

# Hearing Loss in Perinatally HIV-infected and HIV-exposed but Uninfected Children and Adolescents

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**Background:** Little is known about hearing loss in children with HIV infection (HIV+). We examined the prevalence of hearing loss in perinatally HIV+ and HIV-exposed but uninfected (HEU) children, compared these with the percentage with hearing loss in the general population and evaluated possible risk factors for hearing loss in HIV+ and HEU children.

**Methods:** Audiometric examinations were completed in children who met any prespecified criteria for possible hearing loss. The hearing examination consisted of a tympanogram in each ear and pure-tone air-conduction threshold testing from 500 through 4000 Hz. Hearing loss was defined as the pure-tone average over these frequencies  $\geq 20$  dB hearing level. The associations of demographic variables, parent/caregiver, HIV disease and HIV treatment with hearing loss were evaluated with univariate and multi-variable logistic regression models.

**Results:** Hearing testing was completed in 231 children (145 HIV+ and 86 HEU). Hearing loss occurred in 20.0% of HIV+ children and 10.5% of HEU children. After adjusting for caregiver education level, HIV infection was associated with increased odds of hearing loss (adjusted odds ratio = 2.13, 95% confidence interval: 0.95–4.76,  $P = 0.07$ ). Among HIV+ children, those with a Centers for Disease Control and Prevention class C diagnosis had over twice the odds of hearing loss (adjusted odds ratio = 2.47, 95% confidence interval: 1.04–5.87,  $P = 0.04$ ). The prevalence of hearing

loss was higher in both HIV+ and HEU children compared with National Health and Nutrition Examination Survey III children.

**Conclusions:** Hearing loss was more common in both HIV+ and HEU children than in children from a US population sample. More advanced HIV illness increased the risk of hearing loss in HIV+ children.

**Key Words:** perinatal HIV exposure, perinatal HIV infection, hearing loss, antiretroviral therapy

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Children exposed to HIV may be at higher risk for hearing loss, but there is limited research in this area. Researchers have primarily focused on conductive hearing loss as a result of otitis media in HIV-infected (HIV+) children.<sup>1,2</sup> Principi et al<sup>1</sup> showed that symptomatic HIV+ children have significantly more episodes of acute otitis media compared with asymptomatic HIV+ children and with HIV-uninfected children. More recently, Weber et al<sup>2</sup> reported that 152 of 459 (33.1%) HIV+ children <13 years of age were diagnosed with otitis media; 65 of these 152 (42.8%) children were diagnosed with chronic otitis media. In a subsequent stratified analysis, Weber et al<sup>2</sup> observed that younger children (<6 years of age) receiving highly active antiretroviral therapy (HAART) had significantly lower prevalence of chronic otitis media compared with those not on HAART. The lower prevalence of chronic otitis media in the younger age group was attributed to higher CD4+ lymphocyte (CD4) counts. For older children (6–13 years of age), there was no significant difference in chronic otitis media between children on HAART and those not on HAART.

Recurrent otitis media, especially early in life, has been shown to delay phonological development,<sup>3</sup> although other researchers reported no negative effects of persistent otitis media on language development.<sup>4</sup> Antibiotic treatment of acute otitis media episodes generally eliminates the infection and the associated conductive hearing loss. However, chronic otitis media, even if treated with tympanostomy tubes, may lead to higher air-conduction (AC) thresholds and a permanent conductive hearing loss. In fact, Stenstrom et al<sup>5</sup> reported that children who were treated with tympanostomy tubes for chronic otitis media had statistically significant higher thresholds (approximately 2–8 dB) compared with children treated with antibiotics.

Unlike conductive hearing loss caused by otitis media, sensorineural hearing loss involves a distortion of the auditory signal as it leaves the cochlea to be further processed by higher auditory structures and may require a hearing aid as an intervention approach. Because of the distortion, sensorineural hearing loss, especially later-identified losses, impacts language development in young children,<sup>6–8</sup> but no association between this type of hearing loss and HIV infection in children has been reported. There is limited research in this area with HIV+ adults.<sup>9,10</sup> HIV and its treatment are associated with mitochondrial dysfunction,<sup>11</sup> and mitochondrial disorders are associated with sensorineural hearing loss,<sup>12,13</sup> building a plausible mechanism for increased sensorineural hearing loss risk in HIV-infected children.

