International Scholars Journals

International Journal of Medical Sociology and Anthropology Vol. 10 (2), pp. 001-006, February, 2020. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Review

Is there a need for ototoxicity monitoring in patients with HIV/AIDS?

Khoza-Shangase Katijah

University of the Witwatersrand, Johannesburg, South Africa. E-mail: Katijah.Khoza@wits.ac.za.

Accepted 19 November, 2019

This paper reviews published research on hearing loss in adults with HIV/AIDS with a special focus on the possibility of ototoxicity of the medications used in clinical management of this population. Findings from all published papers on the subject, which include but are not limited to case reports, cross-sectional, as well as longitudinal studies where ototoxicity monitoring of patients on antiretroviral therapy (ART) was conducted, are presented. The author offers an introduction to hearing loss in HIV/AIDS with reference to the primary effects of the disease itself as well as effects of opportunistic infections on the auditory function, before delving into iatrogenic hearing loss due to ART and other therapies that this population gets exposed to; and while doing so highlights the need for establishment and implementation of ototoxicity monitoring protocols as part of routine clinical management in Africa; as well as putting forward a recommendation of placing auditory function of adults with HIV/AIDS in developing countries on the healthcare and research agenda. Review of the literature in this field reveals that ototoxicity in adults with HIV/AIDS does exist; although minimal reporting of this morbidity is available in the academic literature. Literature also indicates that the reported causes as well as contributing factors to ototoxicity are varied. Documented information on ART ototoxicity is mainly of case reports, and where bigger samples are described; the studies are based on retrospective cross sectional data review with many of these studies lacking the use of sensitive audiological monitoring tools. Moreover, reports reviewed have mainly been international reports, with only one from Africa. Evidence on ototoxicity related to ART is sparse, however literature reviewed and studies presented highlight the need for intensified research into this area, particularly in developing countries where the volume of evidence is even less; despite these countries being the hardest hit by the pandemic with exposure to ART being an increasing phenomenon.

Key words: Antiretroviral drugs, aminoglycosides, Africa, ototoxic, hearing loss, audiology, monitoring.

INTRODUCTION

During the early stages of the HIV/AIDS pandemic, treatment strategies did not seem to have a positive influence on patients' lives, and therefore hearing loss did not seem to be an important manifestation of HIV/AIDS that required characterisation. However, hearing loss has become one of a number of sensory disabilities associated with HIV/AIDS that must now compete for attention by the research and medical community. Friedman and Noffsinger (1998) were amongst the first to advocate that as primary professionals in hearing health care, audiologists have a responsibility to inform both themselves and other relevant health-care professionals about this issue, hence the current paper.

Understanding the effects and treatment of HIV/AIDS on the auditory system is becoming more important because patients with HIV/AIDS are living longer due to the positive effects of antiretroviral therapy (ART). The discovery of antiretroviral drugs for the treatment of HIV/AIDS has changed the face of the HIV/AIDS pandemic internationally, and has also led to changes in the medical field with people who have HIV/AIDS living for longer periods of time experiencing toxic-related morbidity that influences quality of life indicators (Zapor et al., 2004). There is a concern, however, that HIV-associated auditory disorders may be seriously under-reported. Zuninga (1999) makes reference to anecdotal reports suggesting that hearing loss and dizziness which are often the initial symptoms of underlying auditory system disease may not have been reported by patients prior to HAART because many patients focused on the life-threatening complications of the HIV disease rather than on quality of life issues. This situation is yet to be fully realized in South Africa as ARVs have only been available since April 2004 – and not even to the entire population infected by the virus. People who will benefit from these drugs may in the near future become more

conscious of the quality of life issues and complain about them.

Auditory manifestations may be one of the issues that the population will have to deal with; therefore over and above management of the known side effects of ARVs, research into the identification and monitoring of all other manifestations of the disease is required. With regard to auditory manifestations, both identification and monitoring of ototoxicity require rigorous research to enhance the patients' quality of life, particularly since internationally a link has been established between ARVs and ototoxicity and this link has been described in detail in later sections of this paper.

