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Prevalence and Determinants of Hearing Loss in Multidrug-Resistant Tuberculosis Patients: A Prospective Observational Cohort Study in Kinshasa, Democratic Republic of the Congo.

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Abstract

Purpose. The occurrence of the hearing loss (HL) is a challenge during the treatment of multidrug-resistant tuberculosis (MDR-TB). Aminoglycoside-based regimen, to a lesser extent based on bedaquiline (BDQ), induce ototoxic HL. Identifying associated risk factors is crucial in a resource-limited setting. This study assessed the determinants of the HL in patients with MDR-TB.

Methodology. This prospective observational multicenter cohort study included patients with MDR-TB. It was performed in Kinshasa (Democratic Republic of the Congo) between February 15, 2020 and February 14, 2021. Sociodemographic, clinical, biological, therapeutic, and audiometric data were exported and analyzed using Stata 17 and MedCalc. The fixed-effect linear regression panel model was used to assess the degree of the HL over time according to the following covariates: therapeutic regimen (aminoglycosides, bedaquiline, or alternate), 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 $p < 0.05$.

Findings. Of the 337 patients included, 236 (70%) received an aminoglycoside-based regimen, 61 (18%) received a bedaquiline-based regimen, and 40 (12%) received an aminoglycosides (AG) relayed by BDQ. The frequency of the HL increased from 62% to 96.3% within six months for all therapeutic regimens. The HL 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), aminoglycoside-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 the estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (β coeff: 6.730, Se: 2.70, p= 0.013) were the independent risk factors associated with the HL in MDR-TB patients.

Unique contributor to theory, policy and practice: The hearing loss is more prevalent and worsens during the treatment of the patients with MDR-TB. A systematic audiometric evaluation and monitoring plan are needed for the management of these patients. It should focus on the elderly patients, and those who have an exposure for more than one month, an aminoglycoside-based regimen, a hypoalbuminemia, and have an impaired kidney function. However, further prospective interventional cohort studies are required to assess the incidence of the HL during the MDR-TB treatment.

Keywords*: Multidrug, Resistant Tuberculosis, Determinants, Hearing Loss*

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a major public health challenge in developing countries such as the Democratic Republic of the Congo (DRC) (1-3). For a long time, the treatment regimen for MDR-TB has been dependent on second-line injectable anti-tuberculosis drugs, mainly aminoglycosides (AG), which have been associated with a high prevalence of the sensorineural hearing loss (SHL) among patients, reported to range between 5 and 64% (2-4). Previous studies have identified several risk factors [odds ratio (95%CI)] with the onset of hearing impairment in this patient population, such as age over 40 years [13.47 (3.66-49.49)], a body mass index (BMI) below 18.5 kg/m² [2.34 (1.01–5.44)], creatinine clearance rates less than 60 ml/min/1.73 m² (6.22 [1.09–35.36]), and a positive HIV serostatus [1.18 (1.02-1.36)](3,4). Due to the ototoxic effects of AG, the World Health Organization (WHO) recommended in 2020 to replace them by bedaquiline (BDQ), which is considered to have a lower risk of ototoxicity (4-6). In response to the concerning rates of the hearing loss (HL), reported to range from 8.7% to 21.2% among MDR-TB patients treated with AG, the DRC has committed to implementing these updated treatment guidelines (2,5). While several risk factors associated with AG-induced ototoxicity have been documented, there is little data regarding the relationship between BDQ and the HL (3,5,6). Additionally, the WHO emphasizes the rational use of medications and advocates for a systematic screening for hearing disorders to mitigate the risk of ototoxic HL (7,8). This approach requires the identification of at-risk individuals, highlighting the importance of investigating the determinants of the SHL in MDR-TB patients treated with AG, BDQ, or alternate therapies in Kinshasa, DRC.

