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Is hearing impairment associated with HIV? A systematic review of data from low and middle-income countries

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Abstract

Objectives: To systematically review evidence on the prevalence and characteristics of hearing impairment among children and adults living with HIV in low and middle-income countries (LMIC).

Methods: Articles were identified up to January 2016 through searching four electronic databases. Epidemiological studies conducted in LMIC that explored the association between HIV status and hearing loss, with or without an HIV-uninfected comparison group, were eligible for inclusion. Results were screened and assessed for eligibility and data were extracted by two reviewers, with discussion in the case of disagreement. Findings were narratively synthesized.

Results: The search identified 638 unique references, of which 21 studies were included in the review, including 3491 people with HIV from 13 LMIC. There was lack of consistency in the definition used for hearing loss, making comparability across studies difficult. Among children with HIV, across the three studies that used a cut-off of >15dB in either ear, the prevalence of hearing loss ranged from 22-37%. Among the three studies that used >25dB in either ear, the prevalence ranged from 32-39%. Among adults with HIV, for the five studies that used a threshold of >25dB for either ear, the prevalence ranged from 10-43%. The prevalence of hearing impairment was significantly higher among people with HIV than in controls in eight of the ten studies that assessed this comparison. Conductive hearing loss was the most common type of hearing loss in children with HIV, while sensorineural hearing loss was more common in adults with HIV. There was a lack of evidence for an association between ART use and hearing loss, though there was some suggestion that late stage of HIV disease or low CD4 count was related to hearing loss. There were concerns about the quality of the studies included in the review.

Conclusions: The current evidence is suggestive of a high prevalence of hearing loss among people living with HIV compared to people without HIV, or to WHO estimates for the general population. More research is needed to better understand the aetiology of hearing loss in relation to HIV, and

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whether screening for and treatment of hearing loss can be effectively integrated into HIV treatment services needs further research.

Keywords: Hearing impairment, HIV, screening, epidemiology, low and middle-income countries, systematic review

Introduction

Sub-Saharan Africa contains 70% of the worldwide 35.3 million people living with HIV.[1] Access to anti-retroviral therapy (ART) has become widely available even in these countries in the last decade.[2] Consequently, life expectancy of people living with HIV has increased dramatically, and HIV is fast becoming more of a chronic illness.[3] Evidence is growing that with increased life expectancy there is an emergence of long-term consequences of HIV.[4] The focus of HIV programmes must therefore shift from saving life to improving the quality of life of people living with HIV.

One of the potential long-term consequences of HIV is on hearing impairment. In high-income countries, up to 75% of adults infected with HIV experience various oto-rhino-laryngological symptoms during the course of their disease, including hearing loss.[5] Hearing loss is gradual in most cases, but may be sudden in nature in others.[6] Studies in high-income countries in adults show that sensorineural hearing loss (SNHL) presents in about one-third of all adult individuals infected with HIV, and this can occur as a result of opportunistic central nervous system infections causing meningitis or encephalitis (e.g. toxoplasmosis, syphilis, herpes and CMV) or by the HIV virus itself. [6,7,8,9] Other sensorineural causes can be iatrogenic in nature, for instance, as a result of ototoxic drugs administered for co-infections such as TB, or ARTs.[10] SNHL in HIV is irreversible and so a focus should be on its prevention. Children infected with HIV are also at risk of hearing loss, and studies from the US estimate that about 20% of HIV-positive children have hearing loss.[6] Hearing loss in these children appears to be mainly conductive (i.e. located in the middle ear), probably because the immune-compromised child is at a higher risk of developing otitis media and chronic suppurative otitis media. [11] This means that hearing loss in children with HIV should mostly be treatable, given availability of services.[12]

Assessing hearing function in people living with HIV is therefore potentially important, since good hearing is important for social participation, and inclusion in employment and education. However in most low and middle-income countries (LMIC) access to oto-rhino-laryngological care is limited, ENT doctors are rare and often only available in the capital city.[12] Furthermore, screening programmes are virtually non-existent and access to hearing aids is very rare. Careful consideration

is therefore needed of the prevalence and cause of hearing loss among people living with HIV, in order to show how best to provide prevention and treatment services to mitigate hearing loss in LMICs.

The objective of this study was to systematically review evidence on the prevalence and characteristics of hearing loss among children and adults living with HIV in LMIC, in order to inform HIV programm planning in these settings.

Methods

The systematic review was planned, conducted and reported according to established PRISMA guidelines [13] A systematic literature search was conducted in January 2016 for peer-reviewed articles that presented original research findings on hearing loss among people with HIV in LMICs. A specific review protocol was not published separately.

Search strategy

Four electronic databases, PubMed, Web of Science, EMBASE, and Global Health, were searched in January 2016. Search terms for HIV/AIDS and hearing impairment were identified through MeSH as well as from those used for systematic reviews on similar topics. The date of publication was restricted from 1980 to January 2016 as HIV/AIDS was recognised in the early 1980s. Furthermore, the reference lists of all included papers were screened to identify further eligible papers.