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Recently, researchers have begun to evaluate hearing sensitivity in HIV+ children using pure-tone threshold testing.<sup>14,15</sup> Taipale et al<sup>14</sup> reported that 24% of HIV+ children ( $n = 29$ ) had some degree of hearing loss based on their better ear pure-tone average (PTA) compared with 3% of control children ( $n = 31$ ). The higher percentage of hearing loss in HIV+ children was attributed to middle-ear pathologies. In a larger study, 54 of 139 HIV+ children (39%) had PTAs reflecting some degree of hearing loss.<sup>15</sup> Of the 54 with hearing loss, 48 (89%) had conductive hearing loss, 5 had a mixed hearing loss and only 1 had a sensorineural hearing loss. The rates of hearing loss in these studies suggest an increased risk of hearing loss among children with HIV infection when compared with reported prevalence of 14.9% in the general US population aged 6–19 years.<sup>16</sup> In addition, these studies suggest that HIV infection is associated with middle ear pathologies that could result in conductive hearing loss.

The objectives of this study were (1) to compare the prevalence of hearing loss overall in perinatally HIV+ and HIV-exposed, but uninfected (HEU) children; (2) to compare the adjusted prevalence of hearing loss in perinatally HIV+ and HEU to that of presumably HIV-unexposed children examined in the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 and (3) to evaluate child and caregiver risk factors for hearing loss among HIV+ and HEU children.

## METHODS

### Study Population and Protocol

Our analysis included HIV+ and HEU children enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study. The AMP is a prospective cohort study conducted at 15 sites within the United States and Puerto Rico designed to examine the effects of HIV infection and treatment on children and adolescents with perinatal HIV exposure. All study procedures were approved by the institutional review boards of each participating site and of the Harvard School of Public Health. Written consent was obtained from each child's parent or legal guardian or directly from the older participants, as allowed by the site institutional review board; child's assent was obtained as appropriate.

Children were eligible if they were born to women with HIV infection and were 7–16 years old at study entry. At each semi-annual study visit, information about study participants and their families was gathered through physical examinations, clinical interviews, medical record reviews and neurodevelopmental testing. Lifetime health and antiretroviral treatment (ART) histories were obtained from prior studies or through chart reviews, and current health status was ascertained through physical and laboratory evaluations.

### Hearing Assessments

This cross-sectional analysis includes children in the AMP who had an audiometric examination at the 6-month or 2-year visit between April 5, 2007, and December 10, 2010. Audiometric examinations were performed in children meeting at least one of the following “trigger” criteria: a Core Language Score (CLS) <85 on the Clinical Evaluation of Language Function (CELF-4)<sup>17</sup> at either the 6-month visit or 2-year visit, parent or caregiver report of a child's hearing problem, an abnormal hearing screening as part of routine medical care or a suspected mitochondrial abnormality. The CELF-4 is a standardized measure of language composed of multiple subtests; the CLS is a summary score. The audiometric examination was performed according to a standardized study-defined protocol by an audiologist in a sound-treated test booth and typically was completed within 6 weeks of meeting 1 of the

trigger criteria. At a minimum, the examination consisted of pure-tone AC testing (with bone-conduction testing, if indicated) across the speech-frequency range (500–4000 Hz) and a tympanogram in each ear. In cases where children had repeat audiograms from multiple visits ( $n = 9$ ), the most complete and reliable audiogram was used.

Hearing loss was determined using the pure-tone AC thresholds from an audiometric examination and a PTA of 500, 1000, 2000 and 4000 Hz was calculated for each ear. Once the PTA was calculated, a better ear PTA and worse ear PTA were determined; hearing loss was defined as a worse ear PTA  $\geq 20$  dB hearing level (HL). Unilateral hearing loss was defined as better ear PTA <20 dB HL and worse ear PTA  $\geq 20$  dB HL.

