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Determinants of the Sensorineural Hearing Loss in Patients with Multidrug-Resistant Tuberculosis in Kinshasa (Democratic Republic of the Congo): A Prospective Cohort Study

Mireille Avilaw Mpwate[1], Eddy Mampuya Mbambu[1], Gabriel Mabuaka Lema[1], Christian Nzanza Matanda[1], Dominique Mayuku Mupepe[2], Michel Kayomo Kaswa[3], Murielle Luengiladio Aloni[3], Nicole Muzutie Anshambi[4], Fabrice Mankangu Matuta[4], Luc Losenga Lukasu[5], Serge Katya Mpwate[6], Pierre Zalagile Akilimali[7], Innocent Murhula Kashongwe[8], Zacharie Munogolo Kashongwe[8], Jean Marie Ntumba Kayembe[8], Richard Nzanza Matanda[1*]

[1]Department of Otorhinolaryngology, University Hospital of Kinshasa, Kinshasa 11, University of Kinshasa, Kinshasa, Democratic Republic of The Congo
[2]Division of Cardiology, Department of Internal Medicine, University Hospital of Kinshasa, Kinshasa 11, University of Kinshasa, Kinshasa, Democratic Republic of The Congo
[3]National Tuberculosis Control Program in Democratic Republic of The Congo, Kinshasa, Democratic Republic of The Congo
[4]Provincial Coordination for The Fight against Tuberculosis, Kinshasa, Democratic Republic of The Congo
[5]Multidrug-Resistant Tuberculosis Unit, "Centre d'Excellence Damien", Damien Foundation, Kinshasa, Democratic Republic of The Congo
[6]Department of Anatomy-Pathology, University Hospital of Kinshasa, Kinshasa 11, University of Kinshasa, Kinshasa, Democratic Republic of The Congo
[7]Kinshasa School of Public Health, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of The Congo
[8]Pneumology Unit, Department of Internal Medicine, University Hospital of Kinshasa, Kinshasa 11, University of Kinshasa, Kinshasa, Democratic Republic of The Congo
Email: *rmatanda14@gmail.com

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Abstract

Background: The onset of the hearing loss is a major challenge during the treatment of multidrug-resistant tuberculosis (MDR-TB). Aminoglycoside-based regimens, to a lesser extent based on bedaquiline, induce ototoxic sensorineural hearing loss. Research on risk factors is essential to enable high-risk individuals to benefit from preventive measures in settings with limited resources. **Objective:** This study aimed to assess the determinants of the hearing loss in patients with MDR-TB. **Methods:** This prospective multicenter cohort study included 337 patients with MDR-TB. It was performed in Kinshasa (Democratic Republic of the Congo) between January 2020 and January 2021. Sociodemographic, clinical, biological, therapeutic, and audiometric data were exported and analyzed using Stata 17 and MedCalc. The fixed-effect li-

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near regression panel model was used to assess the degree of the hearing loss over time according to the following covariates: therapeutic regimen (aminoglycosides, bedaquiline, or alternate), stage of chronic kidney disease (CKD), age at inclusion, body mass index, serum albumin level, HIV status, alcohol intake, hypertension, and hemoglobin level. The Hausman test was used to select between fixed- and random-effect estimators. The threshold for statistical significance was set at $p < 0.05$. **Result:** A total of 236 patients (70%) received an aminoglycoside-based regimen, 61 (18%) received a bedaquiline-based regimen, and 40 (12%) received aminoglycosides relayed by bedaquiline. The frequency of the hearing loss increased from 62% to 96.3% within six months for all therapeutic regimens. The Hearing loss worsened, with moderate (72.4%) and profound (16%) deafness being predominant. An Exposure to the treatment for more than one month (β coeff: 27.695, Se: 0.793, $p < 0.001$), AG-based regimen, age ≥ 40 years (β coeff: 6.102, Se: 1.779, $p < 0.001$), hypoalbuminemia (β coeff: 5.610, Se: 1.682, $p = 0.001$), and an eGFR < 60 mL/min/1.73m^2 (β coeff: 6.730, Se: 2.70, $p = 0.013$) were the independent risk factors associated with the hearing loss in patients with MDR-TB. **Conclusions:** The Hearing loss was more prevalent and worsened during the treatment of the patients with MDR-TB. An Exposure for more than one month, AG-based regimens, advanced age, hypoalbuminemia, and CKD have emerged as the main determinants of the worsening of the hearing loss.

