HEARING LOSS AMONG ADOLESCENTS ON ANTIRETROVIRAL THERAPY: A NEED FOR PERIODIC HEARING ASSESSMENT

A.J. Fasunla[1,2], S.A. Ogunkeyede[1,2], and S.O. Afolabi[3]

1. Department of Otorhinolaryngology, College of Medicine, University of Ibadan
2. Department of Otorhinolaryngology, University College Hospital, Ibadan
3. BSA Speech and Hearing Consult, Lagos

Correspondence:
Dr. S.A. Ogunkeyede
Dept. of Otorhinolaryngology, University College Hospital, Ibadan
Email: segunkeyede@yahoo.com

ABSTRACT

Background: **Human immunodeficiency virus-infected adolescents have insufficient CD4 T cell count, and despite attaining viral suppression with HAART regimen, some experience significant hearing loss.**

Objective: **To determine the association between the hearing thresholds in HIV-positive adolescent on highly active antiretroviral therapy and CD4 T cell count.**

Method: **In this cross-sectional study, 63 adolescents receiving highly active antiretroviral therapy had pure tone audiometry and hearing thresholds determined using standard method. Additional data collected using proforma include bio-data type of HAART regimens, treatment duration, the nadir and current CD4-cell count (cells/ml) and viral load (copies/ml) levels. These clinical parameters were correlated with hearing thresholds. Statistical analysis done included univariate analysis and multivariate logistic regression using Statistical Product and Service Solutions (SPSS version 20) and level of statistical significance was determined at $P < 0.05$.**

Results: **There were 63 participants comprising of 26 (41.3%) males and 37 (58.7%) females, age ranged from 13 – 17 years (mean age 14.7years ± 1.65). Hearing loss was found in 20.6% adolescents and was predominantly sensorineural hearing loss. There was asoociation between hearing threshold, nadir CD4 count and viral load, but not with gender, current CD4 count and viral load, HAART regimen, and treatment duration.**

Conclusion: **The high prevalence of adolescents with hearing impairment showed that there might be an association with the disease and/its treatment hence the need for inclusion of periodic hearing evaluation in the routine clincal care of HIV-infected adolescent on HAART.**

Key words: Adolescents, CD4 nadir, HIV, Sensorineural hearing loss, Nigeria

INTRODUCTION

The burden of human Immunodeficiency Virus (HIV) infection in Nigeria is the second highest world-wide with a challenge to the public health.[1] The prevalence of the disease is high among adolescents in sub-Saharan African countries.[2,3] In them, the disease might have been contacted from birth, or via unprotected sexual intercourse, use of contaminated blood products and practice of sharing sharp objects.[4,5,6,7]

HIV-infection is a risk factor for hearing loss and the magnitude seems to increase with the severity of the disease.[8] This may be conductive or sensorineural. The sensorineural hearing loss in HIV patients may be due to direct neurotropic effect of HIV on either the central nervous system or peripheral auditory nerve (neurotoxicity).[9,10,11] Sudden sensorineural hearing loss and demyelination in the brain stem with significant increase in latencies on auditory brain stem has been reported [12, 13] and this may be due to the direct action of the virus on central nervous system. Other causes of hearing loss in HIV infected adolescent may include chronic suppurative otitis media, ototoxicity from antiretroviral therapy and aminoglycosides used in the treatment of tuberculosis which is a common opportunistic infection that is associated with HIV. [8,14,15]

Meningitis and encephalitis may occur as an opportunistic infection in HIV patients because of poor humoral and cell-mediated immunity, with a significant consequence on hearing threshold.[16] The defective chemotaxis and phagocytosis may cause increased vulnerability to middle ear infection[17]. The persistent generalized lymphadenopathy could block the Eustachian tube opening leading to serous otitis media and conductive hearing loss.

The value of CD4 cell count measures the degree of immunosuppression in HIV-positive patients. Highly

active antiretroviral therapy (HAART) often leads to substantial reduction in viral load and immune recovery in HIV-infected individual.[18] CD4 T-cell status is a strong prognostic indicator of mortality and disease progression among individuals living with HIV.[19] Some antiretroviral medications may be ototoxic[20], thus it has been difficult to make conclusions regarding the cause of changes in hearing function in HIV-infected patients on the medication.