### Statistical Methods

Among those with audiometric examinations, demographic variables, caregiver and clinical characteristics were compared between children with and without hearing loss using Fisher's exact test or 2-sample *t* tests, as appropriate. PTA was compared by HIV infection status using Wilcoxon rank-sum tests. Risk factors for hearing loss were evaluated by fitting logistic regression models to obtain estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Factors considered as predictors of hearing loss included child's age, sex, body mass index (which was used as an overall measure of adiposity and nutrition), race, ethnicity and birth characteristics (prematurity and low birth weight). Caregiver characteristics included level of education, Verbal and Performance Scale IQs (as measured by the Wechsler Abbreviated Scale of Intelligence<sup>18</sup>), relationship to child (biological parent versus other) and household income. Socioeconomic status (SES) variables were included based on previous studies demonstrating an increased risk of childhood hearing loss among those with lower SES.<sup>19</sup> Factors with  $P < 0.20$  in univariate models were considered for inclusion in a multivariate model, which was then reduced by a backward selection procedure to include covariates with  $P < 0.15$ . Separate unadjusted and adjusted models were fit using the same strategy but restricted to HIV+ children to evaluate the association of hearing loss with measures of HIV disease severity [plasma HIV RNA concentration (HIV viral load), CD4%, Centers for Disease Control and Prevention (CDC) Disease Classification (Class C versus less symptomatic classes, N, A or B)], as well as summary measures of ART (duration of treatment with HAART and cumulative exposure to nucleoside reverse transcriptase inhibitors).

Because the audiometric examination was a triggered assessment, audiometric data were not obtained on the entire AMP cohort. The estimated prevalence of hearing loss was calculated by multiplying the proportion of children with hearing loss among those with an audiometric evaluation by the proportion who met the trigger. However, this estimate assumed that everyone with hearing loss in the AMP cohort met a trigger for the audiometric evaluation (ie, the trigger sensitivity was 100%). Because some children with hearing loss may not have met one of the study-defined triggers for an audiometric examination, the estimated prevalence of hearing loss would underestimate the true prevalence of hearing loss. To correct for this assumption, adjusted prevalences were estimated by dividing the unadjusted prevalence by a range of possible sensitivities of the trigger, allowing an evaluation of a range of possible hearing loss prevalences. Comparisons of prevalences between the HIV+ and HEU children from the AMP study and between these children and those in the NHANES 1988–1994 were conducted using  $\chi^2$  tests at a range of possible trigger sensitivities. Assessment of hearing in children for the NHANES 1988–1994 is described in detail by Niskar et al.<sup>16</sup> All statistical analyses were conducted using SAS Version 9.1 (SAS Institute, Cary, NC) using

data submitted as of January 1, 2011. Two-sided *P*-values <0.05 were considered statistically significant.

**RESULTS**

Accrual to the AMP study was completed in 2009, with 674 children (448 HIV+, 226 HEU) enrolled and completing the entry visit. Among these 674 children, 301 (45%) met a trigger to have an audiometric examination and 231 of these children (77%) completed this examination (145 HIV+, 86 HEU). The trigger met most often was a CLS <85 on the CELF-4 (n = 154; 92 HIV+, 62 HEU) followed by parent or caregiver report of hearing concern (n = 51; 36 HIV+, 15 HEU). Reasons for not completing the examination included parent or child refusal, missed study visits, inability to schedule an examination or discontinuation of the child from the study before the examination could be conducted. Children who met the trigger for an audiometric examination were more likely to be black (77% versus 69%, *P* = 0.03) and have caregivers with less than a high school education (34% versus 24%, *P* = 0.01) when compared with those not meeting the trigger. Among all children who met a trigger for an audiometric examination, HEU children were more likely to have completed the examination than HIV+ children (83% versus 72%, *P* = 0.02). Those children with *in utero* antiretroviral exposure were also more likely to have audiometric examinations (89% versus 71%, *P* < 0.01). No other statistically significant differences were observed in demographic variables between those with examinations and those without audiometric examinations among children who met the hearing trigger.

The 231 children with a completed audiometric examination ranged in age from 7 to 17 years at the time of the audiometric examination (mean 12.2 years) and were 53% female, 77% black and 29% Hispanic (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B197>). Over half (57%) lived in households with ≤ \$20,000 annual income; 32% of caregivers had less than a high school education. Among the HIV+ children with audiometric examinations, 35% had HIV viral load >400 copies/mL and 23% had a CD4% <25%, while 32% had a CDC class C diagnosis.

The remaining portion of Supplemental Digital Content 1, <http://links.lww.com/INF/B197> shows the demographic variables and HIV characteristics by hearing loss status. The percentage of children with parent/caregiver report of frequent ear infections was significantly higher among those with hearing loss than among those without hearing loss (41% versus 21%, *P* = 0.02). Among HIV+ children, history of CDC class C diagnosis was significantly more common among those with hearing loss (52% versus 28%, *P* = 0.03).