Ototoxicity may be defined as a tendency for certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear and especially of the end organs and neurons of the cochlea and vestibular divisions of the eighth cranial nerve (Cummings, 1993; Hawkins, 1976). It refers to medication-caused auditory and/or vestibular system dysfunction resulting in hearing loss or disequilibrium. Drugs and other chemicals that damage the cochlea do so by destroying sound sensitive hair cells, usually starting at the basal turn and progressing towards the apical turn (Campbell, 2007).

Medical awareness of ARV doses, forms of administration, populations at risk, and possible synergism with other factors is necessary in order to develop appropriate care in the prescription of drugs with possible or established ototoxic side effects. Furthermore, issues such as risk-benefit analysis, patient-informed consent, and quality-of-life considerations, are also crucial factors to be considered in the management of patients with HIV/AIDS. Regardless of whether the effects of the drug are negligible or not, these effects still need to be determined so that proper patient adherence counselling can occur. It is fundamental that audiologists establish and become aware of ototoxic effects of medications used to manage chronic conditions such as HIV/AIDS, and medications prescribed to significant numbers of people – such as the 11% of the population afflicted by HIV/AIDS in South Africa (Dorrington, Johnson, Bradshaw and Daniel, 2006). This awareness is critical to ensure that proper patient education occurs as patients may not notice ototoxic hearing loss until a commu-nication problem becomes evident, signifying that hearing loss within the frequency range, which is vital for understanding speech, has already occurred. Likewise, by the time the patient complains of dizziness, permanent vestibular system damage may have already occurred.

Clinically used drugs and chemical agents may potentially cause adverse effects to the human auditory and vestibular systems (Jackson and Arcieri, 1971). Many of these drugs can play a critical role in the treatment of serious or life-threatening diseases, others offer such important therapeutic effects compared to the ototoxic side effects, that is, ototoxicity risk can be considered to be of minor importance and such may be the case with HIV/AIDS (a sentiment echoed by some physicians). The problem of ototoxic side effects is reported to be more critical in developing countries, where highly effective and low-cost drugs are more easily prescribed without adequate monitoring (Arslan et al., 1999). It is possible that such a situation may exist in some parts of Africa particularly with the high numbers of patients on treatment for HIV/AIDS. An additional concern to the management of HIV/AIDS patients, who may be on potentially ototoxic medication without being audiologically monitored, is that noise exposure following treatment with ototoxic drugs can act synergistically with the drugs that have not been fully cleared from the inner ear (Fausti et al., 2005). Increased susceptibility to hearing loss can continue for several months after completion of treatment or therapy. Due to this likelihood, it is imperative to implement hearing conservation in the form of advising patients to avoid excessive noise exposure for at least six months. In addition, patients who use amplification in the form of hearing aids may need to be counselled and warned to closely monitor and control the hearing aid maximum output during this critical time (Edmunds et al., 2006). Given this scenario, it seems more pressing than ever to endeavour to prevent or ameliorate the possible ototoxic hearing loss in this population, by ensuring ototoxicity monitoring as part of routine clinical management particularly since the treat-ment regimen is varied and the WHO ART guidelines continue to be modified as some drugs get phased out such as the recent suggestion by WHO ART to phase out d4T.

When life-threatening illness necessitates treatment with ototoxic drugs, preserving the quality of the patients' remaining life is customarily a treatment goal. Early detection of ototoxic hearing loss provides physicians with the critical information and opportunity necessary to minimize further impairment and, in some cases, prevent hearing loss from progressing to the point where permanent damage occurs. Although hearing loss is not regarded as a life-threatening condition, it does become a severe threat to essential quality of life indicators unless intervention occurs early during treatment. The adverse effects of a hearing loss on cognitive-linguistic skills and psychosocial behaviour are well documented, as well as the serious vocational, social, and interpersonal cons-quences for the patient.

