

OPEN ACCESS GUIDE TO AUDIOLOGY AND HEARING AIDS FOR OTOLARYNGOLOGISTS



TUBERCULOSIS (TB), AMINOGLYCOSIDE AND HIV-RELATED HEARING LOSS

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This chapter discusses hearing loss related to tuberculosis (TB), HIV, and aminoglycosides. These are significant causes of hearing loss pertinent to developing world countries where the consequences of hearing impairment are exaggerated because of the lack of auditory rehabilitation facilities. In 2013, the global estimate by the *World Health Organization (WHO)* for disabling hearing impairment (>40dB HL in adults and >30dB HL in children) was 368 million (5,3% of the world's population).¹ The prevalence of disabling hearing loss both in children as well as in adults over 65yrs is highest in South East Asia, Asia-Pacific and Sub-Saharan Africa.¹

Tuberculosis (Figure 1) is a major global health problem and is the second biggest cause of death from infectious disease after HIV.² South Africa has one of the highest rates of drug-resistant tuberculosis (MDR-TB) in the world.² Treatment of **drug-resistant tuberculosis necessitates use of 2nd line injectable anti-TB drugs which are associated with sensorineural hearing loss (SNHL).**²

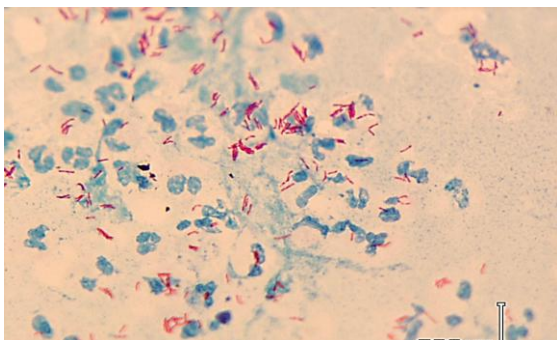


Figure 1: *Mycobacterium tuberculosis* acid-fast bacilli on Ziel-Nielsen staining (Courtesy John Kruger)

HIV is a major health issue in developing countries. *E.g.* the number of patients living with HIV in South Africa increased from 4,2m in 2001 to 5,4m in 2011. In

2010, an estimated 1,16m people (including children) in South Africa were on antiretroviral treatment.³

HIV & TB go hand-in-hand. Fifty percent of TB patients in South Africa test positive for HIV; this necessitates antiretroviral and TB drugs to be given simultaneously. *Harris et al* reported that **HIV-positive multidrug-resistant (MDR) TB patients on highly active antiretroviral therapy (HAART) were more likely to develop ototoxic hearing loss than HIV-negative MDR-TB patients.**² Similarly, *Brits et al* in a study which compared the hearing profiles of gold miners with and without tuberculosis found that miners with TB had significantly poorer hearing thresholds and more pronounced decline over time which was independent of noise exposure. It was found that TB is associated with other predisposing factors for hearing loss including HIV, opportunistic infections and exposure to other ototoxic drugs.⁴

Understanding the effects of these combinations of ototoxic drugs on the auditory system is important as a large number of patients are potentially at risk of SNHL; however the extent of the problem may not be fully appreciated because of a lack of monitoring for ototoxicity.

TB-related Hearing Loss

This can be a consequence of aminoglycosides, TB of the middle ear and TB meningitis. Aminoglycosides are used in MDR-TB and are the principal cause of TB-related hearing loss; this is addressed under **Aminoglycoside Toxicity.**

TB otitis media: The classic features are painless otorrhoea with multiple tympanic

membrane perforations; exuberant granulations; severe hearing loss; and bone necrosis.^{5,6} However, the clinical signs of TB otitis media do not always conform with this description and may be extremely varied. Patients who present with otorrhoea refractory to standard antibiotic treatment and chronic middle ear infection associated with facial nerve palsy should raise a suspicion of TB.^{7,8} Thirty per cent of TB otitis media patients present with acute infection or superinfection and mastoid involvement (*Figure 2*).^{7,8} TB mastoiditis should be considered in the differential diagnosis of a patient presenting with a polyp in the ear canal, particularly where TB is endemic (*Figure 3*). Concomitant pulmonary TB may or may not be present.^{7,8}

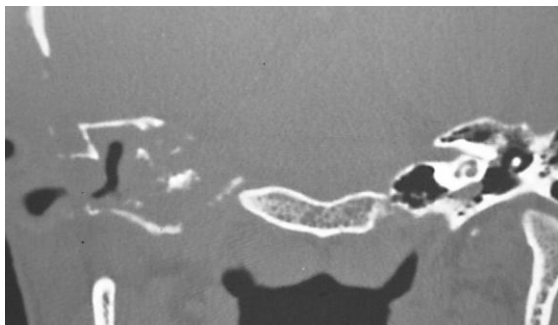


Figure 2: Coronal CT scan showing extensive erosion of the temporal bone in a TB patient



Figure 3: Polyp occluding external ear canal in a patient with TB otitis media

It is valuable to obtain imaging prior to biopsy to exclude underlying chronic suppurative otitis media, cholesteatoma, histiocytosis X, glomus temporale tumor, or a neoplasm. Ziehl-Nielsen staining is often unreliable; a definitive diagnosis is made on culture of tissue specimens or ear discharge.⁹ The diagnosis may also be made on biopsy with histological evidence of TB granuloma. Polymerase chain reaction (PCR) is an alternative to culture to diagnose extrapulmonary TB.⁹ The standard treatment of TB otitis media is anti-tuberculous medication for at least 6 months; disseminated TB and TB meningitis require treatment for 9 - 12 months.¹⁰

TB meningitis: The mortality and morbidity of TB meningitis is very significant; therefore prompt diagnosis and early initiation of treatment are essential. It is one of the most common opportunistic central nervous system (CNS) infections associated with HIV, especially with advanced stages of HIV.¹¹ The duration of symptoms prior to presentation may vary from several days to months. It may present as acute or chronic meningitis.¹¹ In addition to a non-specific prodrome of headache, malaise, nausea and vomiting, patients may present with cranial palsies, most commonly the 6th but also the 2nd, 3rd, 4th and 8th cranial nerves. **Treatment should not be delayed and should be initiated based on clinical suspicion.** Definitive diagnosis requires examination of CSF for acid-fast bacilli, although the yield is often low; in HIV-positive cases the yield of mycobacterium is often better because of greater CNS dissemination.¹¹ *M. Tuberculosis* can take up to 8 weeks to culture on solid media. PCR of CSF samples increases the rapidity of diagnosis, but while specificity is high, sensitivity is low (40-60%). For severe disease, adjunctive steroids reduce mortality, although no significant beneficial effects on intracranial pressure, basal ganglia infarcts, blindness or deafness

were demonstrated in a randomised study.¹²

Aminoglycoside Ototoxicity

Aminoglycosides were introduced in the 1940's and are highly effective treatment of MDR-TB and gram negative infection.¹³ The ototoxic and nephrotoxic effects of aminoglycosides became evident shortly after their introduction and have limited their use although in developing countries they are still widely used due to their broad antimicrobial spectrum and low cost.¹⁴

Patients with TB require retreatment when they fail or default from initial treatment or relapse following initial treatment success. MDR-TB is defined as resistance to both isoniazid and rifampicin. Aminoglycosides are indispensable in treatment of retreatment-TB and MDR-TB. WHO guidelines dictate that injectable aminoglycosides e.g. streptomycin for retreatment of TB and amikacin and kanamycin for MDR-TB (Table 1) should be employed along with residual first-line oral drugs.

