Auditory, video head impulse test and vestibular evoked myogenic potentials findings in adults with human immunodeficiency virus

Waseema Mahomed[a], Barbara M. Heinze[a,*], Bart H.M.E. Vinck[b] and Anton Stoltz[c]

[a] Department of Speech-Language Pathology and Audiology, University of Pretoria, Private bag X20, Hatfield 0028, Pretoria, South Africa

[b] Department of Speech and Hearing Sciences, Ghent University, University Hospital Ghent, 10 Corneel Heymanslaan, 9000 Gent, Belgium

[c] Department of Internal Medicine, Steve Biko Academic Hospital, Private bag X20, Hatfield 0028, Pretoria, South Africa

*****Corresponding author at: Department of Speech-Language Pathology and Audiology, University of Pretoria, Private bag X20, Hatfield 0028, Pretoria, South Africa. Email: barbara.heinze@up.ac.za

Abstract

Objectives: Even though there is an association between hearing loss and human immunodeficiency virus (HIV), particularly in low- and middle-income countries, further research is needed to investigate the nature of such hearing loss. Likewise, despite documented vestibular alterations in people with HIV, the true occurrence, presentation, and nature of these manifestations are yet to be established. Advances in technology for vestibular testing has allowed for objective site-of-lesion tests such as the video head impulse test (vHIT), cervical vestibular evoked myogenic potentials (cVEMPs) and ocular vestibular evoked myogenic potential (oVEMPs). The current study aimed to compare and describe auditory, vHIT, cVEMPs and oVEMPs findings in adults with and without HIV.

Methods: The current study included an HIV positive group (n = 30) and an HIV negative group (n = 30) who underwent an auditory assessment (tympanometry and pure tone audiometry) and objective vestibular assessments.

Results: The occurrence of hearing loss was 53.3% in the HIV positive group compared to 33.3% in the HIV negative group. A higher occurrence of vestibular involvement was documented in the HIV positive group (73.3%) compared to 13.3% in the HIV negative group.

Conclusion: Auditory assessment and objective measures of vestibular end-organ function (vHIT and VEMPs) can be useful to detect sub-clinical alterations. The equipment is mobile and can be performed in any health care setting such as infectious disease clinics for surveillance and monitoring purposes.

Keywords: HIV; Auditory; VEMP; vHIT

1. Introduction

In 2017 there were 36.9 million people living with HIV (PLHIV) of which 1.8 million were new infections. A total of 940 000 people died from AIDS-related illnesses in the same year [1]. Globally, an expansion regarding access to HIV treatment has occurred and transformed not only the HIV epidemic but also the health sector at large [2]. The advancement in antiretroviral therapy (ART) has allowed for a shift in emphasis, currently focusing on quality of life [3].

Auditory and otological manifestations are common occurrences in PLHIV and usually increases as the disease advances [4]. Hearing loss can be conductive, sensorineural or mixed in nature [5]. A systematic review revealed that one in three PLHIV from low- and middle-income countries presented with a hearing impairment, indicating an established association between hearing loss occurrence and HIV [3]. Furthermore, it was found that a statistically significant association was found between HIV and hearing loss in both adults and children and that these findings corroborated with other studies conducted elsewhere, proving that the occurrence of hearing loss is quite common in the HIV population [6,7]. Even though a correlation between hearing loss and HIV has been established, further research is needed to investigate the aetiology of hearing loss in relation to HIV [3].

Previous studies reported an association between HIV and vestibular dysfunction, which may be peripheral or central in nature [8], [9], [10]. Taking into consideration the shared anatomy of the auditory and vestibular end-organs, it's not surprising that vestibular involvement occurs [9]. A systematic review [9] reported on previous studies in which central vestibular abnormalities were suggested as indicated by poor visual suppression and abnormalities in saccade and pursuit tracking [11,12]. Another study indicated a high occurrence of peripheral and central vestibular involvement [13].

Despite documented vestibular alterations in individuals with HIV, the true occurrence, presentation, and nature of these manifestations are yet to be established. To date, research reports on vestibular end-organ function in adults with HIV focused on caloric and rotary chair that evaluates horizontal canal function, as well as air conduction (AC) cVEMPs that evaluates the saccule [8,11,12,14,15]. To our knowledge there are no known objective data on individual semicircular canal function as determined by vHIT and of utricular function as determined by AC oVEMP. The current study aimed to compare and describe auditory, vHIT, cVEMPs and oVEMPs findings in adults with and without HIV.

2. Methods

2.1. Sample characteristics

This cross-sectional, descriptive study was conducted at two sites, namely the Infectious Disease Clinic and the Antiretroviral Clinic at a tertiary referral academic hospital in Pretoria, South Africa. Ethical clearance was obtained from the Institutional Review Board (reference: 38/2018 and 13007263 (GW20180206HS)), and data collection for the current study commenced in February 2018 and ended in July 2018. Each participant provided written informed consent. The current study was structured according to the Declaration of Helsinki [16]

The total sample consisted of 60 individuals aged 18 to 45 years. Participants belonged to one of two groups: (1) diagnosed with HIV and on ART treatment (n = 30); and (2) the age and gender-matched control group (n = 30). Twenty-nine out of 30 HIV positive participants were on a first-line fixed-dose combination ART regime consisting of these three drugs: Tenofovir (300 mg), Emtricitabine (200 mg) and Efavirenz (600 mg). There was only one participant tested who was on the 2nd line ART regime which consisted of Zidovudine (300 mg), Lamivudine (150 mg) and Lopinavir/Ritonavir (400/100 mg). After giving consent for participation, the control group verified their HIV negative status by voluntarily partaking in HIV screening at their local clinics.

Exclusion criteria were as follows: (1) known causes of inner ear dysfunction such as history of recreational or occupational noise exposure, history of ototoxic medication particularly for tuberculosis and cancer, and syphilis; (2) history of chronic alcohol abuse and/or smoking and poor neck range of motion; and (3) participants identified with an outer or middle ear pathology.