Among the 231 children with audiometric examinations, 16.5% (n = 38) were defined as having hearing loss based on a PTA ≥20 dB HL in the worse ear and HIV+ children were twice as likely to have hearing loss than HEU children (20.0% versus 10.5%, *P*=0.07), although this difference did not reach statistical significance (Table 1). Fifteen HIV+ children and 3 HEU children had unilateral hearing loss. Among these 18 children, 61% had less than a 20-dB difference between PTAs for right and left ears and the remaining 39% of children had differences >20 dB between ears, indicating more of an asymmetric unilateral hearing loss. The average worse ear PTA was significantly higher for HIV+ children than for HEU children (14.9 dB HL versus 11.3 dB HL, *P* = 0.04). There was a nonsignificant trend for higher better-ear PTA in the HIV+ children compared with the HEU children (10.5 dB HL versus 8.6 dB HL, *P* = 0.09). The PTAs for right and left ears were similar for both HIV+ and HEU children. Two children did not have PTA data but were classified as having hearing loss. One child had known hearing loss and the other child was deaf.

Tympanogram and bone-conduction data for the 38 children (29 HIV+ and 9 HEU) defined as having hearing loss were evaluated to classify hearing loss as conductive, sensorineural or a mixed combination of the two. When a flat tympanogram was reported, bone-conduction data were used to confirm the presence of a conductive component to their hearing loss. Based on this evaluation, which was blinded to HIV status, 14 of 38 (37%) children had a conductive hearing loss, of whom 11 (79%) were HIV+ children. The determination of a conductive hearing loss for 1 child was a result of open pressure equalization tubes. The remaining 24 (63%) children had sensorineural hearing loss, of whom 18 (75%) were HIV+ children.

**TABLE 1.** Hearing Loss by HIV Infection Status Among 231 Participants of the AMP Study With Audiometric Examinations

Audiometric Outcome	Infection Status			<i>P</i> †
	HIV-infected (HIV+) (N = 145)	HIV-exposed Uninfected (HEU) (N = 86)	Total* (N = 231)	
PTA ≥20 dB (worse ear)	29 (20%)	9 (10%)	38 (16%)	0.07
PTA ≥20 dB (better ear)	14 (10%)	6 (7%)	20 (9%)	0.63
Unilateral hearing loss	15 (10%)	3 (3%)	18 (8%)	0.08
PTA, in dB				
Worse ear, median (IQR)	11.3 (7.5–16.3)	9.4 (6.3–13.8)	10.0 (7.5–15.0)	0.04
Minimum, maximum	0.0, 112.5	2.50, 38.8	0.0, 112.5	
Mean (SD)	14.9 (14.3)	11.3 (7.7)	13.6 (12.3)	
Better ear, median (IQR)	8.8 (5.0–12.5)	7.5 (5.0–10.0)	8.8 (5.0–11.3)	0.09
Minimum, maximum	0, 95	0.00, 28.8	0, 95	
Mean (SD)	10.5 (10.4)	8.6 (6.0)	9.8 (9.1)	
Right ear, median (IQR)	10.0 (6.3–13.8)	8.8 (6.3–11.3)	8.8 (6.3–13.8)	0.05
Minimum, maximum	0.0, 112.5	1.25, 38.8	0.0, 112.5	
Mean (SD)	12.8 (13.0)	10.0 (7.1)	11.7 (11.3)	
Left ear, median (IQR)	10.0 (6.3–13.8)	8.8 (6.3, 12.5)	10.0 (6.3–13.8)	0.14
Minimum, maximum	0, 95	0.00, 38.8	0, 95	
Mean (SD)	12.5 (12.4)	9.9 (6.9)	11.5 (10.7)	

\*Two subjects did not have a value for worse or better pure-tone average, 3 did not have right ear PTA and 4 did not have left ear PTA.

†*P* by Fisher's exact test for percent with hearing loss by infection status and by Wilcoxon rank-sum test for comparisons of PTA.

dB, decibels; SD, standard deviation; PTA, pure-tone average; IQR, interquartile range.