Articles were screened by two reviewers (RE and HK), first by titles, then by abstract and finally by full text to determine eligibility in the final sample. There was discussion until consensus was reached in the event of disagreement. The search strategy is presented in Figure 1.

Study selection

Studies were eligible if they met the following criteria: (1) Original research that included HIV and hearing impairment, (2) results reported or allowed calculation of prevalence of hearing impairment among people with HIV, (3) all people in the sample were screened for hearing impairment, and (4) conducted in an LMIC as defined by the World Bank country classification 2015.

Both HIV status and hearing impairment could be assessed through self-report, clinical assessment or medical records. Any study with an epidemiological design was eligible for inclusion (survey, case-control, cohort, trials). Given the expectation that there would be a dearth of information, studies with and without comparison groups were included.

Exclusion criteria comprised: (1) full text unavailable, (2) duplicate reports from the same study, (3) studies that investigated hearing impairment as a risk factor for HIV infection, (4) qualitative studies, (5) case reports (i.e. sample size <10), and (6) study population comprised patients with HIV presumed to be at high risk for hearing loss (e.g. those attending ENT services, those with multi-drug resistant TB).

Data extraction and analysis

The following data were extracted from articles that met the inclusion criteria: General study information (title, author, year of publication), study design, study setting and dates conducted, and population characteristics. The primary research outcomes extracted were: prevalence of hearing impairment among people with HIV, and odds ratio for the relationship between hearing impairment and HIV if a comparison group was available. Furthermore, odds ratio for the relationship between measures of HIV disease status (CD4 count or WHO stage) and hearing impairment were recorded. All these estimates were calculated from available data when they were not presented in the paper.

All data were extracted by the two authors and compared for any differences, which were discussed so that a consensus was reached.

Meta-analysis was not used to pool results, due to the lack of standardised measures of hearing loss and heterogeneity in study designs and consequently a narrative approach was taken. Studies using a comparison group were described separately from those without.

Quality assessment

Quality assessment of the eligible studies was conducted using a modified version of the quality assessment tool for systematic reviews of observational studies (QATSO). Criteria included the following: (1) two measures on representativeness of the sampling method (use of probability sampling to select study participants, population-based recruitment), (2) objectivity of measurement of HIV, (3) validated hearing impairment measurement, (4) acceptable response rate (60% of higher) and (5) control for confounding in studies with a comparison group.

Results

The search identified 638 unique references, after removal of duplicates. Of these, 435 records were excluded after screening titles, and a further 162 records after screening abstracts. 41 papers were

identified for full text review. Twenty-two studies were not eligible, because they did not include a measure of hearing loss (n=10) or HIV (n=3), were conducted in a high income setting (n=2), were an ineligible research design (n=4, e.g. reviews or included an ineligible group of HIV participants such as people with HIV and MDRTB), were not in English (n=1)[14] or the full text could not be retrieved (n=2). [15,16] Two further eligible studies were identified through screening references of eligible papers [20,27] Finally, 21 eligible articles were included in the review. These 21 studies included 3491 people with HIV in 13 LMIC settings.

The characteristics of the eligible studies are summarised in Table 1.[17-37] Eleven studies focused on children, nine on adults, and one on people of all ages. Eleven of the studies included both cases with HIV and HIV uninfected controls, while the remaining ten included only patients with HIV. The majority of the studies were conducted in sub-Saharan Africa (n=13), with the remainder undertaken in Latin America (n=6) or India (n=2). Almost all of the studies were carried out in clinical settings. None of the studies included self-reported HIV status; in all HIV status was clinically verified. None of the studies used probability sampling, and none reported the response rate. Hearing was assessed clinically in twenty studies; only one study assessed hearing impairment through self-report and none extracted the data from medical records.

Most of the studies included in the review used pure tone audiometry (PTA) to measure hearing loss, but a range of different cut-offs was used for hearing loss, particularly among the children. (Table 2) There was also a lack of consistency as to whether hearing loss was determined on the basis of either ear or in the better ear. Among children with HIV, the prevalence of hearing loss varied from 4% to 85% overall. Across the three studies that used a cut-off of >15dB in either ear, the prevalence of hearing loss among children with HIV ranged from 22-37%. Among the three studies that used >25dB in either ear (or did not state whether it was for either ear), the prevalence ranged from 32-39%. Among adults the prevalence of hearing loss ranged from 10%-68%. Among adults, a threshold of >25dB was used more consistently to determine hearing impairment. There were five studies that used this threshold for either ear (or did not state whether it was for either ear), and the prevalence ranged from 10-43%. The prevalence of hearing impairment was consistently higher among people with HIV than in controls. Among children, four of the five studies that compared children with and without HIV found a significant association between HIV and hearing loss (Figure 2). Similarly, among adults, four of the five studies that included cases and controls found a significantly higher odds of hearing loss among people with HIV compared to uninfected controls. These comparisons were mostly unadjusted.

