Review Article

Middle ear Pathologies in Adults Living with Human Immunodeficiency Virus: A Systematic Review

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Abstract

Introduction: Middle ear pathologies have been linked with HIV. The onset and development of these pathologies in individuals with HIV have not been categorized; and clarity has not been gained regarding whether their presentation is any different in this population when compared to HIV negative control group.

Purpose: The aim of this study was to explore and document published evidence reflecting trends in middle ear pathologies in adults living with HIV.

Methods: A systematic review of literature from January 1982 to December 2018 was conducted using Medline, CINAHL, PubMed, and Psych Info. Studies that reported the occurrence rate of middle ear pathologies in adults with HIV and published in English were included.

Results: Twelve articles met the inclusion criteria. Evidence suggests that the reported occurrence rates of middle ear pathologies ranges from 2.5% to 58% in this population. The variability in assessment measures as well as the different cut-off criteria used in studies seem to have an influence in the findings, with pure tone audiometry identifying more middle ear pathologies in the current review than tympanometry with 226 Hz probe tone and clinical examination. Otitis media, conductive hearing loss, and type B tympanogram were common findings reported in this study. No evidence of an association between the use of antiretroviral therapy (ART) and the rates of middle ear pathologies was found.

Conclusion: Although there are very few studies that have reported on middle ear pathologies in adults living with HIV, the available studies have sufficiently established a link between HIV and middle ear disease in this population, and have revealed that the rate of occurrence is influenced by a number of factors. Key amongst these is the type of assessment measure used. Careful analysis of middle ear pathologies in this population through well controlled research designs that include different assessment measures. The use of case-control and longitudinal designs to determine differences between groups and to establish the time of onset and development of middle ear pathologies is required.

Keywords

adults, HIV, middle ear disorders, systematic review

Introduction

The human immunodeficiency virus (HIV) continues to increase globally with over 1.8 million new infections recorded in 2017.[1] Sub-Saharan countries remain the most affected regions in the world, accounting for approximately 70% of the pandemic.[1] Statistics South Africa (SSA) reports that the prevalence of HIV in South Africa was 6 million in 2017, a figure that has quadrupled when compared to prevalence reported in 2002.[2] Given this constant increase, there are continued global efforts and initiatives to combat HIV, including the use of antiretroviral therapy (ART).[3] With the availability and provision of ART in South African state health facilities since the first quarter of 2004; significant progress has been seen in the achievement of sustaining lives of the infected. Furthermore, South Africa forms part of the laudable setting of UNAIDS 90:90:90 by 2030 targets which show a clear focused strategy efficient management of this disease.[4] These factors have a clear goal of sustaining life and preventing and/or eliminating the spread of the disease. Khoza-Shangase[5] argues that as part of the rehabilitation team, it is important that audiologists constantly insert the importance of also focusing on the *quality* of the life that is sustained by highly active ART (HAART)

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in the clinical management strategy of this population. The additional focus on quality of life would include ear health, hearing and balance function as part of the sensory disabilities that may be experienced by people living with HIV/AIDS – and for the intention of this paper, middle ear disease.

A growing body of research has indicated that ART inhibits one of the enzymes that is necessary for the replication of HIV,[6] lowers the viral load, and improves the immune system.[7-9] Reports show that ART significantly reduces the number of deaths associated with HIV and improves life expectancy.[1,10] Despite these advancements, occurrence of middle ear pathologies seems to persist in individuals living with HIV.[11,12] Disorders of the auditory and vestibular system, including otitis media, are often associated with HIV/AIDS.[13,14]

There has been increasing evidence that suggests that HIV increases the risk of middle ear pathologies by causing the CD4 cell count to decline in the body and thus incapacitating the immune system,[15] allowing the viruses and bacteria to enter the middle ear system causing middle ear disorders.[16] Several studies have reported that otitis media with effusion (OME), serous otitis media (SOM), retracted tympanic membrane (TM) and perforated TM occur in adults with HIV,[12,16-18] and this has an influence in patients' quality of lives.