Classes	Anti-TB drugs	Comments
1 st line drugs	Rifampicin (RIF)	Core of initial TB treatment
	Isoniazid (INH)	
	Pyrazinamide (PZA)	None are ototoxic
	Ethambutol (EMB)	
2 nd line drugs	Streptomycin (SM)	Aminoglycoside used in retreatment TB Ototoxic & nephrotoxic
	Kanamycin/Amikacin	Aminoglycoside used in MDR-TB Ototoxic & nephrotoxic
	Capreomycin*	Polypeptide drug used in MDR-TB Ototoxic & nephrotoxic
	p-Aminosalicylic acid	No ototoxic potential documented
	Levofloxacin	
	Moxifloxacin	
	Gatifloxacin	
	Cycloserine	
	Ethionamide	

Table 1: Classes of TB drugs

MDR-TB patients often have to be treated for at least 18-24 months with these 2nd line TB drugs; this places patients at high risk of developing aminoglycoside-induced SNHL.¹⁵ Aminoglycosides affect both the vestibular and cochlear functions of the inner ear; however individual aminoglycosides exhibit variable degrees of cochleo- and vestibulotoxicity.¹⁶ **Streptomycin and gentamicin are primarily vestibulotoxic; amikacin, neomycin, kanamycin are primarily cochleotoxic.**⁷ Patients are generally able to compensate for vestibular damage; however ototoxic hearing loss is permanently disabling.⁷ **Hearing loss is usually gradual, and symmetrically bilateral (Figure 4).**¹⁷

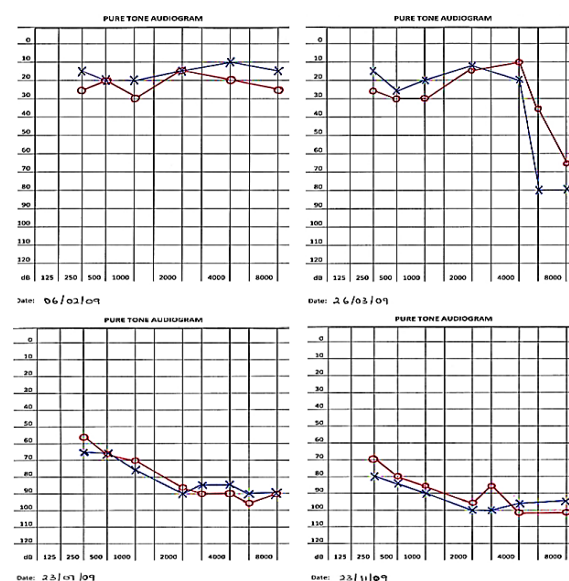


Figure 4: Baseline and follow-up audiograms of a patient on treatment for MDR-TB showing bilateral symmetrical progressive sensorineural hearing loss (SNHL)

Mechanisms of Aminoglycoside-induced Ototoxicity

Aminoglycosides target the sensory neuro-epithelium of the inner ear.⁷ Outer cochlear hair cells are more susceptible to injury than inner hair cells; the basal region of the cochlea is more susceptible than the apical

region.¹⁶ Loss of cochlear hair cells causes secondary degeneration of the auditory nerve. ***This is clinically expressed as high frequency hearing loss; with increased exposure this progresses to involve the lower frequencies (Figure 4).***

Aminoglycosides can remain sequestered within cells of the inner ear for up to 6 months; thus ototoxic injury and associated ***hearing loss may progress for weeks following cessation*** of treatment.¹⁸ Wang *et al* demonstrated that ***ototoxicity may persist for up to one year, even after stopping the drug.***¹⁸ This is relevant when managing ototoxicity in MDR-TB, as patients may be exposed to aminoglycosides for up to 18-24 months.¹⁵ In a study of hearing loss in children with MDR-TB, Seddon *et al* reported that 7/11 patients with audiometric evidence of hearing loss had ***progression of hearing loss after cessation of treatment.***¹⁹

Risk factors for aminoglycoside-induced ototoxicity²⁰

1. Renal dysfunction: Aminoglycosides are primarily excreted by the kidney; hence serum aminoglycoside levels can increase with renal dysfunction²⁰
2. Advanced age
3. Bacteraemia
4. Cumulative dose
5. Concomitant ototoxic drugs
6. Higher serum aminoglycoside concentrations
7. Genetic predisposition

Monitoring aminoglycosides to reduce ototoxicity

Serum trough levels should be monitored to prevent toxicity when treating acute infection *e.g.* gram negative sepsis, or when multiple daily doses of aminoglycoside are administered.¹⁷ However measuring serum trough levels may not be

practical with retreatment-TB and MDR-TB as most patients are treated in the community and are treated for prolonged periods. In such cases the risk of toxicity may be more strongly associated with a larger cumulative dose as patients on MDR-TB regimens are exposed to aminoglycosides for a prolonged period of time. This concurs with a randomised trial by Peloquin *et al*²¹ who looked at the incidence of toxicities associated with two recommended dosing regimens (daily vs. three times per week of intravenous streptomycin, kanamycin, or amikacin) in TB patients; the magnitude of the dose and frequency of administration were not associated with ototoxicity; ototoxicity was associated with a larger cumulative dose and older age.²¹

Genetic screening for aminoglycoside-induced ototoxicity

Genetic factors contribute to aminoglycoside-induced ototoxicity. Aminoglycosides bind to highly conserved sequences of bacterial 16S rRNA and thereby interfere with protein synthesis and cause apoptosis. Human mitochondrial ribosomes share similarities with bacterial ribosomes. Therefore it has been proposed that hair cell mitochondria may be an early target of aminoglycosides. A higher incidence of aminoglycoside-induced hearing loss is likely in individuals with an inherited mitochondrial RNA defect. In patients carrying certain mitochondrial mutations (12S rRNA mutations), the structure of the mitochondrial rRNA has an even greater resemblance to that of the bacterial ribosome. This close resemblance increases the potential for aminoglycosides to bind to rRNA; this in turn increases the potential for ototoxic effects on the hair cells following exposure to aminoglycosides. The first mitochondrial mutation shown to increase aminoglycoside-induced ototoxicity is the 1555 A→G.²² To date there are

six known mitochondrial mutations which have been linked to aminoglycoside-induced hearing loss: A1555G, C1494T, T1095C, T1291C, 961delT+C(n) and A827G, with A1555G being the most common.²³ **Screening individuals before commencing aminoglycosides detects those who are more susceptible to hearing loss, and allows genetic counselling and informed consent.** The Genetics Department at Tygerberg Hospital in Cape Town, South Africa has developed a method to simultaneously detect the 6 known aminoglycoside-induced mutations which facilitates detection of susceptible individuals prior to commencing aminoglycosides.²²

