Original Investigation

Hearing Loss Among HIV-Seropositive and HIV-Seronegative Men and Women

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IMPORTANCE Age-related hearing loss affects quality of life. Data on hearing loss among aging human immunodeficiency virus–seropositive (HIV+) adults are limited.

OBJECTIVE To evaluate pure-tone hearing thresholds among HIV+ and HIV-seronegative (HIV−) adults and to determine whether HIV disease variables and antiretroviral therapy are associated with pure-tone threshold levels.

DESIGN, SETTING, AND PARTICIPANTS A total of 262 men (117 HIV+) from the Baltimore, Maryland/Washington, DC, site of the Multicenter AIDS Cohort Study and 134 women (105 HIV+) from the Washington, DC, site of the Women's Interagency HIV Study participated. Pure-tone air conduction thresholds were collected in a sound-treated room for each ear at frequencies from 250 through 8000 Hz. Linear mixed regression models tested the effect of HIV on hearing after adjustment for age, sex, race, and noise exposure history.

MAIN OUTCOMES AND MEASURES Low-frequency pure-tone average (LPTA) at 250, 500, 1000, and 2000 Hz and high-frequency PTA (HPTA) at 3000, 4000, 6000, and 8000 Hz. Differential HIV effects for LPTA and HPTA and better/worse ear were also examined. $CD4^+$ and $CD8^+$ T-cell counts, $\log_{10}$ plasma HIV RNA concentrations, receipt of AIDS diagnosis, and cumulative duration of antiretroviral therapy were included in the models for HIV+ participants only.

RESULTS HPTA and LPTA were significantly higher (18%: estimated ratio, 1.18 [95% CI, 1.02-1.36]; $P = .02$; and 12%: estimated ratio, 1.12 [95% CI, 1.00-1.26]; $P = .05$, respectively) for HIV+ participants compared with HIV− participants for the better ear. The direction of the effect was consistent across both the better and worse ears. There were no significant associations between HIV disease variables or treatment variables and LPTA or HPTA.

CONCLUSIONS AND RELEVANCE The HIV+ adults had significantly poorer lower-frequency and higher-frequency hearing than HIV− adults. High-frequency hearing loss is consistent with an accelerated aging (presbycusis); low-frequency hearing loss in middle age is unexpected. Because some vowels and consonants have predominantly low-frequency acoustic energy, poor low-frequency hearing may impair communication in HIV+ individuals.

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The relationship between human immunodeficiency virus (HIV) infection and hearing loss in the era of highly active antiretroviral therapy (HAART) has not been extensively investigated. In one of the few studies to prospectively evaluate possible changes in hearing sensitivity in HIV-seropositive (HIV+) individuals, Schouten et al[1] evaluated pure-tone averages (PTAs) in adults who began receiving zidovudine or didanosine, alone or in combination, from 1996 through 1999 with other antiretroviral therapy (ART) not specified. Low-frequency PTAs (500, 1000, and 2000 Hz) and high-frequency PTAs (4000, 8000, and 12 000 Hz) were calculated at baseline, 16 weeks, and 32 weeks. For the participants who had PTA data and returned at 32 weeks (n = 19), there were no significant changes in either high-frequency PTA (HPTA) or low-frequency PTA (LPTA), after accounting for age, noise exposure, $CD4^+$ T-cell count, and viral load.

Recently, van der Westhuizen et al[2] collected pure-tone threshold data among HIV+ and HIV-seronegative (HIV−) adults matched for age, sex, and race. The HIV+ participants had a significantly higher prevalence of hearing loss (calculated using PTA of 500, 1000, and 2000 Hz >25 dB hearing level [HL]) compared with controls; furthermore, this was true across all of the individual frequencies measured (500, 1000, 2000, 3000, and 4000 Hz). Centers for Disease Control and Prevention (CDC) classifications for HIV were also evaluated. The CDC classifications are defined as stage 1, 2, and 3, with CDC stage 3 defined as the greatest HIV disease severity (<200 $CD4^+$ T-cell count/μL).[3] There was a significantly higher prevalence of sensorineural hearing loss in those individuals with CDC stage 3 disease status, who were the only patients in that study receiving HAART. In the disease status analysis, PTA was defined using the aforementioned frequencies, but with a greater than 15 dB HL cut point. This definition of hearing loss, however, is commonly used for children and one that is rarely used in adult populations.