Keywords

Multidrug-Resistant Tuberculosis, Determinants, Hearing Loss, DRC

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a major public health concern in developing countries such as the Democratic Republic of the Congo (DRC) [1] [2] [3]. Aminoglycoside (AG)-based regimens were used for a long time in the management of MDR-TB before being replaced with bedaquiline (BDQ) because of its ototoxic effects [2] [3] [4] [5]. However, a study conducted by our team revealed that the sensorineural hearing loss was frequent and worsened during the treatment with both therapeutic regimens, although it was more marked with the AG-based regimen. The mean degree of the hearing loss was significantly greater in the AG group [AG (60.5 dB) vs BDQ (44 dB); $p < 0.001$]. The double difference was also significant, with a greater increase in the hearing loss in the AG group (diff-in-diff 18.3; $p < 0.001$) [6]. This observation suggested that other risk factors could contribute to the occurrence of the hearing impairment in patients with MDR-TB.

In low- and middle-income countries with limited resources, the World Health Organization has requested public health measures and clinical interventions implemented across the life course, a systematic screening for the detection of

the hearing loss, and the rational use of medicines to prevent ototoxic deafness [7] [8]. This strategy requires the identification of high-risk individuals and the major risk factors [7] [8]. Therefore, we aimed to assess the determinants of the sensorineural hearing loss during the treatment of the patients with MDR-TB in Kinshasa, DRC.

2. Methods

2.1. Study Design and Participant Sampling

This prospective multicenter cohort study was conducted between January 2020 and January 2021 at 42 centers for the screening and the treatment of MDR-TB in Kinshasa (DRC). The study population consisted of the patients with MDR-TB receiving AG and/or the BDQ-based regimens "under directly observed treatment" (DOT). Patients with MDR-TB (diagnosed by molecular methods such as Xpert MTB/RIFR or Genotype MTBR-plusR), aged ≥ 14 years with a normal otoscopy examination, and who signed an informed consent form were enrolled in this study. Pregnant women were excluded from this study.

2.2. Data Collection

Sociodemographic (age, sex, education, and marital status) and clinical (hypoacusis, tinnitus, dizziness, hypertension, diabetes, tobacco and alcohol use, HIV status, and MDR-TB therapeutic regimen) data were obtained through interviews and a review of the patient files. Anthropometric variables (height, weight, body mass index [BMI]) and the blood pressure were measured during the physical examination. Laboratory variables (serum creatinine, serum albumin, glucose, and hemoglobin) were obtained from the patient registers.

The hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive drugs [9]. Diabetes mellitus was defined as a fasting serum glucose ≥ 126 mg/dL or the use of antidiabetic medication [10]. Underweight was defined as BMI < 18.5 kg/m^2 [11]. An excessive alcohol use was defined as more than two standards drink for men and one for women [12]. Smoking was retained for anyone who smoked at least one cigarette/day for > 5 years or weaned for < 5 years [13]. Anemia was defined as the hemoglobin (Hb) level < 12.0 g/dL in women and < 13.0 g/dL in men [14]. Hypoalbuminemia was defined as a serum albumin level < 35 g/L [15]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73m^2 [16].

The Liminal-tone audiometry was used to determine the degree of the hearing loss. This was performed using a shoebox brand audiometer. It is an audiometry software incorporated in an iPad, which does not require a soundproof cabin. The examiner sends sounds of different frequencies (from 250 Hz to 8000 Hz) and intensities (from fies −5 dB to 90 dB). At the end of the examination, the automatic tracing and the average values indicating the degree of the hearing

appears on the electronic tablet. The follow up considered audiometric data collected at 1 (M1), 3 (M3), 6 months, and more (≥M6). Deafness was defined as hearing loss ≥ 21 dB (1). The degree of the hearing loss was classified according to the Pujol and Dubreuil scale [17]: mild (21 - 40 dB), moderate (41 - 60 dB), severe (61 - 80 dB), or profound (≥81 dB).

