abnormalities despite the administration of ARV therapies might be attributed to possible vestibulo-toxic properties. A detailed summary of reports on ototoxicity related to ARV can be found elsewhere (Stearn & Swanepoel, 2010) and some of the therapies included in this summary are, among others, Zidovudine (AZT), Didanosine (ddI), Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP). The majority of these studies demonstrated that NRTIs were the most likely cause of the subjects' hearing loss. A recent study (Matas, Silva, de Almeida Marcon, & Gonçalves, 2010) indicated that their sample of HIV positive subjects who received ARV therapies showed more abnormalities in their auditory evoked potentials, such as auditory brainstem response, than those who did not receive ARV therapies. They suggested that the auditory nerve and brainstem structures were at-risk due to the ototoxic effect of these agents. This is a complex interaction, because it seems to result in ototoxicity for specific cases with specific ARV combinations, even involving interactions with other drugs, alongside possible person-specific susceptibility factors (Stearn & Swanepoel, 2010). Reports on ototoxic ARV agents may suggest this as a possibility to explain the occurrence of vestibular involvement in HIV in earlier stages of the disease. Antiretroviral therapies improve general immunity avoiding secondary infections, therefore the improvement in the advanced stages may not just be due to ARV therapies but may include to central compensation. .

5.4. Conclusion

There is a high occurrence of vestibular involvement in adults with HIV/AIDS. Primary health care providers could screen HIV positive patients to ascertain if there are symptoms of vestibular involvement. If there are any, then they may consider further vestibular assessments and subsequent vestibular rehabilitation therapy.

Subjects infected with HIV have a high risk for vestibular abnormalities; these may occur despite being asymptomatic and/or receiving ARV therapies.

Chapter 6

Does the human immunodeficiency virus influence the vestibulocollic reflex pathways? A comparative study

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Abstract:

Background: This study compared vestibulocollic reflex (VCR) and vestibulo-ocular reflex (VOR) functioning in subjects with and without the human immunodeficiency virus (HIV). It also described test results throughout progression of the disease and compared it in HIV positive subjects with and without antiretroviral (ARV) therapies.

Methods: Subjects comprised 53 adults with HIV/AIDS (mean age 38.5±4.4) and 38 without HIV/AIDS (mean age 36.9±8.2). Clinical examinations included cervical vestibular evoked myogenic potentials (cVEMPs) and bithermal caloric tests.

Results: Abnormal cVEMP and caloric results were significantly higher in the HIV positive group (p=.001), with an odds ratio of 10.2. Vestibulocollic reflex and VOR involvement increased with progression of the disease. There were more abnormal test results in subjects using ARV therapies (66.7%) compared to those not using ARV therapies (63.6%), but this difference was insignificant.

Conclusion: HIV/AIDS seems to influence VCR pathways. Combining cVEMP and caloric tests may be useful to detect early neurologic involvement in HIV positive subjects.

6.1. Introduction

The vestibular system senses movement and sends this information to the cerebellum and vestibular nuclei in the brainstem. Motion and other sensory information get processed and integrated, to stabilize gaze during head movement by means of the vestibulo-ocular reflex (VOR) and to maintain body and head stability by means of the vestibulospinal reflex (VSR) and vestibulocollic reflex (VCR), respectively (Fife, 2010; Goebel, 2008a). A pathway that includes the saccule, inferior vestibular nerve and vestibulospinal tract mediates and actives the VCR (Ito, Ishimoto, & Murofushi, 2001; Wilson et al., 1995). Cervical or collic vestibular evoked myogenic potentials (cVEMPs) are a manifestation arising from the VCR of the vestibulospinal tract (Rosengren et al., 2010) and are mediated ipsilaterally by a three neuron arc. Uchino and colleagues (Uchino et al., 1997) described the anatomic pathway of the VCR, also known as the sacculocollic reflex. Primary vestibular neurons that travel from the saccule via the inferior vestibular nerve, project into second order vestibular neurons in the lateral vestibular nucleus in the brainstem. From there, neurons descend in the medial vestibulospinal tracts and connect to the motor nuclei of the accessory nerve. Third order vestibular neurons descend to the flexor and extensor neck muscles via the medial vestibulospinal tract (Uchino et al., 1997).

Cervical vestibular evoked myogenic potentials are ipsilaterally evoked short latency responses measured with an active electrode over a contracted sternocleidomastoid (SCM) muscle (Colebatch et al., 1994), capable of evoking the VCR (Colebatch & Rothwell, 2004) and are perhaps the most direct way of testing VCR functioning (Welgampola & Colebatch, 2005). Therefore, abnormalities of the cVEMP may indicate a lesion at any point along the VCR pathway.

Testing of the VOR pathways, which include the horizontal semicircular canal, superior vestibular nerve and ascending neural path to the extra-ocular muscles (Wester, 2012), is well characterized and the basis of many commonly used vestibular tests (Fife, 2010). These include, but are not limited to the caloric test (Baloh & Kerber, 2011) and rotational tests (Brandt & Strupp, 2005). Testing of the VSR pathways may include posturography (Baloh & Kerber, 2011).

The VOR and VSR pathways have been examined and described among individuals with the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). A recent systematic literature review summarized all vestibular tests and findings in subjects with HIV/AIDS demonstrating that tests of vestibular function concentrated on the VOR and VSR pathways only (Heinze et al., 2011). To date no studies have investigated the VCR pathways, as tested with cVEMPs, in subjects with HIV/AIDS. This lack of information may in part be attributable to that fact that cVEMPs have only recently been included as part of clinical test-batteries for vestibular function and have proved useful in identifying vestibular disorders (Welgampola & Colebatch, 2005). Therefore, this study aimed (1) to describe and compare the functioning of the VCR with the well characterized VOR in subjects with and without HIV/AIDS; (2) to describe the VCR and VOR throughout progression of the disease; and (3) to compare the VCR and VOR in HIV positive subjects receiving ARV therapies to those who were not receiving ARV therapies.

6.2. Methods and materials

The Research and Ethics Review Committee of the University of Pretoria and a tertiary referral hospital approved the present study. A cross-sectional comparative research design was employed and the method of convenience sampling was used to recruit subjects. Each subject provided written informed consent to participate in the study.

6.2.1. Subjects

Subjects with HIV/AIDS formed part of the experimental group and were drafted from the Infectious Disease (ID) Clinic at a tertiary referral hospital in South Africa. Blood serological tests confirmed the subjects' HIV status and this was documented in their medical records. The researchers obtained written informed consent to access their medical records containing this data. The subjects without HIV/AIDS were employees of the tertiary referral hospital and acquaintances of the researchers who agreed to undergo a blood serological test for HIV. The subjects who were confirmed to be HIV negative formed part of the control group. A total of 91 subjects, 53 adults with HIV/AIDS and 38 without HIVAIDS were evaluated for

participation in the study. Table 6.1 summarizes the description of participating subjects. There were no statistically significant differences in mean ages between the groups (p=0.26; t-test). Literature demonstrated that age affected the vestibular system after 55 to 65 years (Maes et al., 2010) therefore, in order to minimize the likelihood of age affecting the results, only subjects below the age of 50 were allowed to participate in the study.

Table 6.1

Description of subjects

Description	HIV negative group	HIV positive group
Number of subjects (n)	38	53
Mean age	36.9 (SD= 8.2)	38.5 (SD= 4.4)
Min-Max age	20-50 years	23-49 years
Gender distribution	Male = 47.4% (n=18) Female = 52.6% (n=20)	Male = 55% (n=29) Female = 45% (n=24)
CDC categories	Not applicable	CDC category 1: n=15 CDC category 2: n=20 CDC category 3: n=18
ARV therapy users	Not applicable	ARV therapy users: n=42 non-ARV therapy users: n=11

Note: ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; SD = Standard Deviation;

The subjects with HIV/AIDS were further divided into categories according to their cluster of differentiation 4+ (CD4+) cell counts as documented in their medical files at the ID clinic at the time of participation in the study. Subjects with counts higher than 500 cells/uL were assigned to the Centers for Disease Control and Prevention (CDC) classification system for HIV infection (CDC, 1993) category 1, while those with counts of 200-499 cells/uL and less than 200 cells/uL were assigned to CDC categories 2 and 3 respectively. The HIV positive subjects were evenly distributed between the three CDC categories. Fifteen subjects were in category 1 (eight male, seven female), 20 subjects in category 2 (eight male, 12 female) and 18 subjects in category 3 (eight male, 10 female).

The subjects with HIV/AIDS were also divided into two other groups, namely those who received ARV therapies (n=42) and those who were not receiving ARV therapies (n=11). The subjects who were exposed to ARV therapies received at least three of the following drug combinations: tenofovir, lamivudine, efavirenz, emtricitabine, nevirapine, stavudine, zidovudine and lopinavir/ritonavir.

6.2.2. Otologic and audiological examination

An otoscopic examination was performed to inspect the external auditory canal for any, debris or foreign objects that might cause occlusion of the ear canal and to identify any possible perforation of the tympanic membrane. Subjects with obstructed ear canals were referred to a clinician for extraction prior to participation in the study. Tympanometry was performed using a diagnostic Y-226 Hz probe tone (GSI Tympstar, Grason-Stadler). The following criteria (Jerger, 1970) were used for normal adult admittance profiling: ear canal volume (0.8 to 2.0ml), compliance (0.3 to 1.8ml) and middle ear pressure (-100daPa to +50daPa). Type A tympanograms were revealed for 49 subjects with HIV/AIDS and for 38 subjects without HIV/AIDS. Pure tone audiometry (air and bone conduction) was performed to determine the presence of air-bone gaps (GSI 61, Grason-Stadler). Air-bone gaps larger than 10 dB in the four HIV positive subjects with abnormal compliance and middle ear pressure were found, suggesting a conductive component. The 49 HIV positive and 38 HIV negative subjects with type A tympanograms showed no air-bone gaps.

6.2.3. Vestibulo-ocular reflex test

Caloric tests were used to describe the VOR. Rotational testing was not available to the researchers. Tests of spontaneous nystagmus, with and without fixation, preceded caloric stimulation. Videonystagmography (Visual Eyes infrared video-based system from Micromedical Technologies Inc., Chatham, Illinois, U.S.A.) was used to record any spontaneous nystagmus and caloric induced nystagmus. Bithermal (cool 24°C, warm 47°C) air caloric testing (AirFX, Micromedical Technologies Inc.) was used to irrigate the external auditory canal. Air caloric was chosen over water irrigation, because water irrigation of the external ear canal may result in damage to the delicate skin lining of the outer ear, which in turn places it at

risk for invasive external otitis due to bacterial invasion (Zikk et al., 1991). This frequently occurs in those who are immunocompromised, such as persons with HIV/AIDS. Subjects were placed in a supine position with the head tilted forward at an angle of 30° from the horizontal plane for correct positioning of the horizontal semicircular canals. Air was irrigated for 60 seconds, with 5-minute intervals between stimuli. The peak of the slow phase eye velocity (SPV) of caloric nystagmus post-irrigation was used as a parameter of superior vestibular nerve and horizontal canal function. Jongkees' formula (Jongkees et al., 1962) was used to calculate unilateral weakness or asymmetry and directional preponderance. A unilateral weakness or asymmetry of ≥20% (Baloh & Kerber, 2011; Jacobson et al., 1997), directional preponderance of ≥30% (Baloh & Kerber, 2011), bilateral weakness and hyperreflexia was considered abnormal. Bilateral weakness or hypoactive responses were regarded as the total warm responses from both sides less than 11 degrees per second, and the total cool responses from both sides less than 6 degrees per second (Barber & Stockwell, 1980). Hyperreflexia or hyperactive responses were regarded as total responses from both sides of more than 221 degrees per second (Jacobson et al., 1997).

