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Original Article

Types and Severity of Hearing Loss among Patients with Tuberculosis receiving Anti-Tuberculosis Treatment in Nigeria: A Single Center Study.

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Abstract

Background: Tuberculosis (TB) is a contagious and potentially fatal infectious disease with significant global morbidity and mortality. Both the disease and some anti-TB medications have been linked to hearing loss. The study objective is to determine the Types and severity of hearing loss among patients receiving anti-tuberculosis drugs at NAUTH, Nnewi, Nigeria.

Methodology: This prospective cohort study, conducted over one year at Nnamdi Azikiwe University Teaching Hospital (NAUTH) among adults enrolled in TB patients 18-60years and healthy controls using convenient sampling. GeneXpert/AFB testing was used for TB diagnosis, and pure tone audiometry was done for all participants, with follow-up assessments at 2 and 3 months for TB patients. Statistical analysis was performed using STATA version 16.0, with significance set at $p < 0.05$.

Results: A total of 196 participants, which included 98 Tb cases (80 drug sensitive TB(DSTB),18multi drug resistant TB(MDRTB), and 98 controls, with a male:female ratio of1.13:1, mean age 33.82 ± 12.22 years, with an age range of 18-60 years, were recruited. After 90 days of anti-TB treatment, 4.1% of participants developed sensorineural hearing loss, with 3 cases classified as moderate seen among the MDRTB group and 1 case as mild among the DSTB group. There was no significant difference in mean pure tone hearing thresholds between the treatment and control groups in both ears ($p = 0.395$).

Conclusion: Incidence of Bilateral demonstrable hearing loss after anti-TB drugs, which is common among MDRTB, has dropped with the introduction of all oral shorter regimens.

Keywords: Tuberculosis, Anti-tuberculosis drugs, Hearing loss, Types, Severity, Nigeria.

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Quick Response Code:

Introduction

Tuberculosis (TB), a potentially fatal and contagious infectious disease caused by Mycobacterium tuberculosis, remains a significant public health challenge globally, particularly in sub-Saharan Africa.[1,2] TB can affect various body parts, including the ear,manifesting as tuberculous otitis media, leading to hearing loss[3-5]

Tuberculous otitis media can cause conductive hearing loss through granulomatous lesions in the middle ear, ossicular chain destruction, and multiple tympanic membrane perforations.[6–8]Additionally, certain anti-TB drugs, such as aminoglycosides, can induce sensorineural hearing loss by selectively destroying hair cells and spiral ganglion cells in the inner ear[9]

This can significantly impact an individual's quality of life, social interactions, economic productivity, and increasethe cost of healthcare.[10,11]

With the introduction of the "all oral shorter treatment" regimen for multidrug-resistant TB by the World Health Organization (WHO) in 2016, there isa paucity of data and a knowledge gap on the effect of the drugs on hearing health in comparison with the previously used injectables, hence thejustification for this study.[12,13]

This study aims to determine the types and severity of hearing loss among TB patients receiving first-line anti-TB medications for drug-sensitive TB and all oral shorter regimens for MDRTB after 3 months of initiation of treatment.

Methods

Study design: This prospective cohort study was conducted over a one-year period, from October 1, 2022, to September 30, 2023, at the Nnamdi Azikiwe University Teaching Hospital (NAUTH) in Nnewi, Nigeria, and its Neni outpost. The study was carried out among patients attending the TB clinic, ENT clinic, and/or those admitted into the ward.

Participants: The study included tuberculosis patients aged 18 to 60 years old, who were attending the DOTS Clinic, ENT Clinic, or admitted to the wards of NAUTH during the study period. The control group consisted of age- and sex-matched individuals without TB, recruited from hospital staff, patient relatives, and medical students.

Inclusion Criteria: consented and confirmed tuberculosis patients aged between 18 and 60 years.

Exclusion Criteria: Individuals with pre-existing hearing loss, tympanic membrane perforation, or those outside the 18-60 age range were excluded. Patients with comorbidities like diabetes, HIV, hypertension, or those taking ototoxic medications other than anti-tuberculosis drugs were also excluded.