**TABLE 2.** Logistic Regression Models for Hearing Loss (PTA  $\geq$ 20 dB) by Child Demographics and Caregiver Characteristics, Among all 231 Children With Audiometric Examinations and Restricted to 145 HIV+ Children With Examinations

Variable	N	Odds Ratio	95% CI	P
Univariate associations among all 231 children*				
HIV-infected	231	2.14	(0.96–4.77)	0.06
Age at examination	231	1.04	(0.92–1.17)	0.58
Body mass index Z-score at examination	231	1.02	(0.77–1.35)	0.89
Female sex	231	1.43	(0.70–2.90)	0.33
Black	214	0.83	(0.36–1.92)	0.67
Hispanic or Latino	230	0.70	(0.31–1.57)	0.39
Gestational age <37 weeks	157	1.62	(0.64–4.14)	0.31
Birth weight <2500 g	207	0.88	(0.38–2.02)	0.76
Caregiver is biological parent	231	0.61	(0.30–1.23)	0.17
Caregiver completed high school	231	1.99	(0.87–4.59)	0.11
Caregiver married	231	0.66	(0.30–1.43)	0.29
Caregiver VIQ <70	160	0.61	(0.13–2.85)	0.53
Household income $\leq$ \$20,000	229	0.71	(0.35–1.42)	0.33
Univariate associations of HIV disease severity and ART among all 145 HIV+ children†				
Viral load >400 copies/mL at examination	137	0.85	(0.34–2.14)	0.73
CD4% <25% at examination	145	1.10	(0.42–2.86)	0.84
Nadir CD4% <20%	145	2.07	(0.87–4.94)	0.10
Peak viral load $\geq$ 500,000 copies/mL	145	0.97	(0.42–2.20)	0.93
CDC class C	145	2.81	(1.22–6.48)	0.02
Duration on HAART $\leq$ 7 yr	145	1.63	(0.71–3.78)	0.25
Duration on NRTI >7 yr	145	0.82	(0.21–3.23)	0.77
ART regimen at examination	145	—	—	0.40
HAART with PI		1.00 (ref)	—	—
HAART without PI		1.27	(0.45–3.59)	0.65
Non-HAART/no ART		0.27	(0.03–2.19)	0.22

\*HIV infection status, caregiver relationship to child and caregiver education level all considered for final model. Only HIV infections status (aOR = 2.13, 95% CI: 0.95–4.76,  $P = 0.07$ ) and caregiver education (aOR = 1.98, 95% CI: 0.85–4.59,  $P = 0.11$ ) were retained in final adjusted model.

†CDC class and nadir CD4% were considered for final model. CDC class remained significant in the final adjusted model (aOR = 2.47, 95% CI: 1.04–5.87,  $P = 0.04$ ). aOR, adjusted odds ratio; PI, protease inhibitor; VIQ, Verbal Intelligence Quotient; NRTI, nucleoside reverse transcriptase inhibitor.

Table 2 presents a summary of the logistic regression models for hearing loss. In univariate logistic models of hearing loss including all 231 children with hearing examinations, HIV+ children had more than double the odds of hearing loss (OR = 2.14, 95% CI: 0.96–4.77,  $P = 0.06$ ) when compared with HEU children. This association remained marginally significant after adjustment for caregiver education level (adjusted OR = 2.13, 95% CI: 0.95–4.76,  $P = 0.07$ ; see Table 2 footnotes). No other factors showed significant associations with hearing loss.

Among the 145 HIV+ children with audiometric examinations, those with a current or prior CDC class C diagnosis had nearly a 3-fold higher odds of hearing loss (OR = 2.81, 95% CI: 1.22–6.48,  $P = 0.02$ ) compared with children with other CDC classifications (Table 2, lower panel), and this association remained significant after adjusting for nadir CD4% (adjusted OR = 2.47, 95% CI: 1.04–5.87,  $P = 0.04$ ; see Table 2 footnotes). Having a history of poor immune status, as reflected by nadir CD4% <20%, was borderline significantly associated with hearing loss, either in unadjusted models (OR = 2.07, 95% CI: 0.87–4.94,  $P = 0.10$ ) or after adjustment for CDC class. No other HIV characteristics were associated with hearing loss.

