HEARING LOSS AND IN UTERO ARV EXPOSURE IN CHILDREN WHO ARE HIV EXPOSED BUT UNINFECTED

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BACKGROUND

- Early identification of hearing loss is needed to allow for interventions that minimize subsequent adverse effects on children's speech and language development, academic performance, and social interactions.
- Little is known about hearing sensitivity following fetal exposure to maternal antiretroviral (ARV) drugs among children who remain HIV-uninfected.
- Specific Research Questions:
  1. To evaluate pure-tone air-conduction threshold data in 5-year-old children who were HIV-exposed but uninfected (CHEU) enrolled in the Surveillance Monitoring for ART Toxicities (SMARTT) cohort of the Pediatric HIV/AIDS Cohort Study (PHACS)
  2. To evaluate the association of fetal ARV exposure and pure-tone threshold data in 5-year-old CHEU, stratified by timing of fetal ARV exposure initiation.

METHODS

- We included all 5-year-old CHEU enrolled in the SMARTT cohort of PHACS with valid middle ear and pure-tone threshold data from a hearing test conducted after August 2010.
- A pure-tone average (PTA), defined as the average of air-conduction thresholds in decibels (dB) over the frequencies of 0.5, 1, 2, and 4 kHz, was calculated for each ear.
- Hearing loss was defined as a worse-ear PTA >15 dB.
- Log-binomial models were fit using generalized estimating equations to assess the association between fetal ARV exposure and hearing loss, stratified by timing of fetal ARV exposure, either from conception versus after conception.

RESULTS

- Of 1265 CHEU with audiometric exams, 1081 CHEU (49% female; mean age=5.16 [SD=0.25] years, 64% Black, and 35% Hispanic) had valid middle ear and pure-tone threshold data for at least one ear.
- Out of the 1081 CHEU, 1033 had valid middle ear data in both ears and 48 in only one ear. Out of the 1033 CHEU, 969 (93.8%) had bilateral type A tympanograms, indicating normal middle ear function; 17 (1.6%) had bilateral flat tympanograms (type B) (N=1) or negative middle ear pressure (type C) (N=16), indicating abnormal middle ear function, and 47 (4.5%) had one ear type A and the other ear type C. Out of the 48 CHEU, 41 (85%) had type A and 7 (15%) had type C.

Prevalence of hearing loss in 5-year-old CHEU was 15%. For CHEU with ARV exposure initiated _after conception_, TDF/FTC-containing regimens may be protective for hearing loss relative to ZDV/3TC-containing regimens.

	Unadjusted[a]			Adjusted[a,b]		
Exposure from conception	RR	95% CI	p value	RR	95% CI	p value
TDF/FTC, without ATV/r (N=170, 16%[c])	Ref					
TDF/FTC, with ATV/r (N=85, 18%[c])	1.10	(0.62, 1.96)	0.74	1.10	(0.63, 1.89)	0.74
ZDV/3TC, without ATV/r (N=111, 11%[c])	0.69	(0.36, 1.33)	0.27	0.70	(0.37, 1.31)	0.27
Exposure after conception	RR	95% CI	p value	RR	95% CI	p value
TDF/FTC, without ATV/r (N=88, 10%[c])	Ref					
TDF/FTC, with ATV/r (N=84, 12%[c])	1.16	(0.75, 1.79)	0.50	1.03	(0.67, 1.59)	0.88
ZDV/3TC, without ATV/r (N=359, 16%[c])	1.57	(0.88, 2.79)	0.13	1.57	(1.01, 2.44)	0.04

[a]: Models were fit among children with valid pure-tone data for left or right ear, who were *in utero* (1) exposed to ZDV/3TC without ATV/r, (2) exposed to TDF/FTC without ATV/r, or (3) exposed to TDF/FTC with ATV/r. All three groups could include exposure to other protease inhibitors, non-nucleoside reverse transcriptase inhibitors, or integrase strand transfer inhibitors. Separate models were fit for children whose mothers were on ARV from conception and those whose mothers initiated ARV after conception.
[b]: adjusted for years of age at audiometric examination, sex, race, and Hispanic ethnicity.
[c]: % of hearing loss

RESULTS

- Overall, 157/1081 (15%) had hearing loss. Specifically, 66/447 (15%) among those exposed from conception had hearing loss, and 22/191 (12%), 57/370 (15%), and 9/45 (20%) among those with 1st, 2nd, and 3rd trimester of initial ARV exposure, respectively, had hearing loss.
- Over 80% of hearing loss was sensorineural, regardless of timing of first ARV exposure.
- 897/1081 (83%) were exposed to regimens containing ZDV/3TC backbone without ATV/r, TDF/FTC backbone without ATV/r, or TDF/FTC backbone with ATV/r.
- No association between ARV exposure and hearing loss was identified for those first exposed to ARVs at conception. For CHEU with first ARV exposure after conception, regimens containing ZDV/3TC were associated with a higher risk for hearing loss (RR=1.57, 95% CI=1.01-2.44) compared to regimens containing TDF/FTC (Table).

CONCLUSIONS

- Nearly 94% of CHEU with valid data for both ears had normal middle ear function at the time of testing. For those with valid data for only one ear, 85% had normal middle ear function.
- CHEU had an overall hearing loss prevalence of 15%.
- For those with ARV exposure started after conception, this prevalence was higher the later ARV exposure started.
- For CHEU whose ARV exposure was initiated after conception, TDF/FTC-containing regimens may be protective relative to ZDV/3TC-containing regimens.
- Further research is warranted to better understand the factors (including exposure to more detailed ARV regimens) that contribute to hearing loss in CHEU.

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