Newborn Hearing Screenings in Human Immunodeficiency Virus-Exposed Uninfected Infants

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Abstract

Perinatal HIV infection and congenital cytomegalovirus (CMV) infection may increase the risk for hearing loss. We examined 1,435 infants enrolled in the Surveillance Monitoring of ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) network, a prospective study of the safety of in utero antiretroviral (ARV) exposures. We determined the proportion of perinatally HIV-exposed uninfected (HEU) newborns who were referred for additional hearing testing, and evaluated the association between in utero ARV exposures and newborn hearing screening results. Using a nested case-control design, we also examined congenital CMV infection in infants with and without screening referral. Congenital CMV infection was determined based on CMV DNA detection using a nested PCR assay in peripheral blood mononuclear cells obtained within 14 days of birth. Among the 1,435 infants (70% black, 31% Hispanic, 51% male), 45 (3.1%) did not pass the hearing screen and were referred for further
hearing testing. Based on exact logistic regression models controlling for maternal use of tobacco and ototoxic medications, first trimester exposure to Tenofovir was associated with lower odds of a newborn hearing screening referral [adjusted odds ratio (aOR) = 0.41, 95% confidence interval (CI): 0.14-1.00]. Exposure to Atazanavir was linked to higher odds of newborn screening referral, although not attaining significance [aOR = 1.84, 95% CI: 0.92-3.56]. Maternal ARV use may have varying effects on newborn hearing screenings. These results highlight the importance for audiologists to be knowledgeable of in utero ARV exposures in HEU children because of the possibility of higher referrals in these children.

Keywords
Newborn; Hearing; Human Immunodeficiency Virus; Cytomegalovirus; In Utero Antiretroviral Exposure

Introduction
Universal newborn hearing screening in the United States was implemented following the 1993 NIH Consensus Development Conference that endorsed the screening for hearing loss of all newborns before leaving the hospital [1]. This landmark move led to an unprecedented state-by-state effort to promote mandatory newborn screening, which was bolstered by Congressional passage of the Newborn and Infant Hearing Screening and Intervention Act of 1999 that provided funding for statewide programs [2,3]. Late identification of permanent hearing loss can impair long-term speech and language development, and, subsequently, educational achievement [4,5]. The overall rate of permanent hearing loss has been reported as approximately 2 per 1000 live births [6,7]. Human immunodeficiency virus (HIV) is a risk factor for hearing loss in children and adolescents [8], but the potential link between hearing loss and in utero exposure to maternal HIV infection and HIV medications has not been well studied.

Studies of hearing screening results obtained from babies born to mothers infected with HIV are limited. Two studies have observed about two-fold higher risk of hearing loss for HIV-exposed uninfected (HEU) infants as compared to HIV-unexposed and uninfected (HUU) infants, although neither finding attained statistical significance due to the low prevalence of hearing loss [9,10]. In addition, neither accounted for congenital cytomegalovirus (CMV), which is well-known to be linked to sensorineural hearing loss [11-14] and has a higher prevalence in neonates born to mothers with HIV [15,16]. While the prevalence of congenital CMV in HEU infants has decreased with the advent of highly active antiretroviral therapy (HAART), it remains higher than in the general population [17].

Early identification of newborn hearing loss has important implications for the child’s speech, language and educational development. Since congenital CMV infection has been identified as a risk factor for permanent sensorineural hearing loss [13], screening for CMV co-infection in this group of infants is important in understanding hearing loss in HEU. The objectives of this project were to: 1) determine the proportion of HEU children referred for additional testing following a newborn hearing screening in the Surveillance Monitoring of ART Toxicities (SMARTT) cohort study (a protocol within the Pediatric HIV/AIDS Cohort
Study [PHACS]); 2) evaluate the association of in utero antiretroviral (ARV) exposures with newborn hearing screening results; 3) evaluate the association between newborn hearing screening results and other risk factors and 4) examine congenital CMV infection in a subset of infants with and without further hearing referrals as a result of the newborn screening.