A variety of examination methods were used to identify the type of hearing loss (Table 3). Among the seven studies that explored cause of hearing loss in children, four found that conductive hearing loss was the most common type. In contrast, among the seven studies that assessed cause of hearing loss in adults, five found that SNHL was the most common type of hearing loss. Nine studies articles reported in detail on otoscopy findings.[19,21,25,29-33,37] Chronic suppurative otitis media (CSOM) prevalence varied from 16 to 36% in children and adults with HIV. Two studies reported on the prevalence of eardrum perforations in children, and reported these as 9% [19], and 10% [23] respectively. One article reported prevalence of perforations in adults of 8%. [33] Two articles reported on a prevalence of acute otitis media with effusion (A)OME respectively of 5% [21] and 10% [19], respectively.

Fourteen studies investigated the relationship between clinical features of HIV and hearing loss (Table 4). Ten studies reported on relationship between ART and hearing loss, of which three found evidence of an association, although for one this was restricted to a sub-group. [7] In contrast, three of the five studies that investigated the relationship between low CD4 count and hearing loss found a positive association. Similarly, there was consistent evidence for an association between stage of HIV and hearing loss. There was less evidence of a relationship of hearing loss with low viral load or opportunistic infections.

The quality assessment highlighted several concerns about the studies included in the review (Table 5). None of the studies were population based or used probability sampling, and the response rate was consistently not reported. Furthermore, only one study controlled for confounding in the primary analyses of the relationship between HIV and hearing impairment. In terms of strengths, all studies included objective measures of HIV assessment, and all but one used validated assessment tools to determine the presence of hearing impairment.

Discussion

This systematic review summarizes evidence from 21 studies of hearing impairment prevalence among 3491 people with HIV in 13 LMIC settings. To our knowledge, this is the first systematic review of hearing loss among people with HIV. There was a high degree of variability in estimates, attributable at least in part due to the lack of consistency in thresholds used to define hearing loss or methods used to measure hearing loss. Overall, however, approximately one in three people living with HIV appear to experience a hearing impairment. These figures are greater than the estimates for the general population provided by WHO that suggest that 15% of the world's adults population has some degree of hearing loss (>25 dBHL in better ear) of whom one third have disabling hearing loss (>40 dBHL) [38]. In particular, the level of hearing impairment in children with HIV far exceeds

the estimates from WHO of approximately 1.4% have disabling hearing loss (>35 dBHL).[39] Furthermore, in 8 of 10 studies that compared cases with HIV to HIV-uninfected controls there was a statistically significant association between HIV and hearing loss, and this was apparent in both adults and children. These estimates are in line with those from high income countries, indicating that hearing loss is relatively common among people living with HIV. [6,40]

Several of the studies investigated the cause of hearing loss, among people with HIV, as well as the presence of other ear conditions. There was a great variation in methods used here also, including whether tympanometry, air/bone audiometry, otoscopy and/or other examinations were undertaken. Only 9 of 21 articles included reported their otoscopy results in detail. When middle ear dysfunction is not properly investigated a higher proportion of SNHL will be found. This implies that the percentage of treatable causes of hearing loss might be even higher than calculated in this review. However, there were clear patterns in cause; among children hearing loss was most commonly a conductive hearing loss, while in adults this was more likely to be SNHL. These findings are consistent with those studies from high-income countries. [41,42,43] In children, the conductive hearing loss is likely to result from frequent ear infections; several studies reported frequent CSOM among the children with HIV.[19,21, 25, 26, 29-32,37] Although the study samples were generally small, these CSOM prevalences were similar to the otoscopical abnormalities found in 14-37% of ears in high-income countries. [6,43] Overall, 8-10% of children with HIV had an eardrum perforation. These estimates are far higher than would be expected from the general population. For instance, the largest study in Africa on 5368 schoolchildren (not tested for HIV) showed a prevalence of eardrum perforations of only 2.4% with 1.1% of children having a CSOM. [44]

The high prevalence of hearing loss and ear conditions among people living with HIV reported in this review is consistent with previous studies. For instance, a study from Ivory Coast in children showed that non-specified ENT-manifestations in HIV accounted for one third of HIV related presenting symptoms. [45] Similarly in a study among South Africa children CSOM was often a presenting symptom of HIV in 54% of investigated children under the age of 6 years. [46] In Cameroon approximately 12% of patients discovered their HIV status after an oto-laryngological event. [47]

There was some evidence for a relationship between hearing loss and specific characteristics of HIV disease, in particular, signs of advanced disease, though data were lacking and not always consistent. Three of five studies that investigated the relationship between a low CD4 count and hearing loss found a positive association. The association between ART and hearing loss was less clear. It is likely, however, that ART therapy would prevent the discharging periods of acute otitis media, resulting in a lower prevalence of CSOM, and consequently less hearing loss in children. On

the other hand, ART may be given to people with more advanced disease, which may be independently related to hearing loss, thus concealing the potentially positive impact of ART on preserving hearing. There is also the possibility that ART itself may cause hearing loss, through ototoxicity.