HIV and Hearing Loss

The incidence of hearing impairment in HIV/AIDS varies between 20-40%.²⁴ Hearing impairment may result from pathology in the external, middle and/or inner ear and may be conductive, sensorineural or mixed. **HIV affects the sensorineural auditory system directly or indirectly (Figure 5).**²⁵

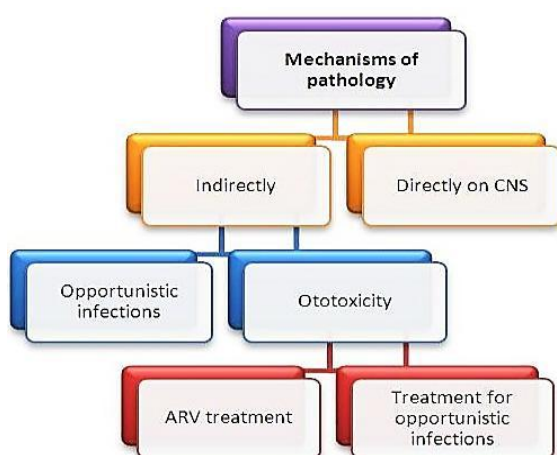


Figure 5: Mechanisms of HIV-related auditory dysfunction¹⁷

Indirect causes can be associated with opportunistic infections that compromise the functioning of the sensory and neural

structures of the inner ear, causing SNHL. **Direct causes** refer to primary HIV infection of the central nervous system or peripheral auditory nerve.

HIV & Conductive/Mixed Hearing Loss

Opportunistic infections or malignancies like otitis media and Kaposi's sarcoma which affect the external and/or middle ear can cause conductive or mixed hearing loss. HIV-positive children appear to have a higher incidence of conductive hearing loss due to middle ear pathology compared to HIV-positive adults who tend to have SNHL.^{25,26} A recent study found that middle ear effusions were present in about 1/3 of patients.²⁶

HIV and SNHL

Van der Westhuizen et al. reported an incidence of SNHL as high as 72%; it was present unilaterally and bilaterally in 32% and 40% respectively, and was more common than conductive hearing loss; the incidence of SNHL increased significantly with disease progression (18% in CDC category 1 and 23% and 31% in CDC categories 2 and 3 respectively).²⁶ SNHL may be attributed to opportunistic ear infections; ototoxic drugs; neoplasia affecting the temporal bone and CNS; opportunistic CNS infections, and direct effects of the virus. These are discussed in detail below.

1. Opportunistic ear infection

The following HIV-related infections of the outer and middle ear may cause conductive or mixed hearing loss

- Middle ear effusion
- Acute otitis media
- Chronic suppurative otitis media
- TB otitis media
- Malignant otitis externa
- Pneumocystis carinii otitis externa

Middle ear effusion (Figure 6): There is a strong association between HIV, adenoid hypertrophy, and middle ear effusions. Middle ear effusion may be the first manifestation of HIV. It is important to examine and if need be, biopsy the nasopharynx to exclude malignancy (Figure 7).²⁷



Figure 6: Left middle ear effusion with a retracted tympanic membrane.



Figure 7: Postnasal space mass seen on nasendoscopy in a patient with HIV

Acute otitis media: This occurs commonly both in immunocompetent and immunocompromised children. The causative organisms are similar to those in HIV negative children (*Streptococcus pneumoniae*, *H. Influenzae* and Group A Beta-haemolytic *Streptococcus*). However the complica-

tions (recalcitrant infection and systemic bacteraemia requiring intravenous antibiotics) appear to be more common in HIV-positive children and correlate with the severity of immune suppression.²⁸ ***Acute otitis media therefore has to be treated aggressively at the outset in HIV-positive patients to prevent complications.*** In HIV-infected children with absent or moderate immune suppression, empiric antibiotic therapy is based on recommendations for immunocompetent children. Given the possible role of *Staphylococcus aureus* in severely immunosuppressed stages, extended spectrum antibiotics should be considered.²⁸

Pneumocystis Carinii otitis media: This may present as otitis media or mastoiditis.²⁹ Organisms gain access to the middle ear from a colonised nasopharynx, from the ear canal, or by haematogenous spread.²⁹ The diagnosis is made histologically using the Gomori methenamine silver stain; this typically reveals cyst formation by organisms which are partially collapsed i.e. "cup-shaped" or "boatshaped".³⁰ Immunohistochemistry with monoclonal antibody to *P. Carinii* in formalin-fixed, paraffin-embedded tissue may be helpful to confirm the diagnosis.³⁰ Management includes 3 weeks' intravenous trimethoprim and dapsone; surgical exploration is rarely required.^{30,31}

Chronic suppurative otitis media (Figure 8): Otitis media is more prevalent and more severe in immunocompromised patients. Persistent otorrhoea in chronic suppurative otitis media is associated with HIV in children. Use of highly active antiretroviral drugs (HAART) reduces the prevalence of chronic otitis media in children, probably due to an increased CD4 count.³²

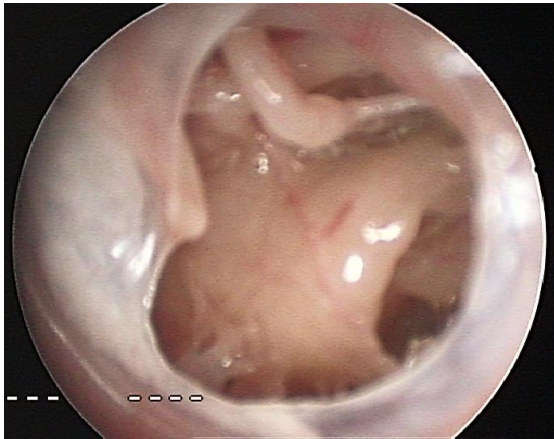


Figure 8: Perforation of left tympanic membrane

TB otitis media: See earlier

Malignant otitis externa: This is a necrotising infection classically caused by *Pseudomonas Aeruginosa* (Figures 9, 10) and involves the external ear canal as well as the surrounding soft tissue.