Accelerated aging has been suggested as a potential explanation for the disproportionate increase in complications of age related problems including hearing loss even in individuals living with HIV/AIDS. Improved medical, nutritional, psychosocial and pharmacological care have converted HIV infection from a terminal to a chronic health condition with increased life expectancy[8], thus making them to need long-term hearing care.

Information is sparse on hearing status of HIV-infected adolescents in Nigeria, hence this study was conducted to determine hearing threshold and the association between it and viral load, CD4 cell counts and HAART administration.

MATERIALS AND METHODS

This was a cross sectional study of HIV-infected adolescents at President's Emergency Plan For AIDS Relief (PEPFAR) clinic, University College Hospital, Ibadan, Nigeria. Ethical approval was obtained from the ethics committee of University of Ibadan/ University College Hospital, Ibadan for the conduct of the study. Participants with clinical history suggestive of risk factors for hearing loss were excluded from the study. Permission was also obtained from the management of the clinic, and Informed consent was obtained from their caregivers and assent was obtained from each participant. A convenient sampling method was done to recruit the participants.

Proforma was used to gather information/data on sex, age, tribe, religion, duration of HIV infection, sources of infection, use of HAART medications, ear symptoms, history of hearing impairment, and family history of hearing loss. Clinical and otoscopic examination of the ear was performed and findings documented. Those with ear-wax and debris had removal done before hearing test was performed.

Pure Tone Audiometry

The procedure was clearly explained to the patients. In a quiet room, patients sat backing the equipment and signified hearing the tone by raising hand above the head level. Pure tones were delivered to each ear consecutively using ear phones to test for air-conduction (AC). The duration of presentation was 2-3 seconds. The test was conducted firstly on the right ear at 250Hz, 500Hz, 1KHz, 2KHz, 4KHz, 6KHz and 8KHz. The test started by presenting pure tone at 40dBHL, if audible then was reduced in 10dB steps till no response occurred, thereafter it was increased by 5dB steps till a response occurred and the result plotted. If no response occurred at 80dBHL, then it was increased by 5dB steps until a response occurred. The left ear was then tested in similar manner. A pure tone average was calculated at the speech frequencies 500Hz to 4 KHz. To test for bone conduction (BC), the bone vibrator was placed on the mastoid of the test ear (the worse ear on AC) delivering different tones at each of the speech frequencies from 500Hz to 4000Hz. Sensorineural hearing loss (SNHL) was diagnosed when the air and bone conduction thresholds on audiogram were within 10dB of each other and thresholds were higher than 25dBHL. Mixed hearing loss (MHL) was diagnosed when the air conduction thresholds were poorer than bone conduction thresholds by more than 10dB, and bone conduction thresholds were less than 25dB.

Conductive hearing loss (CHL) was diagnosed if the bone conduction thresholds were less than 25dB while the air conduction thresholds are higher than 25dB.
In this study, hearing was said to be normal if hearing threshold is less than 26 dB HL. Hearing impairment was classified as Mild (26 to 40 dB HL), Moderate (41 to 55 dB HL), Moderately severe (56 to 70 dBHL), Severe (71 to 90 dB HL), Profound (91 dBHL and above).[21]

In this study, disabling hearing loss is defined as permanent unaided hearing threshold level in the better ear of 31 dB or greater" in the better hearing ear for participants under the age of 15 years and 40dB or greater in older people.[22]

Statistical analysis: Data collected were inputted into Statistical Products and Service Solutions (IBMSPSS version 20). Data analysis was done by univariate analysis and multivariate logistic regression where applicable. Some results were presented in tables and charts where appropriate. The mean and standard deviations were computed for all quantitative variables. Level of statistical significance was set at $P < 0.05$.

