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HIV status and hearing loss among children between 6 to 12 years of age at a large urban health facility in south western Uganda

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Background

Occurrence of hearing loss (HL) among children in the developing countries is common and may even be on the rise[1]. Despite this, hearing loss does not receive sufficient attention in low to middle income countries, probably because of other competing health problems. Nevertheless, HL poses significant threat to social and economic growth and specifically among children, to the development of speech and language [2]. Because of this, HL has attracted significant international audience and WHO has established an international World Hearing Day on March 3rd every year to draw more attention [3].

Hearing loss may be classified as either conductive, sensorineural or mixed hearing loss. Sensorineural hearing loss (SNHL) has the profoundest effect on speech and language acquisition in children[4, 5], but any form of hearing loss can be severe enough to impede language and speech development in a child [1]. When recognized and diagnosed early, hearing loss is commonly addressed by providing amplification using hearing aids. However, secondary prevention of the disability is inferior to primary prevention of hearing loss if possible as this deficit limits the child's communication abilities.

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Hearing loss occurs regardless of age or gender and among children, the common causes are ear infections like otitis media, tympanic membrane perforations, congenitally acquired infections like Cytomegalo virus (CMV), trauma, foreign bodies in the ears and infections like Human Immunodeficiency Virus (HIV) and tuberculosis infections[6]. HIV and TB infections are common in sub Saharan Africa and may increase the burden of HL. HIV is known to increase the risk of both peripheral and central hearing loss among the exposed children by causing abnormal auditory processing [7]. However, there is limited research in sub Saharan Africa where the burden of HIV infection is high.

Few studies on HL and HIV have been done in sub Saharan Africa and additionally, results are variable. For instance, a study among HIV positive children under 5 years in Kampala, Uganda showed about 33% of them had HL and among those with HL, SNHL at 64% was the most prevalent form of HL [8]. Yet, another study to measure prevalence of hearing loss among primary school children in western Uganda estimated it at 3% [9], although the study did not consider the HIV status of the children. In Malawi, prevalence of HL was 24% among HIV infected children [10]. In addition, there are factors that could potentially modify the effect of HIV on HL and these include age, gender and prematurity but evidence regarding these factors is limited [11].

Antiretroviral therapy may have an impact on hearing loss [12]. HIV treatment protocols recommend early testing, diagnosis and treatment of HIV infected children [13]. This means that any child confirmed to be HIV positive is started on antiretroviral therapy (ART) soon after diagnosis. Although this standard of care has improved the health and survival of HIV positive children through protection from opportunistic infections and slowed progression of the disease [13, 14], there is limited knowledge on the otologic effects of long term exposure to ART. Therefore, the aim of this study was to compare the prevalence of hearing loss among HIV positive and HIV negative children between 6 and 12 years of age, to determine the types of hearing loss among this population and to establish whether HIV treatment is associated with the hearing loss types.

Methods

Study design and setting

We conducted a cross sectional study at two referral health facilities in Mbarara, south western Uganda, serving a large region. HIV positive participants were recruited from the Paediatric HIV Clinic while the HIV negative participants were recruited from the Paediatric Out-Patient Clinic at Mbarara Regional Referral Hospital which also serves as the teaching hospital for Mbarara University of Science and Technology (MUST). HIV testing is routinely done at the OPD, and results for the children returned same day to the care givers. We used the results from this routine testing to identify the HIV negatives to enrol. Data collection was carried out by trained research assistants.

Inclusion and exclusion criteria

Children were included in the study if they were aged between 6 and 12 years, able to follow instructions to perform an audiogram the parents or guardians consented to participate and the child provided assent.

Children excluded from the study were those who did not assent or whose parents and guardians declined for them to take part in the study, children below the age of 6 years or over 12 years or those unable to cognitively follow instructions for audiometry using the ShoeBox App on the iPad audiometer. For instance children with Attention Deficit Hyperactive Disorder (ADHD), involuntary muscle movements (chorea) and other conditions that affect concentration were excluded. Also excluded were children with congenital anomalies like microtia and microcephaly and syndromes like Waadenberg and Treacher-Collins. Such conditions increase the likelihood of congenital hearing loss. Children with actively draining (infected) ears were not recruited but instead referred to the ENT clinic for proper diagnosis and treatment.