6.2.4. Vestibulocollic reflex test

The cVEMP procedure was performed using an auditory evoked potential system (Bio-logic Navigator Pro, Natus Medical Inc., San Carlos, California, U.S.A.). Table 3.2 summarizes the stimulus and recording parameters used to record cVEMPs. Subjects were comfortably seated with the head rotated approximately 45° to the opposite side of the ear being tested. A blood pressure manometer with a rolled up inflatable cuff positioned between the subject's hand and jaw was used as feedback method of the contracted sternocleidomastoid (SCM) muscle during the recording of the cVEMP. The subjects pushed with their heads against the rolled up inflatable cuff and were asked to sustain a pressure of 40mmHg. This allowed control of the SCM contractions and ensured comparable muscle contractions between the left and right side (Maes et al., 2009; Vanspauwen et al., 2006). Both the subjects and the investigator monitored this sustained pressure. Insert-type earphones (Etymotic-ER-3, Elk Grove Village, Illinois, U.S.A) with disposable foam tips were used. Every measurement, including absent responses, was repeated twice to test for wave reproducibility and to eliminate potential artifacts. The average

of the two recordings was used for analysis. The first peak on the waveforms was marked as P1, while the second was marked as N1 within a period of 30 milliseconds (ms).

The researchers recorded and measured the latencies of P1 and N1 in ms, inter-peak amplitude in microvolt (µV), and amplitude asymmetry in percentage (%). The asymmetry ratio was determined by calculating the interaural amplitude difference according to the following formula where A_L indicated the amplitude for the left ear and A_R the amplitude for the right ear: $[(A_L - A_R) / (A_L + A_R)]$ x 100. Responses were interpreted as follows: (1) the absence of unilateral or bilateral waveforms were considered abnormal (absence of an identifiable P1 and N1); (2) two standard deviations above the mean of the HIV negative group were used to calculate the upper limits for P1 and N1 latencies (17.0ms and 26.3ms respectively). Latencies above these upper limits were regarded as present yet delayed, and considered abnormal; and (3) the presence of an amplitude asymmetry ratio of ≥40% was considered abnormal, since it indicated side-to-side differences in amplitude (Akin & Murnane, 2008).

6.3. Results and analysis

All analyses of data were performed using the statistical software package SPSS for Windows version 21. Means, standard deviations (±) and percentages (%) were used to describe the data. One-way analysis of variance (ANOVA) was used to compare the distribution of HIV positive subjects between the three CDC categories. The One-Sample Kolmogorov-Smirnov Test was used to demonstrate normality of data. The Independent Samples t-Test was used to compare mean values between the experimental and control groups. *P* values <0.05 were accepted as statistically significant. Odds ratios were calculated. The chi-square non-parametric test was used to compare the findings between the two study groups and the three CDC categories.

6.3.1. Cervical vestibular evoked myogenic potential and caloric test abnormalities

Abnormal cVEMP and caloric test results were found in 66% (n=35) of the subjects with HIV/AIDS, compared to only 15.8% (n=6) of the subjects without

HIV/AIDS, indicating a significantly higher occurrence of pathology in subjects with HIV/AIDS (p=.001; chi-square). Four absent cVEMP recordings were from the four HIV positive subjects with abnormal tympanograms and air-bone gaps. This association between vestibular signs and HIV/AIDS was further confirmed by the odds ratio. An odds ratio of 10.2 was obtained, showing a 10.2 times higher risk for showing abnormal cVEMP and caloric responses in persons who are HIV positive.

Table 6.2 shows the distribution of abnormal cVEMP and caloric test results in the HIV positive and HIV negative groups. Abnormal cVEMP results were found in 43.4% (n=23) and abnormal caloric results in 35.8% (n=19) of subjects with HIV/AIDS. Abnormal cVEMP results due to middle ear pathology were found in 7.5% (n=4) subjects with HIV/AIDS. The cVEMP results were abnormal in 10.5% (n=4) and the caloric results were abnormal in 10.5% (n=4) of the subjects without HIV/AIDS.

Table 6.2

Distribution of abnormal cVEMP and caloric results in the two study groups

	HIV positive group	HIV negative group	*p* value
	n (%)	n (%)	
Abnormal cVEMP	12 (22.6)	2 (5.3)	
Abnormal caloric	8 (15.1)	2 (5.3)	
Abnormal cVEMP with abnormal caloric	11 (20.8)	2 (5.3)	
Abnormal cVEMP due to MEP	4 (7.5)	0	
Total abnormalities	35 (66)	6 (15.8)	.001

Note: % = percentage; cVEMP = cervical vestibular evoked myogenic potentials; n = number of subjects; MEP = middle ear pathology, as demonstrated by abnormal middle ear compliance and pressure, and air-bone gaps

Table 6.3 indicates the occurrence of abnormal cVEMP results according to absent waveforms, delayed P1 and/or N1 latencies and amplitude asymmetry ≥40%. In the HIV positive group, 20.8% (n=11) of subjects showed absent cVEMP recordings, not including the four subjects with middle ear pathology. Of the six subjects with a unilaterally absent cVEMP, five had an absent cVEMP on the left side, and one had an absent cVEMP on the right side. Only one subject in the HIV negative group showed absent cVEMPs bilaterally. There was a significantly higher

occurrence of absent cVEMPs among the subjects with HIV/AIDS than for subjects without HIV/AIDS (p=.003; chi-square). Table 6.3 further indicates that in the HIV positive group 17% (n=9) of subjects presented with delayed latencies. Four subjects showed delayed latencies unilaterally and five bilaterally.

Table 6.3

Description of abnormal cVEMP and caloric test findings in the HIV positive and HIV negative subjects

Abnormal parameters	HIV positive group	HIV negative group
	n (%)	n (%)
cVEMP		
Absent* unilateral	3 (5.7)	1 (2.6)
Absent bilateral	5 (9.4)	1 (2.6)
Delayed unilateral	1 (1.9)	-
Delayed bilateral	5 (9.4)	-
Absent* unilateral with delayed unilateral	3 (5.7)	-
Asymmetry ratio ≥40%	10 (18.9)	3 (7.9)
Caloric		
Unilateral weakness	15 (28.3)	3 (7.9)
Bilateral weakness	1 (1.9)	1 (2.6)
Hyperreflexia	2 (3.8)	-
Directional preponderance	3 (5.7)	-

Note: * = data of the four subjects with middle ear pathology excluded here;
 %= percentage; cVEMP = cervical vestibular evoked myogenic potential; n = number of abnormalities.

There was no significant difference observed regarding mean latencies of P1 and N1 to the left or right side in either of the study groups (p>0.05; t-test). Table 6.4 indicates the distribution of mean P1 and N1 latencies, as well as inter-peak amplitude differences in both the HIV positive and negative groups as recorded from the cVEMP test. P1 latencies were significantly delayed statistically in the HIV positive group. N1 latencies showed no difference between the two groups. Table 6.4 also shows that the HIV positive group had significantly larger inter-peak amplitude cVEMPs that the HIV negative group.

Table 6.4

Mean latency and inter-peak amplitude results in the HIV positive and HIV negative groups from cVEMP recordings

	n	P1 latency (ms)	N1 latency (ms)	I-P amplitude (µV)
HIV positive group	84	15.2 ± 2.2	21.7 ± 2.4	201.2 ± 51.1
HIV negative group	73	13.9 ± 1.6	21.7 ± 4.1	172.7 ± 63.4
p value* (t-test)		.001	.89	.003

Note: n = number of ears (data not used for ears with absent cVEMP);

± = standard deviation; I-P = inter-peak.

6.3.2. Cervical vestibular evoked myogenic potentials and caloric test results throughout disease progression

Figure 6.1 illustrates the cVEMP and caloric test results throughout the progression of the disease. The HIV positive subjects were divided into the three CDC (1993) categories based upon their CD4+ cell counts at the time of participation. Normal cVEMP and caloric test results were recorded in 34% of subjects with HIV/AIDS. The occurrence of abnormal test results increased from 13.3% in category 1, to 22.6% in category 2 and 30.1% in category 3 of disease progression (Figure 6.1).
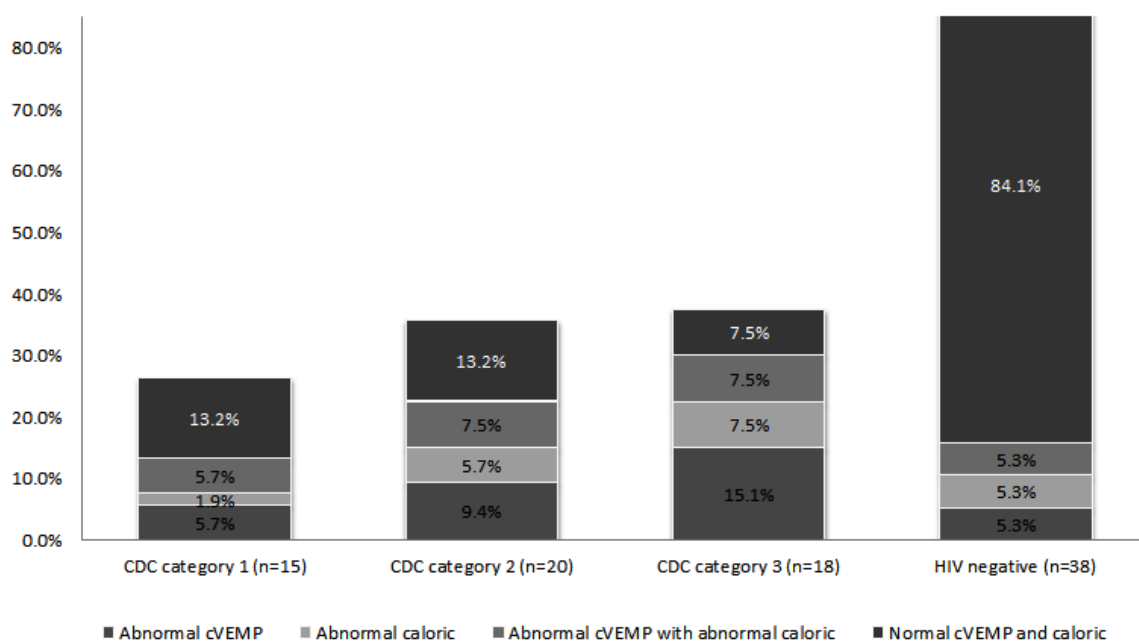
Figure 6.1. cVEMP and caloric test results throughout disease progression

6.3.3. Cervical vestibular evoked myogenic potentials and caloric test results of the HIV positive subjects receiving ARV therapies compared to those who were not receiving ARV therapies

Table 6.5 shows the distribution of abnormal cVEMP and caloric results of the HIV positive subjects receiving ARV therapies compared to those who were not receiving ARV therapies.

Table 6.5

Distribution of abnormal cVEMP and caloric results of the HIV positive subjects receiving ARV therapies compared to those who were not receiving ARV therapies

	ARV users (n=42)	Non-ARV users (n=11)	*p* value
	n (%)	**n (%)**	
Abnormal cVEMP	13 (30.9)	3 (27.3)	
Abnormal caloric	4 (9.5)	4 (36.4)	
Abnormal cVEMP and abnormal caloric	11 (26.2)	0 (0)	
Total abnormalities	28 (66.7)	7 (63.6)	.91

Note: ARV = antiretroviral therapy; cVEMP = cervical vestibular evoked myogenic potential; n = n number of subjects

Of the 42 ARV therapy users, 66.7% (n=28) showed abnormal cVEMP and caloric test results. Of the 11 non-ARV therapy users, 63.6% (n=7) showed abnormal cVEMP and caloric test results. Although the occurrence of abnormal test results were higher among the ARV therapy users, these difference were not statistically significant (*p*=.91; chi-square).

6.4. Discussion

This study demonstrated that subjects with HIV/AIDS presented with significantly more abnormal cVEMP and caloric test findings compared to those without HIV/AIDS. Two-thirds of the subjects with HIV/AIDS (66%) presented with at least one abnormality on the cVEMP and caloric test parameters, compared to only 15.8% of subjects without HIV/AIDS. The calculated odds ratio suggested that

subjects with HIV/AIDS had a 10.2 higher risk of presenting abnormal cVEMP and caloric test results than subjects without HIV/AIDS.