RESULT

There were 63 participants comprising of 26 (41.3%) males and 37 (58.7%) females. Their ages ranged from 13 – 17 years. Thirty-two (50.8%) belonged to the low socioeconomic class, 18(28.8%) belonged to the. middle socioeconomic class and 13 (20.6%) belonged to the high socioeconomic class. All the participants

Table1: Demographic and laboratory parameters of the participants

	Hearing loss in the better ear		
	Present n=13 (20.6%)	**Absent n = 50 (79.4%)**	**p Values**
Sex			
Male	6(9.5%)	23(36.5%)	
Female	7(11.1%)	27(42.9%)	0.45
Mean age	14 ± 2.2	13 ± 2.8	0.35
Viral load (copies/ml)			
Nadir	28,611 ± 419	27,222 ± 433	0.03
Latest	415 ± 22.7	398 ± 25.7	0.35
CD4 cell count cells/mm3			
Nadir	292.8± 98.3	362 ± 27.1	0.03
Latest	499 ± 12.6	508 ± 11.5	0.18
Duration of HAART usage (years)	6.7 ± 2.	7.1 ± 3.5	0.10
HAART regimen			
I	9 (14.3%)	32 (50.8%)	0.08
II	4 (6.3%)	18 (28.6%)	0.53

Note: *Regimen I: Lamimudine+Zidovudine+Nevirapine; Regimen II: Lamivudine+Zidovudine+Efavirez*

were on daily dosage of co-trimoxazole and highly active antiretroviral therapy (HAART) with 41 (65.1%) participants on Lamivudine+Zidovudine+ Nevirapine and 22 (34.9%) participants on Lamivudine +Zidovudine+Efavirez. The period of HAART usage ranged from 10 months to 9 years (mean of 6.9 ± 3.7years). There was no association between duration of HAART usage and the degree of hearing loss (p=0.81) as shown in Table 1. Hearing loss in the better ear was found in 13 (20.6%) participants, which was mild in 12 (92.3%) participants and moderate in one participant. The type of hearing loss was sensorineural hearing loss in 11 (84.6 %) and mixed hearing loss in 1 (7.7%) participant.

Of the participants with hearing loss, 8 (61.5%) had disabling hearing loss. The hearing loss has no association with age (p = 0.2). Hearing loss occurred among patients treated with each of the HAART regimens, but there is no association between hearing loss and the HAART - regimen, after excluding the confounding factors like age, gender and duration of usage of the HAART (p = 0.11). The Nadir viral load of the participants ranged from 29,653 - 76,983 copies/ml, mean of 54,711 ± 11,876 copies/ml while latest viral load ranged from 201 – 4,500 copies/ml, mean of 413 ± 287 copies/ml. The hearing thresholds is associated with nadir viral load (p= 0.03), but not the latest viral load (p = 0.18).

Table 2: Hearing threshold of the participants

Factors		**Disabling Hearing Loss**		
		Yes n = 8(61.5%)	**No n =5(38.5%)**	**Total n = 13(100%)**
Gender	Male	5(38.4%)	3(23.1%)	8(61.5%)
	Female	3(23.1%))	2(15.3%)	5(38.4%)
Degree of hearing loss	Mild hearing loss (26 to 40 dB HL)	7(53.8%)	5(38.5%)	12 (92.3%))
	Moderate hearing loss (41 to 55 dB HL)	1(7.7%)	0(0%)	1(7.7%)
Type of hearing loss	Sensorineural Hearing Loss	6(46.1%)	5(38.5%)	11 (84.6 %)
	Mixed Hearing Loss	1(7.7%)	0(0%)	1(7.7%)
	Conductive Hearing Loss	1(7.7%)	0(0%)	1(7.7%)

The Nadir CD4 cell count of the participants ranged from 227 – 365 cells/mm3, mean of 301.83 ± 28.11 cells/mm 3 while the latest CD4 cell count ranged from 487 cells /mm3 to 1,264 cells/mm3, mean 512 ± 101 cells/mm3. The hearing threshold is associated with the nadir CD4 cell count ($p = 0.03$), but not with latest CD4 cell count ($p = 0.35$) as shown in table 2. Multiple logistic regressions showed that nadir viral load and nadir CD4 cell count could be associated with hearing loss.

DISCUSSION

The participants' age falls within the age group of adolescents with HIV- infection in the previous reports.[23] The prevalence of hearing impairment in this study is higher than the prevalence of hearing loss among children in the general population[24], and lower than the prevalence of 38.8% among HIV infected children in Peru.[25] This difference may be due to environmental factors, viral load and CD4 cell count status of the participants.