Materials and Methods

The study population was the Dynamic Cohort of the SMARTT study which prospectively enrolls pregnant women and their newborns from week 22 of gestation through 72 hours after birth, and follows both the mothers and their children annually. The SMARTT study is a US based, multisite, prospective cohort study designed to evaluate the effects of in utero antiretroviral (ARV) exposure on outcomes across several domains among HEU infants (for additional details of the SMARTT study design, see Williams et al. [18]). Newborn hearing screening and follow-up screening results were collected from the medical record and then reported to the SMARTT study on study-specific data collection forms. Hearing screenings included otoacoustic emission (OAE) measures, automated auditory brainstem response (AABR) measures, or both depending on the hospital protocol. The primary outcome for this analysis was the hearing screening result (pass or refer) using OAE or AABR.

Maternal ARV data were retrospectively collected for the entire pregnancy through chart review or from prior studies; information collected included start and stop dates of each individual ARV drug so that both duration and timing of exposure (by trimester) could be characterized. The primary exposures of interest were in utero ARV exposure overall during pregnancy and within individual trimesters. HAART was considered as any regimen containing at least three drugs from at least two different drug classes. Regimens that included three nucleoside reverse transcriptase inhibitors (NRTIs) were also evaluated, as were individual drug classes (NRTI, non-NRTI, and protease inhibitors) and individual ARV agents. Demographic characteristics and maternal and birth characteristics were collected by questionnaire and medical record review and treated as possible risk factors. Substance use during pregnancy was self-reported by mothers as reported previously [19].

A nested sub-study within SMARTT was conducted to address the issue of congenital CMV, since the SMARTT study itself did not determine CMV infection status on all newborns. Congenital CMV infection was determined in a subset of participants based on CMV DNA detection in peripheral blood mononuclear cells (PBMCs) drawn at the entry study visit (usually at birth) and stored in the PHACS repository using a sensitive nested PCR assay [20]. Samples were chosen in a case-control design with four samples (subject to sample availability) from infants who passed the newborn hearing screen for every one infant who was referred for further testing.

Demographic differences between infants who passed and those who were referred for further hearing testing were examined using chi-square or Wilcoxon tests, as appropriate. The prevalence of hearing screening referral and its exact 95% confidence interval (CI) were calculated under a binomial distribution. Due to the relatively rare outcome of not passing a newborn hearing screening, exact logistic regression models were used to evaluate the association of maternal ARV exposures with newborn hearing outcomes. Adjusted models
Results

As of January 1, 2013, of 1,435 SMARTT infants were enrolled and had newborn hearing screening data. The infants were primarily black (70%), with 31% Hispanic and 51% male. Among these 1,435 infants, 45 (3.1%, exact 95% CI: 2.3% - 4.2%) did not pass the newborn hearing screening and were referred for further testing. Of the 1,435 infants, 1,406 (98%) had detailed information on child demographics and maternal characteristics (Table 1) and subsequent analyses were restricted to these 1406 infants. Almost all infants (1,382 or 98%) were exposed to either HAART or a triple NRTI regimen, with 707 (50%) exposed in the first trimester. The most common ARV exposures (Supplemental Table 2) were lamivudine (67%) and zidovudine (66%); 43% were exposed to Tenofovir, 24% to Atazanavir, and 5% to efavirenz. Only 17 infants (1%) had no recorded ARV exposure.

Based on unadjusted exact logistic regression models, first trimester exposure to Tenofovir was associated with lower odds of a newborn hearing screening referral [odds ratio (OR) = 0.41, 95% CI 0.14-1.00, p = 0.049], and first trimester exposure to emtricitabine was also associated with lower odds of a referral (OR = 0.45, 95% CI 0.15-1.07, p = 0.08), although not attaining statistical significance (Figure 1). After controlling for maternal use of tobacco and ototoxic medications, the association between Tenofovir and screening referral remained significant [adjusted OR (aOR) = 0.39, 95% CI 0.39-0.94, p = 0.03] and the association between emtricitabine and screening referral remained similar (Figure 1). Exposure to Atazanavir during pregnancy was associated with higher odds of newborn screening referral (aOR = 1.84, 95% CI 0.92-3.56, p = 0.09); in addition, a similar magnitude of association was observed for infants with third trimester exposure to Atazanavir (aOR = 1.92, 95% CI 0.94-3.76, p = 0.07; data not shown). There were no significant associations of newborn screening results with either demographic characteristics (including sex, ethnicity, and race) or maternal and birth characteristics (including mother’s age, alcohol, tobacco, or ototoxic medication use during pregnancy, birth weight, or gestation age).