Regarding the recording of reliable cVEMP responses, the use of a correction algorithm remains the favored method, as well as monitoring the electromyographic (EMG) activity of the SCM (Maes et al., 2009). The present study did not have access to these algorithms or EMG systems and, subsequently, this is a limitation of the study. However, results of a recent study concluded that the use of the blood pressure manometer may be a useful alternative in recording reliable cVEMP responses (Maes et al., 2009; Vanspauwen, Wuyts & Van De Heyning, 2006).

The caloric findings in the present study could be compared with those of four previous research reports that employed a group study design of adult subjects with HIV/AIDS (Castello et al., 1998; Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). The abnormal caloric test findings demonstrated the presence of abnormal functioning of the VOR pathway. Three of the four studies indicated similar abnormal caloric test findings in subjects with HIV/AIDS compared to the present study (35.9%; n=19). The two most recent studies (Teggi et al., 2006; Teggi et al., 2008) found abnormal caloric test results in 43.3% and 50% respectively in their sample of subjects with HIV/AIDS. Their samples of subjects were all symptomatic, since they suffered from chronic dizziness. An earlier study found slightly less abnormal caloric test results compared to the present study, namely 11.6% in their sample of subjects with HIV/AIDS (Hausler et al., 1991). In contrast, only one study reported no abnormalities in caloric test findings in their sample of subjects with HIV/AIDS (Castello et al., 1998). No noticeable differences were found between the caloric test protocols employed in these reports, but the subjects in the study by Castello and colleagues (Castello et al., 1998) were all asymptomatic without any vestibular symptoms such as vertigo, dizziness or disequilibrium, which could explain the absence of abnormal caloric responses. It is interesting to note that 66.4% (n=29) of HIV positive subjects in the study by Hausler and colleagues (Hausler et al., 1991) were asymptomatic, yet the authors reported abnormal caloric test findings even among those subjects. However, these authors did not indicate whether their subjects used ARV therapies or any medication for secondary infections that could contribute to the abnormal caloric test findings.

To date, no other research reports have utilized cVEMP in subjects with HIV/AIDS to describe the functioning of the VCR pathways. The present study demonstrated a significantly higher number of abnormal cVEMP results in subjects with HIV/AIDS than in subjects without HIV/AIDS. The mean P1 latencies were statistically significantly delayed in the HIV positive group. The results of the abnormal cVEMP tests suggest a high occurrence of abnormal functioning of the VCR pathways in subjects with HIV/AIDS. The results of the abnormal caloric test also suggest a higher occurrence of abnormal functioning of the VOR pathways in subjects with HIV/AIDS opposed to those without the disease. The caloric test is a nonphysiological, very low frequency test namely 0.003 Hz (White, 2007). One of its disadvantages is that it only assesses the lower frequency responses; the mid and higher physiological frequencies are therefore not assessed, meaning that the VOR as assessed with the caloric test may be even higher.

Possible mechanisms for the increased VCR and VOR abnormalities may include opportunistic infections, ototoxic treatments and direct effects of HIV/AIDS (Heinze et al., 2011). Opportunistic infections may partly affect the functioning and integrity of both branches of the vestibular nerve (and the structures that they innervate). Young (2002) reported five patients with the herpes zoster virus, a common HIV/AIDS related opportunistic infection, suffering from vertigo. Unfortunately, the author did not indicate in the report whether these subjects were HIV positive. Nonetheless, all five subjects (100%) had absent cVEMPs. In addition, four subjects (80%) had absent caloric responses. In another study, 10 subjects with Ramsay Hunt syndrome, also a common HIV/AIDS related opportunistic infection underwent cVEMP and caloric testing (Ozeki, Iwasaki, Ushio, Takeuchi, & Murofushi, 2006). Once again, the authors did not indicate the subjects' HIV status. Similar to Young (2002) the study revealed abnormal cVEMP results in seven subjects (70%) and abnormal caloric results in all 10 subjects (100%). Another study (Zagólski, 2008) demonstrated abnormal cVEMP (23.1%) and caloric (30.8%) test results in subjects infected with cytomegalovirus (HIV status of subjects were not indicated), also a common HIV/AIDS related opportunistic infection that has been reported to cause sensorineural hearing loss and peripheral and central neurologic manifestations in subjects infected with HIV/AIDS (Meynard et al., 1997; Vancíková & Dvorák, 2001). These findings suggest that opportunistic infections like herpes

zoster virus and Ramsay Hunt syndrome may result in involvement of both the VCR and VOR pathways.

The use of ARV therapies could also contribute to the higher occurrence of abnormal cVEMP and caloric test findings in subjects with HIV/AIDS. Those exposed to ARV therapies presented with slightly more abnormalities (66.7%) in cVEMP and caloric testing than those without ARV therapies (63.7%); these differences, however, were not statistically significant. Recent studies found similar results with ABR testing and demonstrated a higher occurrence of abnormal ABR findings in a group of subjects receiving ARV therapies (62.5%) compared to those not receiving ARV therapies (50%), although the difference was not statistically significant (Matas et al., 2010). Such findings suggest that the auditory and vestibular nerves, as well as the structures that they innervate, are at risk due to possible ototoxic effects of some ARV therapies. Antiretroviral therapy regimes may consist of three or more classes of drugs, and one or more of these are nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs) (Moyle, 2000). One adverse effect of NRTIs is mitochondrial toxicity, which is responsible for, among other, myopathy and neuropathy (Warnke, Barreto, & Temesgen, 2007). Neuropathy is a dysfunction of the nervous system, and may therefore include the vestibular branches of the eighth cranial nerve. Additionally, there are case reports of ototoxic sensorineural hearing loss associated with the use of NRTIs which may have been induced by reduction in the mitochondrial DNA content, although ageing and the virus itself could have contributed to mitochondrial DNA mutations (Simdon, Watters, Bartlett, & Connick, 2001). Therefore, if these drugs may cause sensorineural hearing loss and affect the auditory brainstem pathways, it is also likely that they affect the vestibular nerves and/or end organs in subjects who received ARV therapies. A recent study compared the vestibular function of HIV positive subjects that used highly active antiretroviral therapy with age and gender-matched HIV negative subjects (Cohen et al., 2012). They performed vestibular screening tests which consisted of head thrust tests, Dix-Hallpike maneuvers and Romberg balance tests and found no significant difference between the two groups. These subjects had no vestibular complaints, as this could suggest that they might possibly have been centrally compensated. Therefore, the vestibular screening tests that were employed may have been underpowered for the detection of subclinical vestibular involvement in subjects who were centrally compensated.

The occurrence of abnormal cVEMP and caloric test findings increased throughout progression of the disease - from 13.3% in early stages (CDC category 1) to 30.1% in advanced stages (CDC category 3). Three previous studies, that also used a cross-sectional research design, demonstrated an increase in vestibular involvement from early to advanced stages of the disease (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). A detailed summary of their findings has been reviewed elsewhere (Heinze et al., 2011). There is a higher occurrence of abnormal cVEMP and caloric test findings in the advanced stages of HIV/AIDS, due to the reduction in CD4+ cell counts that places the infected individual at-risk for various opportunistic infections. This necessitates the use of ARV therapies to strengthen immunity in order to combat opportunistic infections; however, the vestibular nerves and structures of the vestibular end-organs may be susceptible to ototoxicity and also to the infections themselves, resulting in abnormal cVEMP and caloric test results.

The eighth cranial nerve and brainstem pathways may undergo neuropathologic changes such as subcortical demyelination because of the HIV infection itself (Bankaitis & Keith, 1995; Reyes-Contreras et al., 2002). This may explain the abnormalities in ABR measured in HIV positive individuals with and without clinical features of the disease, irrespective of normal hearing thresholds (Reyes-Contreras et al., 2002). Since the ABR may detect subclinical pathologic changes in the peripheral auditory nervous system, cVEMP and caloric testing may detect pathologic changes in the VOR and VCR pathways respectively in adults infected with HIV/AIDS. Posturography may also be useful in detecting pathologic changes in the VSR pathways (Dellepiane et al., 2005), however this test procedure was unavailable to the researchers.

6.5 Conclusion

There was a significantly higher occurrence of abnormal cVEMP responses and caloric test results in the adults with HIV/AIDS than in those without HIV/AIDS. The abnormalities shown by the cVEMP and caloric tests were probably due to pathology of the VCR and VOR pathways respectively. A combination of cVEMP and caloric tests in the vestibular test battery for adults infected with HIV/AIDS may

offer a tool for detecting early neurologic involvement, irrespective of disease progression and clinical manifestations.

6.6   Summary

- The vestibulocollic reflex (VCR) stabilizes the head during active movements
- Testing of the vestibulo-ocular reflex (VOR) is the basis of many commonly used vestibular tests
- There is a significant high occurrence of abnormal vestibular function in adults infected with HIV, but previous reports concentrated mainly on VOR tests
- It is currently unknown if HIV/AIDS affects the VCR pathways
- Cervical/colic vestibular evoked myogenic potentials (cVEMPs) allow testing of VCR pathways
- Abnormal cVEMP recordings showed a high occurrence of abnormalities of the VCR pathways in adults living with the human immunodeficiency virus (HIV)

PART III

DISCUSSION

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Chapter 7

General discussion, clinical implications and conclusions

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This PhD research project aimed to describe the vestibular functioning and pathology in adults with the human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS). This was achieved through three main research steps: (1) a systematic literature review of the body of peer-reviewed publications on reported HIV/AIDS-related vestibular manifestations and pathology (Heinze et al., 2011); (2) a study to describe peripheral and central vestibular involvement in adults with HIV/AIDS (Heinze, Vinck, Hofmeyr, & Swanepoel, 2013); and (3) a study to determine if HIV/AIDS influence the vestibulocollic reflex (VCR) pathways (Heinze, Vinck, & Swanepoel, 2014).

7.1   Study 1: Systematic literature review of vestibular disorders related to HIV/AIDS

Numerous studies and literature reviews have reported on the auditory and otologic manifestations related to HIV/AIDS (Assuiti, Lanzoni, dos Santos, Erdmann, & Meirelles, 2013; Iacovou, Vlastarakos, Papacharalampous, Kampessis, & Nikolopoulos, 2012; Tshifularo, Govender, & Monama, 2013; Van Der Westhuizen, Swanepoel, Heinze, & Hofmeyr, 2013). This study revealed only 13 records related to the scope of reviews published before 1 February 2010, when the systematic literature review was performed.

7.1.1 Prevalence

In the systematic literature review (Heinze et al., 2011) three studies were identified that reported on the prevalence of peripheral and central vestibular involvement at various stages of HIV infection. The reported prevalence of vestibular involvement was as high as 36% in the early stages of the disease and occurred in up to 100% of subjects in the advanced stages of the disease (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). Vestibular involvement, according to these

literature reports, therefore occurred in HIV positive subjects irrespective of the stage of the disease.

7.1.2 Pathological mechanisms

The systematic literature review further demonstrated that the exact pathological mechanisms playing a role in the vestibular involvement and pathologies are still unclear. Only four case report studies and three postmortem studies, one of which was also a case report, were identified providing information on possible contributing factors. The four case report studies of HIV infected adults demonstrated opportunistic infections as the causal role of the pathologies.

Macher (2008) reported six HIV positive adults with conditions such as syphilitic meningitis, secondary syphilis, syphilitic mass in the internal auditory canal, otosyphilis and neurosyphilis. Song and colleagues (2005) reported an HIV positive adult with otosyphilis, while Hart and colleagues (1989) reported an HIV positive adult with subacute encephalitis. Grimaldi and colleagues (Grimaldi et al., 1993) described an HIV positive adult with bilateral cochleovestibular nerve neuropathy, showing abnormal test results for the auditory brainstem responses (ABR) and during caloric testing. Light microscopic examination revealed also an inflammation of nerve cells. Although this case study did not report a specific opportunistic infection, there was, however, evidence that vasculitis could be responsible for the HIV/AIDS associated cranial nerve neuropathy.