The prevalence of hearing loss in the AMP cohort was higher than that of children from the general US population based on recent analyses of data from NHANES III (H.J. Hoffman, personal communication, 2011). Assuming that all children with hearing loss were identified as meeting one or more study-defined triggers (ie, 100% trigger sensitivity), then the overall prevalence (and 95% CI) for AMP children was 7.4% (5.3%, 10.1%), with a higher prevalence for HIV+ children than HEU children [9.0% (6.1%, 12.7%) and 4.8% (2.2%, 8.8%), respectively] (Table 3). Assuming a trigger sensitivity of 60%, the adjusted prevalence increased to 15.0%

(11.2%, 19.3%) for HIV+ children and 8.0% (4.5%, 12.8%) for HEU children, both of which are significantly higher than the 4.0% prevalence seen in the NHANES III children ( $P < 0.05$ ) (Table 3 and Figure, Supplemental Digital Content 2, <http://links.lww.com/INF/B198>). For the HIV+ children, the adjusted prevalence increased in older age groups, and the percents with hearing loss were consistently higher than the 3–5% prevalences observed in NHANES III. HEU children had a slightly higher estimated prevalence of hearing loss, although not significantly higher, than that in NHANES III whenever the trigger sensitivity was >60%. Once the trigger sensitivity fell to  $\leq$  60%, the difference became statistically significant (Table 3).

## DISCUSSION

This study reports the largest set of diagnostic audiology testing results in a cohort of HIV+ children and one of the few studies in comparisons with HEU children.<sup>20</sup> Hearing loss is common among both HIV+ and HEU children, and HIV+ children had a significantly higher worse ear PTA (ie, poorer hearing) than HEU children. The prevalence of hearing loss in the current study is lower than other recent studies among HIV+ children.<sup>14,15</sup> Those previous studies reported a substantially higher rate of conductive hearing loss whereas more children had sensorineural hearing loss in the present study. The frequencies used to calculate the PTA were consistent across the 3 studies but the definition of hearing loss was slightly different; hearing loss was defined as a PTA >25 dB HL in other studies.<sup>14,15</sup>

The present study used a trigger-based approach for estimating the prevalence of hearing loss, an approach that has been shown to be effective in estimating prevalence rates.<sup>21</sup> Assuming the criteria for triggering an audiology examination identified 60%

**TABLE 3.** Adjusted Prevalence of Hearing Loss in AMP and Prevalence of Hearing Loss in NHANES

Trigger Sensitivity	Age Group at Examination	Overall	HIV+	HEU	NHANES III (1988–1994)*	Significant Pairwise Comparisons (at <i>P</i> < 0.05)
		Prevalence (95%CI)	Prevalence (95%CI)	Prevalence (95%CI)	Prevalence (95%CI)	
100%	7–8 yr†	5.0% (1.4%, 12.3%)	6.2% (0.8%, 20.8%)	4.3% (0.5%, 14.8%)	5.1% (3.5%, 7.5%)	
	9–11 yr	6.2% (3.0%, 11.1%)	8.2% (3.4%, 16.2%)	3.9% (0.8%, 11.0%)	2.7% (1.6%, 4.6%)	HIV+ vs. NHANES
	12–14 yr	8.3% (4.6%, 13.6%)	8.9% (4.5%, 15.4%)	6.7% (1.4%, 18.2%)	4.1% (2.7%, 6.2%)	HIV+ vs. NHANES
	15–17 yr	9.9% (4.9%, 17.5%)	11.1% (5.2%, 20.0%)	4.9% (0.1%, 24.9%)	4.1% (2.4%, 6.8%)	HIV+ vs. NHANES
	Total	7.4% (5.3%, 10.1%)	9.0% (6.1%, 12.7%)	4.8% (2.2%, 8.8%)	4.0% (3.1%, 5.1%)	HIV+ vs. NHANES
80%	7–8 yr	6.3% (2.1%, 14.0%)	7.8% (0.8%, 20.8%)	5.4% (0.5%, 14.8%)	5.1% (3.5%, 7.5%)	
	9–11 yr	7.7% (4.3%, 13.3%)	10.3% (5.0%, 19.2%)	4.9% (1.4%, 12.8%)	2.7% (1.6%, 4.6%)	HIV+ vs. NHANES
	12–14 yr	10.4% (6.5%, 16.4%)	11.2% (6.4%, 18.4%)	8.3% (2.5%, 21.2%)	4.1% (2.7%, 6.2%)	HIV+ vs. NHANES
	15–17 yr	12.3% (6.3%, 19.8%)	13.9% (7.0%, 23.0%)	6.2% (0.1%, 24.9%)	4.1% (2.4%, 6.8%)	HIV+ vs. NHANES
	Total	9.3% (6.8%, 12.1%)	11.3% (8.0%, 15.1%)	6.0% (2.9%, 10.2%)	4.0% (3.1%, 5.1%)	HIV+ vs. HEU, HIV+ vs. NHANES
60%	7–8 yr	8.4% (3.6%, 17.2%)	10.4% (0.8%, 20.8%)	7.2% (1.4%, 17.9%)	5.1% (3.5%, 7.5%)	
	9–11 yr	10.3% (6.2%, 16.3%)	13.7% (7.5%, 23.4%)	6.5% (2.1%, 14.5%)	2.7% (1.6%, 4.6%)	HIV+ and HEU vs. NHANES
	12–14 yr	13.9% (8.9%, 19.8%)	14.9% (8.9%, 22.1%)	11.1% (3.7%, 24.1%)	4.1% (2.7%, 6.2%)	HIV+ and HEU vs. NHANES
	15–17 yr	16.5% (10.1%, 25.6%)	18.5% (10.8%, 28.7%)	8.2% (1.2%, 31.7%)	4.1% (2.4%, 6.8%)	HIV+ vs. NHANES
	Total	12.3% (9.6%, 15.5%)	15.0% (11.2%, 19.3%)	8.0% (4.5%, 12.8%)	4.0% (3.1%, 5.1%)	HIV+ vs. HEU, HIV+ and HEU vs. NHANES