Study procedures

Following enrolment, the parent/guardian was interviewed and a questionnaire completed to document the biodata and demographic factors concerning the child. Each participant underwent otoscopy prior to hearing screening to check for active infection. The hearing screening was carried out in an ambient room using the ShoeBox Application on the iPad audiometer. The iPad and this application have both been validated as tools for hearing screening in children [15]. Unilateral or bilateral failure of the screening test was followed by a Pure Tone Audiology (PTA) to confirm the form and severity of hearing loss.

Data analysis

Data were exported to STATA 11.0 for analysis. Descriptive statistics were generated for demographic and baseline clinical characteristics like age, gender, history of hearing loss and duration of ART treatment. Frequency tables were used to describe the demographics of the study population.

The prevalence of hearing loss among HIV positive children in comparison to HIV negative children was calculated as a fraction of the total number of children screened. Chi square test was used to compare the two proportions. Two by two tables were used to examine the associations between the different factors and hearing loss. Logistic regression analysis was used to calculate the odds ratio of factors associated with hearing loss. In the logistic regression analysis, age of the child was highly correlated with duration on ART hence the latter was omitted from the multiple regression analysis due to collinearity. In the multiple regression analysis we aimed to build a parsimonious model; i.e. included variables that were of statistical significance and with biological importance.

Human subject issues

The study was approved by the Mbarara University of Science and Technology Research Ethics Committee UST Institutional Research and Ethics Committee. Individual informed

consent was obtained from the parents or caregivers of the children and children were also asked to assent for the study procedures.

Results

Baseline characteristics

We consecutively enrolled a total of 227 children of which 79 were HIV negative and 148 were HIV positive children all aged between 6 and 12 years. The demographic and clinical history data are shown in Table 1. There was no significant difference in the distribution of males and females among the HIV positive and negative children. Patient and family history of hearing loss were reported more frequently among HIV negative children compared to the HIV positives. History of infections associated with hearing loss namely cerebral malaria, meningitis and ear infection was similar in both group, however measles was reported more common among HIV negatives compared to the positives (p= 0.02). In the medical history, HIV positives were more likely to have received TB drugs and HIV negatives were more likely to have used quinine.

Frequency of hearing loss

The prevalence of hearing loss among HIV positive children was 13 out of 148 children or 8.8% and 8 out of 79 HIV negative children or 10.1% and the difference was not statistically significant (p=0.74). Overall, a total of 21 (9.3%) children were found to have some form of HL. Among the children with HL (n=51), conductive HL was the most frequent form of HL with n= 36 or 15.9%, followed by SNHL with n= 14 or 6.2%. Only one respondent was diagnosed with mixed HL.

Figure 1 suggests conductive hearing loss is more frequent in the HIV negative children with n= 15 of 79 (18.9%) when compared to HIV positives n= 21 of 148 (14.2%). On the other hand SNHL is more frequent among HIV positives n= 11 (7.4%) compared to n= 3 (3.8%) among the HIV negatives. The only child found to have mixed type of HL was HIV positive. However, this result is not statistically significant with a Fisher's exact of p= 0.21.

Factors associated with hearing loss

Bivariate logistic regression results are presented in Table 2 to show the factors associated with hearing loss. Older children had higher the odds of having hearing loss (OR=5.97, p=0.01). Receiving an ART regimen containing NVP was associated with lower odds of having HL but this relationship was not significant (OR=0.62, p=0.41). Duration of taking ART was significantly associated with increased the odds of having HL and children with more than 6 years of ART history had an eight-fold increase in the odds of having HL (OR=8, p <0.01). History of ear infection significantly increased the odds of having HL by 4.4 (p <0.01). Significantly, anti-TB drugs increased the odds of a child presenting with HL by 6.12 (p <0.01).