7.1.3 Effects of HIV/AIDS on the vestibular system

Postmortem studies, captured in the review, did show that HIV/AIDS may have a direct effect on the peripheral and central vestibular system. Findings by Pappas and colleagues (1995) showed viral-like particles, characteristic of HIV/AIDS, in the peripheral vestibular labyrinth neuroepithelium. They observed pathology within the cristae ampullares, utricle and saccule. Chandrasekhar and colleagues (1992) reported similar findings, in addition to precipitations in the fluid-filled semicircular canals. Hart and colleagues (1989) indicated neuronal loss in the area of the vestibular-cerebellar projections, with inflammation in the vestibular nuclei, suggesting central vestibular involvement.

This systematic review showed evidence in literature suggesting that peripheral and central vestibular functioning may be affected, irrespective of disease stage (Castello et al., 1998; Dellepiane et al., 2005; Teggi et al., 2006; Teggi et al., 2008). The prevalence of central vestibular disorders seemed higher, compared to peripheral disorders, especially in more advanced stages of the disease.

It is clear that the aetiology of HIV/AIDS-associated vestibular dysfunction is complex and includes dealing with both the direct effect of the virus and with the indirect effects such as various opportunistic infections.

7.2 Study 2: Peripheral and central vestibular involvement in adults with HIV/AIDS

The second research step in this project comprised of three aims, namely (1) to describe the occurrence and nature of vestibular involvement among a group of adults infected with HIV; (2) to describe and compare the vestibular function of symptomatic and asymptomatic HIV positive adults; (3) to describe the vestibular function of a group of adults with HIV/AIDS receiving antiretroviral (ARV) therapies and to compare these with the corresponding functioning of those not receiving ARV therapies.

7.2.1 Occurrence and nature of vestibular involvement in adults with HIV/AIDS

The present study demonstrated a significantly higher occurrence of vestibular involvement among adults with HIV/AIDS (79.2%) than among those without HIV infections (18.4%). The odds ratio (16.6) demonstrates that there is a high likelihood of vestibular involvement in individuals with this disease. These findings correspond with previous group studies indicating a higher occurrence of vestibular dysfunction among adults with HIV/AIDS than among adults without HIV/AIDS (Castello et al., 1998; Dellepiane et al., 2005; Hausler et al., 1991; Johnston et al., 1996; Teggi et al., 2006; Teggi et al., 2008). Table 7.1 summarizes the comparison of the occurrence of vestibular involvement between previous studies and the present study.

Table 7.1

Occurrence of abnormal vestibular findings in previous studies and the present study

Study		HIV positive group	HIV negative group
Authors	**Year**	**n [ ] (%)**	**n [ ] (%)**
Present study	2013	42 [53] (79.2)	7 [38] (18.4)
Mathews et al.	2012	18 [60] (30)	0 [30] (0)
Cohen et al.	2012	47 [247] (19)	42 [200] (21)
Teggi et al.	2008	43 [60] (71.6)	4 [30] (13.3)
Teggi et al.	2006	16 [30] (53.3)	NCG
Castello et al.	1998	24 [29] (82.7)	NI
Hausler et al.	1991	20 [43] (46.5)	2 [33] (6.1)

Note: n = the number of subjects with abnormal vestibular findings; [ ] = the total sample size is indicated in square brackets; %= percentage; NCG = no control group; NI = data not indicated in report.

It can be seen that the data from the present study correspond to existing research findings, indicating that there is a higher occurrence of vestibular involvement in adults with HIV/AIDS than those without the disease. The occurrence of vestibular involvement ranged from 19% to 82.7% among adults with HIV/AIDS, compared to vestibular involvement in 6.1% to 21% of the adults without the disease (Table 7.1).

Vestibular dysfunction may occur in the general public as well and is not primarily associated with HIV/AIDS only. A large-scale study of balance and vestibular function among 6785 Americans in the United States aged 40 years and older revealed an overall prevalence of balance and vestibular dysfunction of 35.4% (Agrawal et al., 2009). However, this study did not include prevalence data of vestibular dysfunction among adults younger than 40 years of age. The prevalence of vestibular dysfunction in the 40-49 year group was 18.5%;— this prevalence increased significantly with age. It is therefore expected that the prevalence of vestibular dysfunction in adults below 40 years of age would be even less. Therefore, data obtained from this large-scale study might correlate with findings of vestibular dysfunction in the present study's control group.

The report by Cohen and colleagues (2012) showed some surprising and unexpected results. HIV positive subjects showed a slightly lower prevalence of abnormal vestibular test findings than their HIV negative counterparts (Table 7.1). All the HIV positive subjects were using ARV therapies, which aimed to improve general immunity and to avoid secondary opportunistic infections. Therefore, the observation of a lower occurrence of abnormal vestibular test findings in this study, in comparison to the present investigation and previous studies, may not only be due to the ameliorating effect of ARV therapies, but may also include an effect of central compensation. Subjects were excluded from participation in the Cohen and colleagues (2012) study if they presented with vestibular impairment. Although not specified, it seems as if the subjects were without any self-perceived vestibular symptoms and therefore possibly compensated centrally. This could explain the very low prevalence of abnormal findings compared to the present study and different other previous studies.

Vestibular involvement was found throughout all Centers for Disease Control and Prevention (CDC) categories of HIV/AIDS disease progression. The occurrence of vestibular involvement increased from Category 1 (18.9%) to Category 2 (30.2%), but not from Category 2 to Category 3 (30.1%). This was quite surprising, considering the fact that three earlier studies showed a marked increase in vestibular involvement (Table 5.2 in Chapter 5) and particularly a higher occurrence of vestibular involvement in the advanced categories (Hausler et al., 1991; Teggi et al., 2006; Teggi et al., 2008). Upon closer inspection, the present study showed that peripheral vestibular involvement decreased slightly with disease progression. This might be related to the influence of ARV treatment. In Category 2, 38.2% of subjects with HIV/AIDS used ARV therapies, while 40.5% of subjects in category 3 used ARV therapies. Administering ARV therapies and highly active antiretroviral therapy (HAART) have shown to prevent the progression of HIV/AIDS (Schneider et al., 2005).

A recent study (Cohen et al., 2012) demonstrated no association between peripheral vestibular impairment among HIV positive subjects using highly active antiretroviral therapy (HAART) and HIV negative subjects. In this regard, Cohen and colleagues suggested a therapeutic effect on immunity (Cohen et al., 2012). Antiretroviral therapies aim to restore immune function and help protect the body

against secondary opportunistic infections that are associated with vestibular dysfunction. This, in turn, can reduce the occurrence of peripheral vestibular dysfunction in advanced stages of the disease. Another possible explanation for the decrease in peripheral vestibular involvement in the advanced category, where the majority of subjects (n=13/18) were asymptomatic, might be that vestibular function was being compensated for centrally, with increased disease duration. However, since the HIV positive subjects did not know when they became infected with the virus, the relationship between disease duration, disease category and compensated vestibular function is unclear. With such a multifactorial disease, a repeated measure within subjects design would have been more appropriate to provide more conclusive evidence.

The present study, together with two other studies (Teggi et al., 2006; Teggi et al., 2008), showed that signs of central vestibular involvement increased throughout disease progression. These findings are in agreement with other studies (Castello et al., 1998; Johnston et al., 1996; Sacktor et al., 2001) that demonstrated an association with centrally mediated ocular motor abnormalities, consistent with central nervous system (CNS) dysfunction among HIV positive individuals. The occurrence of signs of central vestibular involvement in the present study was smaller compared to those described by Teggi and colleagues (Teggi et al., 2006; Teggi et al., 2008). A possible explanation for this result might be that the sample of subjects in this study consisted of both symptomatic and asymptomatic individuals and that almost two-thirds of them (62.3%) were asymptomatic. The two studies by Teggi and colleagues included symptomatic subjects only, which could explain a higher occurrence of vestibular dysfunction, particularly central vestibular dysfunction, in their studies.

Although it was not the aim of this study to determine the vestibular function of subjects treated for tuberculosis (TB), this could possibly contribute to explain the higher occurrence of vestibular involvement in the HIV positive subjects than in the HIV negative subjects. Tuberculosis, a very common opportunistic infection, often occurs together with HIV/AIDS, especially in developing countries such as South Africa. Therefore, ARV therapies are very often administered simultaneously with TB treatment (Harris, Peer, & Fagan, 2012). Treatment, especially for multidrug-resistant TB, may include the administration of antibiotics such as aminoglycosides.

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Kanamycin, amikacin and neomycin is predominantly cochleotoxic, streptomycin and tobramycin is predominantly vestibulotoxic, while gentamicin is both oto- and vestibulotoxic (Weinstein, 2013). These known vestibulotoxic agents result in loss of vestibular hair cells and are likely to target the vestibular sensory epithelium as well (Xie, Talaska, & Schacht, 2011). Symptoms of vestibulotoxicity, such as dizziness, disequilibrium, nausea and even vomiting can be mistaken for the effect of other medications that cause similar symptoms. These patients are often very ill and need medication to save their lives. Therefore, symptoms cannot accurately be used to determine the presence and degree of vestibular dysfunction and often remain unnoticed (Black & Pesznecker, 2007). Vestibular function tests should rather be employed to determine vestibular ototoxicity.

Regarding the present study, TB was reported, diagnosed and treated with antibiotics in 30.2% (n=16) of the subjects with HIV/AIDS. However, the class or brand of medication prescribed could not be identified since the researcher did not have access to the pharmacological records if the majority of the subjects. However, there were pharmacological records for four of these subjects. Two subjects were prescribed Rifafour, and the other two were prescribed Dapsone. Vestibular involvement was found in 75% (n=12) of subjects that had a history of TB and its related treatment, while 25% (n=4) had normal vestibular function. There was a significantly higher occurrence (p=0.046; Chi-square) of vestibular involvement in subjects with TB than those without TB.

A specific study demonstrated a significant association between an interaction of TB and its treatment and decline in hearing thresholds (Brits, Strauss, Eloff, Becker, & Swanepoel, 2012). There are currently no known published reports on the direct relationship between TB treatment and vestibular involvement in subjects with HIV/AIDS; however, it can be expected that vestibular involvement may also occur, given the shared anatomy.

7.2.2 Vestibular functioning of symptomatic and asymptomatic HIV positive adults

Of the sample of HIV positive subjects with vestibular involvement, 35.9% were symptomatic and 43.3% were asymptomatic. These findings suggest that

vestibular involvement in HIV/AIDS, particularly peripheral vestibular involvement, may be present, but sub-clinical in some patients. To date and to our knowledge, only one study described the vestibular functioning in asymptomatic HIV positive subjects (Hausler et al., 1991). In this study, the researchers found only central vestibular involvement in their sample. None of the asymptomatic subjects had any signs of peripheral vestibular involvement. However, the authors defined an abnormal caloric profile as a unilateral weakness of 40% and higher. In the present study a unilateral weakness was defined as 20% and higher. The occurrence of peripheral vestibular involvement may therefore have been underreported. In addition, the study was performed before the advent of cervical vestibular evoked myogenic potentials (cVEMPs) that were clinically used only since 1994 (Colebatch et al., 1994).

Primary health care providers should be made aware that patients with HIV/AIDS have an increased prevalence of vestibular dysfunction. Once patients have symptoms, primary health care providers could consider referring them for assessments and management. Symptoms of vestibular dysfunction, such as vertigo, dizziness, disequilibrium, disorientation and blurred vision can seriously jeopardize quality of life. Activities of daily living such as walking, driving and working may be compromised. In addition, individuals have the risk of falling and incurring serious injuries. Symptoms and clinical signs of vestibular involvement are not diagnostic of HIV/AIDS. It may however suggest infection or other underlying causes, but clinicians should have knowledge of these manifestations. Early identification of vestibular dysfunction and its associated symptoms warrant management, which may include medical management or vestibular and balance rehabilitation.