The majority of the studies used PTA or ABR to determine hearing loss, and only one study used self-report measures. There was no specific audiological pattern found among HIV patients. A recent study reports on a marked low tone perceptive hearing loss however only described in adult patients [40] and in one study unilateral hearing loss, with a difference of > 20 dB was reported in 40% in an American population and in 20% in South African children. [42,43] Chandreskar and Makau found higher levels of hearing impairment at 4 and 8 kHz among people with HIV, however in these studies many patients were on ART treatment.[6,29] In another study in individuals on ART treatment, high tone hearing loss was absent and but affected more frequencies.[31] In one study where patients were not on ART treatment, a similar high tone hearing loss was described.[30] Various explanations are possible for these high frequency hearing losses; not only HIV itself but also co-existing neurotropic infections such as CMV, herpes; ototoxic drugs for co-existing TB, or ototoxic aminoglycoside drops used in open middle ears can account for these hearing losses. One study was identified that undertook hearing screening by oto-acoustic emissions (OAE) alone, but was not included in this review as the target group was HIV-exposed children, rather than HIV-positive children.[48] Although no statistically significance was found, in 11,1% of neonates a hearing loss over 20 dB was found and correlated with a CD4 % lower than 25 in the neonate. More recent studies report on specific audiological findings by OAE screening, however their results provide so far no adequate tools to implement in screening programs for hearing loss in the younger children with HIV. [27,34]

Overall, this review showed strong evidence supporting a relationship between HIV and hearing loss. Consequently, there is clear justification for routinely screening children and adults living with HIV for hearing loss and other ENT symptoms. Self-report of hearing loss is likely to be insufficient, since the onset of hearing loss is usually slow. OAE screening is likely to be inappropriate for sub-Saharan African setting, given low access to these screening facilities, as well as lower detection rates of severe hearing losses. [49] Clinical screening using audiology is therefore recommended, as often happens in high income settings. This screening is now more feasible with the availability of low cost mobile tools, such as HearTest and HearScreen.[50] An ear examination would also be helpful to identify other ear conditions, such as CSOM, although constraints on the availability of skilled staff may make this difficult to implement.

Protocols will need to be developed and field-tested in order to determine which mode of screening for hearing impairment among people with HIV is most cost-effective in a resource constrained setting. Furthermore, future studies should use standard means for measuring and defining hearing loss, ideally in line with the WHO categories. Greater standardization in the examination of ears, to determine cause of hearing loss, would also be helpful. More evidence is needed on the causes of hearing loss among adults and children with HIV, so that interventions can be developed and tested. The repeated screening for hearing loss within longitudinal studies of people living with HIV will help to improve our understanding of the aetiology of hearing loss associated with HIV.

There are important strengths to this review. It was the first systematic review on this topic, and included studies from low and middle-income countries, across children and adults. There are also limitations. There was a high degree of variability in how hearing loss was categorised, and concerns about the quality of the data. The studies did not routinely investigate the aetiology of the hearing loss, and so there was potential for bias in reporting of associations between hearing loss and characteristics of HIV. All of the studies were carried out in clinical settings, and so evidence is not available about the prevalence of hearing loss among people with HIV who are not aware of their status and/or not being medically managed. The review was restricted to papers published in English, although in reality this led to the exclusion of only one article.[14] Furthermore, uptake and use of ENT services was not assessed, but is likely to have been low.

In conclusion, the evidence is suggestive of a high prevalence of hearing loss among people living with HIV. More research is needed to consider the aetiology of hearing loss in relation to HIV, and whether screening for and treatment of hearing loss can effectively be integrated into HIV treatment services in low and middle-income settings.