Methods

Study design and participant sampling

This prospective observational multicenter cohort study was conducted between 15 February 15, 2020 and February 14, 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 aminoglycoside (AG) and/or the BDQ-based regimens “under directly observed treatment” (DOT). MDR-TB Patients (diagnosed by molecular methods such as MTB/RIF® or Genotype MTBR-plus sl ®), 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.

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 Liminal-tone audiometry was used to determine the degree of the HL. 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 HL ≥ 21 dB (1). The degree of the HL 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).

Operational definitions

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/m² (11). An excessive alcohol use was defined as more than two standards drink for men and one for women (12). Smoking was considered for anyone who smoked at least one cigarette/day for a year or more or weaned for less than 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). Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m^2 (16). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Statistical analysis

The data were encoded using Microsoft Excel 2013, constituted in the database after the 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 HL over time according to the following covariates: therapeutic regimen (AGs, BDQ, or alternate), 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 $p < 0.05$.

Results

General characteristics of the study population

This study enrolled 397 MDR-TB patients (Figure 1). Among these, 60 were excluded because they were absent during the audiometry testing and/or the interviews. 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.

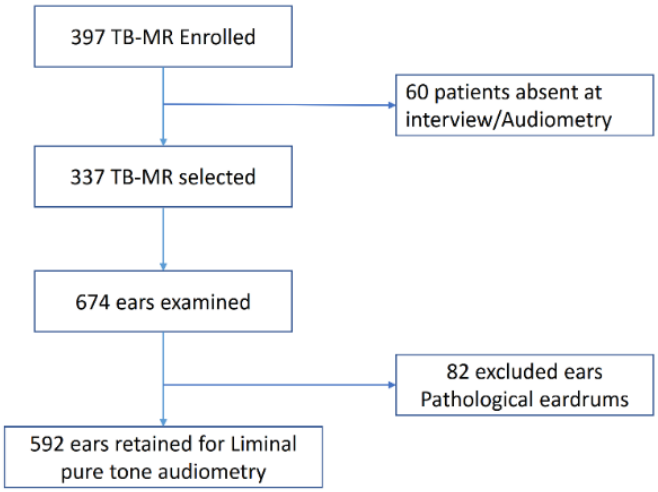

Figure 1. Flow chart of MDR-TB patients.

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 (42.1%) had completed secondary education.

Table 1. Sociodemographic characteristics of the study population

Variable	n	%
Age (mean ± SD) years	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
high school diploma/University	142	42.1

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. Most patients were anemic (84.8%). Among them, almost two-thirds (65%) were underweight and almost half (47.4%) had hypoalbuminemia.

Table 2. Clinical and paraclinical data

Variable	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
Paraclinical		
Anemia	286	84.8
Hypoalbuminemia	160	47.4
Chronic kidney disease	79	23.4

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).

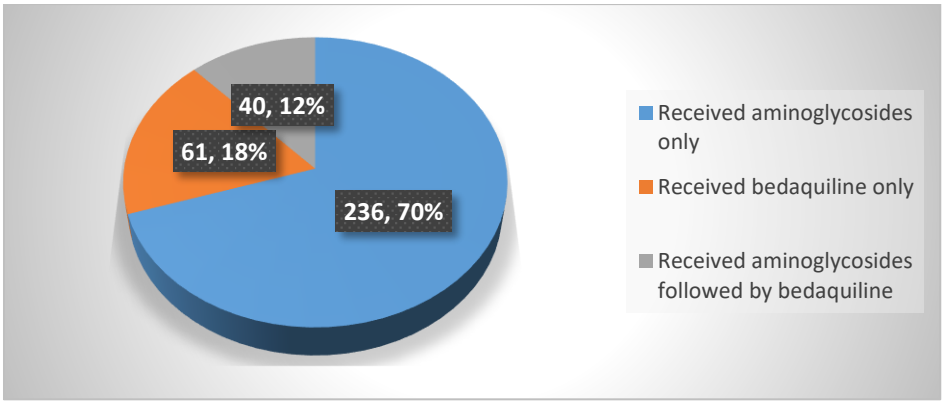

Figure 2. Distribution of patients based on the therapeutic regimen.