Considerable literature has indicated that if middle ear pathologies are not detected and treated early, transient conductive hearing loss (CHL) may occur.[19] Prolonged presence of untreated middle ear pathologies can cause further damage such as permanent sensori/neural hearing loss (SNHL),[20] auditory processing difficulties,[21] and life threatening conditions such as meningitis.[22] Consequently, these conditions can cause communication difficulties and compromised quality of life.[23,24] Therefore, early detection and treatment of middle ear disorders is crucial in order to prevent the listed sequelae. This early detection relies on the use of sensitive assessment measures and availability of ear and hearing care professionals.

A number of assessment measures are used to determine the presence or absence of middle ear pathologies in adults living with HIV. These measures can be divided into subjective (clinical examination techniques) and objective measures. Subjective tests are mainly used by otolaryngologists and have been reported to have higher sensitivity and specificity in detecting the presence or absence of middle ear disorders.[25,26] On the other hand, the objective measures such as the acoustic immittance measure are used primarily by audiologists. The latter measures are widely used because they are simple, quick to administer, cost effective, and time efficient.[27-29] Pure tone audiometry using air bone gap (ABG) as an indicator for middle ear disorder is also used. The use of an appropriate measure for early detection is key in the context of high risk for middle ear disease, as is the case in the HIV population.

In light of the high prevalence of HIV globally, as well as the established link between HIV and middle ear pathologies; the current study aimed to explore and document, through a systematic review, published evidence reflecting trends in middle ear pathologies in adults living with HIV.

Methods

Search Strategy

A comprehensive search of papers that have reported on middle ear pathologies in adults living with HIV was conducted. A computer-aided search of online journal databases, including Medline, CINAHL, PubMed, Psych Info, and Google Scholar was undertaken. The following keywords were used "HIV OR HIV/AIDS AND middle ear disorders OR Middle ear pathologies OR middle ear infection OR Otitis media OR auditory disorders OR hearing loss OR hearing impairment OR deafness OR otologic disorders OR Otolaryngology OR tympanometry, AND adults.

Searches were supplemented by a rigorous manual review of reference lists of the papers included in order to obtain additional papers. The search included articles published between the years 1982 and 2018. This period was chosen because HIV was first reported in the early 1980s.[30] The researcher identified all the articles for review. An additional reviewer reviewed the same articles to ensure the reliability and validity of the process of identifying the relevant articles.

Inclusion Criteria

Studies were included in this review if they were published in peer reviewed journals, included adult participants diagnosed with HIV aged 18 years and older, and documented middle ear status as part of their investigation. Furthermore, studies had to be written in English. Although Cochrane collaboration recommends that only randomized controlled trial (RCT) studies be included for systematic review,[31] due to the focus of the current study, which is concerned about the indicators (middle ear measures) and not the outcome, non-randomized controlled studies were also included.

Data Extraction and Synthesis

A total of 515 titles were retrieved. Of these, 493 were excluded because they were not relevant to the study. These excluded studies were either reviews or focused on vestibular pathologies or other parts of the auditory system (eg, central) in adults living with HIV. A total of 22 articles were