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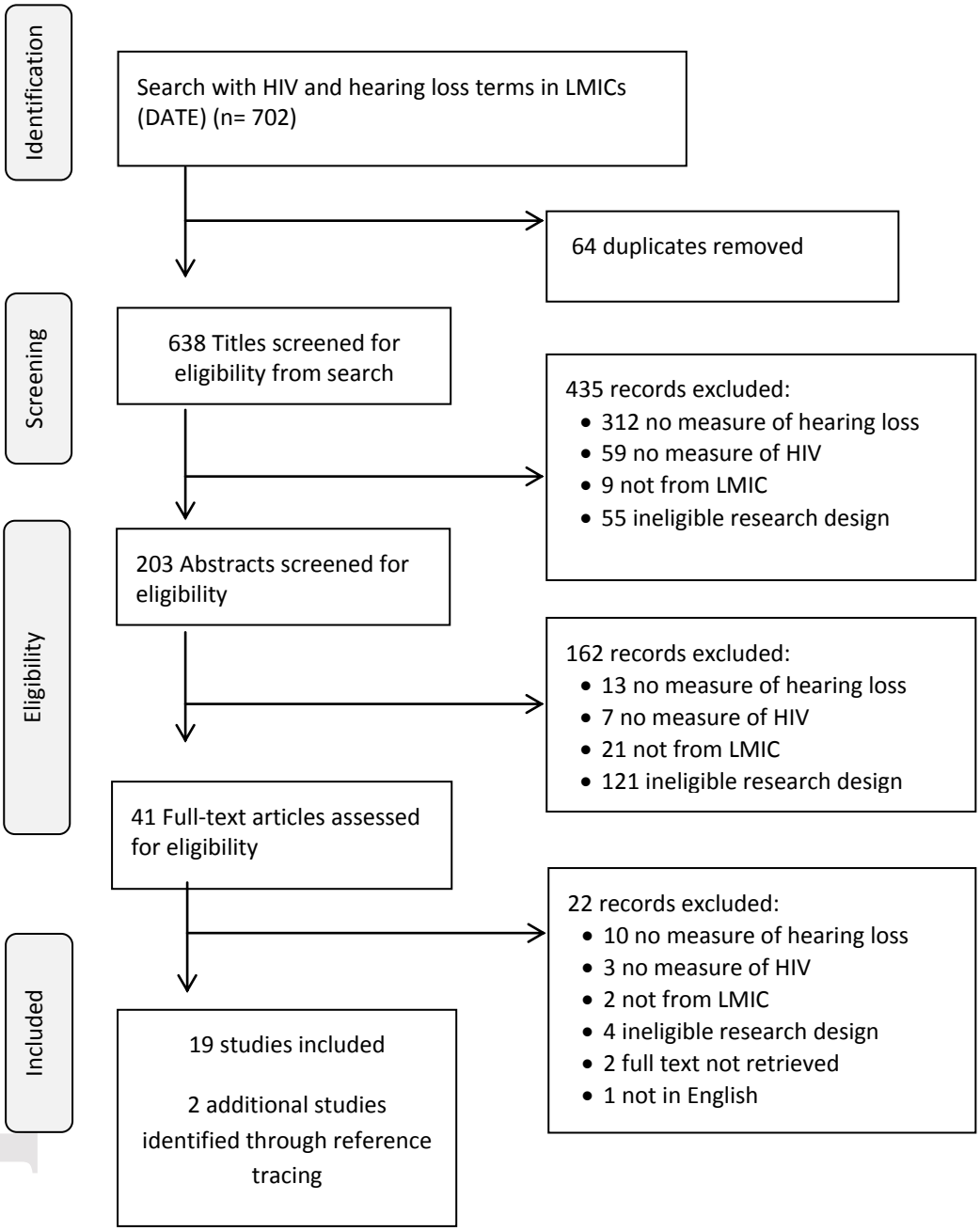

Figure 1 Search strategy with flow diagram

Figure 2: Odds of the association between hearing loss and HIV, among adults and children