Among the 45 infants referred after the initial newborn hearing screening, 22 had acceptable PBMC samples for CMV testing and one (4.5%) was CMV-positive. Of the 1,390 infants who passed the hearing screening, 92 were tested and 5 (5.4%) were CMV-positive. Follow-up hearing testing was not available for the six CMV positive infants.

Follow-up information on subsequent hearing tests for the 45 infants referred for further testing was evaluated through January 1, 2013. Median age at follow-up was three years with the oldest child under six years. Twelve of the 45 (27%) infants did not receive any follow-up hearing testing. Twenty-four (73%) of the remaining 33 infants with subsequent follow-up passed their hearing screenings. Another nine infants (27%) continued to have some degree of hearing problems on additional screenings or testing, including one (3%) with confirmed sensorineural hearing loss after an extensive hearing examination.
Discussion

Exposure to Atazanavir overall and specifically in the third trimester was linked with higher odds of a referral, but this association did not reach statistical significance. A recent report from within the same cohort found a significant association between exposure to Atazanavir and delayed language developmental [21]. In that analysis, the significantly higher odds increased further if the exposure to Atazanavir occurred after the first trimester. This potential relationship between perinatal exposure to Atazanavir and language delay and possibly hearing problems requires further study.

Conversely, exposure to Tenofovir in the first trimester was associated with significantly lower odds of a referral for further hearing testing. Further, first trimester exposure to emtricitabine, typically given in tablets co-formulated with Tenofovir was also associated with lower odds of a referral, but this did not attain statistical significance.

Alternative approaches for evaluating associations between exposures and binary outcomes in the setting of rare events (e.g., hearing screening referral) have also been proposed, such as rare events logistic regression [22]. Utilizing rare events logistic regression (conducted using “relogit” in Stata 11), similar results were obtained to those shown in Supplemental Table 2, providing further support for the current conclusions.

Results of newborn hearing screening in HEU infants in SMARTT showed that 3.1% (45/1435) were referred for further testing, which is lower than the approximate 10% first referral rate previously reported in one statewide program in Rhode Island of all newborns [8]. This referral rate is also lower than that reported by Manfrediet al. [10] but similar to what Olusanya et al. [9] reported in children with HIV infection. Inconsistencies in referral rates are most likely a result of varying equipment used (i.e., OAE or AABR) and referral criteria across studies and even hospitals.

Because CMV-related hearing loss is not always present at birth, and can be progressive with time [11-14], the lack of an association with CMV in this subset at birth is not surprising. Longitudinal hearing testing is critical for these infants and needed to estimate the true risk of hearing loss with congenital CMV in PHEU children. The proportion of congenital CMV infection in HEU children in this study (1/22 = 4.5% in infants with hearing screening referral and 5/92 = 5.4% in infants who passed the hearing screening) was higher than that reported among children in the general US population (0.6%); it is consistent with rates reported in other HEU children [15-16,23]. There was no difference in the CMV infection rates by pass/refer results of the newborn hearing screening.

The Joint Committee on Infant Hearing [3] requires that newborns receive a hearing screening before leaving the hospital or at least by one month of age. The specific protocol for this screening is not standardized across hospitals but the universally accepted measures are OAEs and AABRs. The recording parameters for these measures as well as the pass/refer criteria can also vary. Because of this, one limitation of this study is that newborn screening protocols did vary across sites. Although OAE and AABR measures have different sensitivity and specificity rates for identifying hearing loss, the primary objective of this study was to identify HEU children who were referred for further hearing screening. Initial
hearing screening data were obtained retrospectively and across various SMARTT sites within the U.S. and Puerto Rico so it was difficult to control for the various hearing screening protocols used. Another limitation is the lack of complete follow-up hearing data when a newborn was referred, or whether or not the newborn even had follow-up services after the initial referral.