2.3. Statistical Analysis

The data were encoded using Microsoft Excel 2013, constituted in the database after verification of its consistency, and exported and analyzed using Stata 17 and MedCalc. Descriptive statistical data are presented in tables and figures with the percentages for the qualitative variables. Quantitative variables are expressed as mean ± standard deviation (SD) when the distribution was normal. Pearson's Chi-square or Fisher's exact tests, as appropriate, were used to compare proportions. The fixed-effect linear regression panel model was used to assess the degree of the hearing loss over time according to the following covariates: therapeutic regimen (AGs, BDQ, or alternate), stage of CKD, age, BMI, serum albumin level, HIV status, alcohol intake, hypertension, and hemoglobin level. The Hausman test was used to select between fixed- and random-effect estimators. The threshold for statistical significance was set at $p < 0.05$.

2.4. Ethics Approval

The study protocol was approved by the Ethics Committee of the Kinshasa School of Public Health. All rules of confidentiality complied with the principles of the Declaration of Helsinki. All participants included in the study or their guardians (for participants aged < 18 years) provided written informed consent.

3. Results

3.1. General Characteristics of the Study Participants

This study enrolled 397 patients with MDR-TB (**Figure 1**). Among these, 60 were excluded because they were absent during the interviews and/or the audiometry testing. Thus, 337 participants were selected and 674 ears were examined, of which 592 were retained for the final analyzes. Eighty-two ears (12.2%) were excluded due to a pathological eardrum.

As shown in **Table 1**, the mean patient age was 35.1 ± 14.2 years. More than six of the ten participants were male (63.2%), and the same proportion were single (62.6%). Almost half of the patients were aged between 20 and 34 years (44.2%). Less than half had completed a bachelor's degree (42.1%).

3.2. Clinical and Paraclinical Characteristics of Participants

Table 2 indicates that three of the ten patients (32.6%) complained of tinnitus. Just over a quarter of the participants used tobacco products (27.3%), 38.6% consumed alcohol, and 8% had TB-HIV coinfection. More than six of the ten patients were underweight. Most patients were anemic (84.8%), and almost half

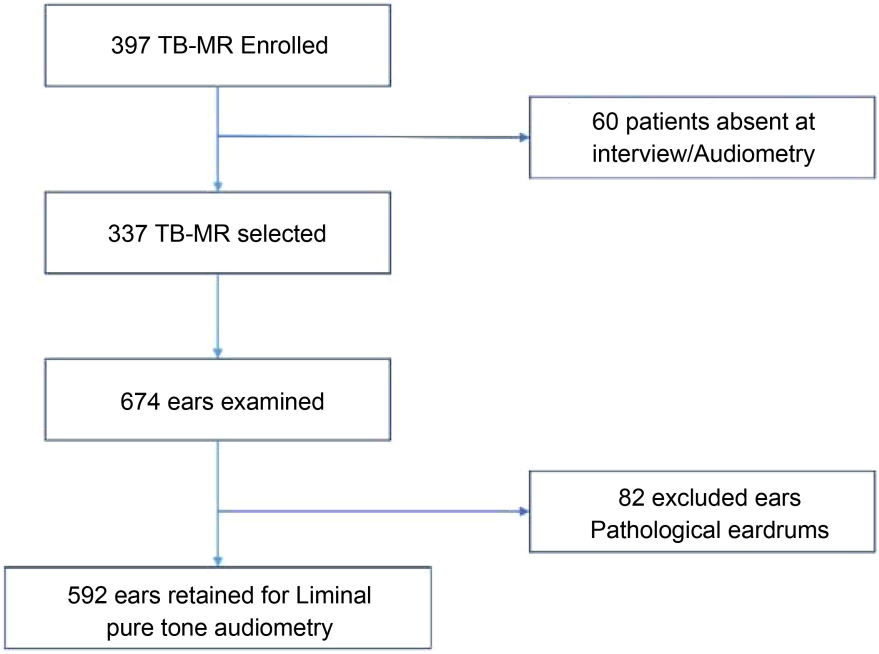

Figure 1. Flow chart of patients with MDR-TB.