7.2.3 Vestibular functioning of HIV positive adults receiving and not receiving ARV therapies

Individuals with HIV/AIDS are now living longer due to the positive effects of ARVs. This has shifted the focus from a life-threatening disease with serious complications, to issues of quality of life (Basavaraj, Navya, & Rashmi, 2010). Vestibular symptoms such as vertigo, dizziness and disequilibrium may therefore have been underreported. The majority of HIV positive subjects used ARV therapies

(n=42/53) at the time of participation in the study. In the group of subjects that used ARV therapies, 78.5% had signs of vestibular involvement, compared to 81.9% of the non-ARV therapy users who had signs of vestibular involvement. Although not statistically significant, the ARV users had slightly less vestibular abnormalities. The findings indicated that the administration of ARV therapies does not reduce the risk of having vestibular abnormalities. The occurrence of vestibular test abnormalities despite the administration of ARV therapies might be attributed to nucleoside reverse transcriptase inhibitors (NRTIs). Of the 42 subjects who used ARV therapies, only eight had unknown drug regimes, or it was not documented in their files. For the remaining 34 ARV users, all of them used 2 nucleoside reverse transcriptase inhibitors (which included tenofovir, lamivudine, emtricitabine, stavudine and zidovudine) as part of their drug regime. A detailed summary of reports on ototoxic related ARV therapies (Stearn & Swanepoel, 2010) have shown that NRTIs such as zidovudine, stavudine and lamivudine, drugs used by subjects in the present study, have been associated with ototoxicity. These ARV agents may in part explain the occurrence of vestibular involvement in HIV/AIDS, particularly in the earlier stages of the disease. However, this is a complex interaction, because it seems to result in ototoxicity for specific cases with specific ARV combinations, alongside possible person-specific susceptibility factors (Stearn & Swanepoel, 2010). It may even involve interactions with other drugs. The regime of ARV therapies may have been potentially ototoxic, but it could have been exacerbated by a history of other ototoxic medications such as antibiotics for the treatment of TB. Early studies have already shown that the risk for ototoxicity increases with current or previous use of other ototoxic agents (Jackson & Arcieri, 1971).

The high incidence of vestibular involvement in the HIV positive subjects, who were not receiving ARVs, could possibly be attributed to opportunistic infections. ARVs have a therapeutic effect; it aims to decelerate the loss of cluster of differentiation 4+ (CD4+) cells that the virus destroys, slows down destruction to the immune system and therefore improve immune function to some extent. A weakened immune system makes the body become more and more predisposed to opportunistic infections. Reported opportunistic infections that not only cause sensorineural hearing loss but also vestibular dysfunction, are otosyphilis (Jae et al., 2005), cytomegalovirus (Zagólski, 2008), herpes zoster and the Ramsay Hunt syndrome (Williams, 2010). There are several case reports of HIV/AIDS-related

opportunistic infections resulting in vestibular dysfunction. These were discussed in the systematic literature review.

7.3   Study 3: The influence of HIV/AIDS on the VCR pathways

The third research step in this project aimed to describe and compare the functioning of the vestibulocollic reflex (VCR) pathways with the well-characterized vestibulo-ocular reflex (VOR) pathways by means of the cVEMP and caloric testing respectively, in subjects with and without HIV/AIDS.

Current studies of vestibular function in individuals with HIV/AIDS used tests of the VOR and VSR. Tests of the VOR include rotatory tests, caloric tests, head impulse tests, head shake tests and other tests that employ videonystagmography (VNG). To date, no other research reports have utilized cVEMP in subjects with HIV/AIDS to assess the functioning of the VCR pathways objectively. This study demonstrated that subjects with HIV/AIDS presented with significantly more abnormal cVEMP and caloric test findings compared to those without HIV/AIDS. Two-thirds of the subjects (66%) with HIV/AIDS presented with at least one abnormality on the cVEMP and caloric test parameters, compared to only 15.8% of subjects without HIV/AIDS. The calculated odds ratios suggested that subjects with HIV/AIDS have a 10.2 higher risk of having abnormal cVEMP and caloric test results than subjects without HIV/AIDS.

The present study's results demonstrated that the VCR pathways may also be affected by HIV/AIDS, considering the significantly higher number of abnormal cVEMP results in subjects with HIV/AIDS than in the subjects without HIV/AIDS. The mean P1 latencies were statistically significantly delayed in the HIV positive group (15.2 ms), compared to 13.9 ms in the HIV negative group; however, these differences were minimal. Such a small difference would not be considered clinically significant and the mean P1 latency for the HIV positive group is well within normal clinical expectations for tone-evoked cVEMP responses. The mean N1 latencies were the same in both groups, namely 21.7 ms. The results of the abnormal cVEMP tests suggest a high occurrence of abnormal function of the VCR in subjects with HIV/AIDS. The VCR stabilizes the head and upper trunk in space during active body movements by means of activation of the neck muscles in response to vestibular and

muscle-stretch receptors (Goldberg & Cullen, 2011). Signs of abnormalities of the VCR include the ocular tilt reaction, which consists of a head tilt and counter-rolling of the eyes toward the side of lesion (Carey & Della Santina, 2005). It could also consist of skew deviation of the eyes, also known as a vertical misalignment (Carey & Della Santina, 2005).

The ABR may detect subclinical pathologic changes in the peripheral auditory nervous system, while cVEMP and caloric testing may detect pathologic changes in the VCR and VOR pathways respectively in adults infected with HIV.

7.4   Clinical implications

Management of HIV/AIDS is a vital component of the South African health care system, given its high prevalence and associated disease processes. Of importance is the high occurrence of head and neck manifestations associated with this disease, particularly vestibular dysfunction as demonstrated by findings of the present study (Heinze et al., 2013). Vestibular involvement has been reported in individuals with varying degrees of HIV infection. The main symptoms of vestibular dysfunction are vertigo, dizziness and disequilibrium and have both physical and social-emotional consequences (Mira, 2008). The physical consequences are reduced postural control and increased risk of falls (Mira, 2008), which lead to incurring serious injuries. Activities of daily living such as walking, driving and working may be compromised. Social-emotional consequences could include anxiety-depression distress, panic disorders and feelings of social isolation when patients are unable to participate in social and leisure activities (Monzani, Casolari, Guidetti, & Rigatelli, 2001). Mira has clearly shown the relationship between vestibular disorders and physical and social-emotional well-being. Patients' general quality of life can therefore be significantly affected (Mira, 2008).

Symptoms and clinical signs of vestibular involvement may suggest infection or other underlying causes, but clinicians, particularly primary health care providers, should have knowledge of these manifestations. The present study has demonstrated that not every subject with signs of vestibular involvement had concomitant vestibular symptoms. Since it would not be time and cost effective to perform vestibular assessments on every patient with HIV/AIDS, primary health care

providers could screen HIV positive patients to ascertain if there are symptoms of vestibular involvement. The questionnaire by Goebel (Goebel, 2008b) in Appendix F could be adapted or used as a guideline to prompt for the subjective perception of any vestibular symptoms such as vertigo, dizziness, disequilibrium, disorientation or blurry vision. In addition to these symptoms, patients with auditory symptoms such as changes in hearing, tinnitus or aural fullness should be referred to an ear-nose-throat (ENT) specialist and audiologist for further investigation. Nonetheless, if there are any vestibular symptoms with or without auditory symptoms, the ENT and/or audiologist may consider performing screening tests of vestibular function. These screening tests will help to separate patients from those who need a more extensive vestibular evaluation. The advantages of these screening or bedside tests are that they can be performed easily and very rapidly and no equipment or technology is needed. The latter is particularly relevant in the South African context where advanced vestibular test equipment such as rotatory chair (to test the VOR), computerized posturography (to test the VSR) or cVEMPs (to test the VCR) is unavailable in most settings, particularly in public or governmental settings. This accentuates the need to advocate performing test procedures that require no equipment and which can be done in an office as a bedside screening test. The vestibular screening tests that fulfil these requirements are listed in Figure 7.1:

VOR
- Dynamic visual acuity (Peters, Mulavara, Cohen, Sangi-Haghpeykar, & Bloomberg, 2012),
- Rapid head impulse test (Curthoys, 2012; Halmagyi & Curthoys, 1988)

VSR
- Romberg on foam/unstable surface with eyes closed (Cohen, Mulavara, Peters, Sangi-Haghpeykar, & Bloomberg, 2013)

VCR
- Observation of a skew deviation and/or ocular tilt reaction (Carey & Della Santina, 2005; Goldberg & Cullen, 2011)

CNS
- Ocular motor function tests which include smooth pursuit tracking and saccade testing (Johnston et al., 1996).

Figure 7.1. Suggested vestibular screening tests for symptomatic HIV positive patients

When patients with HIV/AIDS report any vestibular symptoms and they test positive for a possible vestibular abnormality based on the screening test procedures, further comprehensive assessments of vestibular function is advised.

Chapter 4 summarized the various vestibular tests used in the reports identified by the systematic literature review. These tests include caloric test, pursuit tracking and saccade tests, spontaneous nystagmus test, positional/positioning test, rotatory test, head shake and head thrust/impulse test, posturography, dynamic gait index, gaze stability test and Romberg test.

The present study employed a comprehensive test battery consisting of the majority of the tests used in the reports, together with other tests for peripheral and central vestibular functioning. This is the first study to include cVEMPs in adults infected with HIV. VEMP testing is non-invasive, quick and easy to administer and well tolerated by the patient, contrasting to caloric testing that may often result in vertigo and may even be accompanied by nausea and vomiting. Ocular VEMPs (oVEMPs) have recently been introduced and reports have indicated that air conduction oVEMPs probably measure the utricle and superior portion of the vestibular nerve (Jacobson et al., 2011). If these three test procedures are combined with other tests of vestibular function, it can provide more information about specific structures in the vestibular end organ and its innervating nerves.

Head movements that occur in everyday life are in the frequency range of 1-6 Hz, and are therefore regarded as 'physiological' frequencies. The caloric test is not a physiological test because it only tests at a very low frequency, namely 0.003 Hz. However, testing at low frequencies may provide early signs of vestibular dysfunction, for example due to ototoxicity or other peripheral vestibular dysfunctions (McCaslin et al., 2008; Park, Migliaccio, Della Santina, Minor, & Carey, 2005). Rotational testing can test at higher frequencies than caloric testing, namely between 0.01 Hz and 0.64 Hz (Stockwell & Bojrab, 1997) and may even test up to 1.28 Hz (Handelsman, 2007). Therefore, unlike caloric testing, the frequencies tested with rotational testing are more similar to normal head movements, thus more physiologic. Rotational testing is a recommended procedure in assessing and monitoring of vestibular dysfunction since it allows evaluation of both horizontal semicircular canals

simultaneously (Handelsman, 2007), whereas caloric testing allows evaluation of one side at a time. Vestibulotoxic agents affect both labyrinths, resulting in bilateral vestibular loss. By combining caloric and rotational testing, these tests can quantify the extent of vestibular damage (Handelsman, 2007).

Together with audiologic and caloric tests, oVEMPs and cVEMPs have recently been described as novel tests of inner ear function, particularly for evaluating and monitoring ototoxicity (Yang, Liu, & Young, 2009; Yang, Liu, & Young, 2010). VEMPs have various clinical and diagnostic contributions, other than evaluating and monitoring of ototoxicity. Peripheral vestibular disorders can be determined by (1) presence or absence of responses; (2) threshold at which responses are elicited; and (3) asymmetry ratio between the two sides (Maes et al., 2011; Minor, 2000; Minor et al., 2003; Rauch, Zhou, Kujawa, Guinan, & Herrmann, 2004; Zapala & Brey, 2004). Delayed or prolonged latencies are more associated with retrolabyrinthine vestibular disorders such as acoustic neuroma or multiple sclerosis (Maes et al., 2011; Murofushi, Shimizu, Takegoshi, & Cheng, 2001). Delayed latencies have also been associated with disorders affecting the vestibular nerves, such as Bell's palsy and vestibular neuritis (Wester, 2012). Results from cVEMP responses obtained and described in Chapter 6, indicated that 20.8% (n=11) of HIV positive subjects had unilateral and bilateral absent responses, while only 5.2% (n=2) of HIV negative subjects had absent responses. Regarding the amplitude asymmetry ratio, 18.9% (n=10) of HIV positive subjects had amplitude asymmetry ratio's exceeding 40%, compared to 7.9% (n=3) in the HIV negative group. Delayed latencies occurred in 17% (n=9) of HIV positive subjects, and none in the HIV negative group. Maes and colleagues (Maes et al., 2011) argued that a delayed latency is an ideal parameter for identifying central pathologies; however, findings by Wester (2012) suggested that delayed latencies may also occur in peripheral vestibular pathologies. This necessitates further investigation in order to differentiate between the two sites.