Although, conductive HL is the principal type of hearing loss in HIV infection,[15,16,26] sensorineural hearing loss was predominant in this study. The direct effect of HIV virus on the central nervous system or peripheral auditory nerve might have contributed.[26] The low incidence of conductive hearing loss in our study may be because none of the participants had history of ear discharge.[26] This difference may also be due to age of children investigated as this present study only investigated the hearing of adolescents. Studies have shown the cause

of conductive hearing loss in HIV infected to be Eustachian tube dysfunction and depressed cell mediated immunity, which markedly increase susceptibility to middle ear infection.[27] The Eustachian tube dysfunction in HIV adolescents may be due to nasopharyngeal lymphoid hyperplasia, sinusitis, allergies and their associated mucosal changes that results in obstruction of the Eustachian tube and impairs the middle ear ventilation.[28]

Torre *et al*[29] reported HIV as a factor for hearing loss, and the magnitude of hearing loss seems to increase with the severity of HIV. The association of hearing loss with the nadir viral load and CD4 count in this study supports the notion that high level of HIV virus and low CD4 count may contribute to worsening hearing. Although, mild hearing loss was found in majority of the adolescent, this has been reported to affect school performance and social interaction. In this study, there was no relationship between hearing loss and HAART. Early initiation of antiretroviral therapy may prevent hearing loss as there are no consensus that antiretroviral medications could affect hearing. If care of these hearing impaired adolescent is neglected, it could affect their communication, social and educational development, with significant consequences on the communities and the country.[30] Hearing loss increased with increasing age among the participants, though not statistically significant, probably because the participants were within the same age bracket. The observed none association between hearing thresholds, and latest CD4 cell count and viral load of the participants supports the neurotoxic aetiopathogenesis effect of HIV on the auditory system. The introduction of the HAART reduced the viral load and improved their CD4 cell counts as shown in Table 1. Low CD4 count has been reportedly associated with neural degeneration in HIV-infected individuals.[31]

Limitation of this study is that it is a cross sectional study, the audiological profile were not monitored routinely in the clinic while patients were on the HARRT regimen

REFERENCES

1. United States Embassy in Nigeria. Nigeria HIV Fact Sheet. 2011. Http://photos.state.gov/libraries/nigeria/231771/Public/Decemberhiv factsheet.pdf
2. Diagnoses of HIV Infection in the United States and Dependent Areas, 2014 On the Web: http://www.cdc.gov/hiv/library/reports/surveillance. Accessed on 19/1/2017
3. UNAIDS, AIDS epidemic update 2007, http://www.unaids.org/en/knowledgecentre/hivdata/epiupdate/epiupdarchive/2007/default. asp. Accessed on 19/1/2017
4. **Ana P.** Martinez-Donate, Elaine J. Blumberg, Melbourne F. Hovell, *et al.* Risk for HIV Infection Among Adolescents in the Border City of Tijuana, Mexico Show less. Hispanic Journal of Behavioral Sciences 2004, 14: 407-425
5. Centers for disease Control and Prevention. HIV/AIDS basic information, 2009, http://www.cdc.gov/hiv/topics/basic/index.htm.
6. The World Bank, HIV/AIDS in the Caribbean: Issues and Options, The International Bank for Reconstruction and Development/The World Bank, Washington, DC, USA, 2001.
7. **Gruber E** & Grube JW. Adolescent sexuality and the media: A review of current knowledge and implications. Western Journal of Medicine. 2000;172:210-214.
8. **Chao C,** Czechowicz JA, Messner AH, *et al.* (2012). High prevalence of hearing impairment in HIV-infected Peruvian children. Otolaryngol Head Neck Sur 146:259-265