There have been limited data obtained on the effects of HIV-related medication use on hearing loss, and in the few published studies, it is difficult to attribute the increases in hearing loss specifically to HIV medication use rather than age or cumulative noise exposure. In one of the earliest studies, Bankaitis and Schountz[4] reported drug-induced hearing loss in HIV+ individuals regardless of the stage of the disease. Some researchers have found ototoxic effects in HIV+ individuals treated with nucleoside analog reverse transcriptase inhibitors (NRTIs) such as zidovudine, combinations of stavudine and lamivudine,[5] and combinations of zidovudine and didanosine.[6] Simdon et al[5] suggested caution when interpreting the associations between NRTI use and hearing loss because of confounding variables such as age, previous hearing loss, and noise exposure.

Therefore, the specific aims of this study were as follows: (1) to evaluate the hearing sensitivity characteristics, using pure-tone threshold data, of immunologically and virologically controlled, due to effective use of HAART, HIV+ and demographically similar HIV− men and women, after adjusting for age, sex, race, and noise exposure history, and (2) to determine whether HIV disease status and ART are associated with hearing sensitivity. The primary hypothesis for this study was that being HIV+ was associated with greater loss of hearing sensitivity at both low and high frequencies compared with being HIV−.

Methods

The institutional review boards for San Diego State University, Johns Hopkins Bloomberg School of Public Health, Georgetown University, and Whitman-Walker Health approved this study. All participants provided written informed consent.

Participants in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS)

The MACS is an ongoing, prospective study of the natural and treated history of HIV infection among men who have sex with men in the United States. Approximately 7000 men were recruited beginning in 1984 to 1985 at 4 centers located in Baltimore, Maryland-Washington, DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. Both HIV+ and HIV− men were recruited from a combination of sources including gay-focused public media, personal referrals, promotional events, and through medical practices and other research studies that targeted gay men. Other details about the recruitment and study design have been described elsewhere.[7,8] Participants return every 6 months for a detailed interview, a physical examination, and collection of blood for laboratory testing and storage. For the present study, men were recruited only from the Baltimore, Maryland-Washington, DC, MACS site.

The WIHS is a multicenter prospective cohort study that was established in 1994 to study women with or at risk for HIV infection. A total of 3766 HIV+ and at-risk HIV− women were enrolled beginning in 1994 through 1995 at 6 centers located in New York (Bronx and Brooklyn), New York; Chicago, Illinois; Los Angeles, California; San Francisco, California; and Washington, DC. The HIV+ and HIV− women were recruited from primary care and hospital-based clinics, research studies, community centers, women's support groups, HIV testing sites, and referrals from enrolled participants. Participants return every 6 months for a detailed interview, a physical examination, and collection of blood samples for laboratory testing and storage. Further details of WIHS study methodology have been previously reported.[9,10] For this study, women were recruited from the Washington, DC, site of the WIHS.

Procedures

The hearing research protocol was added to the existing MACS/WIHS protocol. A hearing-related questionnaire was administered by an interviewer and assessed the participant's self-reported hearing loss due to various factors, including perinatal exposure to rubella or cytomegalovirus, factors present at birth other than genetic or infectious disease, measles or meningitis, otitis media, ear trauma, or Ménière's disease or otosclerosis. Questions regarding tinnitus and noise exposure at work or during leisure activities

were also included. All questions were from the National Institute on Deafness and Other Communication Disorders–funded adult Hearing Supplement to the 2007 National Health Interview Survey.[11]

The hearing examination consisted of an otoscopic examination, tympanometry, and pure-tone air and bone conduction testing. Otoscopy and tympanometry were used to examine for possible outer and middle ear disease. Equivalent ear canal volume, peak acoustic admittance, and tympanogram peak pressure were determined from the tympanogram using a GSI Tympstar (Grason Stadler Inc). Pure-tone thresholds, in decibel HL, were obtained according to American Speech-Language-Hearing Association guidelines[12] in a sound-treated booth (Industrial Acoustics Co) using a clinical audiometer (GSI 61; Grason Stadler Inc) with supra-aural earphones (TDH-50P). Pure-tone air conduction thresholds were completed in each ear at 250, 500, 750, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. Bone conduction thresholds were completed at 500, 1000, 2000, and 4000 Hz. Pure-tone averages were calculated as the mean of air conduction thresholds at 250, 500, 1000, and 2000 Hz for the LPTA and at 3000, 4000, 6000, and 8000 Hz for the HPTA. Left and right ear PTA measurements at lower frequencies and higher frequencies were differentiated as (1) LPTA or HPTA and (2) by ear with the better or worse PTA measurement. Better ear was defined as the ear with the lower PTA. When the ears were equal, the ear with a lower threshold at a subsequent frequency, not used in the calculation of the PTA, established the better ear. For the purpose of the present study, an air-bone gap was defined as a difference between air conduction thresholds and bone conduction thresholds that was at least 15 dB at any 2 of the 4 frequencies tested in either ear.