Audiometric data

Figure 3 shows the evolution of the hearing loss (HL) 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.

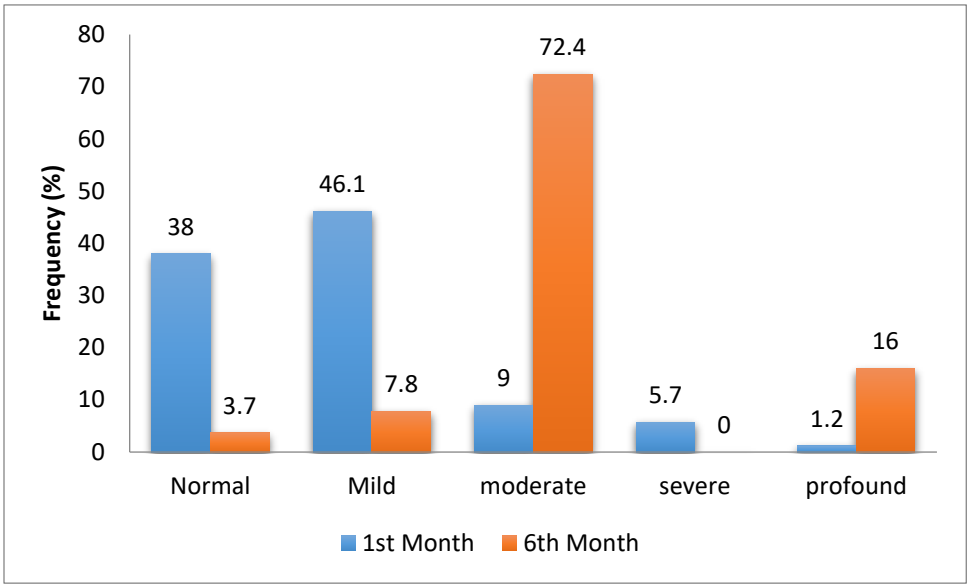

Figure 3. Frequency and degree of the hearing loss.

There was a significant difference of the degree of the HL between the three groups ($p<0.001$). In fact, the worsening of the HL 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).

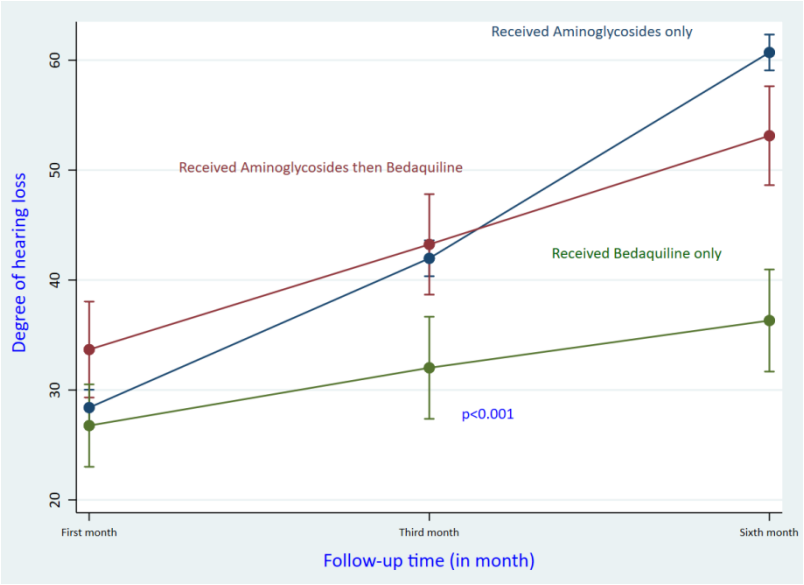

Figure 4. Hearing loss by the therapeutic regimen

Determinants of the hearing loss

Table 3 summarizes the results of a multivariate analysis used to determine the risk factors of the onset and the worsening of the HL in the MDR-TB patients.