The known effects of HIV/AIDS on the auditory system that have been reported in the literature are mainly based on cross-sectional studies and case reports conducted internationally in industrialised countries, with very limited information coming from third world countries where the presentation of the virus and its treatments may be different. Furthermore, because this evidence may not be viewed to be contextually relevant to the developing world, its incorporation into routine clinical assessment and management lags behind significantly. Hence, the need for categorizing the ototoxic effects of HIV/AIDS treatment, in an effort to ensure that ototoxicity monitoring

protocols are established and implemented as part of routine clinical management amongst patients infected. Research into ototoxicity in HIV/AIDS needs to be locally relevant, it should include large sample sizes and longitudinal follow up of cases, and should also utilize sensitive audiological test measures to improve validity and reliability of findings.

SEARCH STRATEGY

The current paper draws on published English language studies available up to July 2009 on the topic of ototoxicity in HIV/AIDS. Studies were mainly identified using keyword searches of electronic databases as well as scanning the reference lists found from these databases. The databases sourced were Academic Search Premier, Index to South African Periodicals, ISI Web of Science, Medline, Pubmed, Science Direct and South African ePublications. The key words used were ototoxicity, HIV, AIDS, auditory function, otolaryngology, otology, antiretroviral therapy, adults, and hearing. In order to be included, the study has recruited HIV–positive adults, and no choice of research design was excluded.

RESULTS AND DISCUSSION Non-

Iatrogenic hearing loss in HIV/AIDS

Review of the literature in this field reveals that auditory manifestations in adults with HIV/AIDS are heterogeneous and possibly caused by varied factors. Auditory presentations including hearing loss, tinnitus and vertigo in varied combinations can occur with the type of hearing loss including conductive, mixed, sensorineural, and central types of hearing loss. This hearing loss can also range from mild to profound in severity either unilaterally or bilaterally, with the type of onset including sudden and gradual progressive onset. The varied causes include HIV/AIDS as a primary cause, opportunistic infections as well as treatments that the patients undergo.

Numerous clinical and mostly medically oriented studies have demonstrated the occurrence of hearing loss and other auditory manifestations in HIV/AIDS. According to the research literature, auditory abnormal-lities associated with HIV/AIDS and its treatments have been reported in persons with varying degrees of HIV infection, in both symptomatic and asymptomatic patients, as well as in patients on antiretroviral treatment. Indications exist that the HIV effects on the auditory system can be direct as well as indirect; however this distinction is not always clear and consistent. Early reports in the literature demonstrated that HIV might directly affect the auditory function due to the fact that the virus is neurotropic and commonly manifests itself neurologically (McArthur, 1987), which may be what Kallail et al. (2008) refer to as HIV/AIDS being the primary cause of auditory system disorders. These direct causes have been reported to possibly give rise to central pathology observed in this population (Bankaitis; 1996; Lalwani and Sooy, 1992). More commonly though, reports in the literature focus significantly on the indirect effects of the virus on the ear. It is believed that indirect causes that result in hearing loss stem from opportunistic infections which require suppressive therapy, thereby leading to ototoxicity (Bankaitis; 1996; Bankaitis and Schountz, 1998; Lalwani and Sooy, 1992); which Kallail et al. (2008) refer to as iatrogenic sources. It is important to note that these findings are mainly from developed countries where the presentation and management of HIV/AIDS is different to that in developing countries, suggesting a need for more research into this area particularly since the numbers of adults living with HIV/AIDS in developing countries such as South Africa is still high, and also because the context is different.

Iatrogenic hearing loss in HIV/AIDS

Because of all the diseases and infections that the population with HIV/AIDS present with, it is not surprising to find patients with hearing loss due to ototoxicity, as this population goes through a drug regimen that often involves potentially ototoxic medications (Birchall et al., 1992). Bankaitis and Schountz (1998) report that the use of experimental antiretroviral drugs with undocumented or unknown side effects contributes to this hearing loss, in addition, ototoxic drugs that are often used in the treatment of opportunistic infections such as tuberculosis may increase the potential for a drug-induced hearing loss in this population (Khoza-Shangase, Mupawose and Mlangeni, 2009).

