



Safety of antituberculosis agents used for multidrug-resistant tuberculosis

Maurice Mbwe Mpoh

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**Safety of antituberculosis agents used for
multidrug-resistant tuberculosis**

By Maurice MBWE MPOH

Under the supervision of Pr. Francesco SALVO

Defended on December 18, 2023

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Title: Safety of antituberculosis agents used for multidrug-resistant tuberculosis

ABSTRACT

Tuberculosis (TB) is a disease caused by Koch's bacillus. It is the ninth leading cause of death worldwide, and the most common infectious cause of death, surpassing HIV/AIDS. The development of resistances due to misuse of anti-tuberculosis drugs has resulted in new forms of TB, including multidrug-resistant tuberculosis (MDR-TB). MDR-TB is a particularly dangerous form of tuberculosis, characterized by its resistance to both isoniazid and rifampicin, the two main and most effective anti-tuberculosis drugs. Developing countries, including Cameroon, are heavily affected. Effectively treating MDR-TB requires the combination of several drugs over several months. Indeed, from 2016 to 2020 the World Health Organization recommended the use of shorter treatment regimen for MDR-TB patients. This lasts for 9–11 months and is divided into two phases: An intensive phase, and a continuous ambulatory phase. The intensive phase involved 4–6 months of daily treatment with 6 antibiotics (moxifloxacin, prothionamide, isoniazid high-dose, clofazimine, ethambutol, and pyrazinamide) associated with kanamycin or amikacin. The continuous ambulatory phase had a fixed treatment duration of 5 months with 4 antibiotics: Moxifloxacin, clofazimine, ethambutol, and pyrazinamide.

The aim of this thesis was to assess the safety of anti-tuberculosis drugs used in the management of MDR-TB in Cameroon.

Initially, we conducted a study to assess the safety profile of treatments used for MDR-TB in the main TB treatment center or hospital in Cameroon. This study identified aminoglycoside-related deafness as the main cause of treatment change or discontinuation.

Secondly, we assessed compliance with WHO recommendations on MDR-TB treatment, as well as patient persistence with the program and the treatment. This study revealed very strong

compliance with the WHO recommendations, although a progressive decline in persistence was recorded notably during the continuation phase.

Finally, in view of the fact that during the course of our thesis, aminoglycosides were replaced by bedaquiline in the WHO-standardized MDR-TB treatment regimen, due to ototoxicity and other problems, we carried out a preliminary study on the safety and persistence of the new MDR-TB regimen. This work showed that ototoxicity problems disappeared, and that treatment persistence improved, while highlighting the risks of joint pain and cardiac problems associated with the new regimen.

These results demonstrate that MDR-TB treatment regimens in Cameroon are consistently associated with adverse drug reactions despite changes in the medicines used. Thus, there is a need to implement a strong drug safety monitoring system which will allow health care providers and policy makers to continuously evaluate the safety profile of drugs in use and improve clinical outcomes. As the current treatment regimen is now bedaquiline-based, the strict monitoring of cardiovascular events is vital since other drugs like clofazimine, and moxifloxacin can also prolong the QT interval.

Key words: pharmacovigilance, public health, MDR-TB, drug safety, adverse reactions.

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Titre: Sécurité des antituberculeux utilisés dans la prise en charge de la Tuberculose Multirésistante.

RÉSUMÉ

La tuberculose (TB) est une maladie causée par le bacille de Koch. Elle est la neuvième cause de décès dans le monde et la première cause de décès d'origine infectieuse, devant le VIH/SIDA. Le développement de résistance due à une mauvaise utilisation des médicaments antituberculeux a donné naissance à de nouvelles formes de tuberculose, dont la tuberculose multirésistante (TB-MR). La TB-MR est une forme particulièrement dangereuse de TB qui se définit par la résistance à la fois à l'isoniazide et à la rifampicine, les deux antituberculeux de première intention les plus efficaces. Les pays en voie de développement, dont le Cameroun, sont particulièrement touchés. Un traitement efficace de la TB-MR passe par l'association de plusieurs médicaments pendant une longue période comme le recommande l'Organisation mondiale de la Santé. En effet, depuis 2016 le régime de traitement court et standardisé recommandé par l'OMS subdivisait la prise en charge de la TB-MR en deux phases distinctes pouvant aller de 9 à 11 mois. La première phase dite intensive durait 4 à 6 mois avec la prise de 7 antituberculeux (Kanamycine/amikacine, moxifloxacine, prothionamide, isoniazide haute-dose, clofazimine, ethambutol, et pyrazinamide). La deuxième phase dite phase continue avait une durée fixe de 5 mois avec 4 antituberculeux (Moxifloxacine, clofazimine, ethambutol, and pyrazinamide).

L'objectif de cette thèse était d'évaluer la sécurité des médicaments antituberculeux utilisés dans la prise en charge de la TB-MR au Cameroun.

Dans un premier temps, nous avons réalisé une étude dont l'objectif principal était d'évaluer le profil de sécurité des traitements utilisés pour la TB-MR dans le principal hôpital de prise en charge de cette maladie au Cameroun. Cette étude a permis d'identifier la surdité liée aux aminosides comme principale cause de changement ou d'arrêt de traitement.

Deuxièmement, nous avons évalué la conformité aux recommandations de l’OMS sur le traitement de la TB-MR, ainsi que la persistance des patients au programme et au traitement. Cette étude a quant à elle révélé une très bonne conformité aux recommandations de l’OMS, mais aussi une baisse progressive de la persistance, en particulier pendant la phase continue.

Enfin, étant donné qu’au cours de notre thèse, les aminoglycosides ont été remplacés par la bédaquiline dans le nouveau régime de traitement court et standardisé recommandé par l’OMS, en raison de problèmes d’ototoxicité et autres, nous avons réalisé une étude préliminaire de la sécurité et de la persistance de ce nouveau traitement. Ce travail a montré que les problèmes d’ototoxicité ont disparu et que la persistance au traitement s’est améliorée, tout en soulignant les risques de douleurs articulaires et de problèmes cardiaques associés au nouveau régime.

Ces résultats montrent que malgré le changement de médicaments, les effets indésirables sont couramment associés aux schémas thérapeutiques de la TB-MR au Cameroun. Il est donc nécessaire de mettre en place un système solide de surveillance de la sécurité des médicaments qui permettra aux prestataires de soins de santé et aux décideurs politiques d’évaluer en permanence le profil de sécurité des médicaments utilisés et d’améliorer les résultats cliniques. Comme le traitement mis en œuvre est maintenant basé sur la bédaquiline, il faut être prudent dans la surveillance des événements cardiovasculaires car d’autres médicaments comme la clofazimine, et la moxifloxacine ont également le pouvoir de prolonger l’intervalle QT.

Mots clés : pharmacovigilance, santé publique, tuberculose multirésistante, sécurité des médicaments, effets indésirables

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ABBREVIATIONS

ADR : Adverse Drug Reaction

aDSM : active tuberculosis drug-safety monitoring and management

AIDS : acquired immunodeficiency syndrome

Am: Amikacin

AMA: African Medicine Agency

ANRS: Agence Nationale pour la Recherche sur le SIDA et les hépatites

Bdq: bedaquiline

BPaL: bedaquiline, pretomanid and linezolid

CDT: center of diagnostic and treatment

CI : confidence interval

Cfz: Clofazimine

CTCAE: Common Terminology Criteria for Adverse Events

DR-TB : drug-resistant tuberculosis

DOT : directly observed treatment

DUS: drug utilization studies

E: Ethambutol

EI: Effet indésirable

EHR: Electronic Health Records

Eto: ethionamide

EMA: European Medicines Agency

ENCePP: European network of centres for pharmacoepidemiology and pharmacovigilance

FAERS: FDA Adverse Event Reporting System

FDA: Food Drug Administration

GVP: Good vigilance practices

HIV: human immunodeficiency virus

H: Isoniazid

Km: Kanamycin

Lfx: Levofloxacin

Lzd: Linezolid

MAH: Marketing Authorization Holders

MDR-TB : Multidrugresistant Tuberculosis

Mfx: Moxifloxacin

NTP: National Tuberculosis control Programme

NIS: Non interventional studies

OMS : Organisation Mondiale de la Santé

Pa: pretomanid

PNLT: Programme National de Lutte contre la Tuberculose

PV : Pharmacovigilance

RR-TB: Rifampicin Resistant Tuberculosis

SNS: Drug social network systems

TB : Tuberculosis

TB-MR: Tuberculose Multirésistante

TSR: Targeted spontaneous reporting

WHO: World Health Organization

XDR-TB: extensively drug-resistant TB

Z: Pyrazinamide

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1.INTRODUCTION

1.1.Tuberculosis

Tuberculosis (TB) is an infectious disease caused by a bacteria called *Mycobacterium tuberculosis* discovered in 1882 by Doctor Robert Koch.(1) Although TB mostly affects the lungs (pulmonary TB), the disease can also be located in other sites like the kidneys, brain, spine and skin (extrapulmonary TB).(2) The contamination mechanisms are similar for both forms of the disease. Indeed, tuberculosis spreads from infected people when they release the bacillus into the air by coughing, sneezing or spitting. Well-known as a disease of poverty, TB can affect anyone anywhere and the common symptoms usually include prolonged cough (sometimes with blood), chest pain, weakness, fatigue, weight loss, fever and night sweats.(2) Meanwhile, symptoms depend on where in the body TB becomes active.

Even as it is preventable and curable, TB has been recognized as a global emergency by World Health Organization (WHO) in 1994 and today continues to be considered as a major public health threat. Indeed, with a higher rate occurrence with men, about a quarter of the world population is infected by the Koch bacillus and 5–10% of people infected will probably get TB symptoms and develop the disease. (1) Moreover, TB is ranked among the top ten causes of death worldwide and identified as the leading cause of death among people living with AIDS in 2020.

According to the 2022 TB Global report, in 2021, about 10.6 million (95% UI : 9.9–11 million) of people were infected and fell ill with TB.(3) Africa is the second most infected region, with 25% of persons who developed TB globally living there, just behind the 44% of cases observed in South-East Asia. More specifically, Nigeria (4.4%) and South Africa (3.6%) are two of the eight countries accounting for two thirds of the global total cases of TB. (3)

In 2021, there was an estimated 1.4 million deaths among HIV-negative people (95% uncertainty interval [UI]: 1.3–1.5 million) and 187 000 deaths (95% UI : 158 000–218 000) among HIV-positive people, for a combined total of 1.6 million.(3)

Cameroon is one of the 30 countries on the global list of high-burden countries for HIV-associated TB.(4) Prevalence of TB is estimated at 150 cases/100,000 inhabitants with 2.89% as mortality rate, ranking Cameroon as the 25th most infected country in the world .(5)

1.2.Multidrug-Resistant Tuberculosis

There was rapid emergence of drug-resistant tuberculosis as the antimicrobial resistance against *Mycobacterium tuberculosis* started with streptomycin - the first introduced treatment for the disease. Meanwhile, the first Multi-Resistant strains appeared in the 90s with the discovery of bacillus simultaneous resistant to isoniazid and rifampicin.(6) The form of TB characterized by the *M. Tuberculosis* resistance to at least rifampicin and isoniazid is called Multidrug-Resistant TB (MDR-TB).(2,7)

If some patients can be directly diagnosed as multidrug-resistant without previously followed TB treatment, it is widely accepted that most of the cases of TB drug resistance are a result of a combination of physician error or lack of patient compliance with anti-tuberculosis (anti-TB) treatment.(8) Specifically, the inappropriate use of drugs, errors in the application of WHO recommendations, use of inefficient drugs, regularity of drug stock-out leading to interrupted or discontinued treatments are potential causes of MDR-TB pointed out by National Tuberculosis Programme (NTP).(9)

Moreover, medical staff and TB patients also contribute through their behaviors to MDR-TB emergence. This generally happens in cases of lack of information or training, early discontinuation of patients to therapy, inadequate management of clinical or safety issues, wrong choice of medication or their posology, lack of supervision of treatment intake, haphazard changes in therapeutic regimens in the event of drug intolerance.

1.3.Multidrug-Resistant Tuberculosis Treatment

Appropriate treatment is very important to cure MDR-TB as the mortality rate in absence of treatment with anti-TB drugs range from 20% to 70% for people with culture-positive (but smear-negative) pulmonary TB and for individuals with sputum smear-positive pulmonary TB respectively.(2) Treatment recommendations are related to the type of tuberculosis. Indeed, with a regularly reported success rate of around 85%, the current recommended therapy of drug-susceptible TB disease is a 6-month treatment regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide.(10) Meanwhile, treatment of drug resistant TB is longer and requires a higher number of drugs more expensive (\geq US \$ 1000 per person) and recognized as more toxic. For MDR-TB patients, WHO generally report a treatment success rate of 57%.(1)

As MDR-TB requires particular and complex therapy, there are several approaches and treatment regimens used in the World. Operational research is routinely done by experts from different parts of the world to improve efficacy and safety of MDR-TB treatment. Meanwhile, the most accepted and implemented treatments in most of the countries are generally those recommended by WHO. Indeed, WHO Guidelines are usually evidence-based and published considering the most common findings and knowledge of the disease and its therapy. According to WHO, evidence for the effectiveness and safety of recommended MDR-TB regimens derives from studies where therapy was administered under fairly standardized conditions with relatively little variation in the content and duration, and with close monitoring.(10)

Thus, published recommendations always request the use of MDR-TB regimens with the same drug composition and duration than those used in observational studies. Moreover, drug replacement and changes to the treatment duration must only be considered within the parameters applied in the referred observational studies.(10)

In light of the worldwide spread of MDR-TB and the growing number of the newer form of tuberculosis called extensively drug-resistant TB (XDR-TB) caused by clinical mismanagement and inappropriate utilization of antituberculosis agents, regimens options of MDR-TB are always changing. Recommended options are based on expected efficacy, safety, patient preference and clinical judgement.(10) Moreover, results of drug resistance tests, patient treatment history, age, severity and site of the disease are also taken into account.

To harmonize practices and reinforce the coordination of efforts done worldwide to eradicate or at least limit the widespread of MDR-TB, WHO Global TB Programme has since 1996 regularly issued policy guidelines and operational handbooks for the treatment of drug-resistant tuberculosis.(10–15) Meanwhile, before the WHO treatment guidelines of resistant TB released in 2016, most of the MDR-TB treatments applied in the world were longer individualized regimens mainly based on drug susceptibility and lasted 18 months or more.(8,10) These regimens were usually designed to include a minimum number of second-line TB medicines considered to be effective based on patient history or drug-resistance patterns.(10)

1.3.1. WHO Guidelines update 2016

- *Shorter treatment regimens*

For the first time a shorter treatment regimen (STR) of MDR-TB lasting 9 to 12 months was recommended by WHO in May 2016. This therapy was recommended in MDR-TB patients who have not been previously treated for more than 1 month with second line drugs used in STR or in whom resistance to fluoroquinolones and second-line injectable agents have been excluded.(10)

The STR was enthusiastically welcomed by physicians, NTPs and MDR-TB patients as it substantially reduced the treatment duration to 9–12 months.(16,17) Indeed, STR refers to a course of treatment for RR-TB or MDR-TB largely standardized, and whose composition and

duration follows closely the one for which there is documented evidence from different settings.(8,10) Thus, MDR-TB therapy based on STR and strongly recommended by WHO is subdivided into 2 parts :

- the first part is an **intensive phase** of four months, including the following seven drugs: levofloxacin or moxifloxacin (Lfx/Mfx), kanamycin or amikacin (Km or Am, protionamide or ethionamide (Pto/Eto), clofazimine (Cfz), high-dose isoniazid (Hh), pyrazinamide (Z), and ethambutol (E). The intensive phase duration could be extended to 6 months when the patient remains sputum smear-positive at the end of 4 months.