Although HIV mother-to-child-transmission rates have declined dramatically in the U.S., [24] the number of HEU children will continue to increase. The decrease in HIV mother-to-child transmission is directly related to the expanded use of HAART during pregnancy. With the increasing number of ARVs and ARV combinations available for HIV treatment, it is important for future studies to further evaluate these potential adverse effects.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

We thank the children and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS. The study was supported by the *Eunice Kennedy Shriver National Institute of Child Health and Human Development* with co-funding from the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the Office of AIDS Research, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, the National Heart Lung and Blood Institute, the National Institute of Dental and Craniofacial Research, and the National Institute on Alcohol Abuse and Alcoholism, through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George Seage; Project Director: Julie Alperen) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Kenneth Rich; Project Director: Patrick Davis). Data management services were provided by Frontier Science and Technology Research Foundation (PI: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (PI: Julie Davidson).

The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2014, in alphabetical order: **Ann & Robert H. Lurie Children’s Hospital of Chicago**: Ram Yogev, Margaret Ann Sanders, Kathleen Malee, Scott Hunter; **Baylor College of Medicine**: William Shearer, Mary Paul, Norma Cooper, Lynnette Harris; **Bronx Lebanon Hospital Center**: Murli Purswani, Emma Stuard, Anna Cintron; **Children’s Diagnostic & Treatment Center**: Ana Puga, Dia Cooley, Patricia Garvie, James Blood; **New York University School of Medicine**: William Borkowsky, Sandra Deygoo, Helen Rozelman; **Rutgers – New Jersey Medical School**: ArryDieudonne, Linda Bettica, Susan Adubato; **St. Jude Children’s Research Hospital**: Katherine Knapp, Kim Allison, Megan Wilkins; **San Juan Hospital/Department of Pediatrics**: Midneta Acevedo-Flores, Lourdes Angeli-Nieves, Vivian Olivera; **SUNY Downstate Medical Center**: Hermann Mendez, Ava Dennie, Susan Belsey; **Tulane University Health Sciences Center**: Chi Dola, Robert Maupin, Karen Craig, Patricia Sirois; **University of Alabama, Birmingham**: Marilyn Crain, Newana Beatty, Dan Marullo; **University of California, San Diego**: Stephen Spector, Jean Manning, Sharon Nichols; **University of Colorado Denver Health Sciences Center**: Elizabeth McFarland, Jenna Wallace, Carrie Chambers, Christine Reed; **University of Florida/ Jacksonville**: Mobeen Rathore, Kristi Stowers, Ann Usitalo; **University of Illinois, Chicago**: Kenneth Rich, Lourdes Richardson, Renee Smith; **University of Miami**: Gwendolyn Scott, Claudia Florez, Elizabeth Willen; **University of Southern California**: Toni Frederick, Mariam Davtyan, Maribel Mejia; **University of Puerto Rico Medical Center**: Zoe Rodriguez, IbetHeyer, Nydia ScalleyTrifilio.

**References**

1. Early identification of hearing impairment in infants and young children. NIH Consensus Statement. 1993; 11:1–24.
2. NIH Fact Sheet. Newborn Hearing Screening. Updated Oct 2010.
3. Joint Committee on Infant Hearing. Year 2007 Position Statement: Principles and Guidelines for early hearing detection and intervention programs. Pediatrics. 2007; 120:898–921. DOI: 10.1542/peds.2007-2333 [PubMed: 17908777]

*J AIDS Immune Res.* Author manuscript; available in PMC 2017 April 27.
4. Yoshinaga-Itano C, Apuzzo ML. Identification of hearing loss after age 18 months is not early enough. Am Ann Deaf. 1998; 143(5):380–7. [PubMed: 9893323]

5. Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. Pediatrics. 1998; 102(5):1161–71. [PubMed: 9794949]

6. Dalzell L, Orlando M, MacDonald M, Berg A, Bradley M, Cacace A, et al. The New York State universal newborn hearing screening demonstration project: ages of hearing loss identification, hearing aid fitting, and enrollment in early intervention. Ear Hear. 2000; 21(2):118–30. [PubMed: 10777019]