In the multiple logistic regression model shown in Table 3, age (11-12 years), previous ear infection and use of TB drugs all remained significantly associated (p= 0.02, p= 0.01 and p= 0.005 respectively) with occurrence of HL with R^2=0.58.

Effect of Nevirapine on hearing loss

In a subgroup analysis among patients receiving antiretroviral therapy (n=148), we assessed the relationship between use of NVP and hearing loss. The frequency of HL among patients with NVP was 6 out of 84 or 7.1% and 7 of 64 patients or 10.9% among those not receiving NVP. There is a difference, however this was not statistically significant (p=0.41). Other antiretroviral drugs in common use were assessed and also no significant difference emerged.

1.4 Discussion

We conducted a cross-sectional study among HIV positive and negative children to compare the prevalence and types of hearing loss between the two groups, and to determine whether HIV treatment regimen is associated with the hearing loss type.

The main findings of the study were first, the prevalence of HL among HIV negative children is similar to that of HIV positive children. Second, the factors associated with HL were older age of the child, history of ear infection, use of TB drugs and long duration on ART medication. Third, the factors that strongly predicted the occurrence of HL were older age of the child and history of ear infections and TB treatment and lastly there was no significant relationship between NVP based ART and occurrence of HL

Our data suggests that frequency of HL was the same among HIV positives and negatives. The finding is surprising, our data has no clear explanation for this discrepancy and disagrees with many other studies conducted before that suggested that HL was higher among HIV positive children [16-18]. A case control study by Taipale et al [19] in Angola using either pure tone audiometry or evoked potentials also showed a higher prevalence of HL among HIV positive children compared to the HIV negative. Studies suggest that higher prevalence of HL among HIV positive children may be because HIV positive children are more predisposed to developmental abnormalities, opportunistic infections and are exposed to several drugs that increase their predisposition to HL [20]. Studies have shown that when a disease process is considered 'serious', there is a higher likelihood of seeking healthcare [21]. Considering the social perception of HIV infection, this may provide more opportunities for HIV positive children to be diagnosed with HL than their HIV negative counterparts. Our study is not in isolation; there are other studies that showed no clear difference in the prevalence of HL among HIV positive and negative children making it difficult to attribute HIV infection as a cause of HL [22, 23].

The commonest type of HL overall, in this population was conductive hearing loss. The result is similar to other studies elsewhere [10, 24]. CHL is mainly attributed to ear infections such as otitis media which is considered a common pediatric infection, ear drum perforations and trauma [25]. Otitis media is also a common diagnosis among children seen in many ENT clinics in resource limited settings and among HIV positive children and this is evident in our study population. For patients with SNHL, the high prevalence of SNHL seen among the HIV positive children is similar to findings from other studies conducted both locally and abroad [8, 11, 20]. Suggested theories of the pathophysiology of SNHL in HIV infection include effect of the disease process and drugs on mitochondrial function

causing ototoxicity in patients who are predisposed [26, 27]. Other studies have attributed the SNHL to neurological effects of the HIV infection and opportunistic infections like meningitis on the central auditory centres leading to neural HL [20].

The presence of factors predisposing to HL such as use of other ototoxic drugs such as aminoglycosides, noise exposure and infections like meningitis and TB further increases the risk for HL [25, 27]. Some of the factors that we found to be associated with HL in our study included increasing age of the child which may be explained by several previous ear infections and long term exposure to ART thus increasing the chances of developing HL. Anti TB drugs especially the macrolide containing regimens contain known ototoxic drugs which would lead to HL during and after treatment [28]. However, there was no child receiving such a regimen in our study. Records showed that they had received rifampicin, isoniazid and pyrazinamide; none of which has been found to be ototoxic. Therefore the relationship between TB treatment and HL in our study could have been a chance finding with no true association between TB treatment and occurrence of HL but may warrant further assessment in larger studies. Other factors known to have neurological and otologic sequelae such as measles and use of quinine drug showed no significant association to occurrence of HL in our study population. However there have been reports published on measles virus causing irreversible SNHL [29, 30] and quinine treatment more commonly leading to reversible high frequency SNHL [31]. Data indicating measles and quinine as causes of HL are scanty however.