While it is important to assess vestibular functioning in symptomatic subjects with HIV/AIDS, a comprehensive vestibular test battery is essential. A baseline assessment is important, because it serves as a basis for comparison that can be used to determine changes in vestibular function. In an ideal world where access to facilities with numerous equipment is available, the vestibular test battery could

consist of the following (Handelsman, 2007): (1) VNG test battery consisting of test of spontaneous nystagmus, ocular motor tests, positional/positioning tests; (2) caloric tests; (3) bedside assessments consisting of head shake nystagmus test, head thrust/impulse test, dynamic visual acuity, Romberg and Fukuda stepping test; (4) rotational testing; (5) posturography; (6) Dizziness Handicap Inventory; and (7) audiologic assessment. This vestibular test battery should also include oVEMP and cVEMP to assess otolith function. This initial or baseline assessment could take several hours to complete and may leave the patient exhausted. Subsequent follow-up and monitoring assessment procedures should be fast and tolerated well, yet it should yield reliable and valuable information about vestibular function.

Table 7.2 indicates a suggested protocol for symptomatic HIV positive subjects who tested positive on the screening tests, irrespective of ARV therapy usage and CDC category. VEMPs require an auditory evoked potential system; a protocol for oVEMP and cVEMP can easily be added to existing auditory evoked potentials software. An audiologic assessment should always accompany a vestibular assessment, because certain disorders or infections that affect hearing can affect the vestibular system too, and vice versa. An audiologic assessment is also an important component in monitoring for ototoxicity and should therefore include high frequency audiometry and, ideally, distortion product otoacoustic emissions (DPOAEs) as well.

This test battery should be performed on patients when they are in CDC category 1, 2 and 3 in order to monitor vestibular function during progression of the disease. In this way vestibular function can be assessed longitudinally and be tracked during disease progression. Once changes in vestibular function are detected, ARV therapies or other ototoxic drug regimes and doses might be adapted. For those individuals receiving aminoglycosides, vestibular monitoring may be done once a week (Harris et al., 2012). Monitoring could allow for preventative measures such as drug dose reduction or drug substitution. It could also allow for counselling of patients and their family to be aware of and recognize symptoms early enough, and reinsure them of rehabilitation that aims to improve quality of life, both physically and social-emotionally.

Table 7.2

Suggested assessment protocol used during disease progression and monitoring

Test procedure	Purpose
Caloric irrigation	To test VOR pathways that include horizontal canals at a low frequency (~0.003 Hz)
oVEMPs	To test VOR pathways that include utricle
cVEMPs	To test VCR pathways that include saccule
Head impulse test	To test VOR pathways that include horizontal canals at high frequencies (up to 5 Hz*)
Dynamic visual acuity	To test VOR pathways at high frequencies (2 Hz)[#]
Romberg (eyes closed on foam)	To test VSR pathways
Pursuit tracking and saccades	To test CNS (brainstem, cerebellum) function
Audiologic assessment	To determine associated SNHL

Note: * = Jorns-Häderli et al. (2007); [#] = Peters, Mulavara, Cohen, Sangi-Haghpeykar and Bloomberg (2012); CNS = central nervous system; cVEMPs = cervical vestibular evoked myogenic potentials; oVEMPs = ocular vestibular evoked myogenic potentials; SNHL = sensorineural hearing loss; VCR = vestibulocollic reflex; VOR = vestibulo-ocular reflex; VSR = vestibulospinal reflex.

The high occurrence of vestibular involvement suggests that primary health care providers, ENT specialists and audiologists are very likely to encounter HIV positive individuals with vestibular symptoms and dysfunction. These health care professionals need to understand these conditions and the related auditory-vestibular dysfunction of an individual with HIV/AIDS to ensure appropriate diagnosis and optimal management. They should also understand that HIV positive individuals often have additional psychosocial complaints due to the impact of the disease on their lives (Mngadi, 2003). When this is coupled with the occurrence of vestibular symptoms and dysfunction, it compromises their physical and emotional health even further. It is important that health care professionals are aware of this and have knowledge of these consequences. Vestibular dysfunction occurs more frequently with the progression of the viral infection. Individuals with the disease should be counselled regarding this possibility and should be reassured that treatment options

are available. They do not have to live with distressing or incapacitating vestibular symptoms. Their vestibular function should be monitored and when noticeable changes are detected, their management plan should be adapted accordingly.

7.5   Critical evaluation of this study

The strengths and limitations of this research study were critically considered. This critical evaluation aided in directing future research projects. The strengths and limitations are discussed below.

7.5.1   Strengths of this study

- This research constitutes the first African study of vestibular function and pathology in adults with HIV/AIDS. Similar studies, as identified in the systematic literature review, were from other countries and continents. Africa, particularly South Africa, might have a different protocol of drug regimes for HIV/AIDS, perhaps causing its manifestations to be different (Khoza, 2007).
- This research design controlled for gender and age with a matched control and experimental group.
- This research utilized a comprehensive vestibular test battery, including various bedside assessments, videonystagmography (VNG) and particularly included objective measures such as cVEMPs. The latter was the first and only of its kind to assess the VCR pathways in adults with HIV/AIDS objectively.

7.5.2   Limitations of this study

- This research used the Fukuda stepping test. This test procedure is not sensitive enough to identify abnormalities and asymmetries in the VSR pathways (Honaker et al., 2009; Honaker & Shepard, 2012) and therefore should not be used and interpreted on its own. In addition, this research did not utilize all objective tests of vestibular function, such as posturography and rotatory chair tests. The very expensive equipment required for these tests was not available at the setting where data collection took place and would also have been too time consuming to add them to the protocol. Also

oVEMPs were not performed, since the protocols (including the stimulus and recording parameters) for this procedure wasn't refined for clinical use yet. The researcher had to use what was available at the time of data collection.

- Regarding the recording of reliable cVEMP responses, the use of a correction algorithm remains the favored method, as well as monitoring the electromyographic (EMG) activity of the sternocleidomastoid muscle (Maes et al., 2009). The present study did not have access to these algorithms or EMG systems and, subsequently, this is a limitation of the study. However, results of a recent study concluded that the use of the blood pressure manometer may be a useful alternative in recording reliable cVEMP responses (Maes et al., 2009).

- Due to the cross sectional nature of this study, causality between vestibular involvement and HIV/AIDS could not effectively be determined. A longitudinal or within-subjects repeated measures design would best determine the occurrence of vestibular involvement between CDC categories. However, this comes with challenges: during the data collection phase of this study, several patients succumbed to HIV/AIDS-related complications that make a longitudinal study quite difficult. In addition, many subjects live hundreds of kilometres away and seldom visit the infectious disease (ID) clinic, particularly those who do not qualify for ARVs yet, or those who choose not to commence with this treatment.

- The researcher did not have access to the medical and pharmacologic records containing information regarding other potentially ototoxic medication such as aminoglycosides for TB, which made it difficult to draw conclusions about the contribution of ototoxicity on vestibular dysfunction. Additionally, opportunistic infections were not documented in the files kept at the ID clinic. These files contained information regarding CD4+ cell counts, viral loads and ARV therapies only. Again, this is also a limitation since it is unknown what opportunistic infections were responsible for the high occurrence of vestibular involvement in this sample.

- The HIV positive group was divided into two sub groups: the ARV therapy users (n=42) and the non-ARV therapy users (n=11). The sample size of the non-ARV therapy group was very small and should have been matched in sample size between the two groups to allow for comparisons that would have been more meaningful.

7.6 Future perspectives

7.6.1 Association between hearing loss and vestibular dysfunction

There is a high prevalence of sensorineural hearing loss in subjects with HIV/AIDS (Van Der Westhuizen et al., 2013); considering the shared anatomy of the vestibular end-organs and the cochlea, it would be expected that vestibular dysfunction should occur. The present study has shown a high occurrence of vestibular involvement in adults with HIV/AIDS. However, an association of hearing loss (sensorineural hearing loss) and vestibular dysfunction is not yet clear. In addition to this, future studies of vestibular function in adults with HIV/AIDS should include a much larger sample size to allow for generalization of results. Also, future studies should include oVEMPs and incorporate new developments in VNG testing such as the video head impulse test (vHIT).

7.6.2 Longitudinal study of vestibular function in subjects with HIV/AIDS

The present study, together with all previous studies of vestibular functioning in HIV positive adults and children with vestibular dysfunction, employed a cross-sectional research design. This may have limited the ability to identify vestibular dysfunction that may have developed during the course of the progression of the disease. Future studies should therefore evaluate vestibular function when subjects are in the early and advanced stages of HIV/AIDS to determine causality between vestibular involvement and HIV/AIDS.

7.6.3 Vestibular and motor function in children with HIV/AIDS

Recent studies have shown vestibular and motor dysfunction in children with hearing loss (De Kegel, Maes, Baetens, Dhooge, & Van Waelvelde, 2012; Maes, De Kegel, Van Waelvelde, & Dhooge, 2013). Another study has shown vestibular dysfunction in children with HIV/AIDS (Palacios et al., 2008). It would therefore be interesting to compare the vestibular and motor function in HIV positive children with and without a sensorineural hearing loss. Also to determine if the prevalence of vestibular and motor dysfunction is higher among HIV positive children with hearing

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loss and to determine its nature and extent. For this purpose, a child-friendly vestibular test protocol should be considered, and could include objective, non-invasive and easily-tolerated cVEMPs, oVEMPs and vHIT. These three test procedures would allow testing of both vestibular nerves and three out of the five vestibular end organs.

7.7   General conclusions

Peripheral and central vestibular involvement was significantly more common in subjects living with HIV/AIDS than in subjects without the disease. The literature showed that the occurrence of vestibular involvement ranged from 19% to 82.7% among adults with HIV. The present study showed an occurrence of vestibular involvement of 79.2% that can be seen throughout the progression of the disease. Not only does this viral disease directly and indirectly influence the VOR and VSR pathways, but also seems to influence the VCR pathways. Primary health care providers could screen HIV positive patients to ascertain if they have any vestibular symptoms. When they have vestibular symptoms, the primary health care providers could perform vestibular screening test procedures easily and rapidly to separate patients from those who need a more extensive vestibular evaluation. HIV positive patients with confirmed vestibular dysfunction should be monitored routinely and offered vestibular and balance rehabilitation therapy to minimize functional and emotional limitations and to improve their general quality of life.

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Note: reference list was created by Refworks 2.0 using the APA 6th edition style.

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PART IV

APPENDICES

_____

Appendix A

Ethical approval letters

_____

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Proposal and Ethics Committee

12 May 2009

Dear Prof Swanepoel

Project:	**Vestibular functioning and pathology in adults with HIV/ AIDS: A comparative study**
Researcher:	**BM Heinze**
Supervisor:	**Prof DCD Swanepoel**
Department:	**Communication Pathology**
Reference Number:	**9701010**

Thank you for your response to the Committee's letter of 15 April 2009.

I have pleasure in informing you that the Research Proposal and Ethics Committee formally **approved** the above study at an *ad hoc* meeting held on 11 May 2009. The approval is subject to the candidate abiding by the principles and parameters set out in her application and research proposal in the actual execution of the research.

The Committee requests you to convey this approval to Ms Heinze.

We wish you success with the project.

Sincerely

Prof. Brenda Louw
Chair: Research Proposal and Ethics Committee
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: brenda.louw@up.ac.za

Research Proposal and Ethics Committee Members: Prof P Chiroro; Dr M-H Coetzee; Dr JEH Grobler; Prof KL Harris; Ms H Klopper; Prof E Krüger; Prof B Louw (Chair); Prof A Mlambo; Prof G Prinsloo; Mr C Puttergill; Prof H Stander; Prof E Taljard; Dr J van Dyk; Prof C Walton; Mr FG Wolmarans

100
1908 - 2008

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Humanities
Research Proposal and Ethics Committee

12 May 2009

Dear Prof Swanepoel

Project:	**Vestibular functioning and pathology in adults with HIV/ AIDS: A comparative study**
Researcher:	**BM Heinze**
Supervisor:	**Prof DCD Swanepoel**
Department:	**Communication Pathology**
Reference Number:	**9701010**

Further to our letter of approval, please note that this approval will be rescinded should the hospital not grant Ms Heinze permission to conduct the research. Proof of hospital's approval is therefore required.