Table 1. Sociodemographic characteristics of the study participants.

	n	%
Age (mean ± SD)	35.1 ± 14.2	
Age group		
<20 years	39	11.6
20 - 34 years	149	44.2
35 - 49 years	102	30.3
≥50 years	47	13.9
Sex		
Male	213	63.2
Female	124	36.8
Marital status		
Single	211	62.6
Married	98	29.1
Widowed/Divorced	28	8.3
Education		
None/Primary	19	5.6
Unfinished high school	176	52.2
Bachelor degree/University	142	42.1

Table 2. Clinical and paraclinical data.

	n	%
Symptoms		
Tinnitus	110	32.6
Hypoacusis	81	24
Dizziness	44	13.1
Medical history		
Alcohol intake	130	38.6
smoking	92	27.3
HIV/AIDS	27	8
Hypertension	7	2
Underweight	219	65
Paraclinic		
Anemia	286	84.8
Hypoalbuminemia	160	47.4
Chronic kidney disease	79	23.4

(47.4%) had hypoalbuminemia.

Regarding the therapeutic regimen, 236 patients (70%) received only an AG-based regimen, 61 (18%) received only BDQ, and 40 (12%) received AG followed by BDQ (Figure 2).

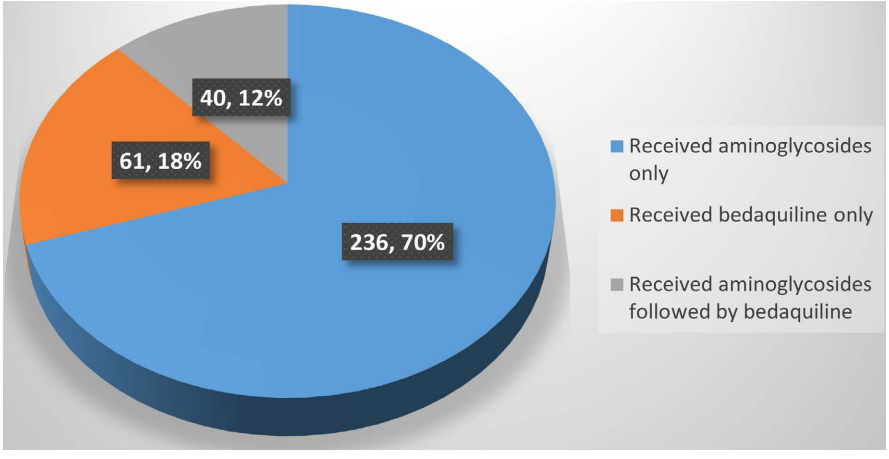

Figure 2. Distribution of patients based on the therapeutic regimen.

3.3. Audiometric Data

Figure 3 shows the evolution of the hearing loss frequency and the severity in liminal audiometry performed at 1 and ≥ 6 months. This frequency increased from 62% to 96.3% within six months for all therapeutic regimens, and moderate (72.4%) and profound (16%) deafness were the most prevalent.