- the latter is followed by a **continuation phase** of five months including 4 drugs: Levofloxacin (Lfx) or Moxifloxacin (Mfx), Pyrazinamide(Z), Ethambutol (E), and Clofazimine (Cfz). The duration of the continuation phase remained fixed at 5 months, regardless of the duration of the intensive phase.

- The treatment regimen was abbreviated as follows (4–6 Am/Km-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E).

The dosage of each of these drugs according to the patient's weight is shown in the following table below.

Table 1: : Recommended doses of drugs during the intensive and continuation phase.

Drugs	Intensive Phase Daily Dose (mg)				Continuation Phase Daily Dose (mg)			
	30-39 Kg	40-54 Kg	55-70 Kg	Over 70 Kg	30-39 Kg	40-54 Kg	55-70 Kg	Over 70 Kg
Amikacin/Kanamycin	500	750	1000	1000	/	/	/	/
Clofazimine	50	100	100	100	50	100	100	100
Ethambutol	600	800	1200	1400	600	800	1200	1400
Isoniazid	300	450	600	600	/	/	/	/
Moxifloxacin	400	600	800	800	400	600	800	800
Prothionamide	500	500	750	1000	/	/	/	/
Pyrazinamide	800	1200	1600	2000	800	1200	1600	2000

Beside the shorter regimen, a longer MDR-TB regimen was also proposed by WHO in 2016 as a conditional recommendation with very low level in the evidence.(18) With a duration of 18–20 months, these regimens are designed with at least four to five effective TB medicine based on the drug-resistance profile.

1.3.2. WHO Guidelines update 2020

In June 2020, WHO has updated the guidelines related to the treatment of drug resistant tuberculosis.(15,19) The *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment* included two new recommendations, one on the composition of shorter regimens and one on the use of the BPaL regimen (i.e. bedaquiline, pretomanid and linezolid).(19)

- **Shorter Regimen**

The new composition recommended a shorter treatment regimen for patients with MDR/RR-TB not resistant to fluoroquinolones (of 9–11 months), with the inclusion of bedaquiline instead of aminoglycosides which were injectables, making the regimen all oral.(15) The doses of all the drugs previously used in the former STR were maintained in this new totally oral regimen. Meanwhile, recommended doses and treatment duration with bedaquiline were different than the replaced aminoglycosides. Indeed, for MDR-TB patients weighing more than 30 kg the bedaquiline recommended dose were: 400 mg daily (200 mg morning and evening) for two weeks, followed by 2 tablets 3 times a week.

- **BPaL Regimen**

To gather more evidence that could potentially lead to the introduction of this regimen in routine care of MDR-TB patients, a new short, 6–9-month regimen composed of bedaquiline, pretomanid and linezolid (BPaL) has been conditionally recommended for use in patients with

MDR/RR-TB and additional fluoroquinolone resistance, under operational research conditions only.(19)

1.3.3. WHO Guidelines update 2022

Following the 2020 revision which highlighted the ongoing need to gather more evidence through clinical trials and other research studies, WHO issued in 2022 a new higher-quality evidence-based policy related to the treatment of MDR-TB.(20) The latter and current WHO consolidated guidelines on tuberculosis recommended two different options of short regimens to be used for the treatment of MDR-TB: BPaLM regimen and 9-month all-oral regimen.

- **BPaLM Regimen**

As new available evidence showed that this regimen much improved treatment success rates (89%) compared with the current STR (52%), as well as lower levels of treatment failure, death and loss to follow-up, a BPaLM regimen is recommended since 2022 as the preferred option or best choice of treatment for MDR-TB patients.(20)

Indeed, it is the shortest totally oral treatment regimen with a duration of 6 months which requires association of 4 different drugs: bedaquiline, pretomanid, linezolid and moxifloxacin. This option regimen is abbreviated as (6 Bdq-Pa-Lzd-Mfx).

This regimen is recommended by WHO for patients with presumed or documented fluoroquinolone susceptibility. When resistance to fluoroquinolone is confirmed, Moxifloxacin could be retrieved and the three-drug therapy abbreviated as BPaL regimen may be resumed. Indeed, this could be explained by the fact that there is no additional benefit in using a drug with confirmed resistance. If not, patients would be exposed to avoidable Adverse drug reaction (ADR) and unnecessary drug toxicity.(20)

- **9-month all-oral regimen**

According to the 2022 revision, STR (9-month regimens) can be used in patients non-eligible for the BPaLM (6-month regimens); also, STR represents a preferred treatment option over the longer regimens.(20,21)

This totally oral regimen lasting 9 to 11 months recommended in absence of fluoroquinolone resistance is also split into 2 phases with the same drugs previously listed in the 2020 update. Meanwhile, during the intensive phase the new recommendation raised that ethionamide could be replaced by 2 months of linezolid (600 mg, daily).(20,21) Indeed, current evidence gained through assessment of two different alternatives, STR including linezolid for 2 months and STR with ethionamide for 4 months, showed similar levels of treatment success (64% vs 66%), failure or recurrence (1.1% vs 1.4%), deaths (20% vs 21%), loss to follow-up (15% vs 12%) and amplification of drug resistance (0.6% vs 0%).(19,20) Moreover, Adverse events were noted in 5% of participants receiving the 9-month regimen with linezolid.(19,20)

Then, the treatment regimen is now abbreviated as follows (4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto or Lzd(2 m) / 5 Lfx/Mfx-Cfz-Z-E).

For patients with MDR-TB who are not eligible for the BPaLM or 9-month all oral regimen, it remains a longer individualized MDR-TB treatment regimens with a duration of at least 18 months, designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history.

1.4. Safety monitoring of Multidrug-resistant Tuberculosis treatment

MDR-TB patients are infected by a *M tuberculosis* resistant to the key drugs of the first line antitubercular agents, rifampicin and isoniazid. To ensure better treatment effectiveness and safety, WHO recommends since 2016 use of standardized and shorter regimens.(10)

Meanwhile, these treatment regimens require a combination of multiple tuberculosis second-line drugs which are more toxic than first-line drugs and consequently,(22) improve the likelihood of safety issues occurrence. Indeed, each of drug composing the regimen is associated with numerous adverse drug reactions which can lead to serious morbidities like liver or renal failure, blindness, hearing loss or even death.(22) These events can negatively impact treatment outcomes and be responsible of patients' treatment discontinuation or failure.

Drug safety monitoring is fundamental for an appropriate and effective use of medicines. Indeed, right and safe medicines strongly contribute to high quality medical care, specifically for diseases that require complex treatments like MDR-TB.(23) Health policies around the world should ensure the existence of National Pharmacovigilance programs which will continuously carry out post-marketing surveillance of the drugs used in the health system.

Generally, second-line anti-TB drugs are more toxic in patients than first-line drugs, increasing the essence of pharmacovigilance in the programmatic management of drug-resistant TB. Even if it has been noticed that some NTPs record occurrence of adverse drug reactions for patients on treatment, in most programs, the nature and frequency of harms caused by the drugs remains poorly profiled and can only be inferred indirectly from the interruption or failure of treatment.(12) That is why WHO strongly recommends NTPs to systematically monitor adverse effects associated with anti-tuberculosis medication because they are better placed to safeguard patient safety, especially when introducing new anti-TB drugs and regimens.(12,24,25)

1.4.1. Drug Safety Monitoring approaches

Pharmacovigilance described by WHO as “the science related to the detection, assessment, understanding, and prevention of adverse effects or any drug-related problem for patient safety”, is essential particularly for the treatment of MDR-TB which are exposing numerous patients of diverse ages, sex and ethnic profiles to complex combinations of drugs, increasing

the likelihood for ADRs.(26) These ADRs could be collected through a passive or active surveillance approach.

Passive surveillance is a pharmacovigilance approach in which Adverse events (AE) are not actively looked for but directly reported to the marketing authorization holder - National Pharmacovigilance Center or any regulatory authority recognized by healthcare professionals or patients.(23,27,28) Thus, it involves the usage of spontaneous adverse event reports voluntarily sent by healthcare professionals or patients. All these safety data collected are then recorded in a local database, at regional or national level for example, and then used at international level, as done by European Medicine Agency (EMA), WHO and in the near future at the African Medicine Agency (AMA) Level. Information collected by the Individual Case Safety Report (ICSR) are administrative (e.g. country, region, or hospital), and concern health status of patients (e.g. age, gender, pre-existing co-morbidities), followed by the description of AE and suspected and concomitant medicines.

Contrarily to the latter, active Pharmacovigilance aims to actively seek AE or drug safety problem at the level of health services, patients and healthcare providers. Indeed, active surveillance consists of a continuous follow-up of patients during and after treatment where ADRs are detected either by asking patients directly or by screening the patient medical records.(29) This approach is very important to identify new drug safety signals or confirm information collected through passive surveillance.(28)

Thus, through active or passive surveillance, there are different methods used to monitor the safety of drugs including antituberculosis drugs.(27–29) All these approaches are important but a preferred approach should be selected each time regarding specific circumstances based on the local situation, experience, expertise, and resources available to achieve the planned objectives.(23,29) Potential methods of drug safety monitoring to consider are as follows:

- **Spontaneous reporting**

It is a passive pharmacovigilance methodology related to the reporting of ADR occurring after therapy and detected by the patient or the healthcare professional. For instance, the direct reporting of hepatotoxicity observed in patients under MDR-TB regimen to the national pharmacovigilance centre.

If a spontaneous reporting system is easy to establish and relatively cheaper to run compared to other drug safety monitoring approaches, its main and severe disadvantage is underreporting. It is estimated that less than 1% of ADRs are reported,(25,28,30,31) patients and health professionals need to be trained and motivated to voluntarily report any suspected adverse events occurring during patient treatment. Many countries have a system of spontaneous reporting of AEs using ICSR.(25) Some of the best database centralizing individual case safety reports in the world are:

- FAERS (FDA Adverse Event Reporting System) database run by FDA
- VigiBase™, the WHO Global ICSR database
- For Europe: EudraVigilance maintained by EMA

- **Targeted spontaneous reporting**

Today, beside spontaneous reporting, drug safety monitoring can be done through targeted spontaneous reporting (TSR). Indeed, TSR is a relatively new method of pharmacovigilance that integrates elements found in cohort event monitoring and spontaneous reporting (40). In this PV surveillance approach, selected ADRs of interest are monitored in a predefined subgroup of patients as part of routine care.(32) In addition to Spontaneous reporting and Cohort event Monitoring (CEM), TSR is one of the pharmacovigilance approaches or methodologies recommended by WHO to be implemented in NTPs for drug safety monitoring of tuberculosis treatment.(33) In fact, in NTPs, TSR can be easily implemented and could be focused on the surveillance of serious adverse events in specific patient groups, such as MDR-TB patients.

Despite the fact that similarly to spontaneous reporting TSR hugely depends on the willingness of patients and health care providers to report, the approach requires less resources (time and fundings) to be implemented in routine pharmacovigilance activities of clinical programs with the advantage of capturing safety measurements over the entire length of treatments.(32,33)

- **Social network monitoring**

Beyond traditional drug safety monitoring methods, there is a growing interest in the development of new approaches linked to technology. Indeed, as there is no way to life today without social media, it is common to see health data shared by patients through these means. Aware of the importance of this new source of information, the European guidelines of good pharmacovigilance practices (GVP) clearly stated in its module VI, that information on suspected adverse reactions should be routinely sought and collected from the internet or digital media.(34–37) Thus, Drug social network systems (SNS) which is at its infancy, could be considered as drug safety monitoring approach based on health data published by patients from internet or social media. Despite the high population coverage of SNS screening where the enormous amount of data is received, information must be filtered to be appropriately used. In fact, information shared are generally unstructured, uncontrolled, non-validated by physicians, pharmacist or any other medical experts and lastly, there is a high chance of duplication due to cross-channel information diffusion.(35)

- **Drug utilization studies**

Assessing drug utilization is vital for pharmacovigilance. Indeed, while focusing on the various medical, social, and economic aspects of drug use, drug utilization studies (DUS) could be helpful to identify patterns linked to risks and benefits of drug therapy. In drug safety monitoring, DUS often employ different methodologies including prospective clinical cohort studies, cross-sectional surveys using questionnaires and retrospective studies using existing

databases or patients' medical records.(38) As non-interventional studies (NIS), DUS could be conducted to assess safety, tolerability and effectiveness of medicines used to treat a defined disease in real life and in line with current clinical practice at the study site.(39)

- **Bibliographic databases or literature reports**

According to GVP, medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. This passive surveillance consists of screening by marketing authorization holders (MAH) and PV authorities of all the reports of suspected ADRs from the medical literature.(37) Thus, relevant published abstracts from meetings and draft manuscripts should be reviewed and assessed to identify and record ICSRs or potentially generate drug safety signals originating from spontaneous reports or non-interventional post-authorization studies.(37) Indeed, literature is one of the vital sources of signal detection and enables the gathering of international scientific information from diverse sources worldwide. Although the main limit of this approach is the fact that it is more time and resource-demanding, due to the high quantity of information that needs to be filtered, assessed, reviewed and analyzed, literature monitoring gives a broad perspective on the topic by including articles containing relevant safety information and/or emerging safety issue processes, a wide range of data, and the inclusion of different cultural, geographical, and socioeconomic contexts.(37,40,41)

- **Cohort event monitoring**

Cohort event monitoring (CEM) is an active form of surveillance, similar in design and management to an epidemiological cohort study. As a drug safety monitoring approach, CEM systems could be implemented to complement ICSRs. Indeed, CEM entails intensifying follow-up and looking for different outcomes such as benefits or risks of selected medicinal products

over a period of time.(29,42) CEM is restricted to a subset of products but has showed its effectiveness in drug safety monitoring in countries where there is no stringent pharmacovigilance system and the collection of ICSRs is not guaranteed as observed with major public health programs in developing countries.(29,42) To encourage National tuberculosis program in CEM implementation, WHO in 2015 published guidelines related to the framework of implementation of the active drug safety monitoring and management (aDSM).(24) Meanwhile, aDSM is related to patients treated with: (i) new anti-TB drugs; (ii) novel MDR-TB regimens; or (iii) extensively drug-resistant TB (XDR-TB) regimens, in order to detect, manage and report suspected or confirmed drug toxicities.(24)

- Sentinel site

In this active surveillance approach, drug safety monitoring is done in preselected and identified treatment sites. Here the method consists of reviewing medical records or interviewing patients and/or physicians to collect or ensure complete and accurate data on reported adverse reactions from these sites.(29) The main advantage of this approach is the possibility to collect relevant information from these sentinel sites such as data from specific patient subgroups or utilization practices of targeted drugs that could not be available in a spontaneous reporting system.(29)

- Clinical Registries

Nowadays, registries increasingly become an important active method used in drug post-marketing surveillance.(29,43) Indeed, disease and product registries that systematically collect data on all eligible patients are an extraordinary resource for capturing key or new safety information.(43,44) Thus, clinical registries could be very helpful as a drug safety monitoring system as they are able to benchmark national standards, monitor trends in patient characteristics, procedural and drug details and most importantly monitor clinical outcomes. This approach could be suitable for MDR-TB patients as registries commonly enroll

complicated patients in terms of the complexity of their underlying disease, their comorbidities, and their concomitant medication.(44)

- **Longitudinal electronic patient records**

Electronic health records (EHRs) are extremely valuable but underused in analyzing real-world use of medicines.(45) Meanwhile, the use of EHRs is a proactive approach to pharmacovigilance as they contain real- time real-world clinical data gathered during routine clinical care. (45,46) Thus, EHRs are a tremendous resource for drug safety monitoring as they provide detailed information on extended parts of patient's medical histories.