In both MACS and WIHS, ART use was assessed at the study visit, and, beginning in October 1998, ART adherence was also captured at each visit. The ART medications were classified as NRTIs, protease inhibitors (PIs), and non-NRTIs (NNRTIs). Cumulative duration (years) of use of each class of ART was calculated on the basis of the number of ART medications reported in each classification and weighted for self-reported adherence. Weights were calculated by multiplying the number of ART medications at each visit by the adherence level, and the weighted values then cumulated. The weights were 1, 0.975, 0.85, 0.375, and 0 for adherence levels of 100%, 95% to 99%, 75% to 94%, less than 75%, and 0%, respectively. Antiretroviral therapy use prior to October 1998 was considered 100% adherent. Any AIDS-defining illnesses including a history of pulmonary tuberculosis were self-reported according to the 1993 CDC definition of AIDS.[13] Data on prevalent diabetes mellitus[14,15] and ever use of hormone therapy or thyroid medication were collected from the medical history questionnaire and/or laboratory results from the enrollment MACS or WIHS study visit through the study visit when the hearing test was performed (August 2008 through October 2012).

In the MACS, plasma HIV RNA concentrations were measured using the COBAS Ultrasensitive Amplicor HIV-1 monitor assay (Roche Molecular Systems), sensitive to 50 copies HIV RNA/mL; or the Taqman HIV-1 Test (Roche Molecular Systems), sensitive to 20 copies HIV RNA/mL. In the WIHS, plasma HIV RNA was measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Molecular Systems), sensitive to 20 or 48 copies HIV RNA/mL. Values were $\log_{10}$ transformed for statistical analysis. CD4$^+$ and CD8$^+$ T-cell counts were measured for HIV+ men and women at each study visit using standardized flow cytometry and a complete blood cell count.[16] Laboratory results (CD4$^+$, CD8$^+$, HIV RNA) collected within 1 year prior to the hearing testing date were used for this analysis.

Statistical Analysis

These cross-sectional data were analyzed using 2 multivariable linear mixed (containing both fixed and random effects) models constructed using PROC MIXED (SAS, version 9.3). The first mixed model was designed to examine the relationship of the primary predictor, HIV status (HIV− as the reference), with the PTA outcome defined as the HPTA and LPTA for each ear, a total of 4 continuous PTA outcomes for each participant. A random-subject effect was included in each model to account for within-person correlation of the 4 repeated measurements (ie, PTA outcomes). The second mixed model was similar to the first model but for HIV+ participants only. Covariables in the multivariable models included frequency (indicator variables LPTA/HPTA, with HPTA as the reference), ear (better/worse, with worse as the reference), sex (female as the reference), age (in decades), race (black/nonblack, with nonblack as the reference), and history of noise exposure (occupational/none and nonoccupational/none, with none as the reference for both variables).

To examine effect modification by frequency and ear, we included the 3-way interaction between HIV status, LPTA/HPTA, and better/worse ear in the mixed model. Because we were primarily interested in the effect of HIV status, we chose to estimate separate HIV+ and HIV− effects for each combination of the 4 groups (HPTA/worse ear, HPTA/better ear, LPTA/worse ear, LPTA/better ear), a total of 8 effects for the 8 categories of the combination of 3 binary variables. In addition, similar 3-way interactions were also included for sex × LPTA/HPTA × better/worse ear (each of 4 regression coefficients compares a specific combination of the 3 variables involving men with the other 4 combinations involving women), race × LPTA/HPTA × better/worse ear (each regression coefficient compares a specific combination involving blacks with the other 4 combinations involving nonblacks), and age × LPTA/HPTA × better/worse ear (with age as a continuous variable, separate linear regression slopes for each of the 4 categories of LPTA/HPTA and better/worse ear were generated). Each analysis included an examination of residuals as a check on the required assumptions of normally distributed errors with constant variance. Standard residual plots indicated that the error distribution was skewed to the right, and a logarithmic transformation of PTA was used to stabilize the variance. Estimates (regression coefficients) from the linear mixed model are presented on the transformed scale. The proportionate difference, expressed as a ratio, between HIV+ and HIV− in each of the 4 LTPA/HTPA × better/worse ear categories was esti-