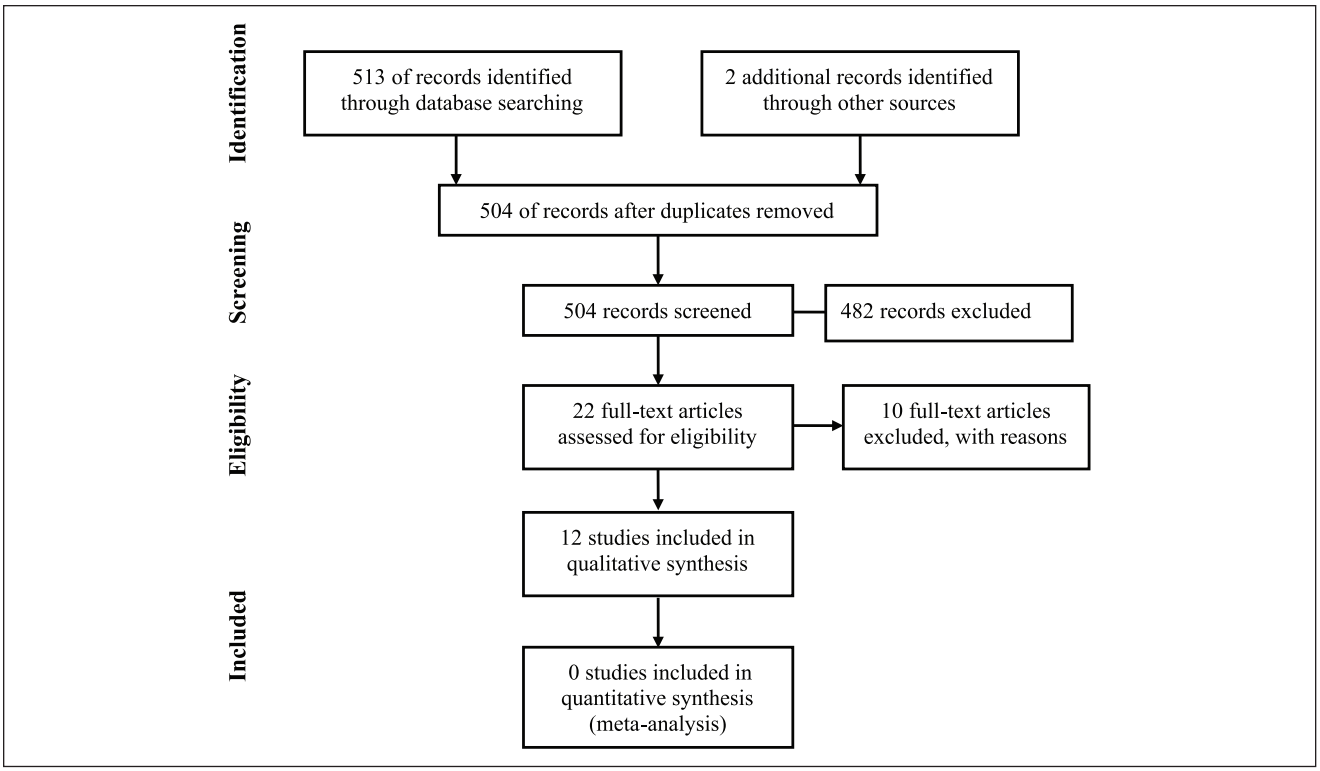

Figure 1. The PRISMA flow diagram describing the inclusion of studies.

included from databases based on their abstract screening. A total of 12 articles were finally included for analysis. The PRISMA flow diagram, showing the process of selecting studies for inclusion in this review is included (Figure 1). The age of the participants in the research papers ranged from 18 years to 60 years, with sample sizes reaching 960.

Results

Three tables that follow summarize the results of the studies included for review. Table 1 summarizes the studies that utilized acoustic immittance (tympanometry) as a measure, Table 2 presents studies where pure tone audiometry (ABG indicator) was used, and Table 3 depicts findings from studies that made middle ear disorders diagnosis based on clinical examination techniques.

Acoustic Immittance

Four studies[12,32-34] reported middle ear disorders based on acoustic immittance measures. Majority of the participants (76%) were females in two studies[10,29] than males. There was no significant difference between female and male participants in one study.[28] Only two studies[12,28] recorded the CD4 T-cell counts, and classified participants according to CDC categories in their reporting. In these two studies, most participants (44% & 47%) fell into CDC category 2, which consists of people living with HIV with CD4 counts of 200 to 499 cell/Ml; with few participants (22% and 39%) in category 3 which consists of $<$200 cell/μL.

All four studies[12,32-34] reported that participants were on medication. In three studies,[32-34] only participants in category 3 of CDC classification were on medication. However, n one study,[10] participants were on medication regardless of CD4 count cells or CDC category. As a result, majority of the participants (99%) were on medications in a study conducted by Sebothoma and Khoza-Shangase[12] compared to 39% and 63% in studies conducted by Van der Weshuizen et al.[33] and Chandrasekhar et al.[34] respectively.

Amongst these four studies reviewed, only one study[32] included an HIV negative control group to make a comparison. Although the percentages were not recorded in this study,[32] it is reported that the HIV negative control group was significantly younger in age, and most participants were males.

All these studies used tympanometry with 226Hz probe tone to assess the middle ear function. Only two studies specified the cut-off range for tympanometric parameters (ie, ear canal volume, statistic compliance and tympanometric peak pressure) to determine normal versus abnormal middle ear function. Both Maro et al.[32] and Van der Westhuizen et al.[33] used 0.9 to 2 ml for ear canal volume, 0.3 to 1.7 ml for static compliance, and −100 to 50 daPa for tympanometric peak pressure.