Beyond allowing follow-up during a long period of time and accessibility to essential clinical information as drug prescriptions, laboratory test results, hospital referrals or admissions, notes on symptoms, signs and diagnoses, one of the added values of EHR is inclusion of information on both exposed and unexposed patients.(42) Moreover, the use of longitudinal database on drug safety monitoring is advantageous because compared to ICSRs, patients EHRs carry more complete information on the medical history, previous treatment undertaken, comorbidities, and medications taken before and after the event of interest.(42)

1.4.2. Drug safety monitoring of MDR-TB treatment in Cameroon

In Cameroon clinical and therapeutic management of MDR-TB treatment are placed under the responsibility of the NTP. The NTP is organized following the health system from the central to the peripheral level. At the central level there is a technical central group that ensures national-level coordination . Each of the ten administrative regions of the country has a regional technical group which is in charge of implementing the national policy and guidance of TB at the regional level. Then, at the peripheral levels, there are TB diagnostics and treatment centers (CDT) within health facilities. As MDR-TB is rarer and more complex to manage than susceptible TB, there is a reduced number of 24 CDT at the national level, among which the

Jamot Hospital of Yaoundé (JHY) which is a referral CDT of the country in charge of 2/3 of MDR-TB patients. (47)

To harmonize practices and ensure efficiency in its functioning, the Cameroonian NTP commonly released under the control of the Ministry of Public Health Guidelines relating to the management of tuberculosis in Cameroon. In terms of content, these guidelines always have two sections dedicated to treatment and pharmacovigilance. In these parts, treatments are described in line with the WHO recommendations and a set of potential ADR are listed with the different levels of severity and potential behaviors to undertake in case of ADR incidence. Physicians are advised to systematically record identified adverse events in the patient's file and grade them according to severity (Table 2). Moreover, only severe adverse reactions are mandatory to be reported using the standardized form of the Ministry of Public Health.(47)

Table 2:Rating of severity of adverse drug reactions in adults

DEGREE	TYPE	DESCRIPTION
DEGREE 1	Mild anomaly	Mild and transient discomfort, without limitation of usual daily activity; does not require medical intervention.
DEGREE 2	Moderate abnormality	Partial limitation of usual daily activity; medical intervention or corrective treatment may not be necessary.
DEGREE 3	Severe abnormality	Limitation of usual daily activity; requires medical intervention and corrective treatment, hospitalization possible
DEGREE 4	Life-threatening or permanent injury	Very limited activity: requires medical intervention and corrective treatment, almost always hospitalized

In a template of MDR-TB patients' medical dossiers, there is a section related to drug safety monitoring where the physician is supposed to report any occurrence of ADR. Internally there is no functional unit of pharmacovigilance in the NTP, but a pharmacist in charge of drug procurement is officially appointed as PV focal point. He is supposed to work with the vigilance service located at the Directorate of Pharmacy, Drugs, and Laboratories (DPML). Hence, there

is no national PV center but a service of 4 staff coordinating this activity in the whole country. Spontaneous reporting is the only Drug safety monitoring approach implemented at the level of the NTP as all the ADRs captured at the level of the NTP are supposed to be reported to the vigilance service of the DPML. Meanwhile, exploiting Vigibase showed that out of the 7,996 ADRs reported from Cameroon, only three cases of AEs were related to anti-tuberculosis ethambutol, isoniazid, and linezolid.

2.PROBLEMATIC AND OBJECTIVES

2.1.Problematic

MDR-TB is a dangerous and mortal disease that requires particular clinical and psychological management by health care providers and society. Its therapy is very complex due to the high number of drugs taken on a daily basis and treatment duration.(48–52) The frequent occurrence of safety issues related to the toxicity of drugs used during MDR-TB treatment decreases expected effectiveness, treatment outcomes and constitutes a barrier for the global progress made towards ending the TB epidemic.(48,53–55) Weaknesses of pharmacovigilance systems in Africa do not favor drug safety monitoring and the optimization of MDR-TB treatment. Beyond the latter, the realization of the current thesis could be justified by different observations in the Cameroonian Health System.

Indeed, there is no stringent pharmacovigilance system in Cameroon and there is a limited implementation of drug safety monitoring activities in the country's public health programs.(56) Additionally, despite the known importance of drug safety monitoring during the length and complex MDR-TB therapy which is associated with the occurrence of numerous ADRs, only three ICSRs related to ethambutol, linezolid and isoniazid were recorded in the national database of pharmacovigilance held by the Cameroonian Ministry of Public Health. Even at the level of the national control program of TB, no safety concerns, or results on drug utilization studies of antituberculosis agents were appropriately documented. More so, in Cameroon there is no existing registry, EHRs or CEM to ease the follow-up of patients treated for MDR-TB. Furthermore, to the best of our knowledge, there are no studies in the literature that specifically aim to describe the burden of safety issues experienced by MDR-TB patients in Cameroon.

2.2.Objectives

The Main objective of this thesis was to evaluate the safety profile of drugs used for the treatment of multidrug-resistant tuberculosis in Cameroon.

To meet this goal, the first study aimed to evaluate the safety issues detected in the most important referent center for MDR-TB management in Cameroon.

The second study aimed to evaluate the MDR-TB drug utilization patterns and the impact of safety issues in drug persistence.

Finally, as during the second year of this thesis WHO launched new guidelines for the management of MDR-TB, we studied their impact in both safety issues and drug persistence.

**3.EVALUATION OF THE SAFETY OF
ANTITUBERCULOSIS AGENTS USED FOR
MULTIDRUG-RESISTANT TUBERCULOSIS IN
CAMEROON.**

3.1. Background

Efficacious pharmacological therapies are always related with a certain extent of risks. Drug safety issues need to be recognized as soon as possible and well managed in order to ensure expected clinical outcomes of drug uses.

The likelihood of AE increases with the number of medications used by patients. As polypharmacy, is an integral part of composition of MDR-TB treatment regimens, incidence of ADRs associated ranges from 20% to 90%.(48,57,58) If joint pain, nausea, vomiting, ototoxicity, are commonly associated with TB treatment, little remains known about their safety profile when used concomitantly for the management of MDR-TB.(48,58–61) This situation is particularly relevant in African countries without strong spontaneous reporting systems, like Cameroon. Indeed, even though NTP highlighted the importance of drug safety monitoring of MDR-TB treatment regimens in the national treatment guidelines of drug resistant tuberculosis, limited pharmacovigilance activities are implemented in real life by CDT. Collaboration with the National PV system is not efficient and a very low rate of ADR occurring during TB treatments are reported to the authorities. At the date of 12th of September 2023 for instance, only three cases of AE following tuberculosis treatment were recorded in Vigibase as ICSRs from Cameroon. Moreover, there is no other database or monitoring system allowing the review of ADRs related to MDR-TB treatment at the national level. Even in the literature, there is not much clinical case reports or studies describing whether adverse events impact treatment outcomes of MDR-TB in Cameroon. Thus, the first study of this thesis aimed to evaluate the incidence, the severity and the clinical presentation of AE related to MDR-TB treatments, and to identify those leading to treatment drug discontinuation or regimen modification. This work was published in the *International Journal of Mycobacteriology* and will be described in the next chapter.

3.2.Safety of antituberculosis agents used for multidrug-resistant tuberculosis among patients attending the Jamot Hospital of Yaounde, Cameroon

Mpoh MM, Deli V, Daniel TT, Salvo F. Safety of antituberculosis agents used for multidrug-resistant tuberculosis among patients attending the Jamot Hospital of Yaounde, Cameroon. Int J Mycobacteriol 2023;12:168-74.

Safety of Antituberculosis Agents used for Multidrug-Resistant Tuberculosis among Patients Attending the Jamot Hospital of Yaounde, Cameroon

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Abstract

Background: Recognized in 1994 as a global emergency by the World Health Organization, tuberculosis (TB) remains an ongoing health threat. In Cameroon, the mortality rate is estimated at 2.9%. Treatment of multidrug-resistant TB (MDR-TB) defined as the resistance to the two most effective anti-TB drugs, and requires therapy of more than 7 drugs taken on a daily basis during 9–12 months. This study aimed to evaluate the safety profile of treatment regimens used for MDR-TB at Jamot Hospital of Yaounde (JHY). **Methods:** This was a retrospective cohort study of patients treated for MDR-TB at JHY from January 1, 2017, to December 31, 2019. Patients characteristics of the cohort, drugs regimen were collected and described. All possible adverse drug reactions (ADR) were described clinically and by severity grade. **Results:** During the study period, 107 patients were included, and 96 (89.7%) experienced at least one ADR. Most parts of the patients (90) experienced mild or moderate ADR. Hearing loss was the most frequent ADR, and led mostly in aminoglycosides dose reduction ($n = 30$, 96.7%). Gastrointestinal events were commonly observed during the study period. **Conclusion:** Our findings suggested that ototoxicity was a prominent safety issue during the study period. The implementation of the new short treatment regimen could be effective in reducing the burden of ototoxicity among MDR-TB patients. Nevertheless, new safety issues could emerge.

Keywords: Adverse drug reactions, Cameroon, multidrug-resistant tuberculosis, pharmacovigilance, safety

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INTRODUCTION

In the last decades, tuberculosis (TB) which is a lung disease caused by *Mycobacterium tuberculosis* becomes a major public health problem worldwide and especially in Cameroon where its mortality rate is estimated at 2.9%.^[1,2] Sneezing, coughing, and spitting are the well-known mode of contamination from person to person.^[2] Due to its related morbidity and mortality, this disease has been recognized in 1994 as a global emergency by the World Health Organization (WHO). Ranked among the top ten causes of death worldwide, TB was also identified as the leading cause of death among patients living with acquired immunodeficiency syndrome (AIDS) in 2020.^[3,4]

Multidrug-resistant TB (MDR-TB) is a serious and mortal disease characterized by the resistance to the two most

effective first-line anti-TB drugs, isoniazid and rifampicin. WHO estimated that 484,000 new cases of MDR-TB were diagnosed in 2020.^[2]

Since 2016, WHO recommend a standardized short treatment regimen (STR) of 9–12 months for MDR-TB patients who

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ABSTRACT

Background: Recognized in 1994 as a global emergency by the World Health Organization, tuberculosis (TB) remains an ongoing health threat. In Cameroon, the mortality rate is estimated at 2.9%. Treatment of multidrug-resistant TB (MDR-TB) is defined as the resistance to the two most effective anti-TB drugs, and requires therapy of more than 7 drugs taken on a daily basis during 9-12 months. This study aimed to evaluate the safety profile of treatment regimens used for MDR-TB at the Jamot Hospital of Yaoundé (JHY).

Methods: This was a retrospective cohort study of patients treated for MDR-TB at HJY from January 1, 2017, to December 31, 2019. Patients characteristics of the cohort, drugs regimen were collected and described. All possible adverse drug reactions (ADR) were described clinically and by severity grade.

Results: During the study period, 107 patients were included, and 96 (89.7%) experienced at least one ADR. Most patients (90) experienced mild or moderate ADR. Hearing loss was the most frequent ADR, and led mostly in aminoglycosides dose reduction (n = 30, 96.7%). Gastrointestinal events were commonly observed during the study period.

Conclusions: Our findings suggested that ototoxicity was a prominent safety issue during the study period. The implementation of the new short treatment regimen could be effective in reducing the burden of ototoxicity among MDR-TB patients. Nevertheless, new safety issues could emerge.

INTRODUCTION

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Since 2016, WHO recommend a standardized short treatment regimen (STR) of 9–12 months for MDR-TB patients who have not been previously treated with second-line drugs and for whom resistance to fluoroquinolones and second-line drugs has not been observed or is considered unlikely. [3]

Despite the narrow monitoring of the observance and the obligation of the directly observed treatment during the entire treatment, MDR-TB therapy remains complex and related to the occurrence of safety issues. Indeed, the high number of drugs taken on daily basis and the length of MDR-TB therapy increase the likelihood of adverse drug reactions (ADRs), mostly ototoxicity and gastrointestinal disorders with symptoms ranging from mild to severe. [4–6]

As there is limited information available on the exact burden of ADR experienced by patients treated for MDR-TB, the first aim of this study was to evaluate the safety profile of treatment

regimens used for MDR-TB management in one hospital of Cameroon. Moreover, this study aimed to assess the severity of adverse events related to MDR-TB treatments, and identify adverse events leading to treatment drug discontinuation or regimen modification.

METHODS

Study design and data source

This was a retrospective cohort study of patients suffering from MDR-TB who received a treatment regimen at Jamot Hospital of Yaoundé (JHY). JHY is the Cameroonian reference hospital for the treatment of TB, and two-thirds (2/3) of MDR-TB cases were treated there. Patients hospitalized between January 1, 2017 and December 31, 2019, were included.

Among them, patients aged with less than 18 years or those with no information available in the medical records were excluded. All information was retrieved from their medical records, which were routinely updated each month.

Patients were followed and data were collected from the 1st day of treatment (Month 1, M1) to: (i) The end of treatment or last visit with available clinical information, (ii) diagnosis of ultra-resistant TB, or (iii) death.

Drug exposure

During the study period the WHO STR was used routinely.[3] This last for 9–11 months and is divided into two phases: An intensive in hospital phase, and continuous ambulatory phase. The intensive phase lasted 4–6 months of daily treatment with 6 antibiotics (moxifloxacin, prothionamide, isoniazid high-dose, clofazimine, ethambutol, and pyrazinamide) associated with kanamycin or amikacin.

For this study the treatment regimen was categorized in relation to the injectable aminoglycosides or any other drug of choice used during the intensive phase.

The continuous ambulatory phase had a fixed treatment duration of 5 months with 4 antibiotics: Moxifloxacin, clofazimine, ethambutol, and pyrazinamide.

Aside from these guidelines, each drug dose modification or drug switch was described as well as its cause (e.g. ADR or drug shortage).

Safety data

Clinical events that occurred during the study period that patients' practitioners considered as possible ADR and reported in the medical files were collected. ADRs were categorized into digestive, kidney, hepatic, neurological, auditory, and other disorders. The physician reported at each visit both ADRs and their severity, using the scale proposed by the French Agency for the Research in AIDS and hepatitis, (National Agency for Research on AIDS and Hepatitis), which corresponds to the first four grades of the Common Terminology Criteria for Adverse Events.[7] As fatal ADRs were not included in this classification, they were considered Grade 5.