Table 1. Characteristics of Participants, Stratified by Human Immunodeficiency Virus (HIV) Status and Sex

Characteristic	HIV+			HIV−			P Value[a]
	Men (n = 117)	Women (n = 105)	All (n = 222)	Men (n = 145)	Women (n = 29)	All (n = 174)	
Age, mean (SD), y	52.3 (7.9)	46.3 (8.0)	49.5 (8.5)	57.8 (9.0)	41.7 (10.5)	55.1 (11.0)	<.001
Race, No. (%)							
Nonblack	56 (47.9)	18 (17.1)	74 (33.3)	117 (80.7)	9 (31.0)	126 (72.4)	<.001
Black	61 (52.1)	87 (82.9)	148 (66.7)	28 (19.3)	20 (69.0)	48 (27.6)	
Noise exposure, No. (%)							
Occupational	31 (26.5)	14 (13.3)	45 (20.3)	35 (24.1)	3 (10.3)	38 (21.8)	.70
Nonoccupational	63 (53.8)	55 (52.4)	118 (53.2)	91 (62.8)	19 (65.5)	110 (63.2)	.06
Ever received, No. (%)							
Diabetes mellitus diagnosis	16 (13.9)	21 (20.0)	37 (16.7)	15 (10.3)	7 (24.1)	22 (12.6)	.26
Hormone therapy	...	28 (26.7)	...	...	5 (17.2)	...	<.001
AIDS diagnosis	19 (16.2)	40 (38.1)	59 (26.6)	...	...	...	
Total duration of therapy, median (IQR), y							
NRTI	20.5 (10.3-29.7)	15.3 (6.2-23.5)	17.4 (8.0-26.4)	...	...	...	...
NNRTI	4.4 (0.4-8.1)	1.4 (0-2.9)	2.1 (0-6.4)	...	...	...	...
Protease inhibitor	3.1 (0-10.0)	5.0 (0-9.4)	3.8 (0-9.6)	...	...	...	...
Current cell count, mean (SD), cells/μL							
CD4+	603 (287)	549 (305)	577 (296)	...	...	...	...
CD8+	940 (417)	782 (356)	865 (397)	...	...	...	...
Log_{10} HIV RNA, median (IQR), copies/mL	1.6 (1.6-1.6)[b]	1.9 (1.7-3.1)	1.7 (1.6-2.5)	...	...	...	...

Abbreviations: ellipses, not applicable; HIV+, HIV seropositive; HIV−, HIV seronegative; IQR, interquartile range; NNRTI, nonnucleoside analog reverse transcriptase inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor.

[a] Comparisons between all HIV+ and all HIV− participants.

[b] 1.6 Denotes a plasma HIV RNA value of less than 50 copies/mL, or undetectable by the assay used.

mated by the exponentiated difference between coefficients (HIV+/HIV−). Separate preliminary analyses also revealed that the error variance was smaller for the LPTA outcome than for HPTA, and we therefore allowed the 2 error variances to be different in the mixed model.