9. **Schouten JT,** Lockhart DW, Rees TS, *et al.* Aprospective study of hearing changes after beginning zidovudine or didanosine in HIV-1 treatment-naïve people. BMC Infect Dis. 2006;6: 28.
10. **Bankaitis AE,** Christensen LA, Murphy G, Morehouse CR.HIV /ADS and auditory evoked potentials. Seminars in hearing. 1998;19: 177-183.
11. The Brain in AIDS: Central Nervous System HIV-1 Infection and AIDS Dementia Complex. Price,Richard W.; Brew, Bruce; Sidtis, John; Rosenblum, Marc; Scheck, Adrienne C.; Cleary, Paul. Science, Volume 239, Issue 4840, pp. 586-592
12. **Timon CI,** Walsh MA.Sudden sensorineural hearing loss as a presentation of HIV infection. J Laryngol Otol. 1989 Nov;103(11):1071-2
13. **Pagano MA,** Cahn PE, Garau ML, *et al.* Brainstem auditory evoked potentials in human immuno-deficiency virus-seropositive patients with and without acquired immunodeficiency syndrome. Arch Neurol. 1992 ; 49(2):166-169.
14. **Weber R,** Pinheiro Neto CD, Miziara ID, Araujo Filho BC. HAART impact on prevalence of chronic otitis media in Brazilian HIV-infected children. Braz J Otorhinolaryngol. 2006;72:509-514
15. **Matas CG,** Santos Filha VA, Juan KR, Goncalves IC. Audiological manifestations in children and adults with AIDS. Pro Fono 2010;22:269-274.
16. **Molyneux EM,** Tembo M, Kayira K, *et al.* The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi. Arch Dis Child. 2003;88(12):1112-8.
17. **Chander J,** Maini S, Subrahmanyan S, Handa A. Otomycosis - a clinico-mycological study and efficacy of mercurochrome in its treatment. Mycopathologia. 1996; 135(1):9-12.
18. **Ronald J. Ellis,** Jayraan Badiee, Florin Vaida, *et al.* CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 2011 10; 25(14): 10.1097
19. **Battegay M,** Nuesch R, Hirschel B, Kaufmann GR: Immunological recovery and antiretroviral therapy in HIV-1 infection. Lancet Infectious Diseases. 2006, 6 (5): 280-287.
20. **Jason Simdon,** Dan Watters, Stephen Bartlett, Elizabeth Connick. Ototoxicity Associated with Use of Nucleoside Analog Reverse Transcriptase Inhibitors: A Report of 3 Possible Cases and Review of the Literature. Clin Infect Dis. 2001; 32 (11): 1623-1627
21. **O'Connor AE.** Examination of the ear. In: Kerr AG, ed. Scott-Brown's Otolaryngology. 6th ed. London: Butterworth-Heinemann. 1997:3/1/ -3/ 1/29.
22. World Health Organisation. Deafness and hearing loss. Http://www.who.int/mediacentre/ factsheets/fs300/en/. Accessed on 25/5/ 2016.
23. **Ana P. Martinez-Donate,** Elaine J. Blumberg, Melbourne F. Hovell *et al.* Risk for HIV Infection Among Adolescents in the Border City of Tijuana,Mexico Show less. Hispanic Journal of Behavioral Sciences 2004, 14: 407-425
24. **Anni Taipale,** Tuula Pelkonen, Marko Taipale, *et al.* Otorhinolaryngological findings and hearing in HIV-positive and HIV-negative children in a developing country. Eur Arch Otorhinolaryngol. 2011;268:1527-1532.
25. **Chao CK,** Czechowicz JA, Messner AH, *et al.* High prevalence of hearing impairment in HIV infected Peruvian children. Otolaryngol Head Neck Surg. 2012;146: 259-265.
26. **Price Richard W,** Brew Bruce, Sidtis John, *et al.* The Brain in AIDS: Central Nervous System HIV-1 Infection and AIDS Dementia Complex. Science; 239(4840): 586-592
27. **Kohan D,** Rothstein SG, Cohen NL. Otologic disease in patients with acquired immunodeficiency syndrome. Ann Otol Rhinol Laryngol 1988;97: 636-640.
28. **Church J.** Human Immunodeficiency virus (HIV) infection at children's Hospital of Los Angeles: Recurrent otitis media or chronic sinusitis as the presenting process in pediatric AIDS. Immunol Allergy. 1987;9: 25-32
29. **Torre Peter III,** Zeldow Bret MS, Hoffman Howard J, *et al.* Hearing Loss in perinatally HIVinfected and HIV-exposed but uninfected children and adolescents. Pediatr Infect Dis J ;31(8): 835 – 841
30. **Ijaduola GT.** The problems of the profoundly deaf Nigerian child. Postgraduate Doctor – Africa 1982;6:180 - 185.
31. **Sophia Pathai,** Stephen D. Lawn, Helen A. Weiss, *et al.* Increased ocular density in HIV-infected individuals with low nadir CD4 counts in South Africa: evidence of accelerated aging. J Acquir Immune Defic Syndr. 2013;63 (3):307-314.