Sincerely

Prof. Brenda Louw
Chair: Research Proposal and Ethics Committee
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail: brenda.louw@up.ac.za

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1MH/302/6

Tel: 012 314 0487
Fax: 012 314-0013
Enquiries: Lt Col MK Baker

1 Military Hospital
Private Bag X1026
Thaba Tshwane
0143
24 June 2009

CLINICAL TRIAL APPROVAL: "VESTIBULAR FUNCTIONING AND PATHOLOGY IN ADULTS WITH HIV/AIDS: A COMPARATIVE STUDY."

1.   The 1 Military Hospital Research Ethics Committee (1MHREC), comprised of the following members, and adhering to GCP/ICH and SA Clinical Trial guidelines, evaluated the above-mentioned protocol and additional documents:

    a. Lt Col M. Baker: Neurologist, male, chairman 1MHREC.
    b. Col H. du Plessis: Surgeon, male, member 1MHREC.
    c. Col H. Ingram: Anaesthetist, male, member 1MHREC.
    d. Lt. Col. D. Mahapa: Dermatologist, female, member 1MHREC
    e. Lt. Col. L. Hofmeyr: Otorhinolaryngologist, male, member 1MHREC (non-voting on this study).
    f. Ms C. Jackson: Layperson, independent of the organization, female, member 1 MHREC.

2.   The following study protocol was evaluated **"Vestibular Functioning and Pathology in Adults With HIV/AIDS: A Comparative Study."**
Documentation submitted included the protocol description and covering letter.
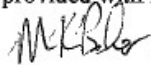
World Class Clinical Service
CONFIDENTIAL

3.   The recommendations are:

The study was ethically approved on 24 June 2009. The principal investigator will be Ms. B. Heinze and supervisor Lt Col. L. Hofmeyr.   Report backs are to be made to the 1MHREC six monthly, in the event of any serious adverse events and on completion or termination of the study. Clinical data may be accessed and analysed, providing that patient anonymity is respected and maintained. The 1 MHREC also requests that a statement be provided outlining finances involved for the study, including whether patient participants will receive monetary compensation.

Addendum 1: On 11 September 2009 the 1MHREC approved additional procedures to be added to the above-stated research protocol, namely horizontal and vertical dynamic visual acuit (DVA) without goggles, and visual suppression in assessing the visual ocular reflex. The 1 MHREC furthermore accepts that study participants will be offered beverages and refreshments during and after assessments and be assisted with transport if required, but not provided with monetary incentives.

(M.K BAKER)
CHAIRMAN 1 MILITARY HOSPITAL RESEARCH ETHICS COMMITTEE: LT COL

DIST

For Info

Ms B. Heinze
Lt Col L. Hofmeyr

World Class Clinical Service
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Telephone:	(012) 671-6807	Department of ENT
Fax:	(012) 671-6902	Institute for Aviation Medicine
Enquiries:	Lt Col LM Hofmeyr	Private Bag X3
		Lyttelton
		0140

/ June 2009

The Officer Commanding
1 Military Hospital
Thaba Tshwane
0187

General

VESTIBULAR FUNCTIONING AND PATHOLOGY IN ADULTS WITH HIV/AIDS: A COMPARATIVE STUDY
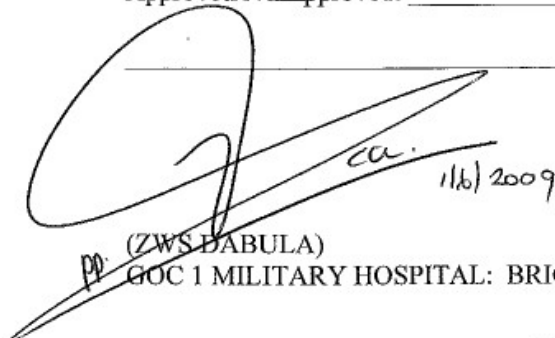
1.   See attached request letters.

2.   Authority is hereby requested to perform the above study at the Institute for Aviation Medicine (IAM).

3.   I, 85565760PE Lt Col L.M. Hofmeyr will be the Military Supervisor for the study.

4.   Your kind consideration is appreciated.

(LM HOFMEYR)
ENT SPECIALIST 1 MILITARY HOSPITAL: LT COL

LMH/LS (h:/Dr L Hofmeyr-VNG/Vest funct and Pathology in Adults-Study)

Approved/Not approved: _____

_____

cc. 1/6/2009

(ZWS DABULA)
pp GOC 1 MILITARY HOSPITAL: BRIG GEN

Appendix B

Covering letter of informed consent

_____

Faculty of Humanities
Department of Communication Pathology

January 2010

Dear Participant,

Thank you for showing interest in this research project. I am a post-graduate student for the Doctoral degree in Communication Pathology at the Department of Communication Pathology, University of Pretoria, and the title of my research project is: **Vestibular functioning and pathology in adults with HIV/AIDS: A comparative study**

Aims of this study

This study will give us a better understanding of the effect of HIV/AIDS on the vestibular (balance) mechanism of the inner ear to assist audiologists and other medical professionals to treat and rehabiliate vestibular complaints proactively and effectively. It will also provide us with knowledge regarding the nature of vestibular manifestations even in the absence of subjective experiences of dizziness or imbalance. We are furthermore aiming at involving participants who are HIV positive as well as those who are HIV negative in order to compare and describe the vestibular functioning between the two groups.

What will be expected from you if you agree to participate:
- Once you have agreed to participate in this research study, you will undergo a hearing and balance assessment.
- Upon completion of this assessment, you will be asked to undergo an HIV test to be conducted by the medical staff involved in this research study. The medical staff will furthermore notify you on the results and perform subsequent counseling if and when neccesary
- After signing the informed consent form that is attached to this letter, you give the researcher permission to note your HIV status and document your CD4+ cell count.

The procedures of the hearing and balance assessment:
- An otoscopic examination (inspection of the earcanal and eardrum), followed by immitance measurements (middle ear test) will be performed. These procedures will not require any response from you and will take five minutes;
- you will undergo a basic hearing evaluation (pure tone audiometry) where you will be required to respond to the presence of a sound. This can take between 10 and 15 minutes;
- next, you will be asked to stand with your feet together in one place for a few seconds, followed by marching with your arms extended for one minute;
- an objective test will then be carried out by placing electrodes on the forehead, and on the neck during which you will hear sounds for approximately 15 minutes;
- afterwards a pair of goggles with an infra-red camera will be placed on your eye during which a series of ocular motor tests will be performed. Here you will be asked to follow moving targets, displayed on a lightbar, with your eyes. This will last about 15 minutes;
- Next is the positional tests where you will be asked to lie on your sides and turn your head sideways. The duration of these tests are approximately 15 minutes;
- finally a small amount of cool (below body temperature) followed by warm (above body temperature) air will be irrigated into both your ear canals consecutively and you might feel slightly dizzy for one to two minutes. The total duration of this test is 30-35

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minutes.

The total duration of this assessment can be expected to last between one and a half hours to two hours.

Risks and discomfort:
There are no medical risks or discomforts associated with this project, although you may experience slight fatigue during participation. You will, however, be given as many breaks as you need during the testing session.

What will happen with the collected data:
All the information obtained from this study will be handled and regarded as highly confidential by assigning codes to each participant. These codes will therefore be used during the data collection as well as the data analysis procedures. No names of participants will be used neither in the thesis nor scientific articles that will be compiled upon completion of ths study. Therefore, the results will be used for research purposes as part of the thesis, as well as future articles and presentations. The data will be kept for 15 years for archiving purposes at the University of Pretoria.

Procedure for participating:
If you agree to participate in this study please sign the attached informed consent form and acknowledge that the data may be used for future research and publication.

How you will benefit from participating
Although you might not directly benefit from participating in this study, your participation will contribute to the understanding of how HIV/AIDS effects the functioning of the vestibular (balance) system, and how the medical professionals can use this information to plan and execute prompt and appropriate intervention and rehabilitation for vestibular disorders.

Participant's rights:
Please note that you are free to withdraw from this study at any point in time without any negative consequences.

Should you require any further information or have any concerns, feel free to contact 0834232925 at any time.

Yours sincerely,

Mrs. Barbara Heinze
Audiologist & Researcher

Prof. De Wet Swanepoel   Prof. Brenda Louw
Research supervisor   Head: Dept of Communication Pathology

Appendix C

Informed consent form

_____

INFORMED CONSENT FORM

Vestibular functioning and pathology in adults with HIV/AIDS: A comparative study

<u>Please complete the following:</u>

Surname: _____

Name: _____

Age: _____

I hereby agree to participate in this project and acknowledge that the data may be used for research purposes. I am aware that I may withdraw form this project, at any time, should I want to.

_____   _____

Signature   Date

Appendix D

Pre-test instructions

_____

Instructions prior to vestibular assessment appointment

Date of appointment: _____

Time of appointment: _____

Dear Participant,

Please read the following information and instructions before your appointment for a hearing and vestibular assessment.

48 hours before the test:
- do not consume alcohol
- do not take medication for dizziness, nausea or motion sickness
- do not take sedatives
- do not take sleep medication or tranquilizers
- do not take antidepressants or pain medication, unless you have been taking them for the past 2 months

On the day of the test:
- do not consume caffeine (coffee, tea, chocolate)
- do not use make-up or oils on skin
- dress comfortable

Two hours before the test:
- do not smoke
- do not eat fatty, oily foods
- eat a light breakfast or lunch
- you may drink milk or fruit juice

You may continue taking the following medication for:
- HIV/AIDS
- heart and blood pressure
- seizures / epilepsy
- insulin / diabetes
- prescription medication taken for more than 2 months

Please contact me for any other information or queries

Kind regards,

Mrs. Barbara Heinze
Audiologist & Researcher
University of Pretoria
(Cell: 0834232925)

Appendix E

Vestibular tests and findings in HIV/AIDS patients:

Literature summary

_____

STUDY			PATIENTS				CONTROLS		TESTS	FINDINGS
Authors	Year	Design	n	Symptom	ARV	HIV staging	n	Symptom		
Teggi et al	2008	Group study	60 HIV+ adults	Yes: chronic dizziness was inclusion criteria	NI	CDC	30 HIV- adults	Yes: chronic dizziness was inclusion criteria	Audiometry, spontaneous nystagmus, positional & positioning tests, caloric tests	Progressive vestibular damage through stages. Higher incidence of central vestibular damage at advanced stages
Palacios et al	2008	Group study	23 HIV+ children	NI	Yes	CDC	No	NA	Audiometry, ABR, ENG (specific tests NI), smooth pursuit, caloric tests, rotatory tests	HIV may directly affect both peripheral & central vestibular systems, although opportunistic infections & drugs can also be responsible
Macher	2008	Case study	6 HIV+ adults	Yes, all cases had dizziness or imbalance	NI	NI	No	NA	Romberg test in one case, informal nystagmus observation in another	CN VIII & peripheral vestibular system involvement in syphilitic meningitis

STUDY			PATIENTS				CONTROLS		TESTS	FINDINGS
Authors	Year	Design	n	Symptom	ARV	HIV staging	n	Symptom		
Teggi et al	2006	Group study	30 HIV+ adults	Yes: history of balance disorders	NI	CDC	No	NA	Dynamic Gait Index, smooth pursuit, saccade, positional tests, caloric tests	Peripheral & central vestibular damage may occur at any stage, although higher incidence of central vestibular damage at advanced stages
Dellepiane et al	2005	Group study	15 HIV+ adults & 15 AIDS adults*	No	NI	CDC	55 HIV- adults	No	Static & dynamic posturo-graphy	Involvement of entire vestibular system, even in early stages & asymptomatic patients
Jae et al	2005	Case study	1 HIV+ adult	Yes: dizziness & progressive HL	NI	NI	No	NA	Audiometry, caloric tests	Otosyphilis is frequently associated with auditory & vestibular symptoms
Castello et al	1998	Group study	29 HIV+ adults	No	NI	CDC	20 HIV- adults	No	ABR, spontaneous & positional nystagmus, pursuit, saccades, caloric tests	HIV infects CNS even at early stages. ABR & caloric tests indicate no effect of HIV on labyrinth or CN VIII