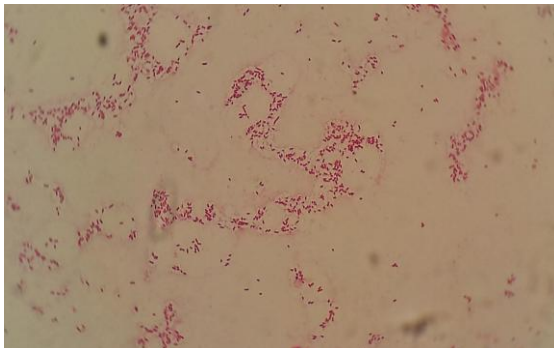


Figure 9: Gram-negative bacilli of P. Aeruginosa

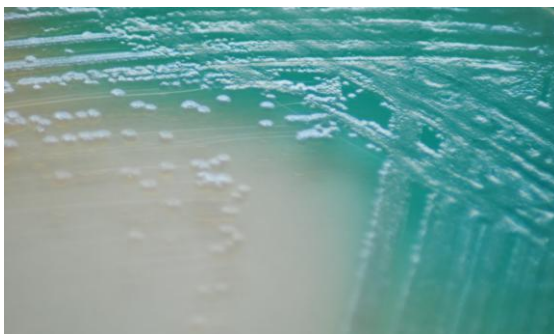


Figure 10: Colonies of P. Aeruginosa on nutrient agar with characteristic green pigmentation (Courtesy John Kruger)

It usually occurs in diabetics, although it may occur in any immunocompromised patient including those with HIV.³³ It should be suspected in the clinical setting of persistent pain and otorrhoea despite conventional treatment. Otoscopy may reveal a tender, oedematous ear canal with granulations at its bony-cartilaginous junction. Fever or other constitutional symptoms may be absent. Cranial nerve palsies may occur; facial nerve involvement is most common, but it can involve the lower three cranial nerves in advanced cases.³⁴ Imaging is used to determine the extent of disease, presence of other complications and to distinguish it from other conditions. CT may be normal in the early stages but as the disease progresses is useful to determine the extent of bony involvement (Figure 11).



Figure 11: Coronal CT shows opacification and erosion of the right external auditory canal

High resolution CT of the temporal bone can identify subtle cortical erosion (may be present in other inflammatory and neoplastic processes) as well as effacement of fat planes beneath the temporal bone and skull base.³⁵ Sclerotic bone can be detected on CT following initiation of treatment or is seen with chronic osteomyelitis.³⁵ Follow-up CT may be useful to determine resolution of soft tissue disease. Static CT findings can exclude recurrence; however remineralisation may not be detected on CT and its use to determine treatment response is limited.³⁵ MRI has superior

contrast resolution and is better to determine soft tissue extent.³³ MRI is also superior to assess intracranial and skull base involvement because it assesses the medullary spaces of bone and identifies subtle dural enhancement.³⁴ Nuclear medicine techniques have been advocated to determine the presence of osteomyelitis of the skull base *e.g.* Technetium 99 and Gallium 67 scintigraphy; these may be more useful for monitoring disease progress.³⁴ Dual antibiotic therapy using a combination of anti-*Pseudomonas* antibiotics such as ciprofloxacin, and either an aminoglycoside or 3rd generation cephalosporin such as ceftazidime, is recommended for *P. Aeruginosa* infection in HIV, especially in severely immunocompromised patients.³³ Combination therapy is suggested to combat resistance.³³ The duration of antibiotic therapy advised varies. The *Bone Infection Unit* in Oxford recommends 6 weeks of intravenous, followed by 6-12 months of oral antibiotics; however this should be guided by clinical findings, normalisation of inflammatory markers *e.g.* ESR, as well as MRI findings. Surgery has a limited role and is used to obtain tissue to exclude malignancy and to obtain cultures to tailor antibiotic therapy.³⁴

Fungal malignant otitis externa, commonly Aspergillus (Figures 12, 13): This constitutes a significant proportion of infections in HIV patients, especially in advanced HIV.³⁶ Invasive *Aspergillus* infection is commonly seen when CD4 counts reach 50/mm.³⁶ Fungal malignant otitis externa often involves the middle ear and mastoid. Management includes surgical debridement and antifungal therapy; amphotericin B is most commonly used.³⁶

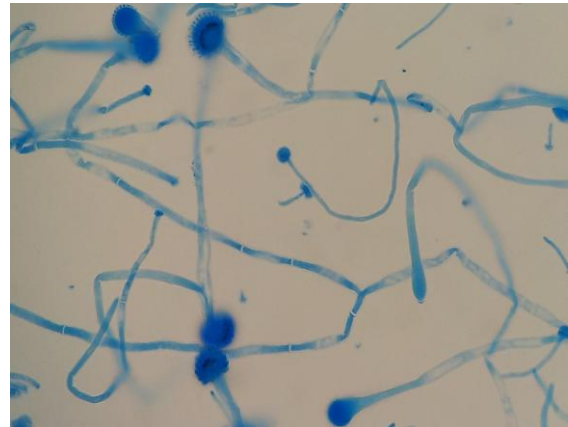


Figure 12: *Aspergillus flavus* conidiophores stained with lactophenol blue

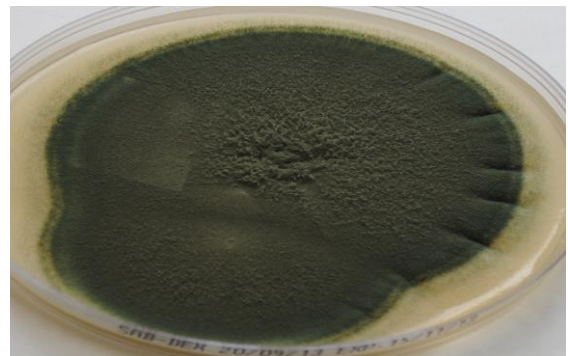


Figure 13: Green velvety growth of *Aspergillus flavus* on Sabouraud's dextrose agar (Courtesy John Kruger)

2. Ototoxic Hearing Loss including HAART

Treating HIV-related opportunistic infections and malignancies with aminoglycosides, amphotericin B, and platinum-based antineoplastic drugs such as Cisplatin may cause SNHL. A number of antiretroviral drugs also affect the hearing. [Highly Active Antiretroviral Therapy \(HAART\)](#) is a combination of antiretroviral drugs (ARVs) and aims to reduce viral load.

There are 3 classes of ARVs *i.e.* nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (Table 2).

NRTIs	NNRTIs	PIs
zidovudine lamivudine stavudine didanosine abacavir tenofovir emtricitabine zalcitabine	nevirapine efavirenz delavirdine	nelfinavir Ritonavir saquinavir indinavir Lopinavir-ritonavir Atazanavir amprenavir Fos-amprenavir

Table 2: Three ARV classes and agents:
From: <http://www.aidsmap.com/Types-of-antiretroviral-drugs> (retrieved 21 June 2013)

NRTIs and NNRTIs suppress HIV replication by inhibiting the action of *HIV reverse transcriptase*; PIs inhibit HIV protease enzyme. Fusion inhibitors are the latest available ARVs. Entry inhibitors mainly prohibit HIV from entering the patient's cells.^{37,38} To date this ARV class includes only Enfuvirtide. HAART regimes typically consist of NRTIs combined with NNRTIs or PIs; NRTIs are the most prevalent components of HAART regimes.³⁹ Table 3 presents a summary of studies that report the effects of ARVs on the auditory system.