Data collection

Data were extracted from medical records in an electronic clinical reporting form, developed using Microsoft office 15.0 Access Database. Three separate sections were produced; the first section was related to the patient's characteristics at baseline namely: sex, age, weight, HIV status, MDR-TB type, TB treatment history, and audiogram status. The second section concerned prescribed treatments, including drug type, doses, eventual switches or dose reduction, start and end date. The third section concerned ADR, with onset month, and severity.

Statistical analysis

A descriptive analysis was conducted on the following variables: gender, mean age and age groups (18–30 years, 31–45 years, 46–60 years, 61–75 years), weight classes (according to the

WHO recommendation for drug doses [30–39 kg; 40–54 kg; 55–70 kg; >70 kg]), TB type (Pulmonary [P]; Extra pulmonary [EP]; both or unknown), TB history (patients never treated for TB before, the patient already treated for TB before, or unknown) HIV status, and initial audiogram status (normal, abnormal). The regimen type (e.g. amikacin, or linezolid based) was also described.

All the data were analyzed using R Software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>). Participants' baseline characteristics were summarized using frequencies and proportions or mean and standard deviation, depending on the type of the variable. To analyze the differences in patient characteristics by main observed adverse events, we used either chi 2 or Fisher exact test for categorical variables and a 2-sample t-test for continuous variables, respectively.

Ethical consideration

The present study was expected to evaluate the safety of drugs used for the treatment of multi-resistant TB. Key information was communicated to the National Program of TB and the Ministry of Public Health, which allowed the beginning of the study.

RESULTS

Study population

During the study period, among 115 potentially eligible patients, five were excluded because no information was available, and three were because they were under 18-year-old. Thus, one hundred and seven patients were included in this study.

Concerning baseline characteristics [Table 1], the sex ratio (M/F) was 1.6 and the mean age was 37 ± 12 years old. Among them, 87 (81.3%) had a pulmonary MDR-TB, one had extrapulmonary and 15 (14.1%) had both MDR-TB. A total of 76 patients (71.0%) had received

a TB treatment before becoming MDR-TB. In our cohort, 39 (36.4%) patients were HIV positive, and 45 (42.1%) reported audiogram abnormalities at baseline.

Table 1. Cohort baseline characteristics.

Characteristics	N= 107 (%)
Sex	
Male	67 (62.6)
Female	40 (37.3)
Age	
Mean age, years (+/- SD)	37.0 (12.0)
18-30	39 (36.4)
31-45	43 (40.1)
46-60	21 (19.6)
61-75	4 (3.7)
Weight classes (WHO)	
30-39 kg	8 (7.5)
40-54 kg	41 (38.5)
55-70 kg	45 (42.05)
>70 kg	13 (12.1)
Type of Tuberculosis	
Pulmonary	87 (81.3)
Pulmonary and/or Extra pulmonary	16 (15.0)
Unknown	4 (3.7)
TB Treatment History	
Never treated	26 (24.3)
Already Treated	76 (71.0)
Unknown	5 (4.7)
Baseline Audiogram status	
Normal	53 (49.5)
Abnormal	45 (42.1)
Unknown	9 (8.4)
HIV status	
Positive	39 (36.4)
Negative	68 (63.6)

Drug use and switches

A total of 99 patients (92.5%) started the intensive phase with kanamycin base treatment, five patients (4.6%) with linezolid, and three patients (2.8%) with amikacin [Table 2].

Table 2: Treatment duration and switch (n=107)

Drug	N=107 (%)
MDR-TB Treatment regimen	
Kanamycin based regimen	99 (92.5)
Linezolid based regimen	5 (4.6)
Amikacin based regimen	3 (2.8)
Drug switch or dose change during follow-up	
Yes	26 (24.2)
No	81 (75.7)

Out of the 107 Patients, 30 (28.03%) changed the drug or its doses during the follow-up period, for a total of 34 changes [2 drug switches, 32 changes in drug doses, 31 doses reduction and 1 dose increase, Table 2].

Adverse drug reactions

A total of 96 patients (89.7%) experienced at least one ADR during the study follow-up, mostly of mild or moderate severity grade (n = 90, 84.1%). Two-thirds of the included patients (70 on 107) developed hearing impairment of grade 1 only (38, 35.5%), grade 2 only (14, 13.08%), or both grade 1 and 2 (18, 16.8%). A total of 448 ADRs have been collected from the patient's medical records [4.5 ADR per patient; Table 3].

Table 3: Adverse drug reaction occurred during multidrug-resistant tuberculosis treatment (n=107)

Type of Adverse event	Total N = 107 (%)	Grade 1 N= 107 (%)	Grade 2 N= 107 (%)	Grade 3 N= 107 (%)	Grade 4 N= 107 (%)	Grade 5 N= 107 (%)
Hearing impairment	70 (65.4)	57 (53.2)	32 (30.0)	-	-	-
Vomiting	32 (30.0)	32 (30.0)	-	-	-	-
Nausea	12 (11.2)	12 (11.2)	-	-	-	-
Abdominal pain	6 (5.6)	6 (5.6)	-	-	-	-
Paresthesia	4 (3.7)	4 (3.7)	-	-	-	-

Sudden death NOS	3 (2.8)	-	-	-	-	3 (2.8)
Arthralgia	3 (2.8)	2 (1.8)	1 (0.9)	-	-	-
Duodenal ulcer	3 (2.8)	-	3 (2.8)	-	-	-
Diarrhea	2 (1.8)	2 (1.8)	-	-	-	-
Acute kidney injury	2 (1.8)	-	-	2 (1.9)	-	-
Hyperuricemia	2 (1.8)	2 (1.8)	-	-	-	-
Hepatic enzyme increased	2 (1.8)	2 (1.8)	-	-	-	-
Pruritus	2 (1.8)	2 (1.8)	-	-	-	-
Myocardial infarction	1 (0.9)	-		1 (0.9)	-	-
Sinus tachycardia	1 (0.9)	1 (0.9)	-	-	-	-
Palpitations	1 (0.9)	1 (0.9)	-	-	-	-
Cholestatic icterus	1 (0.9)	1 (0.9)	-	-	-	-
Cataract	1 (0.9)	1 (0.9)	-	-	-	-
Creatinine increased	1 (0.9)	1 (0.9)	-	-	-	-
Dyspepsia	1 (0.9)	-	1 (0.9)	-	-	-
Eye disorders	1 (0.9)	1 (0.9)	-	-	-	-
Glaucoma	1 (0.9)	1 (0.9)	-	-	-	-
Hypersomnia	1 (0.9)	1 (0.9)	-	-	-	-
Hypothyroidism	1 (0.9)	1 (0.9)	-	-	-	-
HIV-associated nephropathy	1 (0.9)	-	-	1 (0.9)	-	-
Knee pain	1 (0.9)	1 (0.9)	-	-	-	-
Vertigo	1 (0.9)	1 (0.9)	-	-	-	-

Hearing impairment was the most frequently related to a drug switch (n = 1, (50%) or a dose reduction (n = 30, 96.7%). Indeed, among drug switches, linezolid was changed with Kanamycin because of drug shortages, while amikacin was changed with kanamycin because hearing impairment.

Among changes in drug doses, the kanamycin dose was reduced 29 times because of hearing impairment; The amikacin dose was reduced because of hearing impairment in one patient, while the pyrazinamid dose was decreased because of hyperuricemia. Moreover, moxifloxacin was contextually increased because of a risk of progression to ultra-drug-resistant TB (dose increase from 400 mg to 800 mg/day).

Six patients (5.6%) experienced \geq grade 3 adverse events:

Three sudden death occurred in men with pulmonary TB, aged 19, 28, and 56 years (HIV positive). Two patients died in the 1st month of follow-up, one in the 7th month; two patients weighed 55–70 kg and one 40–54 kg. One patient was treated with a linezolid based-regimen, and others with a kanamycin-based regimen.

Two acute kidney injuries occurred in men, both aged 33 years, weighed between 55 and 70 kg or >70 kg. One case was associated with HIV-related nephropathy. Both patients were treated with kanamycin-based regimen and both had pulmonary TB. The event occurred for both the 1st month of treatment.

One myocardial infarction occurred in a man, aged 48, weighted >70 kg, with unknown TB history, and under kanamycin regimen. This event occurred during the 1st month of treatment.

The description of these cases was poor without any element clearly supporting the role of the drugs used for the control of MDR-TB.

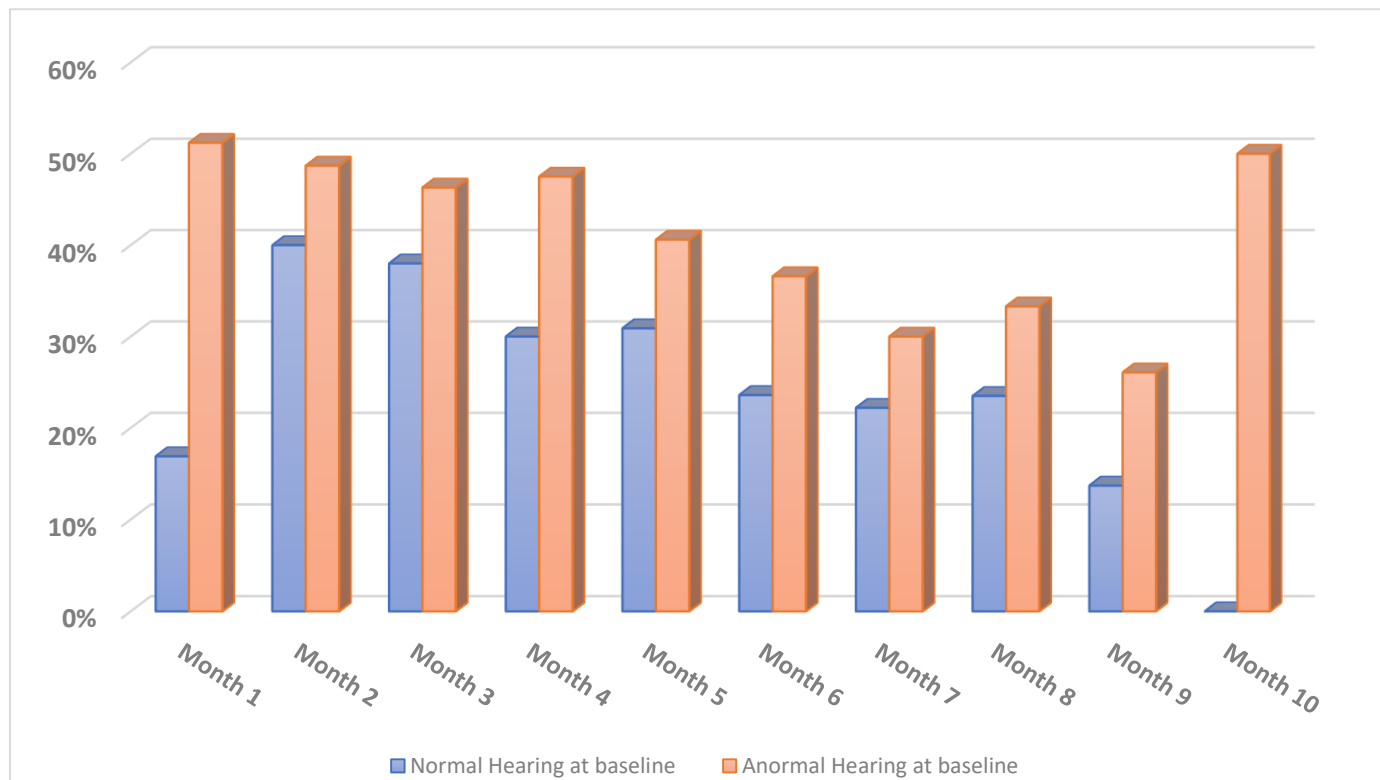
Hearing loss

A total of 70 patients (65.4%) developed hearing loss during the study follow-up. Among them, 53 patients (49.5%) were free of any hearing issues at baseline.

The most frequent hearing impairment was tinnitus ($n = 25$; 23.3%), followed by hearing loss ($n = 20$; 18.7%), bilateral (11 cases, 10.2%) or mono-lateral (9 cases, 8.4%). For 26 patients (24.2%), the detail of the hearing impairment was not recorded.

Out of the 53 patients who had normal hearing at baseline, 70% ($n = 37$) developed a hearing impairment recorded during the study follow-up. Figure 1 shows the reporting time of hearing impairment according to the study visits. Among patients without any hearing impairment at baseline, 16.9% of patients developed hearing impairment at M1. This rate increase up to 40% at M2, and decreased progressively thereafter. Regarding patient of special interest, out of 28 (71.7%) of the 39 patients living with HIV included in this study faced hearing impairment during their treatment while 42 (61.7%) among the 68 patients without HIV experienced it.

Figure 1. Rates of patients with hearing impairment according to follow-up.



DISCUSSION

The key findings showed that most parts of included patients developed an ADR related to the MDR-TB treatments. Most parts of ADR were non severe and probably related to aminoglycoside treatment. The dose reduction because of hearing impairment was the most frequent action for individual risk management.

The study cohort seems quite representative of the Cameroonian population affected by MDR-TB. For example, the sex ratio of the patients involved in this study is globally the same as that reported by the Cameroonian statistics in 2019 in which men represent 61% while women represent 39%.[8] Moreover, the mean age was also in line with the national data which ranks the age of people suffering from TB from 25 to 44 years old. Concerning HIV-TB co-infection, our prevalence is quite higher than the 27% estimated in Cameroon.[8] This could be understood as immunocompromised patients could develop more frequently MDR-TB.[9]

Patients were mainly treated at JHY with the WHO recommended STR with injectable kanamycin as the aminoglycoside of choice during the intensive phase.[10] Among patients that didn't start with kanamycin, three started with amikacin. The latter could be used as an alternative, but is considered at higher risk of ototoxicity.[9,11] Five other patients started with linezolid, which was at the time of the study a well-admitted practice. Indeed in 2018, the international union against TB and lung disease highlighted in their practical guide to the management of resistant TB that delamanid, linezolid, or bedaquiline could be used instead of aminoglycosides.[12] In 2021, Souleymane MB et al. showed that, among patients treated in Niger for pulmonary MDR-TB from 2016 to June 2018 with STR, 12.7% had a linezolid-modified STR, both used at the beginning of treatment or after a kanamycin induced hearing loss.[13]

The safety of MDR-TB is thus an issue that has a high impact on prescription practice. The high frequency of ADR observed in this study was quite similar to the study carried out in a tertiary hospital in Italy from 2008 to 2016. In the latter, Gualano G et al., reported that 66 out of 74 patients (89.2%) had experienced ADRs during their treatment.[14] This occurrence rate was nevertheless higher in comparison to others studies. Indeed, in 3 years 2000–2002, a study carried out in Russia reported that 73% of 244 patients experienced ADR from 2006 to 2007, while an Indian study reported an ADR rate of 58%.[15,16]

The present study showed that severe ADRs were infrequent, and accounted for <3%. Almost all severe ADRs occurred during the 1st month of treatment. This finding is not far from the proportion of patients who experienced severe ADRs during the first 6 months reported in Italy.[14] Our study collected also three sudden death, but any objective element was found to relate them to the prescribed drugs.