We hypothesized that NVP is associated with HL in HIV positive children because case reports and studies have documented ototoxicity as a possible side effect of nucleoside reverse transcriptase inhibitors such as NVP [32, 33]. Literature also shows that ototoxicity effects are heightened in the presence of confounders such noise exposure, ear infections and TB treatment [27], which were common in our study population. In our study however, though several children were receiving NVP based ART regimens, there was no significant difference in the occurrence of HL among children on NVP based ART and those receiving other regimens. The result is similar to that in a study conducted in Malawi to examine the association of ART with HL in children[10]. Though studies on ototoxicity of ART drugs in children are few, association between ART and HL in adults has been reported implicating nucleoside analog drugs such as Didanosine and Stavudine [32-34]. There is a need to study the effect of other ART drugs and their long term exposure on the vulnerable auditory function among children.

The multiple regression model predicted that HL was more likely to occur in HIV positive children if the child was older, had a history of ear infection and TB treatment. The reverse was found true in Malawi where no difference was reported in occurrence of HL with increasing age of the child. However factors such as ear infections and TB treatment increased the odds of HL [10].

The implication of our study results is that hearing loss and ear health are strong factors that need to be assessed routinely and managed adequately especially among HIV positive children.

The strengths of our study are that we compared audiological findings among both HIV positive and negative pediatric populations. We also investigated a less frequently studied age group of pre-adolescents. Limitations in our study included the changing drug regimens and doses for the participants over time. A child may have been exposed to NVP in the past regimens and subsequently changed to other regimens as the disease progressed. Technically therefore they have been exposed to NVP but we only considered the current regimen the child was receiving in our study, therefore some children exposed to NVP may have been misclassified.

In conclusion, the prevalence of hearing loss is similar among HIV positive and negative children with sensorineural hearing loss being the most predominant form among the HIV positive children. Older age of the child, a positive history of ear infection, use of TB drugs and long duration on ART medication are the factors that increase the odds of developing hearing loss among HIV positive children. Based on these features, paediatricians should consider including simple questions and ontological examinations to identify high risk children who may require further attention. Further research should be done to create an algorithm to efficiently identify and manage high risk children.

Acknowledgments

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The chart shows Percentage on the y-axis (0–90) versus Type of Hearing Loss (HL) on the x-axis, with bars for HIV negative and HIV positive:

	No HL	Conductive HL	Sensorineural HL	Mixed HL
HIV negative	77.2	19	3.8	0
HIV positive	77.7	14.2	7.4	0.7
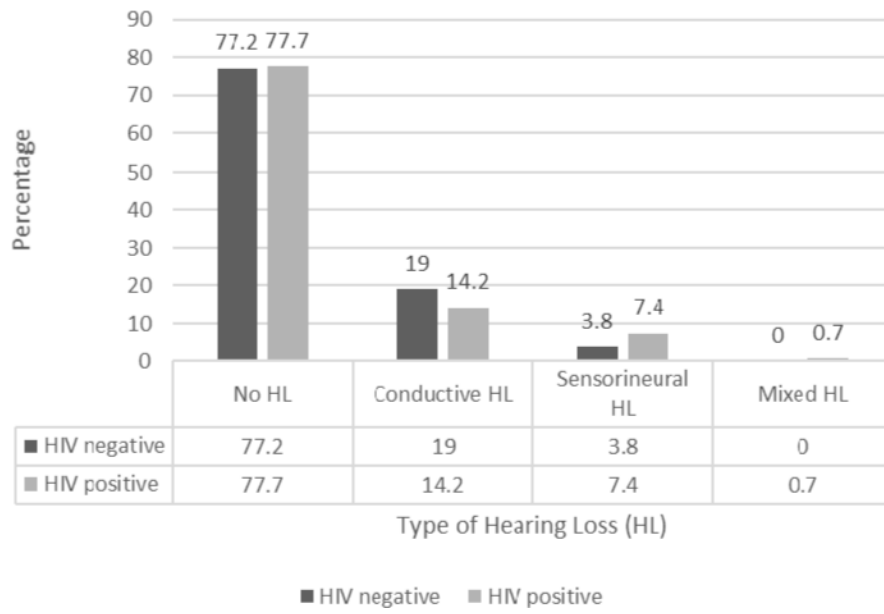
Figure 1.
A graph showing the frequencies of the different types of hearing loss among the HIV positive and negative children

Table 1

Demographic characteristics and clinical history of HIV positive and negative children at Mbarara Hospital.