Table 1. Middle Ear Disorders According to Acoustic Immittance (tympanometry with 226 Hz probe tone).

Study	Age	Sample Size	Middle Ear mMeasure	Findings
1. Sebothoma & Khoza-Shangase[12]	25 to 72 years	n = 87 (161 ears)	tympanometry with 226Hz probe tone	8% (13 ears) presented with abnormal tympanograms (type Ad = 70%). No control group
2. Maro et al.[32]	>18 years	HIV group: n = 449 (889 ears); control group: n = 303	tympanometry with 226Hz probe tone	14% of HIV group presented with abnormal tympanograms. 14% of control group also presented with abnormal tympanogram
3. Van der Westhuizen et al.[33]	18 to 60 years	n = 198	tympanometry with 226Hz probe tone	41% of HIV group presented with abnormal tympanograms (type B = 33%)
4. Chandrasekhar et al.[34]	22 to 58 years	n = 50 (100 ears)		21% presented with abnormal tympanograms (type B = 51%)

Table 2. Middle Ear Disorders According to Pure tone Audiometry.

Studies	Sample Size	Middle Ear Measure	Criteria For Normal	Findings
1. Mathews, Albert, & Job[35]	n = 60, 15 to 45 years	Pure tones (ABG)	≤20 dBHL across frequencies	13% presented with conductive hearing loss
2. Ongulo & Oburra[36]	n = 194; 18 to 50 years	Pure tones (ABG)	Not clear	22% CHL, and 4% MHL
3. Khoza-Shangase[37]	n = 150; 20 to 46 years	Pure tones (ABG)	< 26 dB HL	2.7% Presented with CHL
4. Matas et al.[38]	n = 41; 20 to 60 years	Pure tones (ABG)	not reported in the text	22.25% presented with CHL, 7% MHL; 0% in control group
5. Matas et al.[39]	n = 45; 20 to 60 years	Pure tones (ABG)	≤20 dBHL	58% presented with CHL
6. Torre et al.[40]	n = 396; mean age of 49.5 years	Pure tones (ABG)	≤15 dB HL	2.5% presented with air bone gap

Table 3. Middle Ear Disorders According to Clinical Examination.

Studies	Sample Size	Middle Ear Measure	Findings
1. Prasad et al.[17]	n = 968; 1.5 to 75 years	clinical examination	13% presented with otitis media
2. Tshifularo et al.[18]	n = 153; 1 to 76 years	clinical examination	A total of 42.58% (CSOM = 27%; OME = 15.58)

Overall, the rates of middle ear disorders in adults living with HIV were reported to range from 8% to 41% when tympanometry with 226 Hz probe tone was used. Only one study by Maro et al.[32] included and compared middle ear disorders found to HIV negative control group. This study found no significant difference between the rates of individuals who are living with HIV and those who are HIV negative.

The type of middle ear disorder, based on the type of tympanogram, varied in the studies reviewed. While studies by Chandrasekhar et al.[34] and Van der Westhuizen et al.[33] found type B tympanogram to be associated with a declined number of CD4 cell count and stage of HIV to be common; concurring with findings by Obasineke et al.[41]; a study by Sebothoma and Khoza-Shangase[12] found type Ad (70%) to be the common abnormal tympanogram in individuals living with HIV. One possible explanation for the different types of abnormal tympanograms in these studies could be that in a study conducted by Sebothoma and Khoza-Shangase,[12] 99% of the participants were on HIV treatment regardless of their stage of HIV and the number of CD4 count. On the other hand, in the study by Van der Westhuizen et al.,[33] only participants with CD4 counts lower than 200 cells/uL were on HIV treatment. The use of HIV treatment in majority of the participants in Sebothoma and Khoza-Shangase[12] may have improved the patients' immune systems[8] and prevented the reduction of mucociliary action of the middle ear,[41] thus less severe middle ear disease.