Sample size calculation: The minimum sample size was determined using Fischer's formula,[14]

$N = Z^2P.q / d^2$

Where

N = Minimum sample size,

Z =Normal standard deviation, which corresponds to the 95% confidence interval (i.e., z=1.96)

P = Estimated prevalence is 22.9%.[13]

q = 1 - P,

d = Degree of accuracy, which for this study is 10%

$N = (1.96)^2 \times 0.23 \times 0.77 / 0.01 = 68$

Assuming an attrition rate of 10%

Then 10% of 68 = 6.8

Hence, N is 68+6.8 = 74.8

Therefore, the Minimum sample size was approximately. 75 per study group.

However, 98 participants per study group were recruited into the study.

Study protocol: Sociodemographicdata and clinical information were obtained using aproforma.Physical examinations and ancillary investigations were also conducted. GeneXpert tests were performed using sputum samples to detect Mycobacterium tuberculosis DNA and mutations in the rpoB gene.[15-17]Acid-Fast Bacilli (AFB) smear microscopy was conducted according to International Union Against Tuberculosis and Lung Diseases (IUATLD) guidelines, with two sputum samples (spot and early morning) to confirm TBdiagnosis[18,19].

Audiological assessment: All participants underwent a comprehensive audiological evaluation at baseline (before Anti-TB drugs), 60 days, and after 90 days. The audiological examination was stopped at 90 days so as to compare with previous studies.This included:

- **Otoscopy:** Each participant underwent otoscopic examination using a handheld otoscope to assess the pinna, external auditory canal, and tympanic membrane, with earwax impaction removed as needed.
- **Tuning Fork Tests:** It was conducted using a 512 Hz fork. The Weber Test identified the type of hearing loss by placing the fork on the forehead, while the Rinne Test compared air conduction and bone conduction by placing the fork near the ear canal and on the mastoid process[20]
- **Pure-Tone Audiometry:** Diagnostic pure-tone audiometry was conducted in a soundproof booth using a calibrated audiometer, measuring hearing thresholds for air and bone conduction at various frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz). Hearing thresholds were determined using the Hughson-Westlake method, and results were interpreted based on air and bone conduction thresholds.[21-25]Ototoxicity was assessed using ASHA's 1994 criteria, which include specific threshold shifts[26].Hearing loss was categorized as normal, conductive, sensorineural, or mixed, with severity classified according to World Health Organization standards[22,27]
- **Follow-up:**TB patients underwent pure tone audiometry testing at three time points: before starting anti-TB treatment (baseline), and at 60 and 90 days after treatment initiation.
- Control participants, on the other hand, had pure tone audiometry testing done only once, at recruitment.

Data Analysis: Data analysis was performed using STATA version 16.0.[28].Quantitative variables were summarized using means and standard deviations, while qualitative variables were described using frequencies, percentages, and proportions.

Chi-square test used to testfor association between categorical variables, particularly the relationship between hearing loss and TB status. student's t-test for comparing continuous and categorical variables, and ANOVA for comparing three or more categorical variables. A p-value of <0.05 was considered statistically significant.

Ethics: The study received approval from the Health Research and Ethics Committee (HREC) of NAUTH (approval number: NAUTH/CS/66/VOL.15/VER.3/089/2022/040). Participants were informed

about the study's objectives, assured of confidentiality, and participation was voluntary and cost-free. Written informed consent was obtained from all participants.[29]

Conflict of interest: The Study was self-sponsored, and we have no conflict of interest to declare.

Results

Demographic Profile Of The Patient

196 participants were recruited, comprising 98 treatment groups(80 DSTB,18MDRTB) and 98 control (non-TB) groups.The mean age of the participants was 33.82 ± 12.22 years, with an age range of 18-60 years, and the modal age group was 18-29 years. Both the treatment and control groups had similar demographic characteristics, with 46 (46.9%) females and 52 (53.1%) males in each group. There were no significant differences in age or sex between the two groups ($p > 0.05$). The demographic characteristics are summarized in Table 1.

Table 1: Age and Sex distribution of the treatment and control groups for all participants.