For models restricted to the HIV+ participants, which did not include any 3-way interactions, additional covariables included CD4+ and CD8+ T-cell counts, log_{10} plasma HIV RNA at the study visit closest to the date of the test, ever having had an AIDS-defining condition,[13] and cumulative time receiving PI and/or NNRTI and/or NRTI therapy, adjusted for adherence.
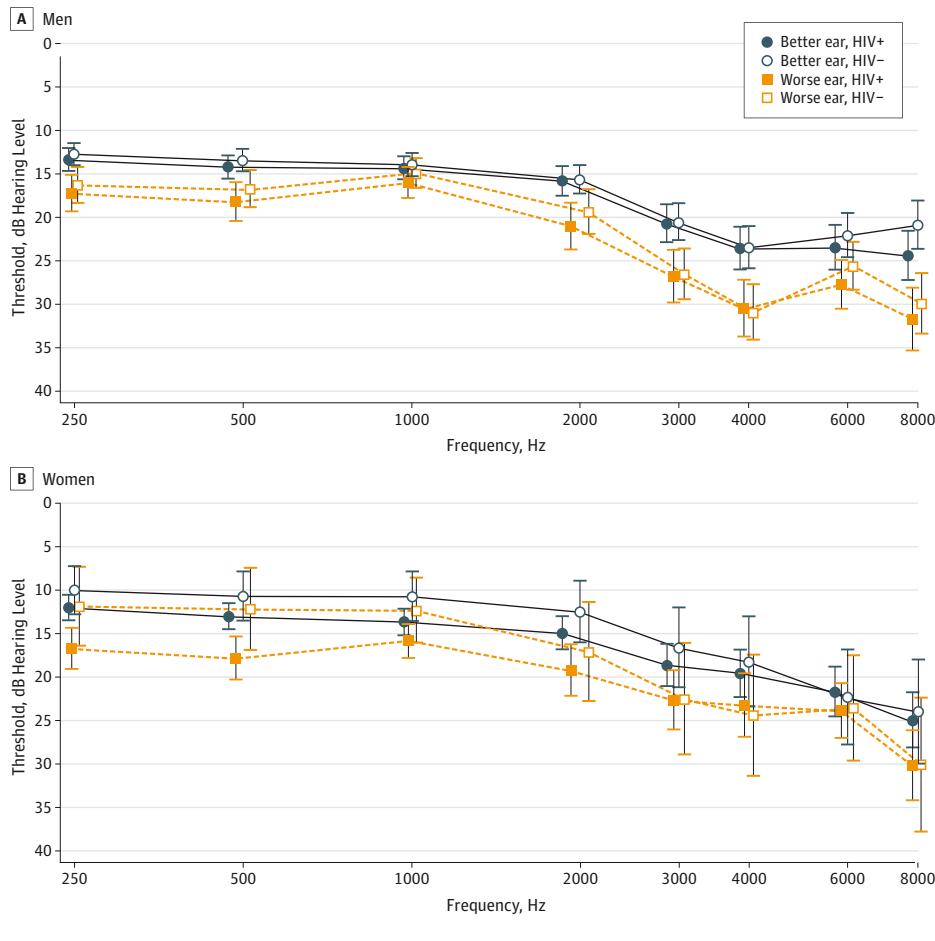
Results

Three hundred ninety-six adults completed pure-tone audiometry testing (90% enrollment of targeted sample); there were 262 men with a mean (SD) age of 57.1 (8.8) years, of whom 117 (44.7%) were HIV+, and 134 women with a mean (SD) age of 47.7 (8.3) years, of whom 105 (78.4%) were HIV+. The proportions of HIV+ in this sample are consistent with those of the entire MACS and WIHS, respectively. The demographic characteristics of the study participants, stratified by HIV status and sex, are presented in **Table 1**. The HIV+ participants were younger and more likely to be female and of black race compared with the HIV− participants. Self-reported occupational noise exposure was simi-

lar between HIV+ and HIV− participants, but men had a higher proportion with occupational noise exposure. The HIV− participants had a slightly higher proportion with nonoccupational noise exposure, but men and women had similar rates for this exposure. Among HIV+ participants, men had longer total duration of NRTI and NNRTI therapy compared with women, but women had longer duration of PI therapy. The HIV+ men and women had similar CD4+ cell counts, but men had a higher proportion with full virologic suppression and higher CD8+ cell counts. Last, more HIV+ women had at least 1 AIDS-defining illness compared with men.

Overall, both HIV+ and HIV− men and women demonstrated a high-frequency sloping configuration for better and worse ear data (**Figure**). In addition, mean threshold data, in decibel HL, show a notched configuration for both HIV+ and HIV− men at 4000 Hz (Figure, A). The figure also shows that HIV+ and HIV− men had similar better ear threshold data although HIV+ men had slightly poorer worse ear threshold than HIV− men. Conversely, HIV+ women had poorer mean thresholds for better and worse ear data across most frequencies tested than HIV− women. The difference between HIV+ and HIV− women, however, was larger for the worse ear than for the better ear, at least up to 2000 Hz (Figure, B). Last, only 3% (n = 12, 10 HIV+ and 2 HIV−) of participants had an air-bone gap, implying that most of the hearing loss was of the sensorineural type, not the conductive or mixed types of hearing loss.