Internationally, iatrogenic hearing loss has been associated with many of the drugs used to treat HIV/AIDS and its associated complications. As early as 1998, the potential for a drug-induced hearing loss in an HIV-infected individual at any stage of the disease was reported to be relatively high (Bankaitis and Schountz, 1998). With all the medications that individuals with HIV are taking and the continual developments in HIV therapies, it is challenging to acquire and maintain a comprehensive knowledge base of HIV-related drugs and associated ototoxicity. Although the side-effects of many antiretroviral drugs are yet to be determined, HIV-infected individuals are often prescribed medications as a prophylaxis or treatment of opportunistic infections that have been long associated with the development of audiological and vestibular changes. Antineoplastic medications such as vincristine, antifungal agents including amphotericin B, flucytosine and ketoconazole, immune modulators, aminoglycoside antibiotics, erythromycin, and azidothymidine (AZT) are all widely used in the management of HIV and are all reported to be associated with significant ototoxicity or decreased hearing (Bankaitis and Keith, 1995; Bankaitis and Schountz, 1998; Campbell, 2007; Gold and Tami, 1998; Kohan et al., 1990; Lalwani and Sooy, 1992). These medications are associated with hearing loss, tinnitus and vertigo. Frequently administered medications for PCP(Pentamidine, TMP /SMX, Primaquine) may cause

tinnitus, vertigo, dizziness, auditory disturbances, deafness, decreased hearing, hearing loss, and otalgia (Bankaitis and Schountz, 1998). Moreover, the use of experimental medications with relatively unknown toxicity as well as the use of ototoxic drugs, such as anti-Tuberculosis (TB) medications, in combination adds to the overall effect on hearing (Simdon et al., 2001).

In South Africa, one of the most frequently administered treatments to the HIV/AIDS population is that of TB treatment. South Africa, like many sub-Saharan countries, witnessed a dramatic upsurge of TB cases over the past decade (Clarke et al., 2006). This upsurge in the number of TB cases is expected to continue, largely due to co-infection with the HIV, with the emergence of drug resistant TB (Aziz et al., 2006) also being reported. This co-occurrence of HIV/AIDS and TB raises serious implications for the audiologist with regard to the possible association between TB treatment and ART. Because some of the drugs used in the treatment of TB fall under the umbrella term 'aminoglycosides' (Smith and MacKenzie, 1997), interactions between these treatments need to be explored. Examples of these aminoglycosides include amikacin, gentamicin, kana-mycin, netimicin, paromomycin, streptomycin, tobra-mycin, and apramycin (Cohn, 1981). These antibiotics are most notorious for being ototoxic, primarily targeting the renal and cochleo-vestibular system (Campbell, 2007) . This impact of medications on hearing function are being reported, although not extensively, with nucleoside analogue reverse transcriptase inhibitors (NRTIs).

Although a variety of adverse effects have been attributed to treatment with nucleoside analogue reverse transcriptase inhibitors (NRTIs) for HIV-1 infection, only a small number of cases of ototoxicity have been reported in the literature. Simdon reported three subjects who experienced ototoxicity, all of whom were over the age of 45 and received combination ART with 2-3 NRTIs plus a NNRTI or a PI. All three of the subjects had prior hearing problems, prior exposure to occupational noise and all developed significant tinnitus (Simdon et al., 2001). Clearly, the presence of these confounding variables (prior hearing loss, noise exposure history, and older age) needs to be taken into consideration when interpreting findings from these cases. The authors suggested that NRTIs should be used cautiously in patients with pre-existing hearing loss. Again, the ability to generalize these results is limited as they were based on case reports and not on large samples. These authors suggest that reductions in mitochondrial DNA content induced by NRTIs, as well as mitochondrial DNA mutations associated with aging and HIV-1 infection may contribute to auditory dysfunction in older patients with HIV-1 infection. They highlight the fact that prospective studies are necessary to determine the incidence of tinnitus and hearing loss among HIV-1 infected patients and their relationship to the use of NRTIs (Simdon et al., 2001).