7. Vohr BR, Carty LM, Moore PE, Letourneau K. The Rhode Island Hearing Assessment Program: experience with statewide hearing screening (1993-1996). J Pediatr. 1998; 133(3):353–7. [PubMed: 978715]

8. Torre P 3rd, Zeldow B, Hoffman HJ, Buchanan A, Siberry GK, Rice M, et al. Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents. Pediatr Infect Dis J. 2012; 31(8):835–41. DOI: 10.1097/INF.0b013e31825b9524 [PubMed: 22549437]

9. Olusanya BO, Afe AJ, Onyia NO. Infants with HIV-infected mothers in a universal newborn hearing screening programme in Lagos, Nigeria. Acta Paediatr. 2009; 98(8):1288–93. DOI: 10.1111/j.1651-2227.2009.01337.x [PubMed: 19519758]

10. Manfredi AK, Zuanetti PA, Mishima F, Granzotti RB. Newborn hearing screening in infants born to HIV-seropositive mothers. J Soc Bras Fonoaudiol. 2011; 23(4):376–80. [PubMed: 22231060]

11. Barbi M, Binda S, Caroppo S, Ambrosetti U, Corpetta C, Sergi P. A wider role for congenital cytomegalovirus infection in sensorineural hearing loss. Pediatr Infect Dis J. 2003; 22(1):39–42. [PubMed: 12544407]

12. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol. 2000; 11(5):283–90. [PubMed: 10821506]

13. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol. 2006; 35(2):226–31. [PubMed: 16386462]

14. Yamamoto AY, Mussi-Pinhata MM, Isaac Mde L, Amaral FR, Carvalheiro CG, Aragon DC, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. Pediatr Infect Dis J. 2011; 30(12):1043–6. DOI: 10.1097/INF.0b013e31822d9640 [PubMed: 21814153]

15. Doyle M, Atkins JT, Rivera-Matos IR. Congenital cytomegalovirus infection in infants infected with human immunodeficiency virus type 1. Pediatr Infect Dis J. 1996; 15(12):1102–6. [PubMed: 8970220]

16. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT, Cervi MC, Duarte G. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. J Pediatr. 1998; 132(2):285–90. [PubMed: 9506642]

17. Guibert G, Warszawski J, Le Chenadec J, Blanche S, Benmeharek Y, Mandelbrot L, et al. Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. Clin Infect Dis. 2009; 48(11):1516–25. DOI: 10.1086/598934 [PubMed: 19388872]

18. Williams PL, Seage GR 3rd, Van Dyke RB, Siberry GK, Griner R, Tassiopoulos K, et al. A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. Am J Epidemiol. 2012; 175(9):950–61. DOI: 10.1093/aje/kwr401 [PubMed: 22491086]

19. Tassiopoulos K, Read JS, Brogly S, Rich K, Lester B, Spector SA, et al. Substance use in HIV-infected women during pregnancy: self-report versus meconium analysis. AIDS Behav. 2010; 14(6):1269–78. DOI: 10.1007/s10461-010-9705-0 [PubMed: 20532607]

20. Taylor-Wiedeman J, Siissons JG, Borysiwicz LK, Sinclair JH. Monocytes are a major site of persistence of human cytomegalovirus in peripheral blood mononuclear cells. J Gen Virol. 1991; 72(1Pt 9):2059–64. [PubMed: 1654370]

21. Rice ML, Zeldow B, Siberry GK, Purswani M, Malek K, Hoffman HJ, et al. Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected
infants. Pediatr Infect Dis J. 2013; 32(10):e406–13. DOI: 10.1097/INF.0b013e31829b80ee [PubMed: 24067563]

22. King G, Zeng L. Logistic regression in rare events data. Polit anal. 2001; 9:137–163.

23. Frederick T, Homans J, Spencer L, Kramer F, Stek A, Oderskalski E, et al. The effect of Prenatal Highly Active Antiretroviral Therapy on the Transmission of Congenital and Perinatal/Early Postnatal Cytomegalovirus Among HIV-Infected and HIV-Exposed Infants. Clin Infect Dis. 2012; 55(6):877–84. DOI: 10.1093/cid/cis535 [PubMed: 22675157]