The majority of studies report that NRTIs are the most likely cause of SNHL, whether permanent or reversible. Only one case report in which ARVs from the PI class were administered was associated with a SNHL.³⁹ One study⁴⁰ showed no evidence of ototoxicity; however this study only used pure tone audiometry and did not include otoacoustic emissions (OAEs) in the monitoring test battery. OAEs are a sensitive test of cochlear damage, particularly outer hair cells, and can be affected long before it is apparent on pure tone audiograms. Although the exact mechanisms are not clear, ARVs are thought to damage mitochondrial DNA.⁴⁶ Nucleoside reverse transcriptase inhibitors (NRTIs) and combinations of drugs have been reported to cause ototoxicity in children and adults.⁴¹ The ototoxic effects of these drugs are influenced by drug type, combinations, dosages and age of the individual and noise exposure.

Studies	Design	ARVs	Hearing loss
Schouten et al. 2006 ⁴⁰	Longitudinal over 32weeks (33 adults)	zidovudine* didanosine*	No significant changes related to ARVs
Rey et al. 2002 ⁴¹	Adult case report	stavudine* lamivudine* nevirapine	Permanent SNHL
Williams et al. 2001 ³⁹	Adult case report	lopinavir-ritonavir	Reversible SNHL
Simdon et al. 2001 ⁴²	3 adult case reports	Case #1: zidovudine* didanosine* stavudine* Case #2: indinavir stavudine* lamivudine* didanosine* Case #3: efavirenz stavudine* lamivudine* zidovudine*	Permanent SNHL
Christensen et al. 1998 ⁴²	Paediatric case report	zidovudine* didanosine*	Permanent SNHL
Marra et al. 1997 ⁴⁴	99 adults with HIV (43 on ARVs)	zidovudine* didanosine* zalcitabine*	9% with SNHL (associated with ARVs for patients >35yrs)
Monte et al. 1997 ⁴⁵	Adult case report	zalcitabine*	Permanent SNHL

* = NRTIs

Table 3: Summary of reports of the effect of ARVs on the auditory system (Adapted from Stearn and Swanepoel²⁵)

3. Neoplasms of temporal bone and CNS

Kaposi Sarcoma (KS): KS may involve the external auditory canal, tympanic membrane and middle ear.²⁹ Treatment involves antiretroviral drugs, the response to which is frequently unpredictable; therefore it is often combined with treatment directed at the KS lesion.⁴⁷ Localised cutaneous KS responds well to surgical excision, cryotherapy, intralesional vinblastine, bleomycin, radiation therapy, interferon- α , and ablation with CO₂ laser.⁴⁷ Lesions which extend onto the tympanic membrane can be ablated using argon laser without causing tympanic membrane perforations.⁴⁸ Radiation therapy may be used for extensive lesions.⁴⁸

Non-Hodgkins lymphoma (NHL): This has been reported to involve the pinna, external auditory canal (Figures 14, 15), tympanic membrane and temporal bone with associated VIIⁿ palsy in HIV patients.⁴⁹ Extra-nodal NHL may mimic otitis externa and squamous cell carcinoma; it should therefore be considered in atypical lesions and biopsies should be repeated if the histological diagnosis does not conform with the clinical picture. A histological diagnosis may be difficult when the disease occurs in such locations; immunohistochemistry may be required to make the diagnosis.⁴⁹



Figure 14: Friable mass involving external auditory canal; biopsy revealed Non-Hodgkins lymphoma



Figure 15: Coronal CT shows mass expanding right external auditory canal

4. Opportunistic CNS infections

Opportunistic CNS infections causing SNHL include TB meningitis, cryptococ-

cal meningitis, otosyphilis, cytomegalovirus infection and Ramsay-Hunt syndrome.

TB meningitis: This is one of the most common opportunistic CNS infections in HIV, especially with advanced HIV.¹¹

Cryptococcal meningitis: As a consequence of the increase in HIV-associated cryptococcosis, it is now the leading cause of community-acquired meningitis, ahead of TB and bacterial meningitis; it accounts for 20-45% of laboratory-confirmed cases of meningitis in Southern Africa.⁵⁰ It is caused by *Cryptococcus neoformans*, an encapsulated, budding, yeast-like fungus (Figures 16, 17).

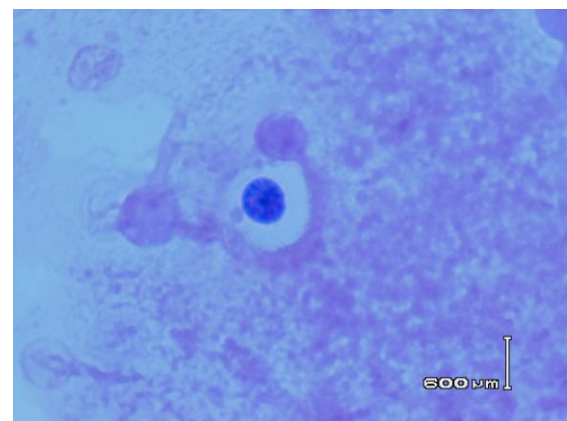


Figure 16: Gram stain of *Cryptococcus neoformans* yeast (Courtesy John Kruger)

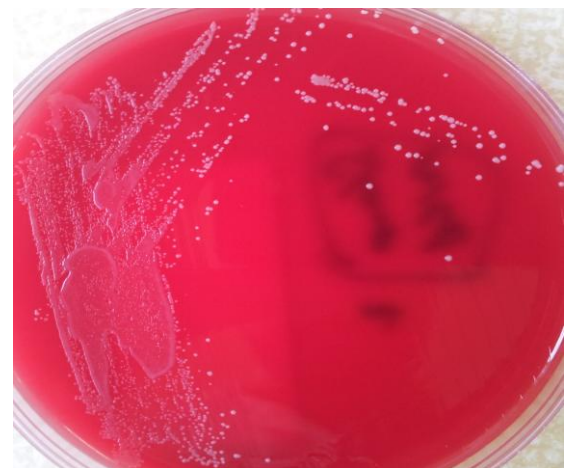


Figure 17: *Cryptococcus* growth on blood agar

It is found in soil and pigeon droppings; humans are infected by inhalation. The infection spreads haematogenously to the brain and meninges. Patients present with headache, nausea/vomiting, disorientation and cranial nerve deficits.⁵⁰ SNHL may be the presenting symptom and may be of sudden onset or progressive in nature.⁵¹ Bilateral SNHL has been reported in 18-30% of cryptococcal meningitis patients.⁵² A temporal bone study demonstrated direct damage to the vestibular and cochlear nerves.⁵¹ Cryptococcal CNS infection has also been associated with auditory neuropathy.⁵¹ Audiological testing may therefore show otoacoustic emissions to be present, abnormal/absent evoked potentials, poor speech perception, and absent acoustic reflexes.⁵¹ Diagnosis is made by the presence of serum cryptococcal antigen and evaluation of CSF by lumbar puncture. It is treated with amphotericin B and 5-fluorocytosine followed by lifelong suppression with fluconazole.⁵⁰