Figure. Age-Adjusted Means and Standard Errors of Pure-Tone Threshold Data for Men and Women

A, Data for 117 human immunodeficiency virus–seropositive (HIV+) and 145 HIV-seronegative (HIV−) men. B, Data for 105 HIV+ and 29 HIV− women.

The results of the multivariable analysis are shown in **Table 2**. The regression coefficients of the HIV+/HIV− × high/low frequency × better/worse ear combinations represent the difference between each combination and the reference group. The log PTAs for the other 7 groups were all significantly higher than the reference (high frequency × better ear × HIV−). The regression coefficients of the combinations involving sex and race represent effects compared with females and nonblacks, respectively. For high frequencies only, being black was negatively associated with hearing loss compared with being nonblack. In other words, black participants were less likely to have poorer high-frequency hearing. Age was significantly associated with higher log PTAs in both ears. Having a reported history of noise exposure, both occupational and nonoccupational, was not significantly associated with poorer hearing sensitivity.

The estimates from Table 2 were used to calculate the ratios of PTAs for HIV+ and HIV− participants (**Table 3**). After adjusting for age, sex, race, and noise exposure, for the better ear, HPTA was 18% higher for HIV+ participants than for HIV− participants, and LPTA was 12% higher; both differences were significant. For worse ear data, HIV+ participants again had higher LPTA and HPTA data compared with HIV− participants, and these ratios were not significant. The HIV-related variables

studied (ie, CD4+ and CD8+ T-cell counts, plasma HIV RNA, history of AIDS, and total years of receipt of any class of ART medications) were not significantly associated with hearing sensitivity (**Table 4**) after adjusting for age, sex, race, and noise exposure.

Discussion

In this study, independent of long-term exposure to antiretroviral medications, current CD4+ cell count, and HIV viral load, HIV+ participants had significantly higher (ie, poorer hearing sensitivity) better ear HPTA (18%) and LPTA (12%) values than HIV− participants, and both results are important. The participants were middle-aged (mean age, approximately 50 years), so an HIV effect on LPTA was not expected, given the speculation that long-term ART exposure or HIV itself contributes to premature aging.[17]

Reports of the prevalence of hearing loss in HIV+ adults have ranged from as low as 14%[2] or 23%[18] to as high as 49%.[19] Hearing loss, in some studies, has been defined as any threshold measured greater than 25 dB HL,[18,19] but this definition will overestimate the prevalence of hearing loss and is rarely used in clinical settings or by the World Health Organization.[20]

Table 2. Estimated Regression Coefficients, Standard Errors, and Confidence Intervals From the Multivariable Linear Mixed Model

Variable[a]	Natural Log dB		P Value
	Estimate (SE)	95% CI	
Intercept	0.95 (0.21)	0.54 to 1.36	<.001
High frequency × better ear × HIV−	1 [Reference]		
High frequency × better ear × HIV+	0.16 (0.07)	0.02 to 0.29	.03
High frequency × worse ear × HIV−	0.67 (0.20)	0.28 to 1.05	.001
High frequency × worse ear × HIV+	0.78 (0.20)	0.38 to 1.17	<.001
Low frequency × better ear × HIV−	0.27 (0.16)	−0.05 to 0.58	.10
Low frequency × better ear × HIV+	0.38 (0.17)	0.05 to 0.71	.02
Low frequency × worse ear × HIV−	0.75 (0.16)	0.43 to 1.07	<.001
Low frequency × worse ear × HIV+	0.85 (0.17)	0.52 to 1.18	<.001
Male × high frequency × worse ear	0.15 (0.08)	−0.01 to 0.31	.06
Male × high frequency × better ear	0.07 (0.08)	−0.09 to 0.23	.39
Male × low frequency × worse ear	0.12 (0.07)	−0.01 to 0.25	.08
Male × low frequency × better ear	0.17 (0.07)	0.04 to 0.30	.01
Black × high frequency × worse ear	−0.23 (0.07)	−0.37 to −0.08	.003
Black × high frequency × better ear	−0.26 (0.07)	−0.40 to −0.11	<.001
Black × low frequency × worse ear	−0.02 (0.06)	−0.14 to 0.10	.74
Black × low frequency × better ear	−0.05 (0.06)	−0.17 to 0.08	.45
Age/10 × high frequency × worse ear[b]	0.28 (0.04)	0.21 to 0.36	<.001
Age/10 × high frequency × better ear[b]	0.37 (0.04)	0.29 to 0.44	<.001
Age/10 × low frequency × worse ear[b]	0.17 (0.03)	0.11 to 0.23	<.001
Age/10 × low frequency × better ear[b]	0.21 (0.03)	0.15 to 0.27	<.001
Noise exposure			
Occupational	0.08 (0.06)	−0.04 to 0.20	.18
Nonoccupational	−0.03 (0.05)	−0.13 to 0.07	.52

Abbreviations: HIV+, human immunodeficiency virus seropositive; HIV−, human immunodeficiency virus seronegative; SE, standard error.