Variable	*Group*		*t/X^2-Value*	*p-value*
	Treatment (n=98)	*Control (n=98)*		
Age (mean ±SD)	*33.82 ± 12.22*	*33.82±12.22*	*0.000*	*1.000*
Age category (years)				
18-29 years	*44 (44.9)*	*44(44.9)*		
30-39 years	*19 (19.4)*	*19(19.4)*	*0.000*	*1.000*
40-49 years	*21 (21.4)*	*21(21,4)*		
50-60 years	*12 (12.3)*	*12(12.3)*		
SEX				
Female	*46 (46.9)*	*46(46.9)*	*0.000*	*1.000*
Male	***52 (53.1)***	***52(53.1)***		

t: Independent t test, X^2: Chi-square test, P: P-value, not statistically significant

The educational status of participants differed significantly between the treatment and control groups (p=0.001). The majority of both groups had secondary education (SSCE) as their highest qualification, with 47 (47.9%) in the treatment group and 37 (37.8%) in the control group. Notably, more controls had diplomas/degrees, 34 (34.7%), compared to the treatment group, 11 (11.2%).

The occupational distribution between the treatment and control groups showed significant differences (p=0.009). The treatment group comprised predominantly self-employed traders, 41 (41.8%), while the

control group had more civil servants, 54 (55.1%). The treatment group also had a higher proportion of artisans and unemployed individuals compared to the control group.

The marital status distribution was similar between the treatment and control groups (p=0.531). In both groups, the majority were either single or married, with 48 (48.9%) single and 48 (48.9%) married in the treatment group, and 52 (53.1%) single and 46 (46.9%) married in the control group. Few participants in the treatment group were separated or widowed. This is shown in Table 2.

Table 2: Demographic profile of the study group

Educational status	**Treatment group**	
Tertiary	11 (11.2)	34 (34.7)
Secondary	47 (47.9)	37 (37.8)
Primary	32 (32.7)	21 (21.4)
None	8 (8.2)	6 (6.1)
Occupation/Profession	**Treatment group**	**Control group**
Artisan	9 (9.2)	3 (3.1)
Business/trader	41 (41.8)	38 (38.8)
Civil servants	37 (37.8)	55 (56.1)
Students	11 (11.2)	2 (2.0)
Marital Status	**Treatment group**	**Control group**
Married	**48 (48.9)**	46 (46.9)
Separated	1 (1.0)	0 (0.0)
Single	48 (48.9)	**52 (53.1)**

X^2: Chi-square test, P: P-value, not statistically significant

Treatment History and Types among TB Patients

In the treatment group, 80 (81.6%) participants were initiated on the drug regimen for DSTB, while 18 (18.4%) were classified as multi-drug resistant TB (MDR-TB) whoreceived the All Oral Shorter Treatment Regimen (AOSTR).detailed in Table 3.

Table 3**: TB Treatment History and Types**

Visit days Monitored	**Sub-groups of Participants by Anti-Tb Medication Types/Diagnosis**		**X^2 Value**	**P Value**
	DSTB (n=80)	MDRTB (n=18)		
Day 0 (On Recruitment)	0 (Commenced Intensive Phase)	18 (On MDRTB Regimen)	58.231	<0.0001
Day 60	80 (Intensive Phase)	18 (On MDRTB Regimen)		
Day 90	80 (Continuation Phase)	18 (On MDRTB Regimen)		

Keys:

DOTS =Directly Observed Treatment Short-Course.

AOSTR = All Oral Shorter Treatment Regimen

Intensive Phase = The initial stage aimed to rapidly reduce the bacterial load.

Continuation Phase = The 2nd stage of TB treatment following the intensive phase.

Type of Hearing Loss Among Study Participants in The Treatment Group: The study revealed that 4 participants (4.1%) developed bilateral sensorineural hearing loss (SNHL) by Day 90, with 3 cases among those with MDRTB and 1 case among those with DSTB, with no statistically significant differences in hearing threshold/loss types among study participants, as shown in Table 4.

Table 4: Type of hearing threshold/loss among study participants.

Type of hearing threshold/loss	**Baseline (1st visit)**	**60 days (2nd visit)**	**90 days (3rd visit)**	**control**	**X^2-value**	**P-value**
Normal hearing	98	98	94	98	12.123	0.207
SNHL	0	0	4	0		
CHL	0	0	0	0		
MHL	0	0	0	0		

X^2: Chi-square test, P: P-value, statistically significant.