24. Centers for Disease Control and Prevention (CDC). Achievements in public health. Reduction in perinatal transmission of HIV infection—United States, 1985-2005. MMWR Morb Mortal Wkly Rep. 2006; 55(21):592–7. [PubMed: 16741495]

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| CMV          | Congenital Cytomegalovirus |
| SMARTT       | Surveillance Monitoring of ART Toxicities |
| PHACS        | Pediatric HIV/AIDS Cohort Study |
| ARV          | Antiretroviral |
| HEU          | HIV-Exposed Uninfected |
| aOR          | Adjusted Odds Ratio |
| CI           | Confidence Interval |
| HIV          | Human Immunodeficiency Virus |
| HUU          | HIV-Unexposed and Uninfected |
| HAART        | Highly Active Antiretroviral Therapy |
| AABR         | Automated Auditory Brainstem Response |
| OAE          | Otoacoustic Emission |
| NRTI         | Nucleoside Reverse Transcriptase Inhibitors |
| OR           | Odds Ratio |
Figure 1.
Estimated associations between maternal ARV exposures and newborn hearing screening referral (or failed screening) using exact adjusted logistic regression, separated by any exposure
(1a) 1st trimester exposure
(1b) Associations were adjusted for maternal use of ototoxic medications and in utero tobacco exposure.
Table 1
Child and maternal characteristics by newborn hearing screening result, among infants with complete maternal antiretroviral exposure information\textsuperscript{a}

| Characteristic                              | Total (N = 1406) | Newborn screening result | p - value |
|---------------------------------------------|------------------|--------------------------|-----------|
|                                             |                  | Pass (N = 1361)          | Refer (N = 45) |
| Female                                      | 682 (49%)        | 663 (49%)                | 19 (42%)  | 0.45      |
| White                                       | 406 (30%)        | 394 (30%)\textsuperscript{b} | 12 (28%) | 0.87      |
| Hispanic                                    | 430 (31%)        | 416 (31%)                | 14 (31%)  | 1.00      |
| Birth Characteristics                       |                  |                          |           |
| Birth weight < 2.5 kg                       | 251 (18%)        | 244 (18%)                | 7 (16%)   | 0.84      |
| Gestational age < 37 weeks                  | 272 (19%)        | 263 (19%)                | 9 (20%)   | 0.85      |
| Mode of delivery – Cesarean                 | 826 (59%)        | 799 (59%)                | 27 (60%)  | 1.00      |
| Maternal Characteristics at delivery        |                  |                          |           |
| Mother < 25 years old                       | 451 (32%)        | 437 (32%)                | 14 (31%)  | 1.00      |
| Maternal viral load > 1000 copies/ml        | 174 (13%)        | 169 (13%)                | 5 (11%)   | 1.00      |
| Maternal CD4 count < 200 cells/mm\textsuperscript{3} | 139 (10%) | 133 (10%)                | 6 (14%)   | 0.44      |
| Maternal substance use during pregnancy     |                  |                          |           |
| Tobacco use                                 | 250 (18%)        | 246 (18%)                | 4 (9%)    | 0.12      |
| Alcohol use                                 | 123 (9%)         | 117 (9%)                 | 6 (13%)   | 0.28      |
| Illicit drug use                            | 123 (9%)         | 118 (9%)                 | 5 (11%)   | 0.59      |
| Exposed to ototoxic medication in utero\textsuperscript{c} | 228 (16%) | 216 (16%)                | 12 (27%)  | 0.06      |

\textsuperscript{a} Twenty-nine infants did not have complete maternal ARV exposure data and are not included. All 29 of these passed the newborn screening.

\textsuperscript{b} Percentages based on non-missing values. Seventy did not report race; 2 ethnicity; 11 birth weight and gestational age; 12 mode of delivery; 11 mother's age at delivery; 28 mother's viral load at delivery; 30 mother's CD4 at delivery; 25 exposure to tobacco, alcohol or illicit drugs.

\textsuperscript{c} Ototoxic medications include gentamicin, neomycin, streptomycin, amphotericin, erythromycin, vancomycin, ibuprofen, indomethacin, naproxen, hydrocodone, furosemide, tobramycin, and misoprostol.