[a] See Methods section for definitions of interaction terms.

[b] Age expressed in decades.

van der Westhuizen et al[2] used an HIV− control group that was age, sex, race, and work environment matched to HIV+ adults and defined hearing loss as a PTA of 500, 1000, and 2000 Hz greater than 25 dB HL; they found significantly poorer thresholds at 500, 1000, 2000, 3000, and 4000 Hz among HIV+ adults compared with controls. That study was limited, however, by the range of frequencies tested (ie, only 500-4000 Hz), so an HIV effect at greater than 4000 Hz was potentially missed by van der Westhuizen et al.[2] In the present study, pure-tone thresholds were extensively evaluated over a range of frequencies that are commonly tested clinically. In addition, the analyses included age, sex, race, and occupational and nonoccupational noise exposure using a clear definition of LPTA and HPTA.

An effect on LPTA, although unexpected, has been reported previously. Bainbridge et al[21] showed that adults with diabetes mellitus were significantly more likely to have hearing loss at both low (LPTA) and high frequencies (HPTA). In fact, the definitions of HPTA for the present study were the same as those used by Bainbridge et al[21]; the only difference was that for the LPTA, 250 Hz was included in the definition for the present study and not by Bainbridge et al.[21] It is possible that both HIV infection and diabetes, being systemic diseases, could affect the neural function of the cochlea.

Our findings that HIV disease-related and treatment-related variables were not significantly associated with a higher LPTA or HPTA contrast with previous research. Ongulo and Oburra[22] reported that among HIV+ adults not receiving ART, those with lower CD4+ T-cell counts and advanced disease were more likely to have hearing loss. van der Westhuizen et al[2] also found greater hearing loss in those with more advanced HIV infection (stage 3), despite HAART. These discrepancies are probably due to differences in study populations because most of the people in the present study experienced virological suppression while receiving ART.

In other research, the prevalence of sensorineural hearing loss increased significantly with disease progression[2,18,23] and pure-tone thresholds were significantly higher in individuals with higher CDC classifications.[24] Comparisons between these studies and the present study are difficult because hearing loss was not defined[22-24] and in one study[22] HIV+ participants were not receiving ART. In addition, HIV-specific variables (eg, CD4+ and CD8+ T-cell counts, plasma HIV RNA) in the present study were clearly defined whereas in previous research, only CDC classification and CD4+ T-cell count[18] were examined. Thus, the present study has evaluated the association between HIV disease characteristics, HIV treatment, and hearing threshold levels more thoroughly than previous studies.

Total years taking any ART were not associated with higher PTAs in our study, which is consistent with other reports. Schouten et al[1] reported no effect of initiating zidovudine or didanosine therapy on hearing sensitivity over a few months.

The LPTA and HPTA definitions between the present study and that of Schouten et al[1] are slightly different. Marra et al[25] found a significant association between ART and hearing loss among older adults, after adjusting for confounding variables. Hearing loss in that study, however, was defined as either a unilateral or bilateral threshold greater than 25 dB HL at 4000 Hz only, an approach rarely used to define hearing loss clinically. Furthermore, Marra et al[25] did not present any characteristics of the HIV+ participants studied. The lack of a significant association between ART and hearing loss in the present study does not eliminate the possibility that ART exposure may be a risk factor for hearing loss. Use of NRTIs has been associated with possible mitochondrial mutation in both perinatally HIV-infected children[26] and HIV+ adults[27] including nonsyndromic sensorineural hearing loss.[28]

The present study has expanded our knowledge of the relationship between HIV infection and hearing loss because aspects of HIV, disease specific and treatment specific, and definitions of hearing loss had not been examined previously. It is well known that higher pure-tone thresholds are the best pre-dictor of poorer word recognition abilities[29,30]; it is not known, however, how HIV and poorer hearing, specifically higher LPTA, affect communication or word recognition. Most of the acoustic energy for English vowels, specifically the first and second formants, occurs at less than 2000 Hz and these formants are the most important for vowel identification.[31] In addition, stop consonants (/p, b/, /t, d/, /k, g/), for example, have lower-frequency energy and formant transitions[32] although other consonants, such as fricatives (/s, z/, /f, v/), have higher-frequency energy.[33] Hence, elevated low-frequency hearing threshold levels can affect the perception of vowels and certain consonants.