Otosyphilis: Otosyphilis is increasing mainly because of the HIV pandemic. It is part of tertiary syphilis; in immunocompetent individuals this occurs 15-20 years after primary infection. In patients with HIV this time interval is significantly accelerated and can occur as quickly as 5 years after primary infection. Otosyphilis can occur in HIV-positive patients despite high CD4 counts.⁵³ It should be considered in any HIV patient complaining of hearing loss or vertigo. Patients may complain of sudden, progressive or fluctuating hearing loss, with or without tinnitus or disequilibrium. SNHL is unilateral or bilateral. Diagnosis may be made with *Flourescent Trepomena Antigen Antibody Absorbed Test* (FTA-ABS); however this cannot distinguish between active and treated disease and remains positive for life despite treatment. Hence the diagnosis of otosyphilis remains controversial.⁵³ *The Venereal Disease Research Laboratory*

(VDRL) and *Rapid Plasma Regain* (RPR) tests are indicators of active disease and become negative once it has been adequately treated. Optimal treatment consists of high-dose intravenous penicillin as well as systemic steroids given over 10-14 days.⁵³

5. Direct effect of HI virus on hearing

HIV is associated with auditory neuropathy (AN). AN is an otologic syndrome characterized by normal otoacoustic emissions and altered/absent auditory evoked potentials in patients with moderate-to-profound SNHL (*Figures 18, 19*).

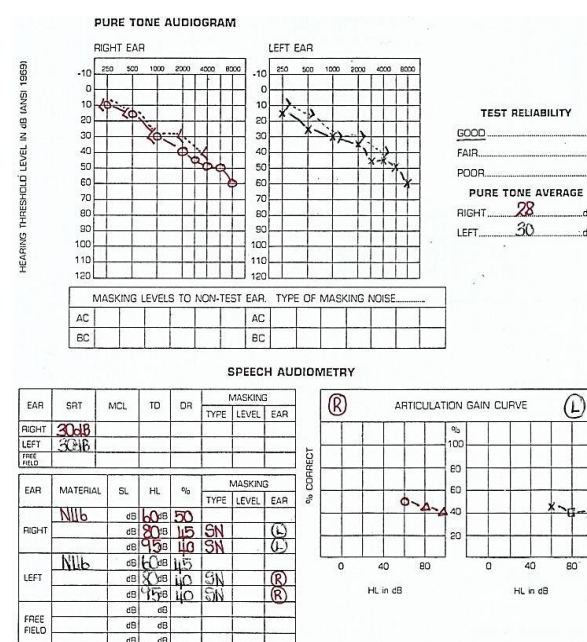


Figure 18: Pure tone audiogram shows bilateral SNHL with poor speech discrimination scores

Patients with AN can present with any configuration or degree of hearing loss; unilateral AN also occurs.⁵² Researchers have proposed several sites of lesion for AN: inner hair cells of the cochlea, synapse between the cochlea and VIII nerve, VIII nerve, or combinations thereof.⁵² A disorder at any of these sites leads to dys-synchrony of the auditory nerve and brainstem. Synchrony is critical for under-

standing speech in the presence of noise.⁵⁴ Abnormalities recorded by auditory brain-stem responses (ABR) in patients with HIV suggest involvement of the peripheral and central auditory nervous systems.⁵⁵⁻⁵⁷ These abnormalities may be due to demyelination as a result of direct infection of glial and neurological cells.⁵⁷ Post mortem studies^{58,59} demonstrated microstructural changes as well as viral-like particles characteristic of HIV within the epithelium and endolymphatic spaces of the end-organs suggesting that the HI virus may be directly ototoxic. The majority of these studies also showed structural abnormalities within the CNS. SNHL associated with HIV is typically high-frequency with a pattern similar to that seen in presbycusis.

Audiological Screening and Monitoring for Ototoxicity

Screening, identification and monitoring for ototoxic hearing loss allows one to counsel patients and their families, to possibly stop ototoxic drugs or to adjust the treatment regimen, to provide and to rehabilitate hearing. Developing countries often lack resources to implement effective screening and monitoring for ototoxicity; research needs to be directed at practical and cost-effective screening tools.³

Symptoms of ototoxicity include tinnitus, dizziness, and difficulty understanding speech in noise. ***Patient self-reporting to detect early hearing or vestibular impairment is neither reliable nor sensitive.***^{60,61} By the time patients complain of difficulty understanding speech or vertigo, permanent ototoxic damage has occurred.

Patients with life-threatening illnesses such as MDR-TB and cancer may need to continue with medication despite ototoxicity. The purpose of screening such patients is to provide auditory rehabilitation.

A multidisciplinary discussion including e.g. a physician, audiologist, oncologist and patient may be required to determine appropriate management.

The American Academy of Audiology position statement and clinical practice guidelines for monitoring ototoxicity (2009) includes

- Basic audiologic assessment (including air conduction audiometry & bone conduction when indicated)
 - High frequency audiometry (HFA)
 - Otoacoustic emission (OAE) measurements
- <http://www.audiology.org/resources/documentlibrary/documents/otomonpositionguideline.pdf>

Comprehensive baseline evaluation (1st step to monitor ototoxicity) should include

1. ***Otoscopy & tympanometry*** to evaluate outer and middle ear function, particularly since otitis media is a very common opportunistic infection in immunocompromised individuals and may cause conductive hearing loss
2. ***Pure tone audiometry*** to determine pre-existing hearing loss and to establish a clear association between the drug and ototoxin-induced hearing loss. Pure tone audiometry also allows one to evaluate the range of hearing loss relevant to speech communication
3. ***HFA*** is essential because ototoxicity tends to affect the basal turn of the cochlea first, well before changes become evident in the conventional range of 250-8000 Hz. HFA includes pure tone testing above 8000Hz, ranging up to 16 or 20 kHz. *Figure 20* illustrates an audiogram of typical ototoxin-induced hearing loss. Note the sharply sloping hearing loss in the high and very high frequencies above 8000Hz

4. **Speech audiometry (word recognition)** should always be included in the baseline evaluation to determine if hearing loss progresses to involve the conventional frequency range. In such cases the focus is to preserve speech frequencies as best possible and to maintain effective communication
5. **OAE measurements** are done to evaluate outer hair cell function (OHC) as drug toxicity tends to be expressed first as OHC dysfunction. In addition, OAE responses tend to change before hearing thresholds do in the conventional frequency range, but not before changes are observed in HFA thresholds. It should be remembered that otitis media or other middle ear pathologies may affect OAE measurements and would therefore not yield reliable results.

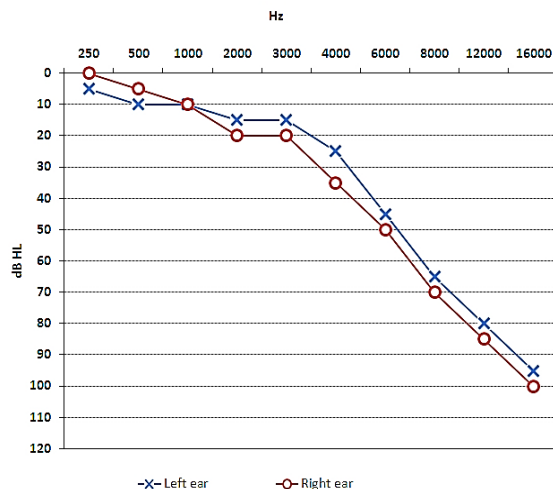


Figure 20: Typical ototoxin-induced high frequency sensorineural hearing loss

Basis for comparison

A basis for comparison is required to determine drug-induced changes in hearing and auditory function. Criteria for clinically significant changes in hearing are ⁶²

- ≥ 20 dB pure tone threshold change at any one test frequency

- ≥ 10 dB pure tone threshold change at any two adjacent frequencies
- Loss of responses at three consecutive test frequencies that were previously present

In addition, an effective referral system and appropriate follow-up testing are required.