Several cases of ototoxicity have been reported in HIV-infected patients treated with zalcitabine (Martinez and French, 1993; Monte, Fenwick and Monteiro, 1997; Powderly, Klebert and Clifford, 1990); didanosine (Colebunders, Dipraetere, Van Wanzeele and Van Gehuchten, 1998); zidovudine (Simdon et al., 2001); and combinations of zidovudine and didanosine (Christensen et al., 1998); stavudine and lamivudine (Simdon et al., 2001); stavudine, lamivudine, didanosine, and hydroxyurea (Simdon et al., 2001); and post exposure prophylaxis with stavudine, lamivudine, and nevirapine (Rey et al., 2002). Moreover, a study of 99 HIV-infected individuals who received antiretroviral drugs showed that hearing loss was common in this population. Hearing loss was significantly associated with those that are 35 or older and with a history of ear infection, and there was a trend toward an association with documented receipt of therapy with antiretroviral drugs in the preceding 6 months (Marra et al., 1997).

As earlier illustrated, previous cross-sectional studies and case reports have shown an association between hearing loss and NRTI therapy (Marra et al., 1997; McNaghten et al., 2001; Simdon et al., 2001). There have been two case reports of hearing loss in persons receiving ART regimens that included NRTIs and a second class of antiretroviral drugs; one with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Nevirapine) and one with a protease inhibitor (PI) (lopinavir/ritonavir) each combined with NRTIs, (both these subjects were also receiving stavudine and lamivudine). One case reported sudden hearing loss two weeks subsequent to the person completing one month of post- exposure prophylaxis which resulted in long-term hearing loss (Rey et al., 2002). The other case described hearing loss in a subject with extensive HIV pre-treatment, and suggested a possible relationship with the protease inhibitor, although there were other possible explanations noted in Simdon's reply to this case report (Simdon et al., 2001; Williams, 2001).

One should note that not all of the aforementioned studies utilized sensitive ototoxicity monitoring protocols such as ultra-high frequency audiometry and/or otoacoustic emissions. Furthermore, some of these studies also did not follow longitudinal research designs that could have allowed the researchers to investigate within-subject changes; but they rather followed cross sectional methodology designs. In addition, the reports that other factors such as age, drug interactions, concomitant noise exposure, and so on may have an influence on the ototoxicity of ARVs should be taken into consideration when reviewing the effects of ARVs on hearing.

While ototoxic hearing loss has been described in HIV-infected people after beginning NRTIs, there have been extremely limited prospective studies, with one published example of a prospective study by Schouten et al. (2006). Hence there still needs to be extensive investigations to clearly establish and confirm this relationship. The study by Schouten et al. (2006) investigated hearing changes

longitudinally in treatment-naïve HIV-infected subjects following initiation of regimens containing NRTIs. The goal of their study involved performing a prospective assessment of the contribution of zidovudine (ZVD) and didanosine (ddI) to hearing loss. Changes in hearing levels at all frequencies and in low and high frequency pure tone averages were measured at baseline, 16, and 32 weeks after initiating antiretroviral therapy.

In Schouten et al.'s (2006) study, treatment with ZVD and ddI did not result in loss of hearing, even after taking into account noise exposure, immune status and age. The results of this prospective pilot study did not support the view that treatment with nucleoside antiretroviral drugs damages hearing. This finding contradicts reports from previous cross-sectional studies and case reports that have indicated that hearing loss may be common among HIV-infected people due to ototoxic drug therapy (Khoza and Ross, 2002; Marra et al., 1997). The results of the prospective study by Schouten et al. (2006) did not corroborate this relationship and are consistent with the report from the Adult/Adolescent Spectrum of HIV Disease Project Group that demonstrated no association between hearing loss and drugs used in the treatment of HIV. Of note, however, the Adult/Adolescent Spectrum of HIV Disease Project Group study was centred on a retrospective chart review for International Classification of Diseases (ICD) -9 coding for hearing loss and not on formal audiometry (McNaghten and Dworkin, 2001). This represents a significant weakness in the methodology for a study attempting to determine ototoxic effects which can be subclinical in nature, hence requiring sensitive audiological monitoring tools.