3. Procedures

3.1. Auditory assessment

Otoscopic examination, followed by tympanometry and acoustic reflexes was performed using a diagnostic Y-226 Hz probe tone (GSI Tympstar, Grason-Stadler, Eden Prairie, MN, USA) and normal middle-ear functioning was classified following established clinical norms [17]. Automated diagnostic pure tone audiometry AC and bone conduction (BC) was conducted at 250, 500, 1000, 2000 and 4000 Hz, in a quiet room using the KUDUwave Type 2 Clinical Audiometer (IEC 60645-1/2) manufactured by eMOYOdotNET, Johannesburg, South Africa. A 4-tone pure tone average (PTA) was calculated across 500, 1000, 2000 and 4000 Hz and was used to classify hearing status in terms of degree (normal = −10–15 dBHL, slight hearing loss = 16–25 dBHL, mild hearing loss = 26–40 dBHL, moderate hearing loss = 41–55 dBHL, moderately-severe hearing loss = 56–70 dBHL, severe hearing loss = 71–90 dBHL, profound hearing loss = 91+ dBHL) and laterality (unilateral or bilateral) [18]. A high frequency pure tone average (HFPTA) was also calculated across 2000, 4000 and 8000 Hz.

3.2. Video head impulse test (vHIT)

The vHIT procedure was conducted using the Otometrics ICS Impulse® manufactured by Natus Medical, Denmark, using the Video Frenzel goggles. The same examiner (author WM) conducted this test at the two sites. Two authors (WM and BH) who has experience with vHIT for the accuracy of VOR gain and for the presence of overt/covert saccades reviewed the data. Participants were seated on a standard fixed armchair with an eye-level target at a distance of 1.5 m in front of them. Before commencing with any testing, it was ensured that the goggles were secured tightly to minimize goggle slippage and thereafter calibration was performed for each participant to ensure reliable results were obtained. For lateral vHIT, the patient's head was turned horizontally at a small angle of about 10°–20° in a brief, abrupt and unpredictable manner making sure to vary the direction of the turns. Vertical vHIT was performed with small, abrupt movements in the direction of the planes; left anterior right posterior (LARP) and right anterior left posterior (RALP) [19,20]. When a HIT was elicited, the goggles collected both head and eye data. Simultaneous displays of the data were recorded for both head and eye movement and allowed the clinician to determine if the

response was within normal limits or not. Furthermore, the software system displayed the gain values obtained in each canal as well as if there were any catch-up saccades recorded. The interpretation of test results was considered abnormal if: (1) the VOR gain value was <0.8 for the lateral canals and <0.7 for vertical canals; or (2) either covert or overt catch-up saccades were present [19,20].

3.2.1. Vestibular evoked myogenic potentials (VEMPs)

The VEMP testing was performed using the Bio-logic Navigator® Pro, manufactured by Natus Medical, USA, connected to an Acer Laptop programmed with software version 7.2.1. An AC 500 Hz toneburst was presented at an intensity of 95dBnHL using rarefaction and alternating as the polarity for cVEMPs and oVEMPs respectively with a rate of 5.1 Hz. A total of 120 and 200 sweeps were measured for cVEMPs and oVEMPs respectively in each ear. The stimuli applied was repeated to confirm wave reproducibility. Insert earphones (ER3A, Etymotic Research, Elk Grove Village, IL, USA) with disposable ear tips were used.

3.2.2. Cervical VEMP (cVEMP) procedure

During testing, participants were seated on a standard chair. The investigator ensured that impedances were kept under 5 kΩ. Thereafter, reusable gold cup electrodes were positioned onto the skin. During cVEMP testing, ipsilateral electromyography recordings were performed. Neck flexion of the sternocleidomastoid (SCM) muscle was achieved by instructing participants to turn the head contralateral to the side of stimulation, ensuring a cVEMP response with robust amplitudes and without early fatigability [21,22]. The active electrode was placed on the ipsilateral mid-portion of the SCM muscle of the test ear, the reference electrode was placed on the sternoclavicular junction, and the ground electrode was placed on the forehead [22]. When marking the waveform, P1 was identified as the first distinctive peak in the waveform between 11.81 and 15.59 ms, followed by N1, identified as the first distinctive trough in the waveform between 18.15 and 25.64 ms [23]. Responses obtained were repeated, and the weighted average was calculated. Additionally, the peak-to-peak amplitude was also recorded and rectified for the baseline SCM muscle activity during the 10 ms interval before stimulus onset. This was achieved by utilizing the ratio of the peak-to-peak amplitude relative to the baseline SCM activity.

3.2.3. Ocular VEMP (oVEMP) procedure

During testing, participants were seated on a standard chair and were instructed to keep their head horizontal while maintaining an upward gaze during the stimulation and recording, focusing their gaze on a stationary target, at an approximate 30° angle, on the ceiling. Electromyography recordings from the extra-ocular muscles in the infra-orbital region were recorded while the stimulus was presented in the contralateral test ear. The active electrode was placed on the inferior oblique muscle, on the opposite eye from the test ear; the reference electrode was placed on the side of the nose bridge, and the ground electrode was placed on the forehead [24]. When marking the waveform, N1 was identified as the first distinctive trough in the waveform between 8.77 and 12.37 ms, followed by a positive peak P1, identified as the first distinctive peak in the waveform between 13.26 and 18.88 ms [23]. Responses obtained were repeated, the weighted average calculated and the peak-to-peak amplitude was then also recorded for each ear.

4. Data analysis

This study utilized descriptive statistics, i.e., means, medians, standard deviations, standard error, 95% confidence interval level for means, frequencies, and percentages as well as inferential statistics in order to determine whether there was a significant difference between both test groups. The Kolmogorov–Smirnov statistic was used to test for normality. Where it was found that the data was not normally distributed, nonparametric tests were used. The Chi-Square test of independence was used to determine whether there was a significant relationship between two nominal (categorical) variables. If the expected count was less than 5, then the Fisher's Exact test was used. The Mann–Whitney *U* test was used to determine if there were statistically significant differences between the two groups for all the continuous variables. A level of significance of 5% was used, i.e., if the *p*-value was less than 0.05, there were statistically significant differences between the groups. Data was analyzed with IBM Statistical Package for the Social Sciences (SPSS Inc. version 25).

5. Results

5.1. Demographics of participants

Results were obtained from 60 participants, 30 HIV positive and 30 HIV negative. A Mann–Whitney *U* test was run to determine if there were differences in age (years) between the HIV positive and the HIV negative control group. Distributions of the ages for both groups were similar. Age was statistically not significantly different between the HIV positive group (Mdn=38,50) and the control group (Mdn=38,00), $U = 433$, $z = -0.252$, $p = 0.801$, using an exact sampling distribution for *U* [25]. Both groups had more female participants with 83.3% and 86.7% in the HIV positive and HIV negative groups respectively. It was 'not possible to determine disease duration, since participants were 'not aware of when becoming infected with the virus, however duration of ART use was known and documented. For the ART duration, a mean of 8.71 (SD=4.31) years, a minimum of 4 months and a maximum of 19 years were documented. Concerning the cluster of differentiation 4+ (CD4+) cell count, a mean value of 580.47 cells/µL (SD=321.66 cells/µL), a minimum of 235 cells/µL and a maximum of 1473 cells/µL were documented. The CD4+ cell count is used to determine degree of immunosuppression; immunological staging of disease reverses with ART use which is administered when CD4+ cell counts are below 350 cells/µL. Table 1 summarizes the of CD4+ levels in relation to the severity immunosuppression and shows the distribution of participants with HIV within this immunological staging. None of the participants that visited the two sites had levels below 200 cells/µL, while more than half had no significant immunosuppression. When probed for subjective perception of vertiginous symptoms and chronic disequilibrium at the time of testing, none reported any.