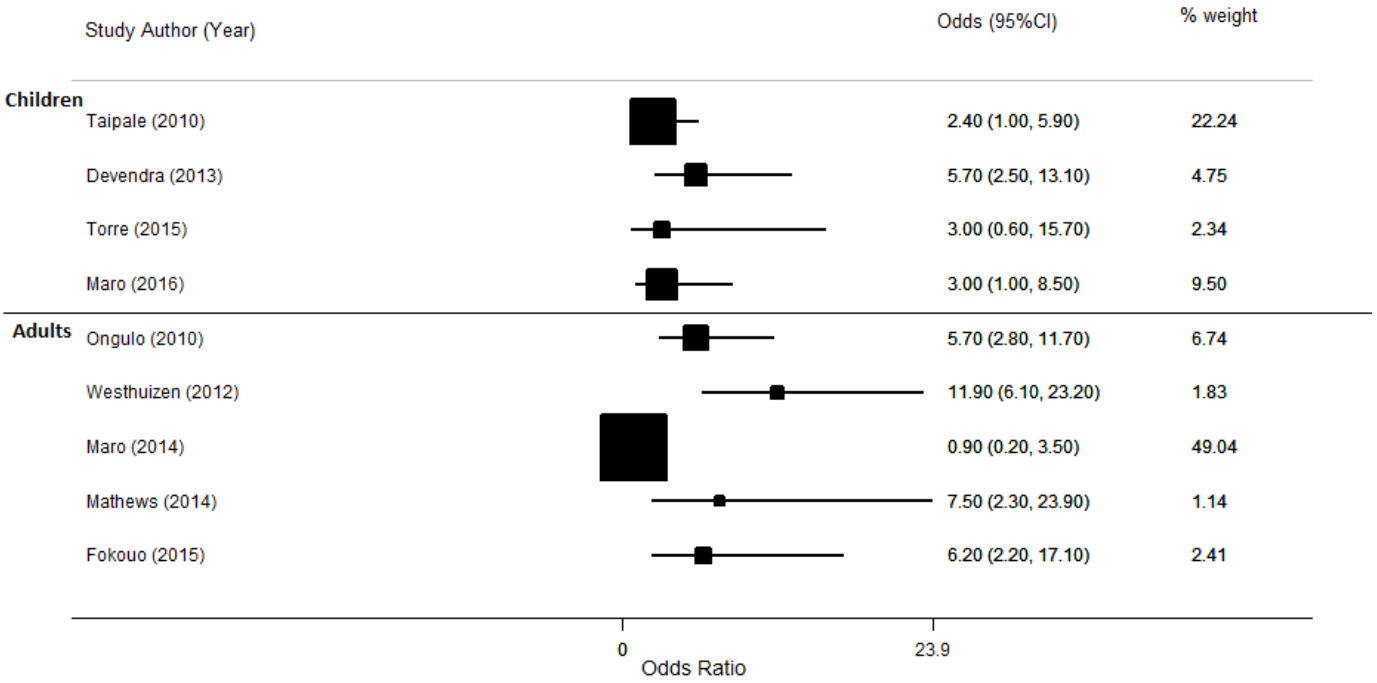

Table 1: Description of studies included in review

Author, year	Country	Study design	Clinic or population sample	Population	PLHIV (n)	HIV – controls (n)	Age range (years)	Mean age (years)	% female
Child sample									
Matas, 2006 **[17]**	Brazil	Case-control	Population	Children	51	50	3-10	-	50%
Palacios, 2008 **[18]**	Mexico	Survey	Clinic	Children	23	-	0-17	4.5	48%
Taipale, 2010 **[19]**	Angola	Case-control	Clinic	Children	78	78	0.75-14.8	5.4	54%
Buriti, 2012 **[20]**	Brazil	Survey	Clinic	Children	23	-	2-10	5.7	56%
Chao, 2012 **[21]**	Peru	Survey	Clinic	Children	139	-	4-19	9.9	52%
Makar, 2012 **[22]**	India	Survey	Not stated	Children	67	-	4-16	11.1	42%
Ndoleriire, 2012 **[23]**	Uganda	Survey	Clinic	Children	370	-	0.5-5	3.0	47%
Devendra, 2013 **[24]**	Malawi	Case-control	Clinic	Children	296	296	2-9	5.9	50%
Matsekete, 2014 **[25]**	Zimbabwe	Survey	Clinic	Children	380	-	5-17	11	55%
Torre, 2015 **[26]**	South Africa	Case-control	Clinic	Children	37	24	4-14	7.1	51%
Maro, 2016 **[27]**	Tanzania	Case-control	Clinic	Children	131	113	<18	10.1	49%
All ages									
Matas, 2010**[28]**	Brazil	Case-control	Population	51 children,	50 children,	75	3-10.1	-	Children: 57%

				22 adults	25 adults		18-50	-	Adults: 36%
Adults									
Makau, 2010 **[29]**	Kenya	Case-control	Clinic	Adults	544	-	18-50	-	-
Ongulo, 2010 **[30]**	Kenya	Case-control	Clinic	Adults	194	124	18-50	35	61%
Khoza Shangase, 2011 **[31]**	South Africa	Survey	Clinic	Adults	150	-	20-46	33.9	65%
Suleyman, 2011 **[32]**	Nigeria	Survey	Clinic	Adults	89	-	18-56	36.4	47%
Westhuizen, 2012 **[33]**	South Africa	Case-control	Clinic	Adults	200	184	18-60	37	44% (cases)
Maro, 2014 **[34]**	Tanzania	Case-control	Clinic	Adults	449	202	>18	39	64%
Matas, 2014 **[35]**	Brazil	Case-control	Clinic	Adults	45	30	20-60	40	49%
Mathews, 2014 **[36]**	India	Survey	Clinic	Not stated	60	30	Not stated	Not stated	Not stated
Fokouo, 2015 **[37]**	Cameroon	Case-control	Clinic	Adults	90	90	15-49	33	72%

Table 2: Prevalence of hearing impairment in relation to HIV

Author, year	Measure of hearing	Cut-off for hearing loss	Either ear or best ear	Prevalence of hearing loss PLHIV	Prevalence of hearing loss HIV-controls	Unadjusted OR	Age- sex adjusted OR
Child							
Matas, 2006 **[17]**	PTA, ABR,	>15dB for ABR and PTA	Either ear	37%	Not available	-	-
Palacios, 2008 **[18]**	ABR (all ages) PTA (aged 4+)	>20dB for PTA and ABR	Not stated	26% for ABR 33% for PTA	-	-	-
Matas, 2010 **[28]**	PTA	>15dB	Either ear	28%	0%	NA	
Taipale, 2010 **[19]**	BERA (all ages) PTA (aged 5+)	>60 dB (BERA)	All ears and better ear	All ears: 8% Better ear: 4%	All ears: 3% Better ear: 0%	All ears: 3.0 (1.0-9.7)* Better ear: NA	
		>25 dB (PTA)	All ears and better ear	All ears: 33% Better ear: 23%	All ears: 15% Better ear: 3%	All ears: 2.4 (1.0-5.9)* Better ear: 9.5 (1.1-83.3)*	
Buriti, 2012 **[20]**	PTA	>15dBHL	Either ear	85% of ears	-	-	
Chao, 2012 **[21]**	PTA	>25dB	Either ear	39%	-	-	