\* Not affected by AMP trigger sensitivity.

†Youngest age group for NHANES is 6–8 yr. 95% CIs adjusted for complex sample design.

of the children with hearing loss, the prevalence estimates of hearing loss for both HIV+ and HEU children were significantly higher than the prevalence of hearing loss in children in the NHANES III database. From a clinical standpoint, the mean worse ear PTAs for both groups of children would be defined as diagnostically normal. Specifically, the mean worse ear PTA for HIV+ children (14.9 dB HL) and for HEU children (11.3 dB HL) were lower than the 16-dB level used to determine slight hearing loss in children and the 20- or 25-dB level used to define mild hearing loss in adolescents and adults. Caution must be used, however, when evaluating these worse ear PTA data. Because audiometric testing was a result of meeting a study trigger, not all AMP participants had completed a hearing test. These PTA data only represent a targeted subset (ie, children who met a trigger for a hearing problem) of AMP participants and not the entire cohort. Given that only the subset identified to be at greater risk of hearing concerns was tested, this could have led to higher mean PTAs for both HIV+ and HEU children compared with PTAs that might have been obtained with a random, nontargeted subset.

In analyses that included only HIV+ children, disease history (defined by CDC class C diagnosis) was associated with hearing loss while current disease status was not. In fact, having a CDC class C diagnosis was the only factor that increased the odds of having hearing loss among these children; no other measure of HIV disease severity or ART was associated with hearing loss. Chao et al<sup>15</sup> did not report an association between HAART and hearing loss in HIV+ children, but did observe an association between low CD4 count ( $\leq 500$  cells/mm<sup>3</sup>) and hearing loss.

Fourteen of the 38 children with hearing loss had a conductive component to their hearing loss, and most were HIV+. The percent of children in AMP with conductive hearing loss was similar between HIV+ children compared with HEU children. This result is not consistent with previous work where a higher rate of conductive hearing loss in HIV+ children has been reported.<sup>1,2</sup> Researchers in those prior studies specifically identified otitis media as the cause of the conductive hearing loss.<sup>14,15</sup> The conductive component identified in the current study is most likely a result of the residual effects of otitis media but unlikely to be a result of acute otitis media as these children were undergoing scheduled audiometric examinations

as part of a research protocol and not in response to acute otalgia or other illness complaints. The type of hearing loss (eg, conductive or sensorineural) was defined in the present study using pure-tone AC and bone-conduction thresholds with tympanometry results, whereas Weber et al<sup>2</sup> had very specific criteria (ie, results from pneumatic otoscopy, a nonintact tympanic membrane and/or purulent otorrhea or results from audiometric measures) for a diagnosis of acute, chronic or serous otitis media in their HIV+ children.