As reported by several studies, the high frequency of ADR occurrence among MDR-TB patients can lead to drug dose reduction, switch of drugs, or treatment interruption.[14,17] This is particularly observed with hearing loss as it can impact an individual's life by causing social isolation, reduced quality of life, and threatening employment stability and family prosperity.[9] That is corroborated by our findings as we observed that almost all of the observed drug switches and dose reductions were due to hearing impairment and related to kanamycin.

During the study period, ototoxicity was the most frequently reported safety issue, and hearing impairment affected almost two out of three patients. It is well known that a high proportion of MDR-TB patients develop hearing loss due to ototoxicity caused by aminoglycosides used during the STR's intensive phase.[9] However, the rate found in this study is clearly above the 10%–50% of aminoglycosides-induced hearing loss reported in 2018 by WHO from different continents.[18,19]

Several studies have reported that antiretroviral therapy is highly associated with an increased risk of ototoxicity, particularly in sub-Saharan African countries and patients co-infected need narrow and special audiometric monitoring.[9] In our study the prevalence of hearing loss was also slightly increased in patients with HIV compared to the rest of the cohort (71.7% vs. 61.7%).

Regarding the common occurrence of ototoxicity with aminoglycosides, systematic audiometry monitoring is recommended at baseline and during MDR-TB treatment.[18,19] In Cameroon, audiometry was systematically done at baseline, the second, and the 4th month. Nevertheless, even with a high proportion of auditory issues, any case of hearing impairment was reported to the Cameroonian pharmacovigilance system during the study period. Thus, if clinicians in Cameroon are well aware of the importance to carry out audiometric measures, actions are needed to increase the culture of spontaneous reporting that helps authorities to implement adequate risk minimization strategies.

Nowadays, bedaquiline is used in Cameroon as a drug of choice in the intensive phase regimen in alternative to aminoglycoside. In June 2020 WHO recommended a new STR for MDR-TB patients without previous exposure to second-line medicines for more than 1 month, where there is no fluoroquinolone resistance and the patients do not have extensive TB disease or severe extrapulmonary TB.[20] Those WHO recommendations followed the findings of several studies which have shown that the replacement of aminoglycosides with bedaquiline has better efficacy and safety with a high therapeutic success.[21–23] One of the advantages of bedaquiline is the fact it is orally administered allowing for easy administration. Meanwhile this drug reserve also safety issue as adverse events other than hearing impairment have to be monitored, such as QT interval (QTc) prolongation.[23,24] Thus, in Cameroon aminoglycosides were replaced with bedaquiline, and the safety monitoring of this new STR

regimen is now mainly based on the control of the cardiac function via standardized ECG at baseline and each month during the treatment period.

This will represent a new challenge for the Cameroonian pharmacovigilance system. Very few cases of ADRs occurred during the study period were reported. In the meantime, these safety data were searched and collected by clinicians. For future safety assessment, new tools could be envisaged in the context of the national TB Control Program, which could allow having data directly in a data warehouse that facilitates data extraction and analysis for data driven regulatory decisions. Besides hearing loss, gastrointestinal events were the most common adverse events observed in this study and affected more or less 1/3 of included patients. These findings are higher than the frequency retrieved in a Vietnamese cross-sectional study (14.2%).[25] The rate of patients who have developed a nephrotoxic event is also in line with the findings from other studies reporting a prevalence of 4%–10% of nephrotoxicity related to injectable anti-TB drugs.[26–30]

This study has some limitations. The sample size is relatively small, and it was a retrospective study based on already collected data in which some information was lacking, for example, the cause of death, and the evolution of ADRs. Moreover, ADRs were collected during monthly visits; it was thus not possible to correctly identify the actual start of the symptoms and the actual ADR evolution. As the study only aimed to collect ADRs reported by a physician in the medical files, laboratory changes were not systematically sought, thus an underestimation of ADRs needs to be accounted for.

CONCLUSION

To our knowledge, this study is the first specifically designed to estimate the incidence of ADR among MDR-TB patients in Cameroon, and describe their clinical features. As our findings suggested that ototoxicity was a prominent safety issue, the implementation of the new STR in

which aminoglycosides are abandoned could globally reduce the burden of ADRs among MDR-TB patients. Nevertheless, as aminoglycosides were replaced with bedaquiline, new safety issues could emerge. Thus, efficient and modern safety data flow need to be implemented in the context of a national program of TB to ensure the patients' safety.

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3.3.Key results and research perspective

This study allowed the identification of safety issues associated with MDR-TB treatment in Cameroon. The frequency and severity of most common adverse effects have been determined. Indeed, ADRs were commonly associated with MDR-TB treatment particularly during the first four months. If ADR were generally mild and moderate, serious adverse effects were also observed. Among the latter were sudden death, cardiovascular events, and kidney injuries. Far beyond gastrointestinal disorders, ototoxicity was the prominent safety issue and its occurrence deeply impacted the treatment regimen. Indeed, most of the drug switches and dose modification concerned aminoglycosides (amikacin and kanamycin) and was due to hearing loss.

We noticed that audiogram monitoring was only done during the second and the fourth month of treatment and was not always followed by appropriate action. Moreover, these safety concerns were known but not documented at the level of NTP neither were they reported to the vigilance service of the Directorate of Pharmacy, Drugs and Laboratories acting as a Cameroonian National pharmacovigilance center. Regarding the observed burden of hearing loss in MDR-TB patients, an appropriate drug monitoring system would have surely led to recommendation, requesting the replacement of aminoglycosides by other less toxic drug in the MDR-TB regimen in Cameroon. Meanwhile, insufficient funds for drug procurement, the expensiveness of the better alternatives like linezolid or bedaquiline and the obligation for the NTPs to implement treatment regimens granted by international organizations could be responsible of these weaknesses. Drug safety monitoring should be national duty and systematically conducted irrespective of the drugs' procurement source.

In fact, without an early detection and appropriate management, these safety concerns could damage public confidence, affect patient adherence and even lead to other complicated comorbidities like XDR-TB. Patients who stop taking anti-TB medicines pose a risk to

themselves and to others. The generation of drug resistance is a very real risk.(62) Implementing a framework of active drug safety monitoring at the national level would have helped data collection on serious adverse drug reactions and signal generation. Findings of this study emphasize the urgent need to improve adverse events reporting in the NTP. Thus, pharmacovigilance should be considered as an essential component of MDR-TB therapy and a close collaboration between the national NTP and the national authorities of pharmacovigilance is necessary.

ADRs occurring during MDR-TB treatment should be systematically sorted and documented to gather evidence of the safety profile of drugs used. NTP should ensure training of medical staff in pharmacovigilance and exploitation of safety data to locally improve patient therapy.

Findings from this study showed the ADRs incidence, severity and identified drug safety monitoring problems encountered during the treatment of MDR-TB patients, the issue thereafter was to understand the impact of these issues in the prescription habits and treatment compliance. Thus, the next step of our thesis aimed to assess drug utilization patterns and persistence.

4.DRUG UTILIZATION STUDY OF ANTITUBERCULOSIS USED FOR MULTIDRUG- RESISTANT TUBERCULOSIS TREATMENT IN CAMEROON

4.1. Background

Management of MDR-TB requires multiple medicines for a longer treatment duration with drugs that are more expensive and difficult to tolerate.⁽⁸⁾ As confirmed with our first study, previous research reported that ADR are common with STR and could lead to major morbidity, including gastrointestinal disturbances, hearing loss, renal failure, or liver failure. Up to date, there is no drug utilization assessment in Cameroon, or at least at the level of the NTP, allowing the continuous evaluation of drug utilization practices. Indeed, Drug Utilisation review (DUR) is a program that aims to determine whether patients receive, or are prescribed, appropriate medication to improve patient health status.⁽⁶⁴⁾ If safety issues could lead to treatment discontinuation or at least decline patient persistence to treatment, inappropriate utilization of drugs could also improve the toxicity or contribute to development of drug resistance. Thus, the clinical outcomes of any therapy are heavily related to drug utilization practices specifically for patients suffering from different comorbidities and following different comedications like MDR-TB patients.

In line with the common occurrence of AE which ranges from mild to moderate as observed in our first study, it seemed important to establish a potential link between the drug prescriptions, ADRs occurrence and persistence to treatment. Also, we intended to identify the patterns related to the treatment regimens implemented in Cameroon. Thus, our second research specifically aimed to assess the respect of WHO recommendations in terms of prescribed drugs and doses, and describe the persistence of patients. Persistence was then evaluated in two ways: firstly, persistence to program by evaluating the overall treatment completion and secondly, persistence to the drugs initially prescribed during each phase of MDR-TB treatment.

4.2. Research submitted to publication: Multidrug-resistant tuberculosis in Cameroon: respect of WHO recommendations and treatment persistence

Multidrug-resistant tuberculosis in Cameroon: respect of WHO recommendations and treatment persistence

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SUBMITTED

ABSTRACT

Background: Extensively drug resistant tuberculosis is mainly related to inadequate or incomplete treatment of Multidrug-resistant tuberculosis (MDR-TB). This study firstly aimed to assess the respect of WHO recommendation on MDR-TB treatment and secondly, to assess treatment persistence.

Methods: Using a retrospective study design, medical records were used to follow all patients treated for MDR-TB between 2017 and 2019 at Yaoundé Jamot Hospital, in Cameroon. The following evaluation criteria were assessed: the respect of WHO recommendations, and overall, intensive and continuous phase persistence, both to program and medications.

Results: A total of 107 patients were included in the cohort, and 91.5% (n=98) were treated according to the WHO recommendations. Thirty patients (28%) changed either drug or its doses during their treatment period. The overall treatment persistence was 51.4%, and was mostly due to a program withdrawn mainly during the first 30 days of each phase. The persistence for the intensive phase was 90.6%, while it was 61.8% for the continuous phase.

Conclusions: The WHO recommendation were mostly respected. Nevertheless, the persistence to MDR-TB decreased over time, and need tailored measure for increasing the rate of patients completing the regimen recommended by WHO, in particular in the continuous phase.

Keywords: anti-tuberculosis agents, drug safety, pharmacovigilance

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is described when *Mycobacterium tuberculosis* also known as Koch's Bacillus become resistant to at least isoniazid and rifampicin which are the two most effective medicines for susceptible tuberculosis (1).

During the two last decades, the worldwide spread of MDR-TB and the inappropriate utilization of antitubercular drugs led to the development of a newer form called extensively drug resistant tuberculosis (XDR-TB). Nowadays, it is widely known that MDR-TB and XDR-TB are man-made problems as they are mostly related to incorrect physicians' prescribing practices leading to inadequate or incomplete treatment, and low treatment adherence (2–4). Indeed, rational use of drugs is essential to ensure treatments' efficacy, safety and prevent the occurrence of drug resistance. That is why to avoid the development of new form of resistance, the basic rule is to make directly observed treatment (DOT) mandatory for each case of tuberculosis. Thus, DOT is a strategy usually used in tuberculosis therapy which consists for the patient, to take his medication in the presence of a health care professional or another designated person. This is particularly true for MDR-TB treatment regimens, which last between 9 and 12 months as recommended by the WHO treatment guidelines (5).

In Cameroon, there are no previous studies that evaluate the drug use and persistence in patients with MDR-TB. Thus, this study firstly aimed to evaluate the actual implementation of the Shorter Treatment Regimen (STR) of MDR-TB recommended by WHO in terms of prescribed drugs and doses. Secondary objectives were to describe persistence of patients to STR, overall and for each STR phase.

METHODS

Study population

Patients aged 18 or older following a MDR-TB treatment at the Jamot Hospital in Yaoundé (JHY) from January 1, 2017 to December 31, 2019 were included in this three year retrospective study. Only patients owning medical records with available information on treatment prescription and history of drug consumption were selected. Patients were followed up to the end of the study treatment (9 or 11 months) or up to when they were lost. Data were collected in a daily basis from the first to the last day of treatment.

During the study period, STR proposed by the WHO for management of MDR-TB were normally used in routine by all the treatment centres of tuberculosis in Cameroon (5), suggesting a treatment of at least 9 months divided into two phases: an intensive phase, followed by a continuous ambulatory phase.

In Cameroon the intensive phase was an in-hospital phase and lasted between 4 and 6 months of daily treatment with seven antibiotics: an aminoglycoside between kanamycin or amikacin associated with moxifloxacin, protionamide, isoniazid high-dose, clofazimine, ethambutol, and pyrazinamide. The continuous phase had a fixed treatment duration of 5 months with 4 antibiotics: moxifloxacin, clofazimine, ethambutol, and pyrazinamide.

Data source and collection

Data were extracted from patients medical records on an electronic reporting form, developed using Microsoft office 15.0 Access Database. Two separate sections were used to collect data. The first section was related to the patient's characteristics at baseline, namely: sex, age, weight and HIV status and the TB treatment history. The second section concerned drug utilization and included all the following information: the starting date of MDR-TB treatment, prescribed

drugs, daily doses (mg/d) or weekly doses (mg/w) when needed, the treatment duration, doses changes, drugs switches, the end date of treatment.

Evaluation criteria

STR implementation was evaluated by comparing drugs, doses, frequency of administration, and treatment duration prescribed by physicians to those recommended in the guidelines related to drug resistant tuberculosis treatment released in 2016 (Table 1).

Table 1: Recommended doses of drugs during the intensive and continuous phases.

Drugs	Intensive Phase Daily Dose (mg)				Continuous Phase Daily Dose (mg)			
	30-39 Kg	40-54 Kg	55-70 Kg	Over 70 Kg	30-39 Kg	40-54 Kg	55-70 Kg	Over 70 Kg
Amikacin/Kanamycin	500	750	1000	1000	/	/	/	/
Clofazimine	50	100	100	100	50	100	100	100
Ethambutol	600	800	1200	1400	600	800	1200	1400
Isoniazid	300	450	600	600	/	/	/	/
Moxifloxacin	400	600	800	800	400	600	800	800
Protionamide	500	500	750	1000	/	/	/	/
Pyrazinamide	800	1200	1600	2000	800	1200	1600	2000

Prescription changes, i.e. drug dose modification and drug switches, were identified and described as well as their cause (e.g. ADR or drug shortage).

The overall program persistence concerned patients that were followed for at least 9 months. Intensive or continuous phase persistence concerned patients the concluded each phase, while persistence to the proposed initial therapy concerned patients that completed intensive or continuous phase, without any drug or dose modification.

Statistical analysis

A descriptive analysis was conducted to characterize the sample of this study. Participants' baseline characteristics were summarized using frequencies and proportions or mean and

standard deviation, depending on the type of the variable. Patients were grouped by sex, Age (18-30 years, 31- 45 years, 46-60 years, 61-75 years), weight classes (according to the WHO recommendation for drug doses [30-39 kg; 40-54 kg; 55-70 kg; >70 kg]), HIV status and TB treatment History (already treated for TB before (F) and Never treated for TB before (N)).