Makar, 2012 **[22]**	PTA	Not stated	Not stated	33%	-	-	
Ndoleriire, 2012 **[23]**	ABR, Tympanometry	>25dB ABR	Not stated	33%	-	-	
Devendra, 2013 **[24]**	Self-report	Difficulty hearing	Either ear	12%	2%	5.7 (2.5-13.1)*	6.2 (2.7-14.3)
Matsekete, 2014 **[25]**	PTA	>25 dB >40 >60	Not stated	32% 11% 3%	-	-	
Torre, 2015 **[26]**	OAE, PTA,	>15dB	Either ear	22%	8%	3.0 (0.6-15.7)*	
Maro, 2016 **[27]**	OAE,PTA	>25 dB	Better ear	12%	5%	3.0 (1.0-8.5)*	
Adults							
Matas, 2010 **[28]**	PTA, ABR, Tympanometry	>25dB	Not stated	41%	0%	NA	
Makau, 2010 **[29]**	PTA, tuning fork	>25dB	Not stated	31%	-	-	
Ongulo, 2010 **[30]**	PTA	>25dB	Not stated	34%	8%	5.7 (2.8-11.7)	
Khoza Shangase, 2011 **[31]**	PTA	>25dB	Either ear	10%	-	-	
Suleyman, 2011 **[32]**	PTA	Not stated		68%			
Westhuizen, 2012 **[33]**	PTA, OAE, tympanometry	>25 dBHL	Either ear and better ear	Either ear: 43% Better ear: 26%	Either ear: 6% Better ear: 2.5%	Either ear: 11.9 (6.1-23.2)* Better ear: 12.6 (4.9-32.0)*	

Maro, 2014 **[34]**	PTA, ABR	>40 dB HL	Better ear	3.1%	3.5%	0.9 (0.2-3.5)*	
Matas, 2014 **[35]**	ABR	>20 dB	Average across ears	40%	0%	-	
Mathews, 2014 **[36]**	PTA	Not stated	Not stated	53%	13%	7.4 (2.3-23.9)*	
Fokouo, 2015 **[37]**	PTA (air/bone)	>20dB	Either ear**	27%	6%	6.2 (2.2-17.1)*	

* Calculated from figures in paper

**Estimate of proportion of ears with hearing loss

Table 3: Type of hearing loss among people living with HIV

Author, year	Examination	Conductive HL	SNHL	Mixed
Children				
Palacios, 2008 **[18]**	PTA, ABR, vestibular assessment	50% (children>4) 75% (children<4)		
Chao, 2012 **[21]**	PTA, Tympanometry, Otoscopy	89%	2%	9%
Makar, 2012 **[22]**	Not stated	33%	45%	55%
Ndoleriire, 2012 **[23]**	ABR, Tympanometry	36%	64%	
Torre, 2015 **[26]**	dpOAE, Tympanometry, PTA,	63%	38%	
Matas, 2010 **[28]**	PTA, Tympanometry,ABR	25%	2%	0%
Adults				
Matas 2010 **[28]**	PTA, tympanometry, ABR	14%	18%	9%
Makau, 2010 **[29]**	PTA, tuning fork, Otoscopy		Most common	Least common
Ongulo, 2010**[30]**	Otoscopy, PTA, tuning fork	22%	74%	4%
Khoza Shangase, 2011**[31]**	Otoscopy, PTA, Tympanometry	73%	27%	
Suleyman, 2011 **[32]**	PTA, Otoscopy	32%	14%	52%

Westhuizen 2012 **[33]**	PTA, Otoscopy, dpOAE, Tympanometry	29%	64%	7%
Matas, 2014 **[34]**	PTA, Tympanometry	28%	61%	11%
Fokouo, 2015 **[37]**	Otoscopy, PTA	18%	62%	20%

Table 4: HIV characteristics and prevalence of hearing loss

HIV characteristic	Studies investigating	Association with hearing loss	Description	Effect estimate
ART	Chao **[21]**	Positive	Yes versus no	OR=9.6, 1.2-75.4
	Buriti **[20]**	Positive	Yes versus no	OR=7.3 (1.3-41.4)*
	Taipale **[19]**	Null	Yes versus no	Not significant
	Makau **[29]**	Null	Yes versus no	P=0.12
	Torre **[26]**	Null	Yes versus no	
	Fokou **[37]**	Null	Yes versus no	Right ear: OR: 0.9 (0.3-2.5)* Left ear: OR: 1.5 (0.6-4.2)*
	Maro **[34]**	Null	Yes versus no	OR=2.5 (0.6-11.3)*
	Maro **[27]**	Null	Yes versus no	Not statistically significant
	Matas**[28]**	Null	Yes versus no	OR=2.4 (0.7-8.7)*
CD4 count	Chao **[21]**	Positive	Low versus high: Cut-off: 500	OR=3.5, 1.2-10.5
	Matsekete **[25]**	Positive	Low versus high: Cut-off <350	P<0.02
	Torre **[26]**	Null		
	Ongulo **[30]**	Positive	Not stated	"Found to be related"
	Palacios **[18]**	Null	Mean CD4 count	0=0.08
viral load	Chao **[21]**	Inverse	High versus low: Cut-off: 400 copies/mL	OR=0.2 (0.1-0.6)
	Buriti **[20]**	Positive	High versus low: Cut-off: 50 copies/mL	OR = 6.4 (0.9-46.1)
	Torre **[26]**	Null		
Opportunistic infections	Buriti **[20]**	Positive		P=0.003
Stage of disease	Westhuizen **[33]**	Null	CDC category	P>0.05
	Torre **[26]**	Positive		OR=2.47 (1.0-5.9)
	Ongulo **[30]**	Positive	WHO clinical staging	P=0,003
	Mathews**[36]**	Significant – direction not specified	AIDS	P=0.001