Table 1. Immunological staging of disease according to CD4+ levels (cells/µL).

Stage	CD4+ levels	Severity of immunosuppression	*n* (%) of HIV participants
1	>500	Not significant immunosuppression	17 (56.7)
2	350–499	Mild immunosuppression	4 (13.3)
3	200–349	Advanced immunosuppression	9 (30)
4	<200	Severe immunosuppression	0

World Health Organization, 2007.

5.1.1. Auditory assessment

Acoustic tympanometry and acoustic reflexes were carried out first, wherein all 60 participants obtained type A tympanograms and at least one reflex present at 1000 Hz or 2000 Hz. Furthermore, bone conduction was also conducted at 250–8000 Hz, but none of the participants in the current study presented with air-bone gaps.

A Mann–Whitney *U* test was run to determine if there were significant differences in thresholds (dBHL) for all octave test frequencies, the 4-tone PTA and the HFPTA between the left and right ears of our study population. Distributions of the thresholds for both ears were similar, and each side was statistically not significantly different between the left and right ears ($p > 0.05$). Therefore, a comparison was drawn between both test groups, which did yield statistically significant differences, rather than between both ears. Table 2 describes the AC pure tone audiometry across the test frequency spectrum 250–8000 Hz per test group. Within each test group, all the ears tested was considered as one group and therefore parametric statistics was carried out. A one-way ANOVA was performed for all octave frequencies, 4-tone PTA and HFPTA. Results indicated statistically significantly differences ($p = 0.05$) or borderline statistically significant differences ($\pm p = 0.05$) at all of the above listed octave variables except at 2 kHz ($p = 0.149$).

Table 2. Auditory findings: octave frequencies (250–8000 Hz), 4-tone PTA and HFPTA.

	Group	*n*	M	Mdn	SD	SE	95% confidence interval for mean		*p*-value
							Lower bound	Upper bound	
250 Hz	HIV+	60	20.75	20.00	13.62	1.76	17.23	24.27	
	HIV−	60	11	10.00	8.72	1.13	8.75	13.25	
	Between groups								0.001[b]
500 Hz	HIV+	60	20.67	20.00	12.77	1.65	17.37	23.97	
	HIV−	60	11.75	10.00	8.63	1.11	9.52	13.98	
	Between groups								0.001[b]
1000 Hz	HIV+	60	15.42	15.00	10.35	1.34	12.74	18.09	
	HIV−	60	11.58	10.00	11.10	1.43	8.71	14.45	
	Between groups								0.053[a]
2000 Hz	HIV+	60	13.58	15.00	10.05	1.3	10.99	16.18	
	HIV−	60	11.08	10.00	8.79	1.13	8.81	13.35	
	Between groups								0.149
4000 Hz	HIV+	60	8.75	5.00	10.99	1.42	5.91	11.59	
	HIV−	60	5.50	0.00	7.8	1.01	3.49	7.51	
	Between groups								0.064
8000 Hz	HIV+	60	8.17	5.00	11.53	1.49	5.19	11.15	
	HIV−	60	2.75	0.00	5.16	0.67	1.42	4.08	
	Between groups								0.001[b]
4-Tone PTA	HIV+	60	14.68	13.00	9.43	1.22	12.25	17.12	
	HIV−	60	9.95	10.00	7.98	1.03	7.89	12.01	
	Between groups								0.004[b]
HFPTA	HIV+	60	10.17	7.50	8.93	1.15	7.86	12.47	
	HIV−	60	6.44	5.00	5.60	0.72	5	7.89	
	Between groups								0.007[b]

[a]Borderline statistically significant. [b]Statistically significant, HIV+= HIV positive, HIV−= HIV negative, *n*= number of ears (left and right ears combined), SE=standard error, SD=standard deviation, M=mean, Mdn=median, SE=standard error, SD=standard deviation.

Hearing status was described based on the calculated 4-tone PTA regarding degree and laterality [18]. Normal hearing was regarded as any PTA ≤15 dBHL per ear [18]. Normal hearing was indicated to be 58.3% (*n* = 35 ears) in the HIV positive group and 76.7% (*n* = 46 ears) in the HIV negative group. Fig. 1 illustrates the degree and lateralization (unilateral or bilateral) of hearing loss in both groups when considering affected ears.