The persistence was evaluated on daily basis and expressed as the cumulative rate of patients that have completed each phase of the program on the total number of eligible patients. For intensive phase, only the first four months were considered, while the continuous phase was considered started from the first day of the initiation of pertinent treatments.

Per each phase, patients were considered persistent to the program if they were not lost to follow-up, while were considered persistent to the treatment if they continued up to the end of each phase with the proposed initial treatment. For the latter analysis, only patients that were not lost to follow up were considered. All the data were analyzed using Microsoft Excel ® 2018.

Ethical consideration

National Program of tuberculosis and Ministry of Public Health consent was obtained before the beginning of the study. The confidentiality of the information was ensured because neither the names of the patients, nor their date of birth, nor their origin were recorded.

RESULTS

Patients characteristics

During the study period, 107 patients were included during the three-year period. The sex ratio (M/F) was 1.54 and the average age 37 +/-12 years old. A total of 24.3% were considered naïve patients as they didn't have any TB treatment story. Almost all patients started the intensive STR phase with WHO recommended drug regimen: kanamycin-based regimen (92.5%), and

amikacin-based regimen (3 patients; 2.8%). Only 5 patients (4.6%) started with a linezolid-based regimen (Table 2).

Table 2. Baseline characteristics of patients

Characteristics	N= 107 (%)
Sex	
Male	67 (62.6)
Female	40 (37.3)
Age	
Mean age, years (+/- SD)	37.0 (12.0)
18-30	39 (36.4)
31-45	43 (40.1)
46-60	21 (19.6)
61-75	4 (3.7)
Weight classes (WHO)	
30-39 kg	8 (7.5)
40-54 kg	41 (38.5)
55-70 kg	45 (42.0)
>70 kg	13 (12.1)
HIV status	
Positive	39 (36.4)
Negative	68 (63.6)
TB Treatment History	
Never treated	26 (24.3)
Already Treated	76 (71.0)
Unknown	5 (4.7)
MDR-TB Treatment regimen at baseline	
Kanamycin based regimen	99 (92.5)
Linezolid based regimen	5 (4.6)
Amikacin based regimen	3 (2.8)

Respect of WHO recommendations

Overall, 91.5% (n=98) of patients started MDR-TB treatment according to the WHO recommendations. Among the others (n=9 patients), all non-conformities occurred in the intensive phase, mostly in women (n=6; 66.6%), and in patients weighted 30-39 kg (n=7; 77.7%). They mostly concerned clofazimine (n=7; 87.5%, sole non-conformity in four patients), for which patients received the double of the expected dose (100 mg instead of 50 mg daily). Four patients had more than four non-conformities, mostly receiving the double of expected dose (Table 3).

Table 3: non-conformities observed on initial prescription of MDR-TB treatment

Drugs	Daily Dose (g)					
	30-39 Kg		40-54 Kg		55-70 Kg	
	RD/PD*	Patients** n=8 (%)	RD/PD	Patients n=41(%)	RD/PD	Patients n=45(%)
Kanamycin	500/1000	1 (12.5)	750/1000	1 (2.4)	1000/-	-
Clofazimine	50/100	7 (87.5)	100/-	-	100/-	-
Isoniazid	300/600	1 (12.5)	450/-	-	600/-	-
	300/900	1 (12.5)				
Protionamide	500/750	3 (37.5)	500/750	1(2.4)	750/1000	1(2.2)
Pyrazinamide	800/1600	3 (37.5)	1200/1600	1(2.4)	1600/-	-
Moxifloxacin	400/800	1 (12.5)	600/-	-	800/-	-
Ethambutol	600/1200	3 (37.5)	800/1200	1(2.4)	1200/1400	1(2.2)

**RD/PD: Recommended Dose/Prescribed Dose*

***One patient could have reported several non-conformities. Thus, numbers and rate are not mutually exclusive.*

Dose modification or drug switch

Out of the 107 Patients, 30 (28%) changed the drug or its doses during their treatment period, for a total of 34 changes. Only one dose increase was observed; in this case moxifloxacin was increased from 400 mg to 800 mg/day because of a risk of progression to ultra-drug-resistant tuberculosis. Among the 31 observed dose reduction, aminoglycosides (kanamycin or amikacin) dose was reduced in 26 patients (24.3%), because of hearing impairment. In one patient, pyrazinamide dose was reduced because of hyperuricemia.

Almost all dose modifications occurred during the intensive phase of treatment, but one pyrazinamide dose reduction occurred at the first month of the continuous phase. This patient thereafter was lost to follow-up. Indeed, 4.6% (n=5) of patients experienced dose reduction during the first month of treatment, 8.4% (n=9) during the second one or the third one each,

1.8% (n=2) during month 4, and 0.1% (n=1) during the month 5. The only moxifloxacin dose increase occurred during the fourth month of treatment.

Among the 25 patients (23.3%) who experienced only one dose reduction during the treatment period, the initial prescribed dose was decreased to at least 25%: 17 patients have seen their dose reduced by 57.1 %, four by 25%, one patient by 33.3 % and one to 66.6%. Two other patients stopped the concerned drug, with a consequent switch, both during the first month of treatment. Linezolid and amikacin taken in a daily basis were both switched to kanamycin on weekly basis, because of drug shortage and hearing impairment, respectively.

Persistence to the MDR-TB Program

The mean of treatment duration was 217 ± 73 days, while the median was 270 days.

Over the 107 patients who started the MDR-TB treatment, 90.6% (n=97) were persistent to the intensive phase. Among the latter, 44.8% (n=48) have completed this phase after four months, 34.5% (n=37) after five months, and 10.2% (n=11) after six months.

Eight patients (7.4%) were lost after completing the initial phase and 89 patients (83.2%) actually started the continuous phase. Among them, only 61.8% (n = 55) were persistent at the end of the continuous phase.

Overall, 51.4% of initial patients were persistent to the entire MDR-TB program (i.e. at least 9 months). Both during the intensive and the continuous phase, the most part of non-persistence occurred during the first 30 days (Figure 1).

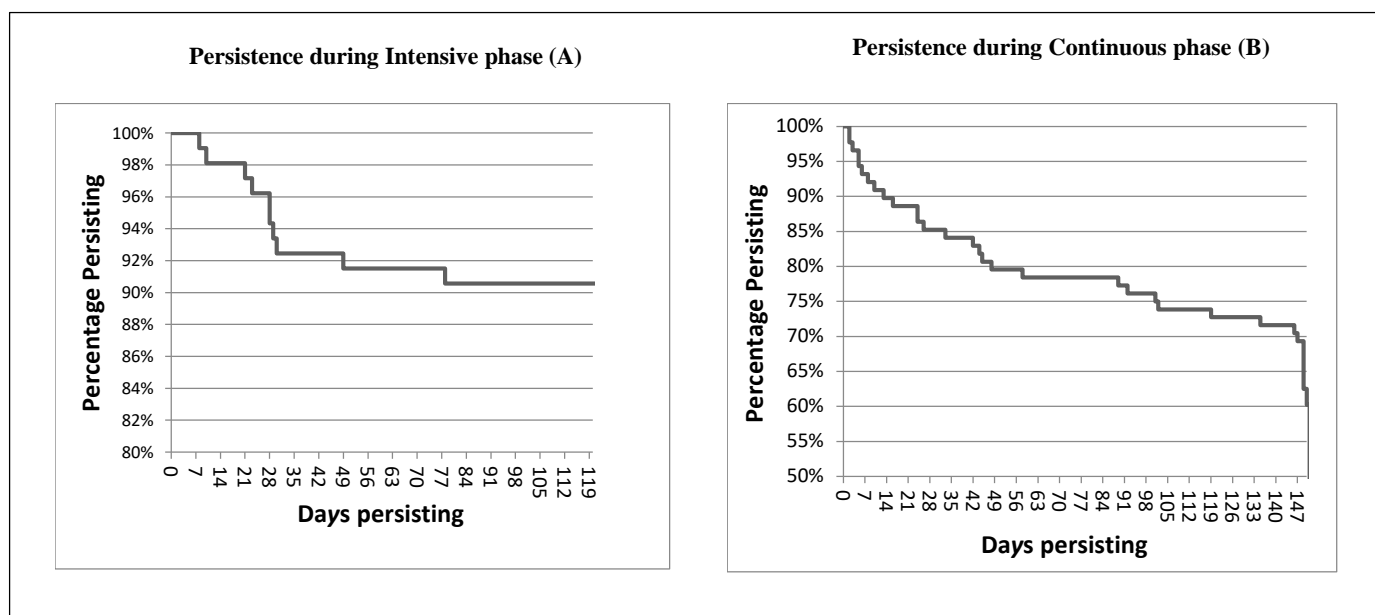


Figure 1: Evolution of MDR-TB program persistence in intensive (A) or continuous (B) phase.

Persistence to initial therapy

Among the 97 patients who finished the intensive phase, persistence to initial therapy was 72.1% as 27 patients experienced drug switch or dose changes (Figure 2). Among the 55 patients that finished the continuous phase, any dose change or drugs switch occurred.

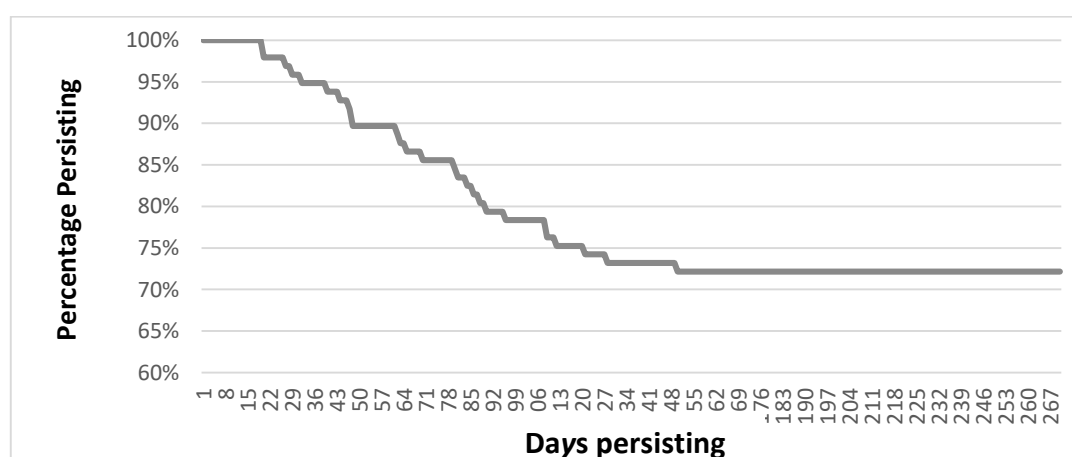


Figure 2: Initial therapy persistence among patients who finished the intensive phase

DISCUSSION

This study showed that most parts of the patients at JHY were treated according to the WHO STR during the study period. Physicians' prescriptions were in most of the cases respecting the WHO recommendations. Meanwhile, persistence to treatment was continuously decreased during the follow-up period, and around half of initially treated patients completed the STR for MDR-TB. Almost all the drug switches or dose modifications occurred during the intensive phase, but the most part of program withdrawal occurred in continuous phase.

Almost all the drugs used to treat MDR-TB patients during the study period were recommended by the WHO STR, almost every time with a kanamycin based therapy. Even if linezolid was not recommended by WHO at that time it was prescribed in five patients. Several studies reported its relevant efficacy in MDR-TB treating regimens (6–10), and its preference over the aminoglycosides could be related to its better tolerability on auditory system, and growingly repurposed among new options for MDR-TB therapy (8,11).

WHO recommended doses of drugs were well implemented as only 8.5% of patients experienced non conformities of the prescribed doses. It concerned mostly clofazimine, in particular in patients weighting 30-39 Kg for witch clofazimine is recommended at 50 mg, instead of 100 for patients of at least 40 kg. As less than 10% of the included patients were weighting 30-39 Kg, prescribers need to be more aware about this possible prescription error.

Patients living with HIV and others who observed more than one non conformities of the recommended dose were highly exposed to drug toxicity. Meanwhile none particular safety issue has been observed among those patients in this study.

Hearing loss was very frequently related to dose reduction and drugs switches. This finding is in accordance with expected, as hearing loss is well-known as a dose dependent adverse drug reaction (12–16), and physician could reduce the dose or increase its interval instead of directly

withdrawn it from the patients therapy (17). Meanwhile, decision should be made regarding some parameters like, drug resistance profile of the microorganism, the status of the disease and responsiveness to treatment, availability of alternative drugs and the duration of aminoglycosides administration (17). The other dose reduction was related to pyrazinamide and the reason reported was occurrence of hyperuricemia, which is another well-known adverse reaction (18–21).

Concerning persistence, a continuous decline of persistence all along the duration of MDR-TB treatment was observed. Meanwhile data showed patients were greatly more persistent during the intensive phase than during the continuous phase. This could be related to the efforts of Cameroon health system to hospitalize patients during the intensive phase, with a consequent increased monitoring of drug use, adherence and persistence to the proposed drugs.

The most part of non-persistence was seen during the first 30 days of treatment, both in the intensive and in the continue phase. For the first one, it is particularly due to adverse reactions, while for the second one it could be due to a sudden decrease of monitoring, or patients misunderstandings concerning the importance to the five months of ambulatory treatment.

As near of half of patients were lost during the continuous phase; this rate is very high and could lead to treatment failure or increase in XDR-TB (22). Thus, appropriate strategies should be developed for increasing the persistence in particular in the ambulatory phase. Moreover, an appropriate follow-up is necessary to support and enrich the DOT approach, with for example safety monitoring, patient counselling, patient education and any form of follow-up (e.g. psychological).

This study has some limitations. Firstly, this study was conducted only in one centre, reducing its external validity. Nevertheless, Jamot Hospital take care of 1/3 of MDR-TB patients in Cameroon, and could be considered representative of the benefit in persistence for the intensive

in hospital phase. Secondly an inappropriate recording of patients information in source document could not be entirely excluded, in particular for continuous phase. However, if it could concern the doses or the drug used in this phase, it should not impact the number of patients persistent up to the end of the program.

The most important strength of this study is that it was conducted in the largest Cameroonian center for the management of MDR-TB. It provides evidence for optimizing the WHO persistence programme in Cameroon, and could apply also in other countries in which the burden of MDR-TB and its evolution to XDR-TB is of concerns (23,24). Indeed, the findings of this study can be used by as a starting point in the implementation and strengthening of Antimicrobial Stewardship Programs, also known as ASPs (25,26).

CONCLUSION

The present study suggests that the intensive in hospital phase is related to higher persistence. It also suggests that the first 30 days of each treatment phase are the most important to increase persistence to the MDR-TB program. If the recent changes in the WHO recommendation avoiding aminoglycosides could increase persistence in the initial phase, as a reduction of burden of hearing loss is expected, other measures need to be thought in order to increase the persistence in continuous phase.

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4.3. Key results and research perspectives

After description of the occurrence frequency and type of adverse drug reactions in a cohort of MDR-TB patients in our first study, this drug utilization study aimed to identify the potential causes and the negative impact of the safety issues previously identified on the treatment outcomes. Specifically, this study aimed to assess the respect of WHO recommendations then patients' persistence to program and to initial therapy.