There are at least three criticisms that can be levelled against the aforementioned study by Schouten et al. (2006). Firstly, this study did not incorporate otoacoustic emissions (OAEs) as part of their monitoring battery, and this could have had a significant impact on their results since OAEs have been shown to be sensitive to cochlear damage in ototoxicity monitoring. Secondly, only 33 participants were included in their study, a small sample size which significantly reduces the strength of the study in terms of the ability to generalize the findings. Moreover, a small sample size limits the power of this study to detect a difference and also limits ability to accurately interpret results. Thirdly, there was no control group, although the researchers did acknowledge that this was a pilot study. To their credit, these authors' pure tone testing included 12 kHz, which is an ultrahigh frequency. Ultrahigh frequencies have been reported to be finely tuned to the effect of damaging environmental factors such as noise and ototoxic drugs (Campbell, 2007).

Replication of studies such as Schouten et al.'s (2006) longitudinal study in developing countries such as South Africa may be challenging due to a number of factors. Firstly, the nature of the HIV/AIDS disease and the population being studied may preclude complete control over confounding variables that could have had an influence on the results such as interactions of ARVs with other therapies; especially traditional medicine in the form of '*ubhejane'* which has been reported to be in widespread use (Bateman, 2006). The current researcher is of the opinion though that isolating all the possibly contributing confounding variables may provide a more accurate answer but may not necessarily provide a practical, relevant, and context-sensitive finding. Within the South African AIDS population for an example; it may be impossible to find participants who are only exposed to just one strict ARV regimen without any other medications coming into play. Secondly, securing descent sized comparison groups may be difficult, thereby preventing randomized matching of participants in the comparison group with those in the experimental group.

Challenges in obtaining large enough sample sizes for control groups may be due to factors such as attrition due to patients commencing treatment during the study as well as loss to follow up. Thirdly, ultra-high frequency audiometry which does not form part of the routine audiological test battery may influence the type of results found; and this influence could reflect in clinical changes in the ultrahigh frequencies depicted on the audiogram being entirely missed. Lastly, the length of time for which the audiologic monitoring occurs due to attrition may be too short to allow for clinical hearing loss possibly caused by ART to manifest and therefore be detected on the audiogram.

Nevertheless, such longitudinal studies of patients on various regimens of ARVs need to be conducted. These studies need to be carried out in order to determine if any hearing changes occur during the period when the patients were receiving ARVs. Both clinically significant and statistically significant changes need to be investigated as presence of statistically significant changes does not necessarily translate to clinically significant findings. It is also critical that measures such as DPOAEs, which are sensitive to microcochlear changes, form part of the methodologies employed since DPOAE have been shown to be superior to pure tone audiometry in this regard (Hall, 2000).

Conclusion

In view of the increase in the number of patients who are reported to be infected with HIV/AIDS and now receiving ART in developing countries, it is anticipated that drug-induced hearing loss might be one of the adverse effects of ART. This is because ART improves survival for those with HIV, side effects and morbidities are increasingly becoming increasingly important. Audiologists and physicians are generally not fully informed about these side effects on hearing. As a profession; over and above identifying HIV/AIDS primary auditory manifestations, audiologists also need to ensure the safe and effective use of antiretroviral drugs and other therapies that may have a negative effect on hearing function. Because the

evidence base is largely from the developed world; research from developing countries needs to be intensified. Lack of context specific data from developing countries may have implications for the management of this population since contextual factors in developing countries are arguably different to those in first world countries.