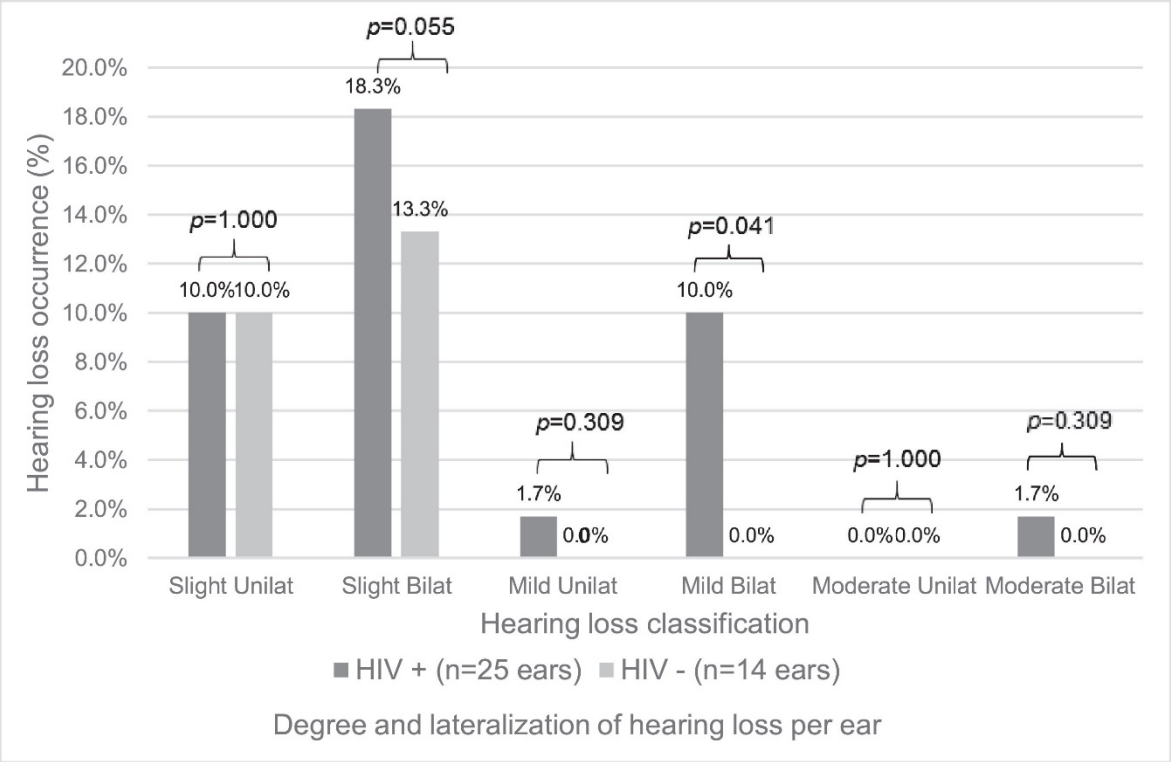

Fig. 1. Degree and lateralization of hearing loss.

A total occurrence of 41.7% (*n* = 25 ears) and of 23.3% (*n* = 14 ears) hearing loss was found in the HIV positive and HIV negative test group respectively. It was found that bilateral slight hearing loss had the highest occurrence in both test groups. In the HIV positive group, the degree of hearing loss was mostly slight and mild. The HIV positive group had a statistically significantly higher occurrence of slight ($p = 0.055$) and mild ($p = 0.041$) bilateral sensorineural hearing loss than the HIV negative group.

However, when considering hearing status per participant, and classifying hearing loss as either having a unilateral or bilateral hearing loss, then 16 HIV positive participants (53.3%) demonstrated a hearing loss compared to 10 HIV negative participants (33.3%). In the HIV positive group, nine participants had a bilateral hearing loss (five had bilateral slight hearing loss, one had bilateral mild hearing loss, two had slight hearing loss in the one ear and mild hearing loss in the other ear, and one had slight hearing loss in the one ear and moderate hearing loss in the other ear) while seven had a unilateral hearing loss (six participants with slight hearing loss, one with mild hearing loss). In the HIV negative group, four participants had a bilateral slight hearing loss and six participants had a unilateral slight hearing loss.

5.2. Vestibular assessment

To report on the vHIT results, a Mann-Whitney U test was first run to determine if there were differences in lateral, anterior and posterior gain between the left and right ears of both HIV positive and the HIV negative groups. The gain distributions between both ears of the same participant were significantly different for the lateral and anterior measurements. Gain was statistically significantly different between the left ears and right ears for lateral gain results, where $U = 965.00$, $z = -3.63$ and $p = 0.001$ and for the anterior gain results ($U = 1184.00$, $z=-2.37$ and $p = 0.018$). However, for posterior gain measurements ($U = 1485.50$, $z = -1.08$, $p = 0.279$) no significant difference was obtained. Because of the observed asymmetry between left and right ears, vHIT data from this study are reported for left and right ears separately. Table 3 summarizes the median vHIT gain results for the HIV positive group and HIV negative group in the right and left ears respectively for all six semicircular canals.

Table 3. Median vHIT gain values for all six canals.

Canal	vHIT gain: left ears (*n* = 60) Mdn (25, 75 percentile)			Canal	vHIT gain: right ears (*n* = 60) Mdn (25, 75 percentile)		
	HIV+ Group	HIV− Group	*p-value*[a]		HIV+ Group	HIV− Group	*p-value*[a]
Lateral	0.92 (0.86, 0.99)	0.91 (0.86, 1.00)	0.903	**Lateral**	1 (0.90, 1.07)	1 (0.97, 1.01)	0.651
Anterior	1.01 (0.88, 1.07)	0.96 (0.84, 1.02)	0.200	**Anterior**	0.85 (0.71, 1.04)	0.97 (0.78, 1.10)	0.146
Posterior	0.86 (0.78, 0.98)	0.91 (0.84, 1.00)	0.193	**Posterior**	0.87 (0.80, 1.02)	0.90 (0.88, 0.98)	0.264

[a]The Mann–Whitney test was run for differences between two independent samples, Mdn=median, *n*=number of ears.

The median gain values obtained for both test groups in both ears for all six vHIT testing conditions were within the normative data used in this study. However, nine participants (33%) in the HIV positive group had abnormally low gain values in one or more of the semicircular canals, while two participants (6.7%) in the HIV negative group had low gain values. The presence of catch-up saccades were recorded in eight participants (26.7%) in the HIV positive group and four (13.3%) in the HIV negative group. The presence of both abnormally low gain together with catch-up saccades were recorded only in the HIV positive group among two participants (6.7%).

In the HIV positive group, five participants (16.7%) had absent cVEMPs; one participant had a unilaterally absent cVEMP while four had bilaterally absent cVEMPs. All the participants in the HIV negative group had present cVEMPs. Regarding oVEMPs in the HIV positive group, seven participants (23.3%) had no identifiable wave forms; two participants had unilaterally absent oVEMPs while five had bilaterally absent oVEMPs. Upon closer inspection of the data, it was found that four participants had both absent cVEMPs and oVEMPs, three had absent oVEMPs only and one had absent cVEMPs only, thus a total of eight (26.7%) HIV positive participants with absent VEMPs. Only the data of participants with present cVEMPs were included in statistical analyses and summarized in Table 4. The Mann–Whitney *U* test, the Wilcoxon W test and the *Z* test were used to assess if there were statistically significant differences between both ears in each test group. Results indicated that there were no statistically significant differences for the cVEMP (P1 and N1) and

oVEMP (N1 and P1) latencies between the groups. There was however a significant difference concerning cVEMP inter-peak amplitudes, but not for oVEMP inter-peak amplitudes. Descriptive statistics were run between both test groups instead of both sets of ears.

Table 4. Summary of cVEMP and oVEMP latencies (ms), inter-peak amplitudes (µV) and asymmetry ratios (%).