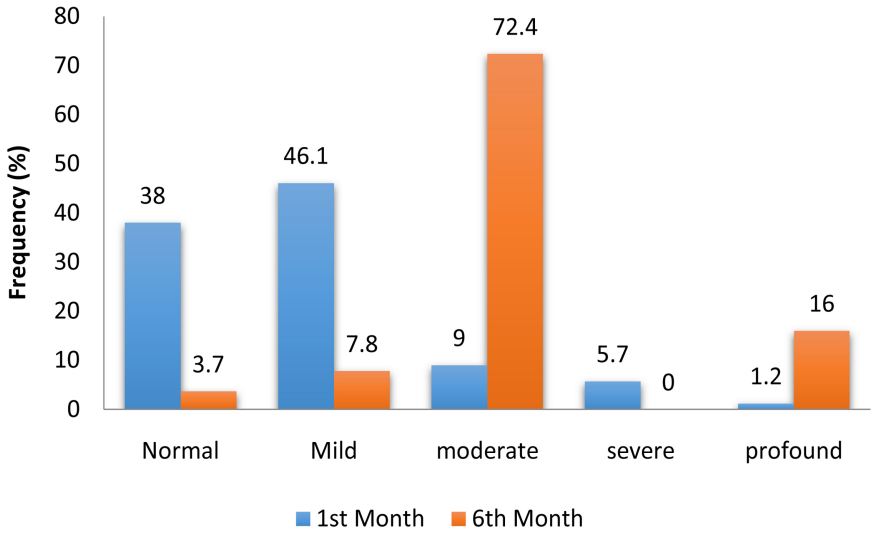

Figure 3. Frequency and degree of the hearing loss.

There was a significant difference of the degree of the hearing loss between the three groups ($p < 0.001$). In fact, the worsening of the hearing loss was more marked in the patients on the AG-based regimen than in the other two groups. The patients on the BDQ-based regimen had less hearing impairment than the other groups (**Figure 4**).

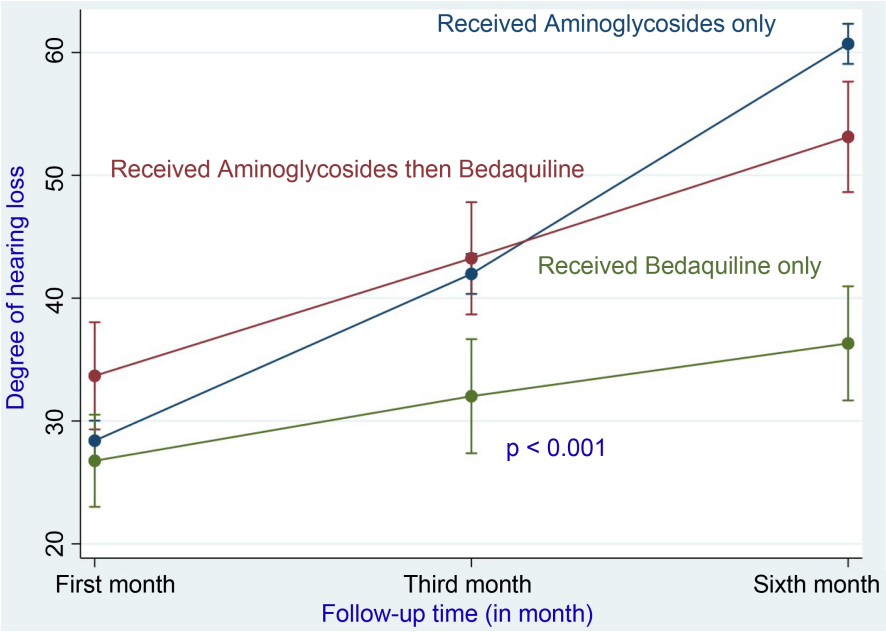

Figure 4. Hearing loss by the therapeutic regimen.

3.4. Determinants of the Hearing Loss

Table 3 shows the results of a multivariate analysis used to determine the risk factors of the onset and the worsening of the hearing loss in the patients with MDR-TB.

Table 3. Determinants of hearing loss in patients with MDR-TB.