Study results showed that WHO policy recommending the use of STR for MDR-TB treatment regimen was generally implemented by the NTP. Persistence to treatment was generally good. Meanwhile, nonconformities or medical errors were observed, and could lead to inefficiencies of proposed regimen. Regarding the burden of this disease and the likelihood to a development of new form of resistance, strict implementations of the recommended therapy is required and medical staff should be systematically trained before using and continuously supervised to ensure appropriate clinical management of patients.

Our findings also showed the negative impact of ADR occurrence in drug utilization. Indeed, drug changes and dose modification observed because of hearing loss occurrence neither favoured rapid elimination of *M tuberculosis* nor patient persistence to treatment. The toxicity of aminoglycosides influenced the safety profile of the entire MDR-TB treatment regimen.

Nonconformities observed in prescribed doses raised the problem of insufficient knowledge of treatment guidelines of tuberculosis by medical staff. This finding is very important because misuse of antibiotics is the leading cause of antimicrobial resistance spread worldwide.(65,66)

Additional efforts should be made to ensure patients persistence to treatment during the continuation phase. Indeed, persistence to program was excellent during the intensive phase as patients were hospitalized but strongly decreased when they went home and theoretically must continue to take their treatment ambulatorily for other 5 consecutive months. The continuous

decrease of persistence in this study shows that monitoring, documenting, assessing and managing of drug utilization and related ADRs is important to ensure patient persistence and consequently, improve treatment outcomes.(54)

Knowing that tuberculosis is a disease of poverty, patients usually face economic difficulties after spending 4 to 6 months in the hospital. They need to be well educated to understand that they are not yet safe but need to continue taking their medication till the end of their treatment. This is crucial as treatment discontinuation can lead to treatment failure and consequently exacerbate the risk of Extensively Drug-Resistant TB (XDR-TB). It is therefore vital for the Ministry of Public Health and National Tuberculosis Control Programme to work together to find, new strategies beyond the DOT approach and implement antimicrobial stewardship to promote patient persistence to treatment.

The replacement of aminoglycosides by bedaquiline in current guidelines could have an impact for patient safety, main ambition of WHO, but also in treatment persistence. This is why our last study aimed to evaluate the evolution of the safety profile of drugs and persistence, after introduction of this new STR in Cameroon.

**5.EVOLUTION OF THE SAFETY PROFILE AND
PERSISTENCE AFTER INTRODUCTION OF A NEW
MULTIDRUG-RESISTANT TUBERCULOSIS
TREATMENT**

5.1. Background

Shorter MDR-TB regimen is recommended by World Health Organization since 2016 with the aim to improve safety and effectiveness of MDR-TB treatment.(10) Its worldwide implementation and the continuous collection of evidence through operational research and observational studies led to new recommendations.(15,20,21) Thus, in 2020 new guidelines of drug resistant tuberculosis recommended use of a 9-month all oral treatment regimens in which aminoglycosides (kanamycin, amikacin) were replaced by bedaquiline during the intensive phase.

Beyond the injection pain elimination, aminoglycosides are known to highly contribute to occurrence of hearing impairment among MDR-TB patients.(67–70) Thus, among the treatment benefits expected with bedaquiline introduction, there were oral administration and absence of hearing loss.(51,52) The latter could significantly influence patient persistence to treatment.

A retrospective study carried out at Jamot hospital of Yaoundé from 2017 to 2019 which aimed to evaluate the safety profile of MDR-TB treatment regimens used showed that ototoxicity and gastrointestinal toxicity were the most common observed safety issues.(71) Moreover, specifically because of ototoxicity, patients experienced drug switch, dose modification and treatment discontinuation; non-conformities were also observed both what should have increase the burden of ADRs, or increasing the risk of further drug resistance.

Following new WHO recommendations issued in June 2020, Cameroon through its National Control Tuberculosis Program introduced in November 2021 the above mentioned bedaquiline based regimens for the treatment of all cases of MDR-TB.(15,21) More than 12 months after and as far of our knowledge, none drug utilization study or observational studies have been carried out at the national level to evaluate the potential benefits of the new STR.

This study mainly aimed to evaluate the impact of bedaquiline in the safety profile of STR regimen of MDR-TB and secondly, to assess the respect of WHO recommendations, persistence to program and persistence to initial therapy during the intensive phase.

5.2.Evaluation of drug safety profile and persistence 18 months after initiating short, all-oral bedaquiline treatment regimen for Multidrug-resistant tuberculosis (article in preparation)

ABSTRACT

Background: Cameroon National Control Program of tuberculosis (TB) introduced new standardized treatment regimen (STR) for the treatment of Multi-Drug Resistant TB (MDR-TB) in which aminoglycosides have been replaced by bedaquiline in 2021. Thus, the aim of the present study was to evaluate its implementation in term of prescription patterns, persistence and safety.

Methods: This was a retrospective cohort study of patients included in the intensive phase of the program and treated for MDR-TB at HJY from November 2021, to July 31, 2023. Patients' characteristics of the cohort were described, while prescription practices, persistence to program, persistence to initial therapy and occurring adverse drug reactions observed, were analyzed.

Results: During the study period, 53 patients were included, and 38 (71.7%) experienced at least one ADR, mainly of grade 1 (n=47; 88,6%) and grade 2 severity (n=9; 16,9%). Vomiting (n=14; 26.4%), arthralgia (n=14; 26.4%), peripheral neuropathy (n=5; 9.4%;) and increase of hepatic enzyme (n=4; 7.5%) were the most common ADR with the frequency and respectively. No case of hearing loss has been observed. Persistence to initial therapy was almost perfect, and none drug change or dose modification related to ADR have been reported. A systematic misuse of clofazimine and moxifloxacin was observed in some patients' weight categories.

Conclusions: Ototoxicity was no more observed in MDR-TB with the bedaquiline introduction. Meanwhile, serious ADRs like neuropathy peripheral, increase of hepatic enzyme, QT prolongation and sudden death were rarely observed. A trained staff and an adapted drug safety monitoring system are needed to improve clinical outcomes of MDR-TB therapy.

Evaluation of drug safety profile and persistence 18 months after initiating short, all-oral bedaquiline treatment regimen for Multidrug-resistant tuberculosis

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INTRODUCTION

Since the last decades, there is a continuous spread of Multidrug-tuberculosis resistant in the World.(72–74) Management of this complex disease remains a challenge regarding the treatment duration and related drug safety issues.(48)

In light of new evidence collected from observational studies and operational research conducted all over the world, WHO regularly published guidelines with the aim to improve efficacy and safety of MDR-TB treatment regimens.(10,15,20) Thus, regarding the burden of related safety issues reported and the need to improve expected clinical outcomes, guidelines related to the management of MDR-TB treatment has been updated twice from 2016 to 2022. (10,15,20) Indeed, In June 2020, WHO published new guidelines for the treatment of MDR-TB in which aminoglycosides, commonly associated with a high incidence rate of hearing impairment have been replaced by bedaquiline during the intensive phase. Meanwhile, it is only in 2021 that the Cameroon National Control Program of tuberculosis (TB) introduced that new short and standardized treatment regimen (STR) for the treatment of Multi-Drug Resistant TB (MDR-TB). This new STR could improve management of MDR-TB patient as studies

suggested that ototoxicity was a prominent safety issue and led to drug switch and dose modification in Cameroon.(71) As far of our knowledge none study have been carried out till now to determine the safety profile of that treatment in Cameroon. Thus, this study aimed to evaluate implementation of that all oral regimen in term of prescription patterns, persistence and safety.

METHODS

Study design and data source

This was a preliminary prospective cohort study of patients suffering of MDR-TB who received a treatment regimen newly bedaquiline based STR recommended by WHO since 2020. All patients who started their MDR-TB treatment regimen after its implementation at the Jamot Hospital of Yaoundé (JHY) were included in this study. Only data related to the intensive phase which lasts 4 to 6 months have been collected. Patients aged 18 years or above were included, irrespective of the presence of a previous treatment for TB. Patients with no information available in the medical records treatment were excluded.

The index data was defined as the date in which they received their first MDR-TB drug during the hospitalization or intensive phase. Every information was retrieved by the screening of medical records of patients managed at the Pneumology Department of the JHY. The medical records of each patient were routinely updated monthly. Patients were followed and data were collected for each month from day 1 of treatment (Month 1, M1) to: i) the end of intensive phase (Month 4 to 6), ii) death or iii) last visit with available clinical information for patients lost during the study period.

Drug exposure during the intensive phase

During the study period, in Cameroon the orally shorter MDR-TB regimen proposed by WHO in 2020 was used routinely.(19) This lasts for 9-11 months and was divided in two phases: an intensive, or hospitalization phase, followed by a continuation or ambulatory phase. For this study, only the intensive phase was analyzed. It lasted 4 to 6 months of daily treatment with 6 antibiotics (moxifloxacin, prothionamide, isoniazid high-dose, cefazoline, ethambutol, and pyrazinamide) associated to bedaquiline.

Evaluation criteria

Patterns of drug utilization during the intensive phase was evaluated by comparing drugs, doses, frequency of administration, and treatment duration prescribed by physicians to those recommended in the guidelines related to drug resistant tuberculosis treatment released in 2020 (Table 1).

Table 1: Recommended doses of drugs during the intensive phase.

Drugs	Intensive Phase Daily Dose (mg)			
	30-39 Kg	40-54 Kg	55-70 Kg	Over 70 Kg
Clofazimine	50	100	100	100
Ethambutol	600	800	1200	1400
Isoniazid	300	450	600	600
Moxifloxacin	400	600	800	800
Prothionamide	500	500	750	1000
Pyrazinamide	800	1200	1600	2000
Bedaquiline	Bedaquiline was taken 400 mg daily (200 mg morning and evening) for two weeks, followed by 200 mg 3 times a week (18).			

The intensive phase duration was calculated using starting and the end date of related therapy.

The actual use of drugs was confirmed by the health professional ensuring the DOT marked a

cross (meaning patient effectively take his drug) or a circle (patient didn't take his drug) on the marking sheet dedicated to this purpose in the medical file.

Persistence

The overall program persistence concerned patients that were followed for at least 4 months. While, persistence to the proposed initial therapy concerned patients that completed intensive phase without any drug or dose modification.

Safety data

Clinical events which occurred during the study period and that patients' practitioner considered as a possible ADR and reported in the medical files were collected. The medical file propose to physicians to insert data concerning digestive, kidney, hepatic, neurological, auditory and others ADRs. The physician reported at each visit both ADRs and their severity, using the scale proposed by the French Agency for the Research in AIDS and hepatitis, (*Agence Nationale pour la Recherche sur le SIDA et les hépatites*, ANRS), which correspond to the first four grades of the Common Terminology Criteria for Adverse Events (CTCAE) (66). Indeed, each ADR was classified ad follows :

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Grade 2:** Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental;
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care;
- **Grade 4:** Life-threatening consequences; urgent intervention indicated;

As fatal ADRs were not included in ANRS classification, they were considered as Grade 5.

Data collection

Data were extracted on an electronic clinical reporting form, developed using Microsoft office 15.0 Access Database. Three separate sections were produced to collect data of MDR-TB patients. The first section was related to patients' characteristics at baseline namely: sex, age, weight, HIV status, TB treatment History, Type of Patients, Type of Tuberculosis, audiogram status. The second section concerned treatments and included all the following information: drugs, doses, eventual switches of drugs or doses, start and end date of treatment. The third section concerned ADR, with onset month and severity. The confidentiality of the information was ensured because neither the names of the patients, nor their date of birth, nor their origin was recorded into the database.

Statistical analysis

A descriptive analysis was conducted on the following variables: gender, mean age and age groups (18–30 years, 31–45 years, 46–60 years, 61–75 years), weight classes (according to the WHO recommendation for drug doses [30–39 kg; 40–54 kg; 55–70 kg; >70 kg]), TB type (Pulmonary [P]; Extra pulmonary [EP]; both), TB history (patients never treated for TB before, the patient already treated for TB before) and HIV status.

For this preliminary study, all the data were analyzed using Microsoft Excel 2018. Participants' baseline characteristics were summarized using frequencies and proportions or mean and standard deviation, depending on the type of the variable.

Ethical consideration

Authorization from National Tuberculosis program and Hospital Jamot have been obtained before starting data collection.

RESULTS

Patients' characteristics

A total number of 53 patients have been included during the study period. The sex ratio (M/F) was 1.5 and the average age 39 +/-14 years old. A total of 32.1% of patients have been never treated for tuberculosis (Table 1).

Table 1. Cohort baseline characteristics.

Characteristics	N= 53 (%)
Sex	
Male	32 (60.3)
Female	21 (39.7)
Age	
Mean age, years (+/- SD)	39 (14.0)
18-30	21 (39.7)
31-45	16(30.2)
46-60	10 (18.8)
61-75	6(11.3)
Weight classes (WHO)	
30-39 kg	3 (5.6)
40-54 kg	22 (41.5)
55-70 kg	27 (50.9)
>70 kg	1 (1.8)
HIV status	
Positive	13 (24.5)
Negative	40 (75.5)
TB Treatment History	
Never treated	17 (32.1)
Already Treated	36 (67.9)
MDR-TB Treatment regimen at baseline	
BDQ based regimen	53 (100)

Adverse drug reactions

During the study period, 38 patients (71.9%) experienced at least one ADR, mainly in the first two months of treatment (n=35; 92.1%). A total of 87 ADRs reported (mean of 2.3 per patient). ADR were mostly of grade 1 (n=47; 88,6%) or grade 2 (n=9; 16,9%). The most common ADR were vomiting and arthralgia that were found in 14 patients (26.4%) each; peripheral

neuropathy and increase of hepatic enzyme occurred in five (9.4%) and four (7.5%) patients, respectively (Table 2).

Table 2. Adverse drug reaction occurred during MDR- Treatment

Type of Adverse event	Total N = 53 (%)	Grade 1 N= 53 (%)	Grade 2 N= 53 (%)	Grade 3 N= 53 (%)	Grade 4 N= 53 (%)	Grade 5 N= 53 (%)
Arthralgia	14 (26.4)	11 (20.7)	3(5.6)	-	-	-
Vomiting	14 (26.4)	14 (26.4)	-	-	-	-
Peripheral neuropathy	5 (9.4)	4 (7.5)	1 (1.8)	-	-	-
Hepatic enzyme increased	4 (7.5)	2 (3.7)	2 (3.7)	-	-	-
Abdominal pain	3 (5.6)	2 (3.7)	1 (1.8)	-	-	-
Eye disorders	2 (3.7)	1 (1.8)	1 (1.8)	-	-	-
Fatigue	2 (3.7)	2 (3.7)	-	-	-	-
Hyperuricemia	2 (3.7)	2 (3.7)	-	-	-	-
Nausea	2 (3.7)	2 (3.7)	-	-	-	-
Palpitations	2 (3.7)	-	-	2 (3.7)	-	-
Pruritus	2 (3.7)	2 (3.7)	-	-	-	-
Sudden death	2 (3.7)	-	-	-	-	2 (3.7)
Thoracic pain	2 (3.7)	2 (3.7)	-	-	-	-
Vertige	2 (3.7)	2 (3.7)		-	-	-
Renal failure	1 (1.8)	-	1 (1.8)		-	-
Skin disorders	1 (1.8)	1 (1.8)	-	-	-	-

Four patients (7.5%) experienced ADR of \geq grade 3 of severity, two sudden death and two cardiac palpitations.