	Group	*n*	M	Mdn	SD	SE	95% confidence interval for mean		*p*-value
							Lower bound	Upper bound	
cVEMP P1 (ms)	HIV^{+}	51	15.29	14.80	2.274	0.318	14.65	15.93	
	HIV^{-}	60	15.04	14.39	1.602	0.207	14.62	15.45	
	Between groups								0.498
cVEMP N1 (ms)	HIV^{+}	51	23.80	23.13	3.206	0.449	22.90	24.70	
	HIV^{-}	60	23.40	23.10	1.849	0.239	22.92	23.88	
	Between groups								0.416
cVEMP amplitude (µV)	HIV^{+}	51	20.50	16.82	14.876	2.083	16.32	24.68	
	HIV^{-}	60	27.10	23.80	12.886	1.664	23.77	30.43	
	Between groups								0.014[a]
cVEMP AR (%)	HIV^{+}	25[b]	22.69	16.82	19.466	3.893	14.65	30.73	
	HIV^{-}	30[b]	19.16	14.22	16.019	2.925	13.18	24.14	
	Between groups								0.505
oVEMP N1 (ms)	HIV^{+}	48	10.06	9.61	1.620	0.234	9.59	10.53	
	HIV^{-}	60	9.74	9.50	0.731	0.094	9.55	9.93	
	Between groups								0.176
oVEMP P1 (ms)	HIV^{+}	48	14.62	14.30	1.990	0.287	14.05	15.20	
	HIV^{-}	60	14.44	14.82	1.217	0.157	14.13	14.76	
	Between groups								0.563
oVEMP amplitude (µV)	HIV^{+}	48	14.51	11.32	10.560	1.524	11.77	17.58	
	HIV^{-}	60	15.31	15.20	9.873	1.275	12.24	18.85	
	Between groups								0.685
oVEMP AR (%)	HIV^{+}	23[b]	28.91	23.50	24.186	5.043	18.50	39.37	
	HIV^{-}	30[b]	17.43	22.67	12.308	2.247	12.84	22.02	
	Between groups								0.001[a]

[a]Statistically significant.
[b]Number of participants with bilateral present VEMPs to calculate asymmetry ratio, AR=asymmetry ratio, HIV.+HIV positive, HIV.
$^{-}$HIV negative, M=mean, Mdn=median, *n*=number of ears with present VEMPs, SE=standard error, SD=standard deviation.

A one-way ANOVA was conducted to determine if the cVEMP latencies differed between the HIV positive and HIV negative group. Results indicated no statistically significant differences between the cVEMP P1 latencies for the HIV positive group (M = 15.29, SD=2.274) and the HIV negative group (M = 15.04, SD=1.602) where $F(1, 109)$=0,463 and p = 0.498. Similarly, there were no statistically significant differences between the cVEMP N1 latencies for the HIV positive group (M = 23.80, SD=3.206) and the HIV negative group (M = 23.40, SD=1.849) where $F(1, 109)$=0,667 and p = 0.416. Furthermore, cVEMP inter-peak amplitudes for the HIV positive group (M = 20.5, SD=14.876) were significantly lower than the HIV negative group (M = 27.10, SD=12.886) where $F(1, 109)$=6, 274 and p = 0.014. Asymmetry ratios (AR) were calculated for those participants with bilateral present cVEMPs; these included data of 25 participants in the HIV positive group and 30 participants in the HIV negative group. There were no statistically significant differences between the groups (p = 0.505).

Likewise, a one-way ANOVA was also conducted to determine if the oVEMP latencies differed between the HIV positive and HIV negative group. Results indicated no statistically significant differences between the oVEMP N1 latencies for the HIV positive group (M = 10.06, SD=1.620) and the HIV negative group (M = 9.74, SD=0.731) where $F(1, 106)$=1.852 and p = 0.176. Similarly, there were no statistically significant differences between the oVEMP P1 latencies for the HIV positive group (M = 14.62, SD=1.990) and the HIV negative group (M = 14.44, SD=1.217) where $F(1, 106)$=0,336 and p = 0.563. Furthermore, there was also no statistically significant differences between the oVEMP amplitudes for the HIV positive group (M = 14.51, SD=10.561) and the HIV negative group (M = 15.31, SD=9.873) where $F(1, 106)$=0.165 and p = 0.685. Asymmetry ratios were calculated for those participants with bilateral present oVEMPs; these included data of 23 participants in the HIV positive group and 30 participants in the HIV negative group. There was a statistically significant difference between the groups ($p < 0.001$); the HIV positive group showed a larger AR (mean 28.91%) compared to the HIV negative group (mean 17.43%). However, these mean values, even for the HIV positive group, can be regarded as clinically within normal limits.

Within the HIV positive test group, 73.3% (n = 22) presented abnormalities in vHIT and/or VEMP in comparison to 13.3% (n = 4) of the HIV negative group.

6. Discussion

6.1. Hearing loss and HIV

A recent systematic review of data from children and adults with HIV from low and middle income countries showed a high prevalence of hearing loss in people with HIV compared to those without HIV [3]. Sensorineural hearing loss was the most common type of hearing loss among adults. The studies summarized in this review that documented hearing loss among adults with HIV, used varied cut-offs for hearing loss; the overall majority used >20dBHL and two did 'not state. The prevalence of hearing loss in adults ranged from as low as 10% to as high as 68%. The degree of hearing loss was 'not reported. The current study, also from a low-middle income country, is in agreement with the abovementioned studies concerning the higher occurrence of hearing loss in adults with HIV compared to those without HIV. In accordance with the current study, a previous study from a low-middle income country that utilized the same criteria for hearing loss, namely ≥16dBHL, reported a 64% occurrence of sensorineural hearing loss [4]. This is very similar to the reported 53.3% in the current study.