The contextual factors include but are not limited to the use of different drugs and/or use of generic drugs, the possible co-use of traditional medicine by a large majority of the patient cohort, as well as the use of different monitoring tools depending on available technology. Evidence of the ototoxic effects of all ARVs in current use needs to be established; with concrete steps being taken towards setting up drug-monitoring programs as well as ensuring efficient and consistent adverse event reporting from drug trials; these being potential resources for more data that could be used to answer the posed question: is there a need for ototoxicity monitoring in patients with HIV/AIDS?

REFERENCES

Arslan E, Orzan E, Santarelli R (1999). Global Problem of Drug-Induced Hearing Loss. Annals New York Acad. Sci., 884: 1-14.

Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, Wells C, Nunn P, Blanc L, Raviglione M (2006). Epidemiology of anti-tuberculosis drug resistance (the global project on anti-tuberculosis drug resistance surveillance): An updated analysis. Lancet, 368(9553): 2142-2154.

Bankaitis AE (1996). Audiological changes attributable to HIV. Audiol. Today, 8(6): 14-16.

Bankaitis AF, Keith RW (1995). Audiologic changes associated with HIV infection. Ear Nose Throat J., 74: 353-359.

Bankaitis AE, Schountz T (1998). HIV-Related Ototoxicity. Semin. Hear., 19: 155-163.

Bateman C (2006). Taking ubhejane by the horn(s). S. Afr. Med. J., 96(5): 382.

Birchall M, Wight R, French P, Cockbain Z, Smith S (1992). Auditory function in patients infected with the Human Immunodeficiency Virus. Clin. Otolaryngol., 17: 117-121.

Campbell KCM (2007). Pharmacology and ototoxicity for Audiologists. United States: Thomson Delmar Learning.

Christensen LA, Morehouse CR, Powell TW, Alchediak T, Silio M (1998). Antiviral therapy in a child with pediatric human immunodeficiency virus (HIV): case study of audiologic findings. J. Am. Acad. Audiol. 9: 292-298.

Clarke M, Dick J, Bogg L (2006). Cost-effectiveness analysis of an alternative tuberculosis management strategy for permanent farm dwellers in South Africa amidst health service contraction. Scandanavian J. Pub. Health, 34: 83-91.

Cohn A (1981). Etiology and pathology of disorders affecting hearing. In F.N. Martin (Ed). Medical audiology: Disorders of hearing. New Jersey: Prentice-Hall, Inc.

Colebunders R, Dipraetere K, Van Wanzeele P, Van Gehuchten S (1998). Deafness caused by didanosine. Microbiol. Infect. Dis., 17: 214-215.

Cummings CW (1993). Otolaryngology – Head and neck surgery. USA: Mosby-Yearbook.

Dorrington RE, Johnson LF, Bradshaw D, Daniel T (2006). The demographic impact of HIV/AIDS in South Africa. National and provincial indicators for 2006. Centre for Actuarial Research, South African Medical Research Council and Actuarial Society of South Africa, Cape Town.

Edmunds AL, Mudd PA, Kalkanis J, Campbell KCM, Rybak LP (2006). Inner ear ototoxicity. Retrieved from the Web October 10, 2006 http://www.emedicine.com

Fausti SA, Wilmington DJ, Helt PV, Konrad-Martin D (2005). Hearing and health care: the need for improved hearing loss prevention and hearing conservation practices. J. Rehab. Res. Dev., 42(4): 45-62.

Friedman JL, Noffsinger D (1998). Hearing loss associated with HIV/AIDS: Social, cultural, and political issues. Seminars in Hearing, 19: 205-214.

Gold S, Tami TA (1998). Otolaryngological Manifestations of HIV/AIDS. Semin. Hear., 19: 2.

Hall JW (2000). Handbook of otoacoustic emissions. San Diego: Singular Publishing Group.

Hawkins JE (1976). Drug ototoxicity. In: Keidel D. (Ed). Handbook of sensory physiology.(Vol. 5). Auditory system part 3: clinical and special topics. pp 707-748. Berlin: Springer.