	β Coefficient	Standard error	p-value
Duration of treatment			
First month	ref		
Third month	11.706	0.793	**<0.001**
Sixth month	27.695	0.794	**<0.001**
Therapeutic regimen			
Only aminoglycosides	ref		
Only bedaquiline	−2.169	2.689	0.420
Received aminoglycosides followed by bedaquiline	−6.843	2.550	**0.007**
Age			
<40 years	ref		
≥40 years	6.102	1.779	**<0.001**
Sex			
Female	ref		
Male	−0.507	1.855	0.785
Body mass index			
≥18.5	ref		
<18.5	1.989	1.631	0.223
Alcohol intake			
No	ref		
Yes	2.469	1.879	0.189
Hypertension			
No	ref		
Yes	−1.866	4.412	0.672
Hemoglobin			
Normal			
Anemia	−1.008	2.214	0.649
Albumin			
Normal			
Hypoalbuminemia	5.610	1.682	**0.001**
HIV status			
Negative	ref		
Positive	−1.435	2.618	0.583
CKD			
Stage I	ref		
Stage II	−1.993	1.891	0.292
Stage III and over	6.730	2.710	**0.013**

A multivariate logistic regression analysis revealed that the exposure to the treatment for more than one month, AG-based regimen, age ≥ 40 years, hypoalbuminemia, and an eGFR < 60 ml/min/1.72m^2 were identified as the main determinants of the hearing loss among the patients with MDR-TB. After adjustment, the duration of exposure, the age, the therapeutic regimen, the serum albumin level as well as the renal function were identified as determinants of the worsening of the hearing loss. Indeed, patients who were at stage 3 or beyond in the staging of CKD (according to MDRD) had a seven-fold worsening of the hearing loss (β coeff: 6.730, Se: 2.710, p = 0.013) compared with those were at stage I. The Hearing impairment worsened six-fold in the older patients (≥40 years) (β coeff: 6.102, Se: 1.779, p < 0.001) and those with hypoalbuminemia (β coeff: 5.610, Se: 1.682, p = 0.001) compared to young and those with normal serum albumin level. Naturally, the hearing loss worsened with the duration of exposure to the treatment. Examinations at three and six months showed a 12-(β coeff: 11.706, Se: 0.793, p < 0.001) and 28-fold (β coeff: 27.695, Se: 0.794, p < 0.001) increased hearing deterioration respectively, compared with the first examination. The Patients who received AG experienced a worsening of their hearing deficit compared to the patients who received BDQ only or AG followed by BDQ. The degree of the hearing loss decreased by seven in the patients who started with AG and then continued with bedaquiline (β coeff: −6.843, Se: 2.550, p = 0.007).

4. Discussion

This study aimed to assess the determinants of the hearing loss among the patients with MDR-TB in 42 centers for the screening and the treatment of MDR-TB in Kinshasa (DRC). Salient points in the results were the worsening of the hearing loss during the treatment with both therapeutic regimens, much more marked with the AG-based regimen. The exposure to the treatment for more than one month, the AG-based regimen, age ≥ 40 years, hypoalbuminemia, and an eGFR < 60 mL/min/1.73m^2 emerged as determinants of the hearing loss among the patients with MDR-TB.

4.1. Clinical and Audiometric Data

This study observed a young male patient with MDR-TB (35.1 years) who complained of tinnitus associated with hypoacusis and, to a lesser degree, dizziness for all therapeutic regimens. Our findings are consistent with the previous reports from Kinshasa (DRC) and Africa [6] [8] [18] [19] [20]. Other studies have reported hypoacusis as the main symptom [2] [4]. However, it is important to note that the interviews with the patients were carried out in the first month of the treatment, which makes tinnitus a warning sign that is often neglected in the hearing loss. It is consensually accepted that tinnitus is caused due to the peripheral hearing loss in most cases [21]. In addition, vestibular and cochlear functions are affected by the AG- and BDQ-based regimens, but more markedly by

the AG. This hearing loss is generally insidious and gradual, and may progress for several weeks or even a year after the treatment has been stopped. It has been shown that the vestibular damage can be compensated, whereas cochlear lesions are permanently disabling [6] [13] [22] [23] [24].

Our results indicated that two-thirds of the patients had malnutrition with a history of smoking, alcoholism, and TB-HIV coinfection. Our findings are consistent with previous studies that reported that tobacco, alcohol, undernutrition, and HIV are risk factors associated with TB due to a reduced immunity [25]-[31]. HIV is also a risk factor for the sensorineural hearing loss (21% - 49% of cases) because of its tropism for the auditory nerve [32].