Regarding the degree of hearing loss in the current sample, the most common degree was slight sensorineural hearing loss followed by mild sensorineural hearing loss. In addition, bilateral sensorineural hearing loss was more common than unilateral hearing loss. According to the World Health Organization a disabling hearing loss refers to a hearing loss greater than 40 dBHL in the better ear in adults [26]. That is regarded as a moderate hearing loss or greater [18]. None of the participants in the HIV negative group had a disabling hearing loss, while 1.7% of participants in the HIV positive group had bilateral moderate hearing loss. The absence of detectable outer and middle ear pathologies as demonstrated by type A tympanograms and absence of air-bone gaps on pure tone audiometry, could likely be explained by ART use. The treatments reduce viral loads and increase CD4+ cell counts, thereby improving immunity and reducing risk for opportunistic infections such as otitis media. Otitis media is usually associated with conductive or mixed hearing loss. The risk for other opportunistic infections, caused by viruses, bacteria and other malignancies associated with sensorineural hearing loss [25,26], could also be decreased. Three earlier studies showed a positive association between low CD4+ cell counts and hearing loss [27], [28], [29]. In the current study the mean CD4+ cell count in the HIV positive group was 580.47 cells/µL, while some were higher than 1000 cells/µL. However, it was recently reported that the combination of ART and the virus, at least in part, causes chronic inflammation and activation of the immune system typically seen in the elderly [30]. It is defined as “inflammaging” that is present in HIV positive adults who experience a type of premature ageing. These authors (page 48) explained that “A persistent, low-grade chronic inflammation that typically characterizes immunological ageing is an essential contributor to several comorbidities in the setting of HIV infection. This inflammation is particularly evident in older adults with chronic, well-treated HIV infection. The precise mechanism(s) of this residual immune activation are poorly understood, and the impact of ageing in treated long-life HIV+ is not yet clear.” The positive association with ageing and sensorineural hearing loss is well documented [31]. This mechanism of pathology could likely be attributed to the higher occurrence of hearing loss in the HIV positive group compared to the control group. Further research on larger study samples and serial auditory assessments longitudinally over the course of HIV treatment is needed for understand this more clearly.

Another possible cause for sensorineural hearing loss is the potential ototoxic effect of ARTs. Previous studies reported on sensorineural hearing loss following administration of ARTs [32], [33], [34], [35]. Although the treatment regime differed among them, they all had at least two nucleoside analogue reverse transcriptase inhibitors (NRTIs) in common. Highly active antiretroviral therapy (HAART) regimes typically consist of NRTIs combined with non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) or protease inhibitors; NRTIs are the most prevalent components of HAART regimes [32]. In the current study all HIV positive participants except one had long-term use of two NRTIs (Tenofovir and Emtricitabine) and one NNRTI (Efavirenz). The basal part of the cochlea is more susceptible to ototoxicity than the apex, resulting in a high frequency hearing loss [36]. The auditory findings of the current study didn't demonstrate the typical sloping high frequency hearing loss. In fact the mean HFPTA was well within normal limits in the HIV positive group despite being statistically significantly higher than in the HIV negative group. Extended high frequencies could provide more insight into the possible ototoxic nature of HAART and warrant further longitudinal research. Ototoxicity isn't limited to the cochlea, but can affect the vestibular end-organs and innervating nerves too, hence referred to as vestibulotoxicity [36].

6.2. Vestibular alterations and HIV

Vestibular dysfunction is common in adults with HIV and the occurrence thereof significantly higher in HIV than in those without HIV [8], [9], [10],12,37]. Previous reports indicated not only involvement of the central vestibular pathways as indicated by abnormalities in visual suppression, saccades and pursuit tracking, but also of peripheral function as demonstrated by abnormalities in calorics and cVEMPs [8,11,12,38]. To the authors' knowledge, the current study is the first to objectively determine function of individual semicircular canal and otolith function by utilizing mobile health equipment within an infectious disease clinic setting: vHIT, cVEMP and oVEMP.

The median vHIT gain for the different canals did 'not yield any statistically significant differences between the groups. However, considering individual canal gain values and the presence of covert/overt saccades, a total of 19 participants in the HIV positive group (63.3%) showed some alteration in one or more of these vHIT response parameters, compared to 20% (n = 6) in the HIV negative group. To date, there are no studies that have utilized the lateral and vertical vHIT protocol to determine individual canal function within an HIV positive cohort. There is only one previous study, a case report, that utilized the lateral and vertical vHIT protocol in order to assess individual semicircular canal function [39]. Results indicated positive involvement of both lateral canals and the left vertical canals. A previous study utilized the bedside equivalent, i.e., the lateral head impulse test (HIT), where the investigator relied on simple observation to determine the presence and absence of overt catch up saccades [8]. Similar to the current study, findings indicated a higher occurrence (20.8%) of abnormalities in the HIV positive group when compared to the HIV negative group (10.5%) suggesting the involvement of the lateral canals and/or superior vestibular nerve. On the contrary, one study that also utilized the lateral HIT reported a mere 5% occurrence in the HIV positive group and a higher occurrence of 17.7% in the HIV negative group [40]. The findings from the current study were not dependant on subjective observation of saccades, but rather, obtained through an objective record of eye movements during the head impulses and allowed for the function of each canal to be measured individually regarding gain and catch up saccades. The current study was thus able to quantify gain and measure catch-up saccades which the previous studies were unable to do and could, as a result, justify the higher occurrences reported currently. However, despite the differences in the medium of testing, the studies are in agreement that there is a higher occurrence of peripheral vestibular involvement in those with HIV than those without HIV.

The cVEMPs were absent in 16.7% (n = 5) of the HIV positive participants, of which four were bilaterally absent. Two previous studies [8,38] reported very similar findings where 15.1% of HIV positive participants had absent cVEMPs. A case report of an HIV-infected adult with syphilis reported bilateral absent cVEMPs [41]. In addition, the current study showed significantly lower inter-peak amplitudes in the HIV positive group than in the HIV negative group, suggesting saccular alterations. These findings together with previous reports suggest involvement of the saccules and/or the vestibular nerves that innervate these end-organs. Regarding oVEMPs, the occurrence of absent findings was higher; it was absent in 23.3% (n = 7) of HIV positive participants, of which five was bilateral. The current study was the first to report functional abnormalities of the utricle in adults with HIV. Earlier post-mortem studies using electron microscopic ultra-structural analysis of temporal bone from deceased adults with HIV, can corroborate involvement of the otoliths [42,43]. The authors showed viral-like particle characteristics of HIV in both the otolith organs. They also showed subepithelial elevation of neurosensory epithelium of the otolith organs.

In total, VEMPs were absent in eight HIV positive participants (26.7%) of which four had absence of both cVEMPs and oVEMPs. Absent VEMPs was found at higher rates compared with age-matched controls. In VEMPs, the stimulus examine primarily the integrity of type I hair cells of the otoliths [44]. Likewise, vHIT that examines individual semicircular canal function, seems to activate irregular afferents which primarily innervate type I hair cells [45,46]. Type I hair cells were shown to be more susceptible to insult from example ototoxic mediations [47], although no anecdotal evidence exist to support it, reports on hearing loss after administration of ART could likely not be limited to the cochlea but can involve the vestibular hair cells too. The higher occurrence of absent VEMPs and abnormal vHIT findings could possibly be attributed to the vestibulotoxic nature of ART. In addition, type I vestibular hair cells also show higher susceptibility to age-related alterations [48], the concept of “inflammaging” caused by ART and the virus could be extended to the vestibular hair cells.