Pure Tone Audiometry

Six studies were identified that utilized pure tone audiometry to determine the presence or absence of middle ear disorders in adults living with HIV. The studies reviewed were heterogeneous in nature. Three studies[35,39,40] reported that male participants constituted the majority; while two studies[36,37] indicated majority of female participants. Only

one study[38] did not report on the gender profile of participants. Only three studies provided the mean CD4 count cells[36,37,39]; with participants in a study by Matas et al.[39] consisting of higher mean (585) CD4 count cell, and male participants in a study by Ongulo and Oburra[36] consisting of the lowest mean (47) for CD4 count cells. Of the six studies, only three studies[35,38,39] included a control group.

While all these studies used air-bone gaps (ABG) as an indicator to determine the presence or absence of middle ear disorders, the cut-off points for determining normal hearing thresholds differed between the studies. Two studies[35,38] used ≤20 dBHL as a cut-off; one study[40] used ≤15 dBHL, while another study[37] used <26 dBHL. Two studies[36,39] did not specify their cut-off points at all. Only one study by Matas et al.[39] included and compared the hearing of adults living with HIV to those of an HIV negative control group.

The overall rates of middle ear disorders reported in these studies ranged from 2.5% to 58%. Maro et al.[39] found a statistically significant difference between middle ear disorders in adults living with HIV (22.25%) and the HIV negative control group (6.7%). Of the types of middle ear disorders found, the rates of conductive hearing loss (CHL) were higher than the rates of mixed hearing loss (MHL). One study by Torre et al.[40] did not classify the type of the hearing disorders (eg, CHL or MHL), but simply recorded the rates in ABG.

Of the three studies that included a control group, only two studies[35,39] reported the results of the control group. Both the studies[31,35] indicated that there was no hearing loss with a conductive component (CHL or/and MHL) in the control group. Only one study[38] compared the results of individuals who were on medication and those who were treatment naïve. In the study, individuals who were on medication presented with higher prevalence (30.8%) of CHL when compared to the treatment naïve (20%).

Clinical Examination

Two studies[17,18] used clinical examination techniques to report on middle ear disorders in adults with HIV. Although the inclusion criteria and age groups of participants in these studies were similar, there was also variability with regards to the rates of middle ear disorders in these studies. One study reported the rates of middle ear disorder to be 13%,[17] while the other study reported the rates to be as high as 42.58%.[18] The sample sizes in these studies were significantly different. Unlike in the studies with other middle ear measures, the specific types of middle ear disorders were reported in these studies. Both studies reported otitis media with effusion (OME) to be the most common type of middle ear disorder. Tshifularo et al.,[18] however, found the rates of chronic suppurative otitis media (CSOM) to be higher (27%) when compared to OME (15.58%) in individuals living with HIV.

Discussion

This systematic review summarized evidence reflecting trends in middle ear disorders in adults living with HIV. To the author's knowledge, this is the first systematic review that explored and documented middle ear disorders in adults living with HIV using various assessment measures. This review identified 12 studies that met the inclusion criteria. Because of the heterogeneous nature of the studies included in this review, only qualitative analysis was conducted. All 12 studies reviewed revealed that middle ear disorders are common in adults living with HIV. These findings are consistent with review conducted by Sanjar and colleagues[42] which indicated that middle ear disorders are among the common otolaryngologic manifestations of HIV. It is worrying that middle ear disorders seem to persist in spite the use of ART.[12,18]

While ART is known to significantly improve the immune system of individuals living with HIV, the expectation that patients on ART should have lower prevalence of middle ear disorders does not necessarily ring true. While the study conducted by Sebothoma and Khoza-Shangase[12] where almost all participants were on ART presented with a small percentage (8%) of middle ear disorders; two other studies[33,38] found participants on ART to have significantly higher percentage of middle ear disorders. However, it is worth noting that participants in the latter studies may have had compromised immune systems due to delayed commencement of treatment. Unlike in the study conducted by Sebothoma and Khoza-Shangase[12] where all participants were on ART regardless of their CD4 cell count, participants in the latter studies were only put on HIV treatment when they were in category 3 of the CDC.

No evidence could be found in the studies reviewed on the relationship between the duration of ART, adherence to ART and middle ear disorders; highlighting a need for inclusion of this in future studies. Studies on cochlear[36] and vestibular function,[43,44] and HIV have revealed that the use of ART may have deleterious effects on these systems in terms of ototoxicity and vestibulotoxicity. However, it is hypothesized that the use of ART may have different effects on middle ear function in this population, and this view needs to be explored.