* Calculated from figures in paper

Table 5: Quality of papers assessed in systematic review

Quality variable	**Quality variable criteria**	**Number of papers**	**Percent**
Sampling	Non probability	21	100%
	Probability (+1)	0	0
	Not population based	21	100%
	Population based (+1)	0	0
Objectivity of HIV measurement	Self-reported	0	0
	Clinical records/laboratory tests (+1)	21	100%
Objectivity of hearing impairment measure	Non-validated assessment tool	1	5%
	Validated assessment tool, clinical evaluation (+1)	20	95%
Response rate	Not reported or below 60%	21	100%
	Reported and over 60% (+1)	0	0
Control for confounding	No	10	48%
	Yes (+1)	1	5%
	N/A	10	48%

Appendix: Search terms for Ovid database

1.	((Hearing or Acoustic or Ear*) adj5 (loss* or impair* or deficienc* or disable* or disabili* or handicap*)).sh,ti,ab.
2.	(Deaf*).sh,ti,ab.
3.	exp Hearing Loss/ or exp Deafness/
4.	1 or 2 or 3
5.	((Developing or Low-income or low income or Middle-income or Middle-income or (Low and middle-income) or (Low- and middle-income) or Less-Developed or Less Developed or Least Developed or Under Developed or underdeveloped or Third-World) adj5 (countr* or nation* or world or econom*)).sh,ti,ab
6.	exp Developing countries/
7.	(LIC or LICs or MIC or MICs or LMIC or LMICs or LAMIC or LAMICs or LAMI countr* or third world).sh,ti,ab
8.	(Transitional countr* or Transitional econom* or Transition countr* or Transition econom*).sh,ti,ab
9.	(Afghanistan or Albania or Algeria or American Samoa or Angola or Antigua or Barbuda or Argentina or Armenia or Azerbaijan or Bangladesh or Belarus or Byelarus or Byelorussia or Belorussia or Belize or Benin or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Bosnia-Herzegovina or Bosnia-Hercegovina or Botswana or Brazil or Brasil or Bulgaria or Burkina or Upper Volta or Burundi or Urundi or Cambodia or Republic of Kampuchea or Cameroon or Cameroons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Congo or DRC or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Cuba or Djibouti or Obock or French Somaliland or Dominica or Dominican Republic or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Georgia or Ghana or Gold Coast or Grenada or Guatemala or Guinea or Guinea-Bissau or Guiana or Guyana or Haiti

	or Honduras or India or Indonesia or Iran or Iraq or Jamaica or Jordan or Kazakhstan or Kenya or Kiribati or Republic of Korea or North Korea or DPRK or Kosovo or Kyrgyzstan or Kirghizstan or Kirgizstan or Kirghizia or Kirgizia or Kyrgyz or Kirghiz or Kyrgyz Republic or Lao or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malawi or Nyasaland or Malaysia or Malaya or Malay or Maldives or Mali or Marshall Islands or Mauritania or Mauritius or Mayotte or Mexico or Micronesia or Moldova or Moldovia or Mongolia or Montenegro or Morocco or Mozambique or Myanmar or Burma or Namibia or Nepal or Nicaragua or Niger or Nigeria or Pakistan or Palau or Palestine or Panama or Papua New Guinea or Paraguay or Peru or Philippines or Romania or Rumania or Roumania or Russia or Russian Federation or USSR or Soviet Union or Union of Soviet Socialist Republics or Rwanda or Ruanda-Urundi or Samoa or Samoan Islands or Sao Tome or Principe or Senegal or Serbia or Montenegro or Yugoslavia or Seychelles or Sierra Leone or Solomon Islands or Somalia or South Africa or Sri Lanka or Ceylon or Saint Kitts or St Kitts or Saint Christopher Island or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Sudan or Suriname or Surinam or Swaziland or Syria or Syrian Arab Republic or Tajikistan or Tadzhikistan or Tadjikistan or Tanzania or Thailand or Timor-Leste or East Timor or Togo or Togolese Republic or Tonga or Tunisia or Turkey or Turkmenistan or Turkmenia or Tuvalu or Uganda or Ukraine or Uruguay or Uzbekistan or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Gaza or Yemen or Zambia or Zimbabwe or Rhodesia).sh,ti,ab
10.	5 OR 6 OR 7 OR 8 OR 9
11.	(HIV or Human Immunodeficiency Virus or Human Immun* deficiency Virus*).sh,ti,ab,cp.
12.	(AIDS or Acquired Immunodeficiency Syndrome or Acquired Immun* Deficiency Syndrome).sh,ti,ab,cp.
13.	Exp human immunodeficiency virus / or exp Acquired Immunodeficiency Syndrome/
14.	11 or 12 or 13
15.	4 AND 10 AND 14