Severity/Degree of hearing loss in each ear in the treatment and control groups: 94 (95.9%) participants had normal hearing bilaterally, 3 (3.1%) had moderate bilateral hearing loss, and 1 (1%) had

mild bilateral hearing loss.All 98 (100.0%) participants in the control group had normal hearing bilaterally. The difference in the degree of hearing threshold/loss between the treatment and control groups was not statistically significant, with a p-value of 0.395, as shown in Table 5.

Table 5: Severity/Degree of hearing threshold/loss among study participants.

Degree/Severity of hearing loss	Mean PTA	Treatment group (n, %)	Control group (n, %)	Mean PTA	X^2-Value	P-Value
		Better ear	**Better ear**			
Normal	21.0	94 (95.9)	98 (100.0)	21.8	4.084	0.395
Mild	35.0	1 (1.0)	0 (0.0)			
Moderate	51.6	3 (3.1)	0 (0.0)			
Severe		0 (0.0)	0 (0.0)			
Profound		0 (0.0)	0 (0.0)			
Total		**98 (100.0)**	**98 (100.0)**			

X^2: Chi-square test, P: P-value, not statistically significant

Average pure tone hearing thresholds of participants:

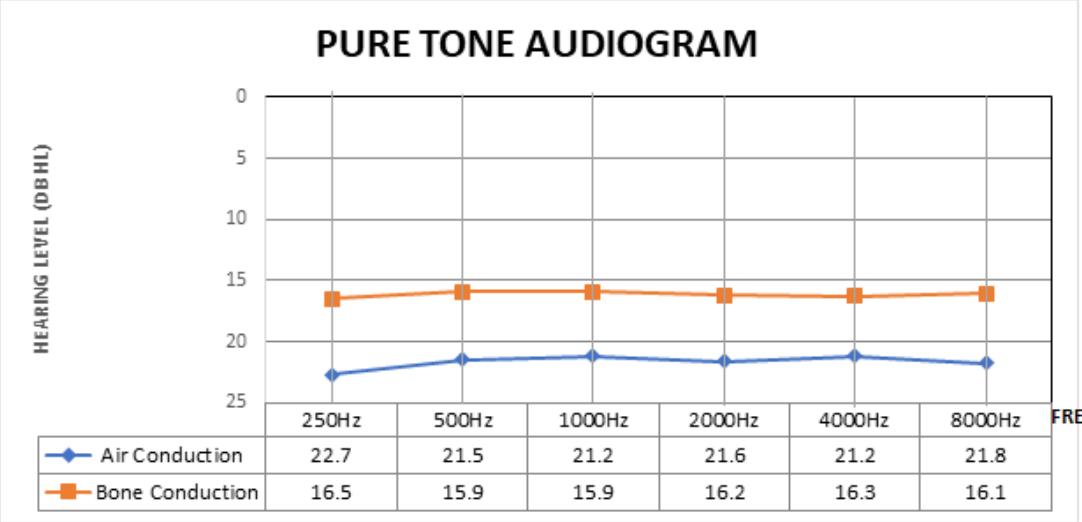


Fig 1: Average Pure Tone Audiogram of Controls

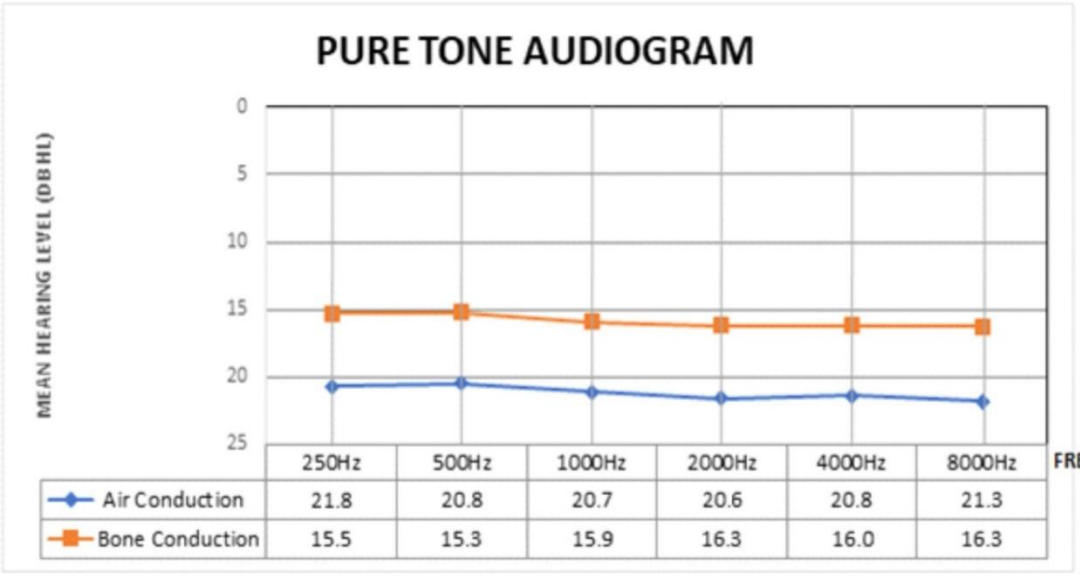


Fig 2: Average Pure Tone Audiogram of treatment group at Day 1 (1st visit).

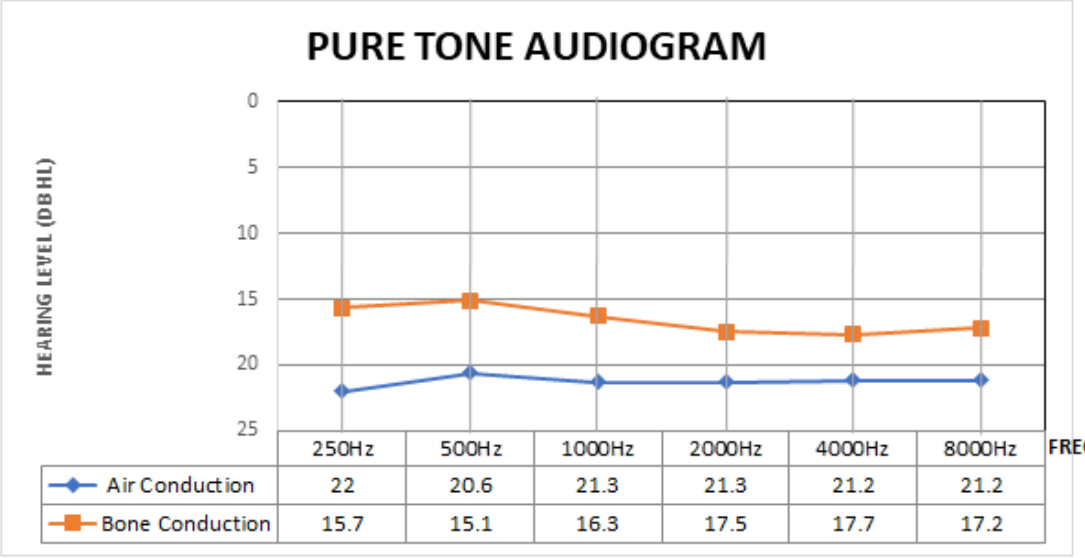
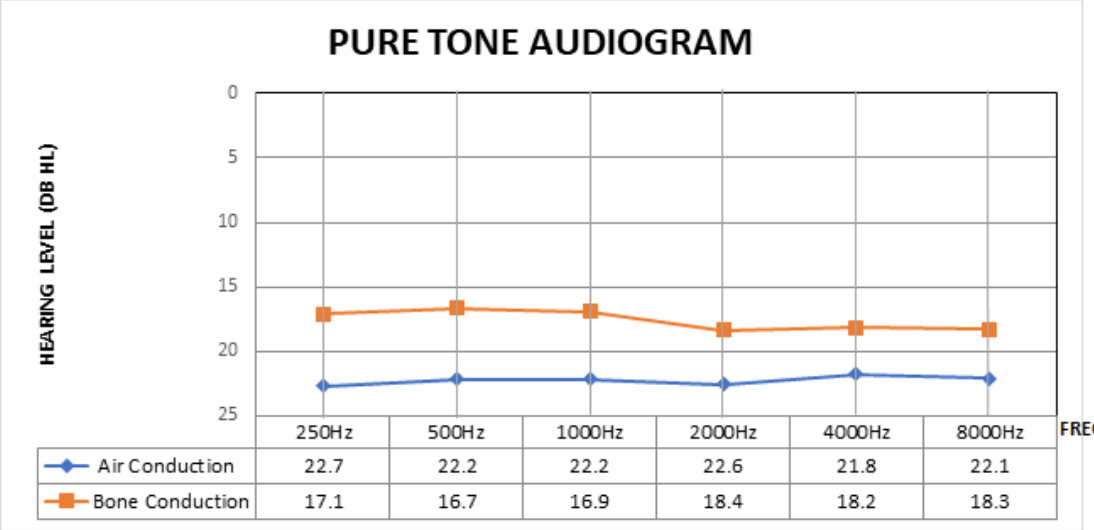