Data from this study indicated that the hearing loss frequency increased within six months for all the therapeutic regimens, with a significantly greater worsening in the group receiving the AG-based regimen. Patients on the BDQ-based regimen had less hearing impairment than the other groups. This observation is in line with the previous reports in Kinshasa [2] [3] [6].

4.2. Determinants of Hearing Loss

The exposure to the treatment for more than one month, the AG-based regimen, age ≥ 40 years, hypoalbuminemia, and CKD were identified as the main determinants of the hearing loss among the patients with MDR-TB. These data are consistent with those reported in the literature [4] [6] [22]. Naturally, the hearing loss worsened during the treatment (AG and BDQ-based regimens), as demonstrated by the deterioration of the hearing at the 6th month follow-up compared to the first examination. However, ototoxic effects are more pronounced in AG-based regimens [4] [6] [22]. The degree of the hearing loss increases with a reduced kidney function. Patients who were at stage 3 or above in the CKD staging system (according to the MDRD) had a high hearing loss. It is the same for patients aged ≥ 40 years compared to young patients, as well as for those on an AG-based regimen compared to those who received BDQ. Several studies have established that the sensory cells of the inner ear in the elder patients have a low recovery capacity due to the precarious vascularization [23] [33] [34]. Decreased GFR and hypoalbuminemia observed in our patients with MDR-TB reduced the urinary excretion of drugs and promoted a large unbound fraction, which intensified the adverse effects [6] [35] [36]. It has been reported that in case of malnutrition, hypoalbuminemia leads to fluid stasis in the interstitium of the hair cells of the inner ear worsening AG ototoxicity because they are water-soluble. The ototoxicity is also exacerbated by the overproduction of reactive oxygen species via oxidative stress [37] [38] [39].

In this study, a positive HIV serology and a BMI < 18.5 kg/m^2 were not associated with the hearing loss in the patients with MDR-TB, although HIV manifests tropism for the auditory nerve and the ototoxicity exacerbated by antiretroviral drugs [40]. Some authors have demonstrated that a BMI of < 18.5 kg/m^2 before the initiation of the treatment and a positive HIV serology are strongly

associated with the ototoxicity of AG [41]. In contrast, other studies did not find any association between sex, age, the duration of the treatment, or the total dose of AG and the hearing loss [42]. This disparity in the results can be explained by different methodological approaches, and some authors suggest the existence of a genetic predisposition through the A1555G mutation in the 12s ribosomal RNA gene of the mitochondrial DNA, which would confer a higher risk of the AG-induced hearing loss [43] [44] [45] [46].

This study had some limitations. The small sample size and the lack of the dosages of serum concentrations of the AG and BDQ may have weakened the power of our observations. The degree of the hearing loss in the patients at the beginning of the treatment was unknown.

5. Conclusion

The sensorineural hearing loss is common and increases during the treatment of the patients with MDR-TB. Audiometric evaluations and the follow-up planning are essential for the management of these patients. It should focus on the older patients, and those who are HIV-positive, undernourished, and have an impaired kidney function.

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Contribution of the Authors

Study design: Mireille A. Mpwate, Zacharie M. Kashogwe, Pierre Z. Akilimali and Richard N. Matanda; data collection: Mireille A. Mpwate, Gabriel M. Lema, Eddy M. Mbambu, Christian N. Matanda, Dominique M. Mupepe, Innocent M. Kashogwe, Michel K. Kaswa, Nicole M. Anshambi, Luc L. Lukasu, Murielle L. Aloni, Fabrice M. Matuta and Serge K. Mpwate; data analysis and interpretation: Mireille A. Mpwate, Pierre Z. Akilimali, Dominique M. Mupepe, Zacharie M. Kashogwe, Richard N. Matanda, Innocent M. Kashogwe, Michel K. Kaswa, Nicole M. Anshambi and Luc L. Lukasu; draft writing and manuscript revision: Mireille A. Mpwate, Pierre Z. Akilimali, Dominique M. Mupepe and Richard N. Matanda. All the authors have read and approved the final version of this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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