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STUDY			PATIENTS				CONTROLS		TESTS	FINDINGS
Authors	Year	Design	n	Symptom	ARV	HIV staging	n	Symptom		
Johnston et al	1996	Group study	13 HIV+ adults	No	NI	NI	9 HIV- adults	No	Ocular motor tests (saccades & pursuit)	Ocular motor tests useful in identifying CNS dysfunction in HIV+ adults
Pappas et al	1995	PM study	12 HIV+ patients¥	NA	NA	NA	NA	NA	Electron microscopic ultra-structural analysis of vestibular end-organs	Pathology of vestibular hair cells, ampullae, otolith organs, labyrinth wall & epithelial lining
Grimaldi et al	1993	Case study	1 HIV+ adult	Yes: sudden bilat HL, fever & weight loss	NI	NI	No	NA	PTA, ABR, caloric tests	Bilateral involvement of both branches of CN VIII
Chandrasekhar et al	1992	PM study	10 HIV+ patients¥	NA	NA	NA	NA	NA	Electron microscopy	Precipitations in peri- and endolymph of vestibule & semicircular canals; subepithelial elevation of neurosensory epithelium of otolith organs

STUDY			PATIENTS				CONTROLS		TESTS	FINDINGS
Authors	Year	Design	n	Symptom	ARV	HIV staging	n	Symptom		
Hausler et al	1991	Group study	43 HIV+ adults	14 stage IV patients were symptomatic	NI	CDC	33 HIV-adults	No	PTA, stapedial reflexes, spontaneous & positional nystagmus, pursuit & rotatory tests, pendular & caloric tests	Asymptomatic HIV+ adults may present with auditory & vestibular findings. At advanced stages both central & peripheral vestibular disorders occur
Hart et al	1989	Case study & PM study	1 HIV+ adult	Yes: dizziness & dis-equilibrium	NI	NI	No	NA	PTA, speech audiometry, ABR, saccade & pursuit tests, caloric tests	Abnormal auditory & central vestibular findings

¥ = temporal bone specimens; * = stage IV; ABR = auditory brainstem response; AIDS = acquired immunodeficiency syndrome; ARV = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; CN VIII = eighth cranial nerve; CNS = central nervous system; HIV = human immunodeficiency virus; HL = hearing loss; NA = not applicable; NI = not indicated; PM = postmortem; PTA = pure tone audiometry.

Appendix F

Structured Interview

_____

Faculty of Humanities
Department of Communication Pathology

Subject code: _____

Date of birth: _____   **Date of visit:** _____

Please describe in your own words the sensation you feel without using the word "dizzy".
_____
_____
_____
_____

1. Do you ever have any of the following sensations?

    Yes   spinning in circles   No
    Yes   falling to one side   No
    Yes   world spinning around you   No

2. The following refer to a typical dizzy spell:

    Yes   do the dizzy spells come in attacks?   No
                     how often? _____
                     how long? _____
                     date of first dizzy spell? _____
    Yes   are you completely free from dizziness between attacks?   No
    Yes   does your hearing change with an attack?   No
    Yes   are you dizzy mainly when you sit or stand up quickly?   No
    Yes   are you more dizzy in certain positions?   No
                     which position? _____
    Yes   are you nauseated during an attack?   No
    Yes   are you sensitive to light when you are dizzy?   No
    Yes   are you dizzy even while lying down?   No
    Yes   have you had a recent cold or flu preceding recent dizzy spells?   No
    Yes   have you had fullness or pressure in your ears?   No
    Yes   have you had pain or discharge in your ear of recent onset?   No
    Yes   have you had trouble walking in the dark?   No
    Yes   are you better if you sit or lie perfectly still?   No

3. The following refer to other sensations you may have:

    Yes   do you black out or faint when dizzy?   No

                 Have you had any of the following:
    Yes   severe or recurrent headaches?   No
    Yes   light sensitivity or nausea with a headache?   No
    Yes   any double or blurry vision?   No
    Yes   numbness in your face or extremities?   No
    Yes   weakness or clumsiness in arms, legs?   No
    Yes   slurred or difficult speech?   No

Yes	difficulty swallowing?				No
Yes	tingling around your mouth?				No
Yes	spots before your eyes?				No
Yes	jerking of arms or legs?				No
Yes	seizures?				No
Yes	confusion or memory loss?				No
Yes	recent head trauma? (if yes, please explain)				No

_____
_____
_____

4. The following refer to your hearing. Indicate which side has been affected:

Yes	difficulty hearing in one ear?	Left	Right	Both	No
Yes	ringing/sounds in one ear?	Left	Right	Both	No
Yes	fullness in one ear?	Left	Right	Both	No
Yes	loud sounds make you dizzy?	Left	Right	Both	No
Yes	change in hearing when dizzy? How? _____				No

Have you had any of the following:

Yes	pain in ears?	Left	Right	Both	No
Yes	discharge from ears?	Left	Right	Both	No
Yes	hearing change?				
Yes	better?	Left	Right	Both	No
Yes	worse?	Left	Right	Both	No
Yes	exposure to loud noises?				No
Yes	previous ear infections?				No
Yes	previous ear surgery?				No
	What? _____				
Yes	family history of hearing loss or deafness?				No

5. The following refer to habits and lifestyle:

Yes	is there added stress to your lifestyle recently?	No
Yes	are you constantly dizzy or unsteady?	No

Is your dizziness related to:

Yes	moments of stress?	No
Yes	menstrual period	No
Yes	overwork or exertion?	No
Yes	do you feel lightheaded or have a swimming sensation when you are dizzy?	No
Yes	did you recently change eyeglasses?	No
Yes	have you ever had weakness a few hours after eating?	No
Yes	do you drink coffee? How much? _____	No
Yes	do you drink tea? How much? _____	No
Yes	do you drink soft drinks? How much? _____	No
Yes	do you drink alcohol? How much? _____	No
Yes	do you smoke? How much? _____	No

Past medical history:

Please list your current medical problems and length of illness:

_____
_____
_____
_____

Please list all surgery performed and approximate dates:

_____
_____
_____
_____

Please list all allergies (including medicine) and reaction:

_____
_____
_____
_____

Please list all medicines you currently take (including pain medicine, non-prescription medicine, nerve pills, sleeping pills, or birth control pills):

_____
_____
_____
_____

Have you had any previous testing (hearing, x-rays, head scans, etc.)?

_____
_____
_____
_____

Family history:

Any family history of:

Yes	migraine headaches or dizziness?	No
Yes	high blood pressure?	No
Yes	low blood pressure?	No
Yes	diabetes?	No
Yes	low blood sugar?	No
Yes	thyroid disease?	No
Yes	asthma?	No

Please list any other diseases that run in your immediate family:

_____
_____
_____
_____
_____

System review:

Tick all applicable symptoms:

Constitutional:			
□ recent weight change	□ fever	□ fatigue	□ n/a
Eyes:			
□ loss of vision	□ pain	□ discharge/tearing	□ n/a
□ left □ right □ both	□ left □ right □ both	□ left □ right □ both	
Ears, Nose, Mouth, Throat:			
□ itchy ears	□ facial weakness	□ nasal obstruction	□ n/a
□ nose bleed	□ sneezing	□ "stuffy" nose	
□ loss of sense of smell	□ growth in nose	□ nasal bleeding	
□ mouth growth, ulcer	□ chewing difficulty	□ lump in neck	
□ pain on swallowing	□ heartburn	□ sore throat	
□ voice changes	□ breathing difficulty		
Cardiovascular:			
□ chest pain	□ irregular heart beat	□ swelling of legs	□ n/a
□ leg pain with rest	□ leg pain with walk		
Respiratory:			
□ wheezing	□ cough	□ shortness of breath	□ n/a
□ coughing up blood	□ mucus		
Gastrointestinal:			
□ decrease in appetite	□ nausea/vomiting	□ blood in stool	□ difficulty swallowing
□ diarrhea/constipation	□ indigestion	□ food intolerance	□ n/a
Musculoskeletal:			
□ neck pain	□ joint pain/stiffness	□ arthritis	□ n/a
Skin:			
□ rash	□ jaundice	□ recent baldness	□ n/a
Neurologic:			
□ headache	□ blackout	□ paralysis	□ n/a
□ tremor	□ seizures		
Psychiatric:			
□ insomnia	□ depression	□ on medications?	□ n/a
Endocrine:			
□ thyroid trouble	□ heat/cold intolerance	□ excessive sweating	□ n/a
□ excessive thirst, hunger, urination			
Genitourinary:			
□ painful urination	□ venereal disease	□ blood in urine	□ n/a
□ difficulty passing urine	□ incontinence	□ frequent urination at night	
Hematologic/Lymphatic:			
□ anemia	□ easy bruising	□ blood disorder (e.g. Sickle cell)	□ n/a
□ bleeding problems			

Do you have anything else to tell us about your particular problem which we have not asked you?

_____
_____
_____

Adapted from:
Goebel, J.A. (2008). Practical management of the dizzy patient (2nd ed.). Wolters Kluwer.

Appendix G

Proof of acceptance of articles

_____

From: <support@jlo.co.uk>
To: Barbara.Heinze@up.ac.za
Date: 10/24/2010 6:26 PM
Subject: Article 103850 has now been accepted

Thank you for submitting your paper 'A systematic review of HIV/AIDS related vestibular disorders' by B Heinze, DeW Swanepoel, LM Hofmeyr to the JLO. It has been reviewed and is acceptable for publication. A further email will be sent if there are final details required or if the paper is acceptable for online publication only.

Rosamund Greensted
Managing Editor

From: "Auris Nasus Larynx" <anl.online@jibika.or.jp>
To: Barbara.Heinze@up.ac.za
Date: 9/24/2013 7:31 AM
Subject: Your Submission ANL-D-13-00241R1

Ms. Ref. No.: ANL-D-13-00241R1
Title: Vestibular involvement in adults with HIV/AIDS
Auris Nasus Larynx

Dear Mrs Barbara Heinze,

We are pleased to inform you that your paper entitled as "Vestibular involvement in adults with HIV/AIDS" has been accepted for publication in Auris Nasus Larynx. Your paper will be handled for publication at the earliest opportunity by Elsevier, the official publisher of Auris Nasus Larynx.

We really appreciate your contribution to Auris Nasus Larynx.

Sincerely yours,

Dr. Kenichi Nibu, Editor in Chief
Dr. Hidenori Inohara, Deputy Editor
Auris Nasus Larynx

****
For further assistance, please visit our customer support site at
http://help.elsevier.com/app/answers/list/p/7923 Here you can search for solutions on a range of
topics, find answers to frequently asked questions and learn more about EES via interactive tutorials.
You will also find our 24/7 support contact details should you need any further assistance from one of
our customer support representatives.

Barbara Heinze - Your JLO article has been accepted

From: <support@jlo.co.uk>
To: <barbara.heinze@up.ac.za>
Date: 1/16/2014 04:35 PM
Subject: Your JLO article has been accepted

Your JLO article has been accepted

Dear Dr Barbara Heinze

Thank you for submitting your paper "Does the human immunodeficiency virus influence the vestibulocollic reflex pathways? A comparative study" to the JLO. It has been reviewed and is acceptable for publication. A further email will be sent if there are final details required or if the paper is acceptable for online publication only

We now publish papers incrementally which means that your article will appear on the website as soon as corrected proofs have been received and can be listed as a published paper.

Thank you again for sending your manuscript to the Journal of Laryngology and Otology

Rosamund Greensted

Managing Editor

The JLO is now able to offer Gold Open Access publication and should you wish to take advantage of this the costs would be £1695 or $2700.

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Kind regards,

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