Fig 3: Average Pure Tone Audiogram at 60days of intensive phase



	250Hz	500Hz	1000Hz	2000Hz	4000Hz	8000Hz
Air Conduction	22.7	22.2	22.2	22.6	21.8	22.1
Bone Conduction	17.1	16.7	16.9	18.4	18.2	18.3

Fig 4: Average Pure Tone **Audiogram at 90days of TB therapy**

Discussion

The study participants had a mean age of 33.82 ± 12.22 years, with a slight male preponderance (46% female, 52% male), consistent with previous studies showing higher tuberculosis prevalence among males.[30,31]The male-to-female disparity may be attributed to increased exposure to risk factors like smoking among males.[33] Most participants in the treatment group had low educational attainment, similar to previous studies showing that lower socio-economic status increases tuberculosis risk.[32]

The study found that the few cases of hearing threshold reductions seen more with MDRTB patients, were all bilateral, sensorineural, and primarily affected the high frequencies, consistent with previous research by Nizamuddin et al., Sagwa et al., Sharma et al., and Tiwari et al.[33-36]These studies have established that ototoxic hearing loss typically presents bilaterally and is most noticeable in the high frequencies unlike hearing loss caused by the disease which may be unilateral although the drugs for the sited studies were the injectables.The cases of hearing threshold reduction in this study were noticed after the third month, supporting findings from other research that hearing losses are noticed with prolonged drug use. [25,37-39]

The hearing loss observed in the treatment group at the 90-day visit predominantly affected the high frequencies, with minimal impact on lower frequencies. This finding is similar with that of Sha et al., Huth et al., Karasawa &Steyger, and Tabuchi et al., which suggests that the basal end of the cochlea, responsible for high-frequency sound processing, is more susceptible to damage than the apical end, which processes low frequencies.[25,38-40].This vulnerability explains why high-frequency hearing losses often precede low-frequency losses in cases of drug-induced ototoxicity.

Regarding the severity of hearing loss, the study found that 94 (95.9%) of the treatment group had normal bilateral hearing, 1 (1%) had mild bilateral hearing loss, and 3 (3.1%) had moderate bilateral hearing loss, although the findings were not statistically significant when compared with the whole participants,it is worthy to note that the hearing loss was more in participants treated for MDRTB than in DSTB at the ratio of 3:1. The isolated cases of hearing loss among the DSTB may be attributed to the systemic effects of tuberculosis on the ear, particularly the inner ear hair cells. Additionally, the co-administration of anti-TB medications with other potentially ototoxic drugs, though not established in this studymay contribute to the observed hearing loss, as reported in previous studies.[41-45]

This study's results are consistent with Khoza-Shengase and Mahamadou's research, suggesting that the new all-oral regimen, non-injectable anti-TB regimen may offer a safer ototoxic profile, with reduced risk of hearing loss.[46]However, this result contradicts findings from other studies, such as those by Duggal and Sarkar, Sagwa et al., Ibekwe & Nwosu, and Sogebi et al., which reported elevated hearing thresholds (i.e increased hearing loss) in patients after anti-TB treatment the sample size may have contributed to this disparity.[26,33,47,48]

There is therefore need for more studies on hearing loss and safety of the current all oral drugs used in MDRTB**.**

Study limitations: Challenge in controlling participants' indiscriminate use of self-medication for other diseases, which may impact negatively on their hearing threshold.

Conclusion

This study investigated the types and severity of hearing loss among tuberculosis patients receiving anti-tuberculosis drugsboth the DSTB and MDRTB patients were recruited.Only 4participants developed bilateral sensorineural hearing loss after 90 days of treatment,Hearing loss was more in MDRTB patients although the small sample size is a big limitation to the actual comparison hence the need for further studies on the ototoxic effect of new all oral regimen for MDRTB.

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