Over 60% of the children with hearing loss in this study had sensorineural hearing loss, and the underlying mechanism of sensorineural hearing loss in these children is unknown. Such sensorineural hearing loss could be a consequence of mitochondrial effects of HIV infection or antiretroviral drugs or past opportunistic central nervous system infections. On the other hand, these children could also have hearing loss on the basis of an undetected mitochondrial, genetic or congenital abnormality, neurologic disorder or damage from congenital infection [eg, cytomegalovirus (CMV)] or ototoxic drug exposure. Mitochondrial abnormality is a risk factor for nonsyndromic sensorineural hearing loss associated, for example, with the A1555G mutation,<sup>12,22</sup> and this mutation has also been shown to predispose for sensorineural hearing loss after aminoglycoside use.<sup>13,23</sup>

Furthermore, the lack of an association in this study between ART regimen and hearing loss does not preclude the possibility that ART regimens in the past may have been risk factors for hearing loss. ART use, specifically from the nucleoside reverse transcriptase inhibitor class, has been noted to be associated with potential mitochondrial dysfunction in perinatally HIV-infected children.<sup>11,24</sup> These findings, together with the above-mentioned association between mitochondrial mutation and sensorineural hearing loss, suggest that further research is needed to evaluate the potential effects of ART on hearing loss.

The finding of a higher rate of hearing loss among HIV+ and HEU children compared with NHANES III children suggests that annual hearing testing should be provided to both HIV+ and HEU children for 2 reasons. First, if a child's hearing loss is allowed to progress, the child is then at risk for delays in the development of both speech and language. In fact, Yoshinaga-Itano et al<sup>8</sup> reported that significantly better language development was associated with

early identification of hearing loss and earlier intervention for that hearing loss. Although Yoshinaga-Itano et al<sup>8</sup> regarded early identification as identification by 6 months, the importance of identification still can apply to children of the age in the AMP study (7–17 years), even though they are substantially older. Second, given the progressive decrease in HLs with increasing age, the mean worse ear PTA in these children, while still considered clinically normal, was poorer than that of healthy children and may put HIV+ and HEU children at risk for early onset hearing loss either in late adolescence or early adulthood. The impact of early onset hearing loss in this age range, without appropriate intervention, has been shown to affect the child's reading vocabulary, language mechanics, spelling and ability in science.<sup>25</sup> Future Pediatric HIV/AIDS Cohort Studies are planned to evaluate the relationship between these variables and hearing loss.

There were no significant associations of SES measures with hearing loss in the current study, which is not consistent with recent work.<sup>19</sup> Although the HIV+ children had a higher rate of hearing loss, these children most likely had more frequent medical appointments than the HEU children, allowing greater opportunity for identification and treatment of otitis media. But SES variables, along with the trigger mechanism used to collect audiometric data, might contribute to why HIV+ and HEU children have higher worse ear PTAs than the NHANES III population.

One limitation of the current study was the inability to determine whether the sensorineural hearing loss was a consequence of congenital CMV infection. A diagnosis of congenital CMV infection requires that CMV be cultured from the neonate within the first 2 weeks of life. Given the age of enrollment into AMP (7–16 years), this diagnosis was not possible. Congenital CMV infection has been shown to be one of the main causes of (progressive) sensorineural hearing loss in children.<sup>26–28</sup> CMV infection causes damage to the inner ear and may not manifest itself as a hearing loss for months or years after the child's birth. The hearing loss may fluctuate and increase in degree over time.<sup>29,30</sup> In fact, this potential late onset, fluctuating and progression of hearing loss require consistent hearing testing.<sup>27</sup>

A second limitation of this study is that distinguishing between categories of otitis media (eg, acute or chronic) was not possible. Although this is a very important distinction, the audiologists were following a research protocol rather than a specific clinical protocol. Tympanometry, pure-tone AC and bone-conduction data were used to define a conductive component of hearing loss; measures such as pneumatic otoscopy<sup>2</sup> and otomicroscopy<sup>3</sup> are used to more thoroughly evaluate the middle ear system in an effort to differentiate types of otitis media. Those 2 measures were not feasible in AMP because hearing loss was just one of many different outcomes that were assessed.

The results of this study show that hearing loss is common among children who were perinatally exposed to HIV. In addition, HIV+ children have a higher rate of hearing loss compared with HEU children and both groups of children had a higher rate of hearing loss compared with HIV-unexposed children. The specific risk factors for the higher rate of hearing loss are not known at this time. Future studies should include evaluation of specific risk factors for hearing loss such as CMV exposure and mitochondrial mutation. However, more importantly, progression of hearing loss should be examined longitudinally to determine whether or not children perinatally exposed to and infected by HIV are at risk for greater hearing loss earlier in life that may affect both educational and social development.

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