If one could make a direct comparison between the mechanisms of pathology between ARTs as potential vestibulotoxic agents and aminoglycosides with well-known vestibulotoxic side-effects that affects semicircular canals more than other vestibular structures [49,50], a higher occurrence of abnormal vHIT findings would be seen. This seemed to be the case in the current study that showed abnormal findings in vHIT response parameters in 63.3% of HIV positive participants, compared to 20% in the HIV negative group. All semicircular canals showed some form of alteration suggesting equal vulnerability among individual canals. The current study showed the potential use of vHIT and VEMPs to detect sub-clinical vestibular alterations even in the absence of apparent vestibular complaints.

A strength of the current study included examination of individual vestibular end-organs by utilizing recently developed tests of vestibular function. The study included in a well-characterized HIV population a from low-middle incoming county with age and gender matched controls. The study sample included adults younger than 45 year to account for age-related degeneration. Participants were purposively selected from a typical public health care facility that provides treatment and counselling. Vestibular function tests were selected for their mobile application, in order to assess participants at the health care facility during their monthly visits. The study had several limitations; we didn't conduct extended high frequency audiometry to detect ototoxic-related hearing loss. The study did not identify a relationship between hearing loss, ART use duration, CD4+ cell counts and viral loads. A reason for not determining the relationship between CD4+ cell counts and vestibular end-organ dysfunction in this cross-sectional study is that once patients with HIV start with treatment, their CD4+ cell counts gradually increase. Although this is monitored regularly, the viral load is a more important indicator of health and treatment effectiveness. Over time, viral loads become undetectable. CD4+ cell counts fluctuate during the day; physical activity, diet and lack of sleep can affect it. Clinicians do not attach too much significance to an individual test result, but rather monitor any trends in changes over time. People living with HIV who have a CD4+ cell count over 500 and undetectable viral load are usually in good health [51]. In the current study the mean CD4+ cell count was 580.47 cells/μL and more than half of the HIV positive participants had counts more than 500, yet 73.3% had some vestibular dysfunction. The relationship between viral loads and vestibular end-organ function are yet to be established. Considering the fluctuating nature of CD4+ cell counts and monitoring of its changes over time, further insight is needed to determine the longitudinal effect of both viral loads and CD4+ cell counts on vestibular function. The study also didn't compare HIV positive adults using ART with HIV positive non-users. The study primarily compared differences in auditory function, vHIT and VEMPs between HIV positive and HIV negative participants

and described the nature in performance on these tests at one point in time. Additional studies should determine the auditory-vestibular function effects of HIV with and without ARTs longitudinally to document alterations. Considering the exploratory, descriptive nature of the study, studies with larger samples are needed to determine clinical implications. Nonetheless, taking into account the dearth of literature of vestibular function in HIV, the study provides findings not yet reported.

7. Conclusion

Auditory and vestibular end-organ alterations has a high occurrence in adults with HIV. The abnormalities reflect a disease-related complication and the effect on quality of life and functional activities should be explored. Auditory assessment and objective measures of vestibular end-organ function (vHIT and VEMPs) can be useful to detect sub-clinical alterations. The equipment is mobile and can be performed in any health care setting such as infectious disease and ART clinics for surveillance and monitoring purposes.

Declaration of Competing Interest

All authors declare that there are no conflicts of interest.

Acknowledgments

The author thanks all those involved throughout the process of the study and the compilation of the article.

References

[1] UNAIDS. *Unaids data 2018*; 2018.

[2] WHO, UNICEF, UNAIDS. *Global Update on HIV treatment 2013: results, Impact and Opportunities*; 2013.

[3] Ensink RJH, Kuper H. Is hearing impairment associated with HIV? A systematic review of data from low- and middle-income countries. *Trop Med Int Heal* 2017; 22:1493–1504.

[4] Van Der Westhuizen Y, Swanepoel DW, Heinze BM, Hofmeyr LM. Auditory and otological manifestations in adults with HIV/AIDS. *Int J Audiol* 2013; 52:37–43.

[5] Mathews SS, Albert RR, Job A. Audio-vestibular function in human immunodeficiency virus infected patients in India. *Indian J Sex Transm Dis AIDS* 2012; 33:98–101.

[6] Chandrasekhar SS, Connelly PE, Brahmbhatt SS, Shah CS, Kloser PC, Baredes S. Otologic and audiological evaluation of human immunodeficiency virus-infected patients. *Am J Otolaryngol* 2000; 21:1–9.

[7] Luque AE, Orlando MS, Cheng Leong U, Allen PD, Guido JJ, Hong-mei Y, et al. Hearing function in people living with HIV/AIDS. *Ear Hear* 2014; 35:282–290.

[8] Heinze BM, Vinck BM, Hofmeyr LM, Swanepoel DW. Vestibular involvement in adults with HIV/AIDS. *Auris Nasus Larynx* 2014; 41:160–168.

[9] Heinze BM, Swanepoel DW, Hofmeyr LM. Systematic review of vestibular disorders related to human immunodeficiency virus and acquired immunodeficiency syndrome. *J Laryngol Otol* 2011; 125:881–890.

[10] Teggi R, Ceserani N, Luce FL, Lazzarin A, Bussi M. Otoneurological findings in human immunodeficiency virus positive patients. *J Laryngol Otol* 2008; 122:1289–1294.

[11] Castello E, Baroni N, Pallestrini E. Neurotological and auditory brain stem response findings in human immunodeficiency virus–positive patients without neurologic manifestations. *Ann Otol Rhinol Laryngol* 1998; 107:1054–1060.

[12] Hausler R, Vibert D, Koralnik IJ, Hirschel B. Neuro-otological manifestations in different stages of HIV infection. *Acta Otolaryngol* 1991; 111:515–521.

[13] Teggi R, Giordano L, Pistorio V, Bussi M. Vestibular function in HIV patients: preliminary report. *Acta Otorhinolaryngol Ital* 2006; 26:140–146.

[14] Song JJ, Lee H, Chae S, Hwang S. Bilateral otosyphilis in a patient with HIV infection. *Eur Arch Otorhinolaryngol* 2005; 262:972–974.

[15] Grimaldi L, Luzi L, Martino GV, Nemni R, Antoneilli A, Canal N, et al. Bilateral eighth cranial nerve neuropathy in human immunodeficiency virus infection. *J Neurol* 1993; 240:363–366.

[16] World Medical Association World medical association declaration of Helsinki ethical principles for medical research involving human subjects. *JAMA* 2013; 310:2191.

[17] Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol 1970; 92:311–324.