The current review revealed that the rates of middle ear disorders in adults living with HIV varied significantly between studies that used similar or different middle ear measures. The rates of middle ear disorders ranged from 2.5% to 58%; with type B tympanogram, CHL, and CSOM being the most prevalent.[18,33,34,38] These variabilities may be attributed to different sample sizes, different middle ear measures used, and different cut-off values used to determine normal versus abnormal. For example, while Khoza-Shangase[37] used <26dB HL as a cut-off point to determine normal versus abnormal, this criterion

is considered to represent mild hearing loss in a study by Torre et al.[40] It can be argued that while it is clear that middle ear disorders exist despite the use of ART, the rates of these disorders may have been either underreported or over reported depending on the criteria and measures used.

The highest rates of middle ear disorders were reported from a study that used air bone gaps from pure tone audiometry.[39] While these findings are supported by a study by Hunter et al.[45] who indicated that CHL (ABG) in children was 20% higher than the rates obtained from tympanometry with 226Hz probe tone, these results were unexpected and surprising given that pure tone audiometry using ABG as an indicator is not a routinely used direct measure of middle ear function.[19] Studies have shown that clinical examination techniques such as otomicroscopy can have sensitivity in identifying middle ear disorders that reaches 100%.[21,46,47] Therefore, one would have expected the rates of middle ear disorders to be higher when measured by clinical examination techniques, instead of the current review findings indicating ABG identifying more middle ear disorders than clinical examination.

The findings of this review may suggest that perhaps evaluation of middle ear disorders in adults living with HIV may need to include multiple measures rather than a single measure. This may provide a better overview of middle ear function in this population. Balatsouras et al.[48] also argue that multiple measures of middle ear function improve the sensitivity and specificity of detecting middle ear disorders. Given the extreme shortage of resources to deal with the consequences of untreated middle ear disorders in developing countries,[49,50] the use of multiple measures may enhance early identification and ensure that management is implemented early. While there is a growing body of evidence that indicates that wideband acoustic immittance (WAI) is one of the single most effective middle ear measures with higher sensitivity and specificity in detecting middle ear disorders,[51,52] and can predict the magnitude of CHL[53]; research is still needed to determine the effectiveness of this measure in adults living with HIV; an implication for future studies.

While this review revealed that middle ear disorders exist and the rates may be high, there is a lack of evidence on whether these trends are similar or different to the HIV negative population. There were only two studies that included HIV negative control groups. Maro and colleagues[32] used tympanometry with 226Hz probe and did not find any statistical significant difference between the rates of middle ear disorders in adults living with HIV and HIV negative control. However, Matas and colleagues[39] used pure tone audiometry (ABG) and reported that adults living with HIV presented with 22.25% while HIV negative control presented with only 6.7% of middle ear disorders. Based on this evidence, whether the rates of middle ear disorders in adults living with HIV are different or similar to those of HIV negative control remains unclear. Further studies that use case-control are needed.

While the existence and rates of middle ear disorders have been reported in the studies reviewed, the time of onset and development of middle ear disorders have not been categorized. The lack of this evidence could partly be attributed to the research designs employed in the studies reviewed. All 12 studies reviewed employed cross-sectional design. As a result, there is a need for further studies that use longitudinal, repeated measures design in order to determine onset, development and changes[54] in middle ear function in adults living with HIV. The lack of evidence about onset and development may prevent audiologists and policy makers from developing ear and hearing monitoring programs for adults living with HIV.

Conclusion

This is the first systematic review to look at the trends and rates of middle ear disorders in adults living with HIV from multiple middle ear measures. This review revealed that middle ear disorders exist in adults living with HIV regardless of the use of ART. These findings highlight the important implications for assessment and management of middle ear disorders in this population. The rates of middle ear disorders in this population varied significantly due to different measures, sample size and criteria used to determine normal versus abnormal. This raises important implications about selection of sensitive and specific measures if cost-effective management programs are to be implemented. The lack of case-control design which made it difficult to determine whether the trends and rates of middle ear disorders in this population differ to HIV negative control raises an implication for future studies. Finally, the time of onset and development was not categorized in the studies reviewed, another implication for future studies.

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