Conclusions

To our knowledge, this is the first study to demonstrate that HIV+ individuals have poorer hearing across the frequency range after many other factors known to affect hearing have been controlled for. Whereas the early literature on possible hearing loss associations with diabetes[34,35] tended to focus on specific frequency ranges (namely, higher frequencies), additional data from the follow-up studies have demonstrated hearing loss in both the low to middle and high-frequency range.[36] The association reported by Bainbridge et al[21] between diabetes and higher audiometric thresholds across the frequency range based on the 1999 to 2004 US National Health and Nutrition Examination Survey was also investigated by Agrawal et al,[37] who supported the association of diabetes, hypertension, and smoking with hearing loss at both high and low PTA frequency ranges. Although we do not understand the mechanism of hearing loss found in our study, our results suggest that HIV+ individuals may have physiologic changes that mimic other chronic conditions that affect hearing levels.

Table 3. Estimated Ratios of Pure-Tone Averages (PTAs) for Human Immunodeficiency Virus–Seropositive (HIV+) People to Those for HIV-Seronegative (HIV−) People, for High and Low Frequencies and Better and Worse Ear

Condition	Ratio of PTA for HIV+ vs HIV− (95% CI)[a]	P Value[b]
High frequency × worse ear	1.12 (0.97-1.29)	.12
High frequency × better ear	1.18 (1.02-1.36)	.02
Low frequency × worse ear	1.11 (0.98-1.25)	.09
Low frequency × better ear	1.12 (1.00-1.26)	.05

[a] Adjusted for age, sex, race, and occupational and nonoccupational noise exposure.

[b] P values for comparing the estimated ratios to the null value of 1.

Table 4. Estimated Regression Coefficients, Standard Errors, and Confidence Intervals From the Multivariable Linear Mixed Model Among the Human Immunodeficiency Virus (HIV)–Seropositive Participants Only

| Variable | Natural Log dB | | |
	Estimated Regression Coefficient (SE)	95% CI	P Value
Intercept	1.72 (0.27)	1.19 to 2.26	<.001
High frequency	0.36 (0.02)	0.31 to 0.40	<.001
Male sex	0.21 (0.09)	0.04 to 0.38	.02
Black race	−0.07 (0.08)	−0.24 to 0.09	.38
Better ear	−0.26 (0.02)	−0.31 to −0.21	<.001
Age, each 10-y increase	0.20 (0.05)	0.11 to 0.29	<.001
Noise exposure			
Occupational	0.02 (0.09)	−0.15 to 0.20	.79
Nonoccupational	−0.02 (0.07)	−0.17 to 0.12	.74
CD4+ cell count, 100-count increase	−0.00 (0.01)	−0.03 to 0.02	.84
CD8+ cell count, 100-count increase	−0.00 (0.01)	−0.02 to 0.02	.66
Total duration of therapy, y			
NRTI	−0.00 (0.00)	−0.01 to 0.01	.50
NNRTI	−0.01 (0.01)	−0.03 to 0.02	.61
Protease inhibitor	0.01 (0.01)	−0.01 to 0.02	.38
Log$_{10}$ HIV RNA, copies/mL	−0.01 (0.04)	−0.08 to 0.07	.90
Ever received AIDS diagnosis	0.07 (0.09)	−0.10 to 0.25	.42

Abbreviations: NNRTI, nonnucleoside analog reverse transcriptase inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; SE, standard error.

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CORRECTION

Missing Conflict of Interest Disclosures Statement: The statement "**Conflict of Interest Disclosures:** None reported." should have been included in the end matter for the article "Staged Laryngotracheoplasty in Adult Laryngotracheal Stenosis: Predictors of Long-term Decannulation" by Liu et al, published online December 26, 2014 (doi:10.1001/jamaoto.2014.3283). This article was corrected online.