	Characteristic	HIV positive children n=148 (%)	HIV negative children n= 79 (%)	Chi p-value
Age	6-8	54 (36.5)	33 (41.8)	
(Mean age= 9.2)	9-10	36 (24.3)	30 (38)	<0.01*
	11-12	58 (39.2)	16 (20.3)	
Gender	Male	73 (49.3)	39 (49.4)	0.995
	Female	75 (50.7)	40 (50.6)	
History of hearing loss	Yes	10 (6.8)	16 (20.3)	<0.01*
	No	138 (93.2)	63 (79.8)	
Family history of hearing loss	Yes	1 (0.7)	8 (10.1)	<0.01*
	No	147 (99.3)	71 (89.9)	
History of infection				
Meningitis	Yes	4 (2.7)	1 (1.3)	0.48
	No	143 (97.3)	78 (98.7)	
Cerebral malaria	Yes	12 (8.2)	10 (12.7)	0.28
	No	135 (91.8)	69 (87.3)	
Measles	Yes	3 (2)	7 (8.9)	0.02*
	No	144 (98)	72 (91.1)	
Previous ear infection	Yes	18 (12.2)	10 (12.7)	0.91
	No	130 (87.8)	69 (87.3)	
Drugs				
Quinine	Yes	54 (36.7)	42 (53.2)	0.02*
	No	93 (63.3)	37 (46.8)	
Tuberculosis (TB) treatment	Yes	15 (10.1)	0 (0)	<0.01*
	No	133 (89.9)	79 (100)	
Trauma				
Head injury	Yes	1 (0.7)	2 (2.5)	0.24
	No	147 (99.3)	77 (97.5)	
Ear trauma	Yes	0 (0)	2 (2.5)	0.05
	No	148 (100)	77 (97.5)	
Ear surgery	Yes	1 (0.7)	2 (2.5)	0.24
	No	147 (99.3)	77 (97.5)	

Table 2

Bivariate logistic regression analysis to determine the factors associated with hearing loss among HIV positive and negative children at Mbarara Hospital, Uganda

Characteristic		Odds Ratio	Confidence interval	P value
Age	6-8	1		
	9-10	2.3	0.53-9.97	0.27
	11-12	5.97	1.63-21.85	0.01*
Gender	Male	1		
	Female	0.71	0.29-1.75	0.45
History of HL	No	1		
	Yes	2.75	0.92-8.28	0.07
History of infection				
Cerebral malaria	No	1		
	Yes	2.44	0.74-8.05	0.14
Measles	No	1		
	Yes	1.09	0.13-9.04	0.94
Previous ear infection	No	1		
	Yes	4.4	1.60-12.1	<0.01*
Drugs				
Quinine	No	1		
	Yes	1.92	0.77-4.76	0.16
TB treatment	No	1		
	Yes	6.12	1.87-20.10	<0.01*
HIV status	Negative	1		
	Positive	0.85	0.34-2.16	0.74
NVP containing	No	1		
ART regimen	Yes	0.62	0.20-1.94	0.41
Duration on ART	<3 years	1		
	3-6 years	0.94	0.15-5.82	0.94
	>6 years	8	1.95-32.83	<0.01*

Table 3

Multiple logistic regression model of the effect of significant factors from the linear regression model on hearing loss

Characteristic		Odds Ratio	95% Confidence interval	p value
Age in complete years	6-8	1		
	9-10	2.11	0.47-9.47	0.33
	11-12	5.23	1.37-19.98	0.02*
Previous ear infection	No	1		
	Yes	4.09	1.35-12.35	0.01*
TB treatment	No	1		
	Yes	6.66	1.77-25.03	0.005*