Frequency of monitoring

This depends on the type of drug *e.g.* individuals receiving aminoglycosides should be monitored once to twice a week.³ The frequency of monitoring for individuals with HIV depends on the use of ARVs. In a typical infectious diseases clinic, such individuals undergo serological testing every 3 months at which time viral loads and CD4 cell counts are monitored; ARV regimes might be adapted according to these tests. This would be the ideal opportunity to evaluate hearing and to document changes that occur.

Post-treatment evaluation

Ototoxic drugs such as aminoglycosides remain in the cochlea long after its administration has been terminated. It is therefore important to perform post-treatment evaluations to confirm that hearing loss has stabilized.

Counselling

Patients should be counselled about the synergistic effect of noise-induced cochlear damage to prevent further hearing loss.

Monitoring ototoxicity in resource constrained settings

Where audiological facilities to screen for and monitor hearing loss are not available, doctors should rely on a careful history

relating to hearing loss, tinnitus, and vestibular symptoms. Community-based mobile systems for reliable pure-tone audiometry with masked air- and bone conduction thresholds are being introduced for hearing screening in TB-treatment (KUDUWave – eMoyoDotNet, South Africa). Mobile phone-based audiometry also shows promise as a screening tool for ototoxicity because of its accuracy to detect high frequency hearing loss (See chapter: [Mobile phone audiometry](#))

References

1. World Health Organization. WHO media centre. <http://www.who.int/mediacentre/factsheets/fs300/en/>. Updated February 2013. Accessed July 15, 2013
2. Statistics South Africa. Statistical release P0302. <http://www.statssa.gov.za/publications/P0302/P03022011.pdf>. Updated 27 July 2011. Accessed May 15, 2013.
3. Harris T, Peer S, Fagan JJ. Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. *J Laryngol Otol*. 2012; 126(6):548-51
4. Brits J, Strauss S, Eloff Z, Becker PJ, Swanepoel de W. Hearing profile of gold miners with and without tuberculosis. *Occup Environ Med*. 2012;69(4):243-9
5. Mongkolrattanothai K, Oram R, Redleaf M, Bova J, Englund JA. Tuberculous otitis media with mastoiditis and central nervous system involvement. *Pediatr Infect Dis J*. 2003;22(5):453-6
6. Cho Y-, Lee H-, Kim S-, et al. Tuberculous otitis media: A clinical and radiologic analysis of 52 patients. *Laryngoscope*. 2006;116(6):921-7
7. Vaamonde P, Castro C, García-Soto N, Labella T, Lozano A. Tuberculous otitis media: A significant diagnostic challenge. *Otolaryngol - Head Neck Surg*. 2004; 130(6):759-766.
8. Lee PYC, Drysdale AJ. Tuberculous otitis media: A difficult diagnosis. *J Laryngol Otol*. 1993;107(4):339-41.
9. Meher R, Singh I, Yadav SPS, Gathwala G. Tubercular otitis media in children. *Otolaryngol - Head Neck Surg*. 2006;135(4):650-2.
10. Nicolau Y, Northrop C, Eavey R. Tuberculous otitis in infants: Temporal bone histopathology and clinical extrapolation. *Otol Neurotol*. 2006;27(5):667-71
11. Vinnard C, MacGregor RR. Tuberculous meningitis in HIV-infected individuals. *Current HIV/AIDS Reports*. 2009;6(3):139-45.
12. Thwaites GE, Bang ND, Dung NH, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004; 351(17):1741-1751+1811
13. Tran Ba Huy P, Bernard P, Schacht J. Kinetics of gentamicin uptake and release in the rat. Comparison of inner ear tissues and fluids with other organs. *J Clin Invest*. 1986;77(5):1492-1500
14. Saunders JE, Greinwald JH, Vaz S, Guo Y. Aminoglycoside ototoxicity in Nicaraguan children: Patient risk factors and mitochondrial DNA results. *Otolaryngol - Head Neck Surg*. 2009; 140(1):103-7
15. Duggal P, Sarkar M. Audiologic monitoring of multidrug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. *BMC Ear, Nose and Throat Disorders*. 2007;7
16. Selimoglu E. Aminoglycoside-induced ototoxicity. *Curr Pharm Des*. 2007; 13(1): 119-26
17. O'Donnell EP, Scarsi KK, Scheetz MH, Postelnick MJ, Cullina J, Jain M. Risk factors for aminoglycoside ototoxicity in adult cystic fibrosis

- patients. *Int J Antimicrob Agents*. 2010;36(1):94-5
18. Wang S, Bian Q, Liu Z, et al. Capability of serum to convert streptomycin to cytotoxin in patients with aminoglycoside-induced hearing loss. *Hear Res*. 1999; 137(1-2):1-7
 19. Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesselink AC, Schaaf HS. Hearing loss in children treated for multidrug-resistant tuberculosis. *J Infect*. 2013;66(4):320-9
 20. Moore RD, Smith CR, Lietman PS. Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. *J Infect Dis*. 1984; 149(1):23-30
 21. Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: Daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis*. 2004;38(11):1538-44
 22. Bardien S, Human H, Harris T, et al. A rapid method for detection of five known mutations associated with aminoglycoside-induced deafness. *BMC Medical Genetics*. 2009;10
 23. Human H, Hagen CM, Jong Gd, et al. Investigation of mitochondrial sequence variants associated with aminoglycoside-induced ototoxicity in South African TB patients on aminoglycosides. *Biochem Biophys Res Commun*. 2010;393(4):751-6
 24. Prasad HKC, Bhojwani KM, Shenoy V, Prasad SC. HIV manifestations in otolaryngology. *Am J Otolaryngol*. 2006; 27(3):179-85
 25. Stearn N, Swanepoel DW. Sensory and neural auditory disorders associated with HIV/AIDS. In: Swanepoel DW, Louw B, eds. *HIV/AIDS related communication, hearing and swallowing disorders*. San Diego, Oxford, Brisbane: Plural Publishing; 2010:243-88
 26. Van der Westhuizen Y, Swanepoel D, Heinze B, Hofmeyr LM (2013). Auditory and otological manifestations in adults with HIV/AIDS. *International Journal of Audiology*. 2013; 52:37-43
 27. Desai SD. Seropositivity, adenoid hypertrophy, and secretory otitis media in adults - A recognized clinical entity. *Otolaryngol - Head Neck Surg*. 1992;107(6 II):755-7
 28. Marchisio P, Principi N, Sorella S, Sala E, Tornaghi R. Etiology of acute otitis media in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 1996;15(1):58-61
 29. Moazzez AH, Alvi A. Head and neck manifestations of AIDS in adults. *Am Fam Physician*. 1998;57(8):1813-22
 30. Rinaldo A, Brandwein MS, Devaney KO, Ferlito A. AIDS-related otological lesions. *Acta Otolaryngol*. 2003;123(6): 672-4
 31. Gherman CR, Ward RR, Bassis ML. Pneumocystis carinii otitis media and mastoiditis as the initial manifestation of the acquired immunodeficiency syndrome. *Am J Med*. 1988;85(2):250-2
 32. Miziara ID, Weber R, Filho BCA, Neto CDP. Otitis media in Brazilian human immunodeficiency virus infected children undergoing antiretroviral therapy. *J Laryngol Otol*. 2007;121(11):1048-54.
 33. Weinroth SE, Schessel D, Tuazon CU. Malignant otitis externa in AIDS patients: Case report and review of the literature. *Ear, Nose Throat J*. 1994; 73(10): 772+774+776-778.
 34. Clark MPA, Pretorius PM, Byren I, Milford CA. Central or atypical skull base osteomyelitis: Diagnosis and treatment. *Skull Base*. 2009;19(4):247-54
 35. Adams A, Offiah C. Central Skull Base osteomyelitis as a complication of necrotising otitis externa: Imaging findings, complications, and challenges of diagnosis. *Clinical Radiol*. 2012; 67:e7-e16
 36. Muñoz A, Martínez-Chamorro E. Radiology in focus. Necrotizing