A multivariate logistic regression analysis revealed that the exposure to the treatment for more than one month, the AG-based regimen, age ≥ 40 years, hypoalbuminemia, and an eGFR < 60 ml/min/1.72 m^2 were identified as the main determinants of the HL among the patients with

MDR-TB. After adjustment, the duration of exposure to anti-tuberculosis drugs, the age, the therapeutic regimen, the serum albumin level as well as the impaired renal function were identified as determinants of the worsening of the HL. Indeed, the severity of the HL intensified with the deterioration of the kidney function. Patients who were at stage 3 or beyond in the staging of CKD had a seven-fold worsening of the HL (β coeff: 6.730, Se: 2.710, p= 0.013) compared with those who 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 levels. Naturally, the HL worsened with the duration of the exposure to the treatment. Specially, 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 the hearing deterioration respectively, compared with the first examination. Finally, 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 HL decreased by seven in the patients who started with AG and then continued with BDQ (β coeff: -6.843, Se: 2.550, p=0.007).

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

	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**

Discussion

This study assessed the determinants of the HL in MDR-TB patients in Kinshasa (DRC). Results showed worsening HL during the treatment with both regimens, significantly more marked with the AG-based regimen. The treatment exposure for more than one month, the AG-

based regimen, age ≥ 40 years, hypoalbuminemia, and an eGFR < 60 mL/min/1.73 m^2 emerged as determinants of the HL in MDR-TB patients.

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 the therapeutic regimens. Our findings are consistent with the previous reports from Kinshasa (DRC) and Africa (6,8,18-20). 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 HL. 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 HL 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, 22-24).

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 HL (21–49% of cases) because of its tropism for the auditory nerve (32).

Data from this study indicated that the HL 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).

Determinants of hearing loss

The treatment exposure for more than one month, the AG-based regimen, age ≥ 40 years, hypoalbuminemia, and CKD were identified as the main determinants of the HL 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 6^{th} 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 HL increases with a reduced kidney function. Patients who were at stage 3 or above in the CKD staging system had a high incidence of the HL. 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 MDR-TB patients reduced the urinary excretion of drugs and promoted a large unbound fraction, which intensified the adverse effects (4,6,35,36). 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 the AG ototoxicity because they are water-soluble. The ototoxicity is also exacerbated by the overproduction of reactive oxygen species via oxidative stress (37- 39).

In this study, a positive HIV serology and a BMI < 18.5 kg/m^2 were not associated with the HL 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 (4,41). 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 HL (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 (43–45).

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 HL in the patients at the beginning of the treatment was unknown.

Conclusion

The prevalence of the SHL is very high and worsens during the treatment of MDR-TB patients. An exposure for more than one month, an aminoglycoside-based regimen, advanced age, hypoalbuminemia and an impaired kidney function have emerged as determinants of the HL. Performing audiometry both prior to and during treatment will facilitate the early detection of signs of ototoxicity in order to provide appropriate and effective interventions. Patients should promptly report any symptoms related to hearing. Further prospective interventional research studies are required to assess the risk of the HL in MDR-TB patients

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Conflicts of interest

The authors declare no conflict of interest.

Contribution of the authors

Study design: Mireille A. Mpwate, Gauthier K. Mesia, Jean Marie N. Kayembe, 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, Luc L. Lukasu; Data analysis and interpretation: Mireille A. Mpwate, Pierre Z. Akilimali, Dominique M. Mupepe, Richard N. Matanda, Innocent M. Kashogwe; Draft writing and manuscript revision : Mireille A. Mpwate, Zacharie M. Kashogwe, Pierre Z. Akilimali, Jean Marie N. Kayembe, Dominique M. Mupepe, Gauthier K. Mesia and Richard N. Matanda. All the authors have read and approved the final version of this manuscript.

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