Jackson GG, Arcieri G (1971). Ototoxicity of gentamicin in man. A survey and controlled analysis of clinical experience in the United States. J. Infect. Dis., 124: 130-137.

Kakuda TN (2000). Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin. Therapeut., *22*(6): 685-708.

Kallail KJ, Downs DW, Schertz JW (2008). Communication disorders in individuals with HIV/AIDS. Kansas J. Med., 1(3).

Khoza K, Ross E (2002). Auditory function in a group of Adults infected with HIV/AIDS in an outpatient clinic in Gauteng, South Africa. S. Afr. J. Comm. Disorders 49: 17-27.

Khoza-Shangase K, Mupawose A, Mlangeni NP (2009). Ototoxic effects of tuberculosis treatments: How aware are patients? Int. J. Med. Sociol. Anthropol., 3(8): 391-399.

Kohan D, Hammerschlag PE, Holliday RA (1990). Otologic disease in AIDS patients: CT correlation. Laryngoscope, 100: 1326-1330.

Lalwani AK, Sooy CD (1992). Otologic and neurologic manifestations of acquired immunodeficiency syndrome. Otolaryngol. Clin. N. Am., 25(6): 1183-1198.

Marra CM, Wechkin HA, Longstreth WT, Rees TS, Syapin CL, Gates GA (1997). Hearing loss and antiretroviral therapy in patients infected with HIV-1. Arch. Neurol., 54(4): 407-10.

Martinez OP, French MAH (1993). Acoustic neuropathy associated with zalcitabine-induced peripheral neuropathy. AIDS, 7: 901-902.

McArthur JC (1987). Neurologic manifestations of AIDS. Medicine, 66, 407-437.

McNaghten AD, Wan PT, Dworkin MS (2001). Correspondence: Prevalence of hearing loss in a cohort of HIV-Infected patients. Arch. Otolaryngol. Head Neck Surg., 127: 1516-1518.

Monte S, Fenwick JD, Monteiro EE (1997). Irreversible ototoxicity associated with zalcitabine. Intl. J. STDs AIDS, 8: 201-202.

Powderly WG, Klebert MK, Clifford DB (1990). Ototoxicity associated with dideoxycytidine. Lancet, 1: 1106.

Rey D, L'Heritier A, Lang JM (2002). Severe ototoxicity in a health care worker who received postexposure prophylaxis with stavudine, lamivudine, and nevirapine after occupational exposure to HIV. Clin. Infect. Dis., 34: 417-418.

Schouten JT, Lockhart DW, Rees TS, Collier AC, Marra CM (2006). A prospective study of hearing changes after beginning zidovudine or didanosine in HIV-1 treatment-naïve people. BMC Infect. Dis., 6: 28.

Seidman MD, Bai U, Khan MJ, Murphy MJ, Quirk WS, Castora FL, Hinojosa R (1996). Association of mitochondrial DNA deletions and cochlear pathology: a molecular biologic tool. Laryngoscope, 106: 777-783.

Simdon J, Watters D, Bartlett S, Connick E (2001). Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: A report of 3 possible cases and review of the literature. Clin. Infect. Dis., 32: 1623-1627.

Simdon J, Watters D, Bartlett S, Connick E (2001). Reply. Clin. Infect. Dis., 33: 2101-2102.

Smith A, MacKenzie I (1997). Hearing loss from ototoxics. WHO Drug Information, 11(1): 7-10.

Williams B (2001). Correspondence: Ototoxicity may be associated with protease inhibitor therapy. Clin. Infect. Dis., 33: 2100-2101.

Zapor MJ, Cozza KL, Wynn GH, Wortmann GW, Scott CA (2004). A(NRTIs, NNRTIs, and Fusion Inhibitors). Psychosomatics, 45(6).

Zuninga J (1999). Communication disorders and HIV disease. J. Intl. Ass. Phys. AIDS Care. Retrieved from the Web October 10, 2006 www.thebody.com/content/art12344.html