- external otitis caused by aspergillus fumigatus: Computed tomography and high resolution magnetic resonance imaging in an AIDS patient. *J Laryngol Otol.* 1998;112(1):98-102
37. Hoffmann C, Rockstroh JK, Kamps BS, eds. *HIV Med.* 2007. 15th ed. Paris, Cagliari, Wuppertal: Flying Publishers; 2007
 38. Shibuyama S, Gevorkyan A, Yoo U, Tim S, Dzhangiryan K, Scott JD. Understanding and avoiding antiretroviral adverse events. *Curr Pharm Des.* 2006;12(9):1075-90
 39. Williams B, Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity may be associated with protease inhibitor therapy [4] (multiple letters). *Clin Infect Dis.* 2001;33(12):2100-2
 40. Schouten JT, Lockhart DW, Rees TS, Collier AC, Marra CM. A prospective study of hearing changes after beginning zidovudine or didanosine in HIV-1 treatment-naïve people. *BMC Infectious Diseases.* 2006;6
 41. Rey D, L'Héritier A, Lang JM. Severe ototoxicity in a health care worker who received postexposure prophylaxis with stavudine, lamivudine, and nevirapine after occupational exposure to HIV [2]. *Clin Infect Dis.* 2002;34(3):418-9
 42. Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: A report of 3 possible cases and review of the literature. *Clin Infect Dis.* 2001;32(11):1623-7
 43. Christensen LA, Morehouse CR, Powell TW, Alchediak T, Silio M. Antiviral therapy in a child with pediatric human immunodeficiency virus (HIV). Case study of audiologic findings. *J Am Acad Audiol.* 1998;9(4):292-8
 44. Marra CM, Wechkin HA, Longstreth Jr. WT, Rees TS, Syapin CL, Gates GA. Hearing loss and antiretroviral therapy in patients infected with HIV-1. *Arch Neurol.* 1997;54(4):407-10
 45. Monte S, Fenwick JD, Monteiro EF. Irreversible ototoxicity associated with zalcitabine. *Int J STD and AIDS.* 1997;8(3): 201-2
 46. Guan M. Mitochondrial DNA mutations associated with aminoglycoside ototoxicity. *J Otol.* 2006;1(2):65-75
 47. Antman K, Chang Y. Kaposi's sarcoma. *N Engl J Med.* 2000;342(14): 1027-38
 48. Michaels L, Soucek S, Liang J. The ear in the acquired immunodeficiency syndrome: I. temporal bone histopathologic study. *Am J Otol.* 1994;15(4):515-22
 49. Fish BM, Huda R, Dundas SAC, Lesser THJ. Clinical records: B-cell lymphoma of the external auditory meatus. *J Laryngol Otol.* 2002;116(1): 39-41
 50. Bicanic T, Harrison TS. Cryptococcal meningitis. *Br Med Bull.* 2004;72:99-118
 51. Celis-Aguilar E, Macías-Valle L, Coutinho-De Toledo H. Auditory neuropathy secondary to cryptococcal central nervous system infection in 2 immuno-compromised patients. *Otolaryngol - Head Neck Surg (United States).* 2012;147(3): 597-8
 52. Cardon G, Campbell J, Sharma A. Plasticity in the developing auditory cortex: evidence from children with sensorineural hearing loss and auditory neuropathy spectrum disorder. *J. Am Acad Audiol.* 2012 Jun;23(6):396-411
 53. McKenzie BJ, Looock JW. Ootosyphilis and HIV: Therapeutic dilemma and out-come of treatment. *BMJ Case Rep.* 2009
 54. Kraus N, Bradlow AR, Cheatham MA, Cunningham J, King CD, Koch DB et.al. Consequences of neural asynchrony: a case of auditory

- neuropathy. *J Assoc Res Otolaryngol.* 2000;1(1):33-45
55. Matas CG, Leite RA, Magliaro FCL, Gonçalves IC. Audiological and electro-physiological evaluation of children with acquired immuno-deficiency syndrome (AIDS). *Braz J Infect Dis.* 2006;10(4):264-8
 56. Matas CG, Sansone AP, Iorio MCM, Succi RCM. Audiological evaluation in children born to HIV positive mothers. *Rev Bras Otorinolaringol.* 2000;66(4): 317-24
 57. Reyes-Contreras L, et al. Brainstem auditory evoked response in HIV-infected patients with and without AIDS. *Arch Med Res.* 2002;33(1):25-8
 58. Chandrasekhar SS, Siverls V, Chandra Sekhar HK. Histopathologic and ultra-structural changes in the temporal bones of HIV-infected human adults. *Am J Otol.* 1992;13(3):207-14
 59. Pappas Jr. DG, et al. Ultrastructural findings in the vestibular end-organs of AIDS cases. *Am J Otol.* 1995;16(2): 140-5
 60. Palmay L, Walker SA, Walker SE, Simor AE Symptom reporting compared with audiometry for the detection of cochleotoxicity in patients on long-term aminoglycoside therapy. *Ann Pharmacother.* 2011;45(5):590-5
 61. Ramma LD, Ibekwe TS. Efficacy of utilising patient self-report of auditory complaints to monitor aminoglycoside ototoxicity. *Int J Tuberc Lung Disease.* 2012;16(2):283
 62. Konrad-Martin D, James KE, Gordon JS, et al. Evaluation of audiometric thres-hold shift criteria for ototoxicity monitoring. *J Am Acad Audiol.* 2010; 21(5):301-4

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