[18] Clark JG. Uses and abuses of hearing loss classification. ASHA 1981; 23:493–500.

[19] Halmagyi GM, Chen L, MacDougall HG, Weber KP, McGarvie LA, Curthoys IS. The video head impulse test. *Front Neurol* 2017; 8:1–23.

[20] McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semi- circular canal function: age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* 2015; 6:1–11.

[21] Isaacson B, Murphy E, Cohen H. Does the method of sternocleidomastoid muscle activation affect the vestibular evoked myogenic potential response? *J Vestib Res* 2006; 16:187–191.

[22] Isaradisaikul S, Navacharoen N, Hanprasertpong C, Kangsanarak J. Cervical vestibular-evoked myogenic potentials: norms and protocols. *Int J Otolaryngol* 2012; 2012:1–7.

[23] Li C, Zuniga MG, Nguyen KD, Carey JP, Agrawal Y. How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: our experience in fifty-three participants. *Clin Otolaryngol* 2014; 39:297–301.

[24] Leyssens L, Heinze BM, Vinck BM, Van Ombergen A, Vanspauwen R, Wuyts F, et al. Standard' versus 'nose reference' electrode placement for measuring oVEMPs with air-

conducted sound: test–retest reliability and preliminary patient results. *Clin Neurophysiol* 2016; 128:312–22.

[25] Dineen LC, Blakesley BC. Generator for sampling distribution of Mann–Whitney U statistics. *J R Stat Soc* C 1973; 22:269–273.

[26] WHO. Deafness and hearing loss 2019; 2019. [27] Chao CK, Czechowicz JA, Messner AH, Alarcón J, Kolevic Roca L, Larragán Rodriguez MM, et al. High prevalence of hearing impairment in HIV-infected Peruvian children. *Otolaryngol Head Neck Surg* 2012; 146:259–265.

[28] Chidziva C, Matsekete J, Bandason T, Shamu S, Dzongodza T, Matinhira N, et al. Hearing impairment and deafness among HIV infected children and adolescents in Harare, Zimbabwe. *Cent Afr J Med.* 2015; 61:56–61.

[29] Ongulo BA, Oburra HO. Hearing disorders in HIV positive adult patients not on anti-retroviral drugs at Kenyatta national hospital. *East Afr Med J* 2010; 87:385–388.

[30] Nasi M, De Biasi S, Gibellini L, Bianchini E, Pecorinin S, Bacca V, et al. Ageing and inflammation in patients with HIV infection. *Clin Exp Imunol* 2016; 187:44–52.

[31] Liu XZ, Yan D. Ageing and hearing loss. *J Pathol* 2007; 211:188–197.

[32] Williams B, Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity may be associated with protease inhibitor therapy. *Clin Infect Dis* 2001; 33:2100–2102.

[33] Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. *Clin Infect Dis* 2001; 32:1623–1627.

[34] Marra CM, Wechkin HA, Longstreth WT Jr, Rees TS, Syapin CL, Gates GA. Hearing loss and antiretroviral therapy in patients infected with HIV-1. *Arch Neurol* 1997; 4:407–410.

[35] Monte S, Fenwick JD, Monteiro EF. Irreversible ototoxicity associated with zalcitabine. *Int J STD AIDS* 1997; 8:201–202.

[36] Ganesan P, Schmiedge J, Manchaiah V, Swapna S, Dhandayutham S, Kothandaraman PP. Ototoxicity: a challenge in diagnosis and treatment. *J Audiol Otol* 2018; 22:59–68.

[37] Dellepiane M, Medicina MC, Mora R, Salami A. Static and dynamic posturography in patients with asymptomatic HIV-1 infection and AIDS. *Acta Otorhinolaryngol Ital* 2005; 25:353–358.

[38] Heinze BM, Vinck BM, Swanepoel DW. Does the human immunodeficiency virus influence the vestibulocollic reflex pathways? A comparative study. *J Laryngol Otol* 2014; 128:772–779.

[39] Jung I, Kim HJ, Kim JS. Fluctuating ataxia and nystagmus in association with anti-GQ1b antibody in HIV infection. *J Neurol Sci* 2017; 382:123–125.

[40] Cohen HS, Cox C, Springer G, Hoffman HJ, Young MA, Margolick JB, et al. Prevalence of abnormalities in vestibular function and balance among HIV-seropositive and HIV-seronegative women and men. *PLoS One* 2012; 7:5–12.

[41] Weder S, Senn P, Caversaccio M, Vibert D. Cochleovestibular deficit as first manifestation of syphilis in a HIV-infected patient. *Case Rep Neurol* 2013; 5:62–67.

[42] Pappas Jr DG, Roland JT Jr, Lim J, Lai A, Hillman DE. Ultrastructural findings in the vestibular end-organs of AIDS cases. *Am J Otol* 1995; 16:140–145.

[43] Chandrasekhar SS, Siverls V, Sekhar HK. Histopathologic and ultra-structural changes in the temporal bones of HIV-infected human adults. *Am J Otol* 1992; 13:207–214.

[44] Curthoys IS, Vulovic V, Burgess AM, Manzari L, Sokolic L, Pogson J, et al. Neural basis of new clinical vestibular tests: otolithic neural responses to sound and vibration. *Clin Exp Pharmacol Physiol* 2014; 41:371–380.

[45] McCaslin DL, Rivas A, Jacobson GP, Bennet ML. The dissociation of video head impulse test (vHIT) and bithermal caloric test results provide topological localization of vestibular system impairment in patients with “definite”Ménière’s disease. *Am J Audiol* 2015; 24:1–10.

[46] Goldberg JM. Afferent diversity and the organization of central vestibular pathways. *Exp Brain Res* 2000; 130:277–297.

[47] Lyford-Pike S, Vogelheim C, Chu E, Della Santina CC, Carey JP. Gentamicin is primarily localized in vestibular type I hair cells after intratympanic administration. *J Assoc Res Otologaryngol* 2007; 8:497–508.

[48] Rauch SD, Velazquez-Villasenor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. *Ann N Y Acad Sci* 2001; 942:220–227.

[49] Nakashima T, Teranishi M, Hibi T, Kobayashi M, Umemura M. Vestibular and cochlear toxicity of aminoglycosides-a review. *Acta Otolaryngol* 2000; 120:904–911.

[50] Rybak LP, Ramkumar V. Ototoxicity. *Kidney Int*. 2007; 72:931–935.

[51] Ying R, Granich RM, Gupta S, Williams BG. CD4 cell count: declining value for antiretroviral therapy eligibility. *Clin Infect Dis* 2016; 62:1022–1028.