Two Sudden death

The first was a male, aged 61 years old, weighted 35 kg, and coinfecting by hepatitis C. He died after 45 days of treatment. The second one was also a male aged 45, weighted 47 kg, HIV positive and died after 16 days of treatment.

Two cardiac palpitations

The first was a male, 26 years old, weighted 56 kg, HIV positive, formerly treated with anti-TB-Drugs. The second was also a male, 48 years old, weighted 57 kg, formerly treated with anti-TB drugs.

Respect of WHO recommendations

All patients started MDR-TB treatment according to the WHO recommendations in terms of prescribed drugs. Nonetheless, non-conformities were found concerning most importantly the doses of clofazimine and moxifloxacin.

Clofazimine doses were double of the expected dose (100 mg instead of 50 mg daily) in all patients weighting 30-39 kg (n=3). A systematic non-conformity has been observed with moxifloxacin in patients weighted more than 39 kg (n=50); they all received 400 mg/day instead of 600 mg/day for patients weighting 40-54 kg (n=22) or 800 mg/day for patients weighting over 54 kg (n=28). Finally, one case of simultaneous non-conformities of ethambutol and pyrazinamide was found, as the recommended doses were received three times per week instead of on a daily basis.

Persistence to the MDR-TB Program

The mean of intensive phase duration was 124 ± 24 days, while the median was 116 days. A total of 51 patients (96.2%) were persistent for at least four months of the intensive phase. Concerning the other two patients, the first was a male, aged 61 years old, weighted 35 kg, and

coinfected by hepatitis C. He died the second month of treatment after 45 days of treatment. The second one was also a male aged 45, weighted 47 kg, HIV positive and lost to follow-up after 16 days of treatment.

Persistence to initial therapy

Among the 53 patients included in this study, nor dose modification or drug switch has been observed during the intensive hospitalized phase because of safety issue related to MDR-TB treatment. Meanwhile, one patient with different comorbidities associated to MDR-TB (*i.e.* diabetes, kidney failure, high blood pressure) has experienced dose modification of all the drugs excepted bedaquiline the second month of treatment.

DISCUSSION

The main result of this study showed that there were common mild and moderate ADRs reported by MDR-TB patients with a predominance of joint pains and vomiting. Meanwhile, some cases of hepatotoxicity, cardiac palpitations and sudden death have been also reported. Moreover, despite the systematic misuse of clofazimine and moxifloxacin noticed in some categories of patients, an excellent persistence to treatment was observed.

Joint pains and vomiting were common ADRs associated with MDR-TB treatment. The incidence rate reported in this study are in accordance with literature.(48) Indeed, different studies reported that gastrointestinal disturbances are very common during MDR-TB treatment. Moreover, arthralgia very common with pyrazinamide treatment and that risk increase when the latter is associated with moxifloxacin, levofloxacin or other fluoroquinolones.(48,72–74)

Comparing to the previous STR including aminoglycosides, our results showed a decrease of ADRs incidence, hearing impairment leading to drug switch and dose modification was no more a safety issue with the new all oral MDR-TB treatment regimen proposed by WHO.

Nevertheless, cases of sudden death and cardiovascular event could be a signal raising the need of a narrow monitoring of cardiac functions with regular electrocardiogram. Thus, regimens can change but there will always remain safety concerns particularly when polypharmacy is mandatory like for MDR-TB therapy.

Severe ADRs were rarely reported in this study but key serious outcomes like peripheral neuropathy, prolongation of QT, palpitations and sudden death which require deep attention of health care providers and NTPs staff happened. In Vigibase ICSRs related to peripheral neuropathy and prolongation of QT are commonly attributed to bedaquiline and linezolid (5). Cardiac toxicities is a very important safety concern to monitor during MDR-TB treatment as several drugs composing the regimens have a potent to prolong QT.(75) Indeed, bedaquiline, clofazimine and moxifloxacin are individually reported in the literature as drugs increasing the risk of QT interval prolongation.(51,52,75–77) This risk is higher with the association of these three drugs during at least four months of treatment. Despite that evidence, it was a surprise to notice during data collection that QTc monitoring was not systematic done. As it is not possible to see what we don't look for, the low number of cardiac events observed in this study could also be related to the weaknesses of the monitoring system. Thus, close monitoring of cardiac parameter is fundamental and should be systematically be implemented during MDR-TB therapy by NTPs.

Persistence to MDR-TB programme and to initial therapy was excellent as treatment discontinuation was only related to death and none drug switch or dose modification related to any safety issue have been recorded on the patient medical records.

The systematic non conformity of the moxifloxacin doses could surely be attributed to an error related to lacking of mastering or understanding of the new MDR-TB treatment by the medical staff. If inappropriate drug utilization doesn't necessarily lead to safety issue, it could at least impact effectiveness of the therapy and contribute to the development of new strains of *M*

tuberculosis. Health care professionals should remind that MDR-TB is a man-made problem caused by weaknesses on clinical and pharmacological management of patients. So, beyond the need of drug safety monitoring, drug utilization studies should be regularly carried out to ensure good practices and avoid emphasizing drug resistance.

Inappropriate use of clofazimine problem for MDR-TB patients weighting less than more than 39 kg followed at the HJY (75). Indeed, by doubling the dose, there is an increase risk to develop its related toxicities which include skin discoloration, gastrointestinal disturbances, hepatic damage, or QT prolongation.(75,78–81) Thus, it should therefore be emphasized that the misuse of drugs during MDR-TB treatment remains a problem that needs to be addressed by medical staff, as it could reduce expected efficacy, increase drug toxicity, or even contribute to the development of a new form of resistance to anti-tuberculosis drugs.

The main limit of this study is the fact that assessment was only done during the intensive phase then, safety and drug utilization of the new TSR were not described during the continuation phase. Another limit is the low number of patients included in our cohort due to the fact this treatment was newly implemented. As for every retrospective study, error on medical records of patients' information surely led to bias while interpreting findings of this study. Meanwhile, this study has the merit to be the first which aimed to evaluate the impact of bedaquiline introduction in the burden of ADR related to MDR-TB therapy in Cameroon.

CONCLUSION

The new oral STR including bedaquiline implemented in JHY is associated with common occurrence of ADRs during the intensive phase of treatment. Ototoxicity was no more observed in MDR-TB patients and ADR did not have an evident impact on treatment persistence, as previously reported with the aminoglycosides-based regimens. Nevertheless, errors in dosages

of moxifloxacin and clofazimine need to be corrected in order to prevent bad utilization practices, and spread of resistant strains. A systematic monitoring of cardiac parameters should be considered in order to prevent potential serious safety concerns that could impact effectiveness of MDR-TB treatment.

6.THESIS GENERAL CONCLUSION

The work conducted through this thesis helped to provide a better understanding of the patterns related to safety issues of shorter treatment regimens used for the management of multidrug-resistant tuberculosis in Cameroon. Common ADRs, their frequencies, prescriber practices and patients' persistence have been identified and assessed.

We started by evaluating the safety profile of STR used in Cameroon from 2017 to 2019. We found that ototoxicity related to aminoglycosides was very common and constituted the main safety problem among MDR-TB patients especially during the first months of treatment. Meanwhile, insufficient management of the cases of hearing loss was noticed as in most cases, only drug dose reduction was observed, and the suspected drug or treatment maintained, which could lead to permanent hearing impairment.

Secondly and within the same period 2017-2019, we assessed potential links between drug usage and observed safety issues. For this purpose, we investigated how the WHO treatment guidelines related to MDR-TB were implemented in Cameroon and what was the patient persistence not only to the program but also to the initially prescribed therapy during both intensive and continuous phase. This study revealed a very good implementation level of WHO recommendations by prescribers. Decrease of persistence to initial therapy has been associated with the occurrence of adverse drug reactions and especially hearing loss during the first months of treatment. Persistence to program strongly decreases during the continuous and ambulatory phase of treatment.

Furthermore, we noticed that persistence to treatment was impacted by occurrence of ADRs which led to drug switch, dose modification and hugely affected treatment persistence. Additional patient education and psychological support could be helpful to raise patients' awareness about the risk of stopping treatment before the expected end date and the importance of adequate use of drugs.

This evidence highlights the need for a close and specific monitoring of patient's persistence to treatment during the second phase of treatment. The excellent persistence observed during the intensive phase was due to the fact that patients were hospitalized and there was close monitoring. Meanwhile, the ambulatory phase constituted a challenge for the national control program of tuberculosis as the persistence highly decreased.

In June 2020, WHO issued new guidance related to MDR-TB treatment in which aminoglycosides, identified in our previous studies as main cause of ototoxicity, drug switch and dose modification, was replaced by bedaquiline during the intensive phase.

Thus, we were interested in knowing the impact of this treatment change on both the burden of safety and persistence to treatment during MDR-TB therapy in the same referent TB treatment center in Cameroon. Results of this study showed that ototoxicity was no more a safety problem and persistence to initial therapy highly improved. Thus, our results could serve as confirmation of the importance and add value to the new WHO treatment recommendations at least at the level of Cameroon. Meanwhile, this study raised new concerns about the safety of bedaquiline which could increase the risk of cardiovascular ADRs, in particular concerning rhythm disorder. This is of particular importance as the intensive phase concomitantly associates three drugs known for increasing the QT time in ECG: bedaquiline, clofazimine and moxifloxacin. Drug misuse during MDR-TB treatment remains a problem to be addressed by medical staff as this could lower the expected effectiveness, increase drug toxicity, or even contribute to the development of new forms of drug resistance.

Results from this thesis are helpful in providing a better understanding of the safety profile of MDR-TB treatment regimen and could be used to improve patient management and treatment outcomes. Indeed, MDR-TB despite all the efforts made remains a major public health threat worldwide. Adequate clinical and drug usage management are essential to ensure the success of the world "End TB" strategy.

As perspective of this work, we strongly suggest the following for the different stakeholders of TB Management.

Ministry of public health and politicians

Emphasizing awareness on the importance of pharmacovigilance and drug safety monitoring during implementation of health programs activities should be a priority for the Ministry of Public Health. In fact, talking about pharmacovigilance in the guidelines and ensuring availability of reporting tools is a good step, however, this is not enough to ensure patient safety. Health professionals need to be continuously sensitized and trained to integrate pharmacovigilance as a normal and relevant part of their routine clinical practices. Thus, there is a need to reinforce the national PV system by reviewing its organizational structures, clarifying roles and responsibilities of actors and elaborating standards operating procedures. In light of the weaknesses of the spontaneous reporting system, MOH through its competent services in charge of pharmacovigilance, should promote implementation of active pharmacovigilance system to collect data, allowing for the continuous gathering of evidence on the safety profile of drugs used in Cameroon. This evidence will then serve when considering the revision of local treatment strategies or guidelines. Creation of an autonomous center of pharmacovigilance could also contribute to the reinforcement of the PV system in Cameroon.

National Tuberculosis programs

As experts of TB management in the country, NTP should monitor both the effectiveness and safety of drugs used in MDR-TB treatment in Cameroon. Generally, TB annual reports always focus on the number of patients treated, treatment success rates and more without emphasizing on the safety profile of drugs used. Efforts should be made to reinforce supervision of pharmacovigilance activities implemented in CDT and reporting of all ADR occurring during MDR-TB treatment. The gap between the number of reporting done and the number of ADRs

recorded in the patients' medical records is evidence of a limit collaboration between NTP and the vigilance service of the Ministry of public health. Creation of PV unit with necessary human and financial resources could be helpful for improving pharmacovigilance in public health programs. Our results reinforce the importance of implementing an aDSM by the National Tuberculosis program to monitor and ensure safety of MDR-TB regimens.

Additional efforts should be made in improving patient persistence to treatment during the continuation phase where they are generally at home.

Technical and financial Partners

TB as Malaria and AIDS is one of the priority diseases for which treatment is ensured through the grants and funding of Technical and financial partners of the Ministry of Public Health. While providing subventions to ensure availability of drugs at the last mile, partners should also consider pharmacovigilance as an integral complement to treatment programs. Indeed, initiatives to promote the rational use of medications, reduce risks, and other steps to assure patient safety result in more cost savings than losses. Given that new strategies are sometimes proposed based on safety data from foreign countries, it is important to highlight that the frequency and expression of ADRs may be influenced by factors linked to the demographic, genetic and nutritional patterns, and to the background comorbidity in a population.(62) Thus, financing PV activities should not be regarded as an additional activity but rather as a core activity of the MDR-TB treatment process.

Health care providers

Treatment of MDR-TB is complex and requires the use of toxic and expensive drugs. Thus, total commitment of health care professionals is core to ensure quality of care. Physicians and pharmacists must ensure that they are well trained, skilled and master treatment guidelines before managing MDR-TB therapy. As treatment regimens change frequently based on new

evidence, regular updating and screening of existing literature to improve clinical practices is key. We can only stop the spread of MDR-TB by constantly monitoring drug safety concerns and ensuring proper drug use.

RESUME SUBSTANTIEL

La tuberculose (TB) est une maladie pulmonaire causée par *Mycobacterium Tuberculosis*, qui se transmet d'une personne à l'autre par les éternuements, la toux et les crachats. En raison de la morbidité et de la mortalité y relative, elle a été reconnue en 1994 comme une urgence mondiale par l'Organisation mondiale de la santé (OMS). (5,82) Aujourd'hui, elle est classée parmi les dix premières causes de décès dans le monde et considérée comme la principale cause de décès chez les patients atteints du VIH-SIDA. Au Cameroun elle constitue l'une des trois maladies prioritaires du Ministère de la Santé Publique et présente un taux de mortalité estimé à 2,9%. (5,82)

La TB devient multirésistante lorsque le patient est infecté par des souches de *Mycobacterium Tuberculosis* résistantes à l'isoniazide et à la rifampicine qui sont les deux antituberculeux de première intention majeurs. Au cours des deux dernières décennies l'expansion de la tuberculose multirésistante (TB-MR) est croissante dans le monde et l'OMS estime qu'environ 500 000 nouveaux cas de TB-MR sont diagnostiqués chaque année.(48)

En effet, il s'agit d'une maladie beaucoup plus grave et complexe dont la prise en charge requiert l'utilisation des antituberculeux davantage toxiques et plus onéreux que les antituberculeux de première intention. De plus, depuis 2016 le régime de traitement court et standardisé recommandé par l'OMS subdivisait la prise en charge de la TB-MR en deux phases distinctes pouvant aller de 9 à 11 mois. La première phase dite intensive durait 4 à 6 mois avec la prise de 7 antituberculeux (Kanamycine/amikacine, moxifloxacine, protionamide, isoniazide haute-dose, clofazimine, ethambutol, et pyrazinamide).(10) La deuxième phase dite phase continue a une durée fixe de 5 mois avec 4 antituberculeux (Moxifloxacine, clofazimine, ethambutol, and pyrazinamide). (10) La prise quotidienne de ces médicaments pendant une longue durée augmente la probabilité de survenue des effets indésirables (EI) chez ces patients qui présentent généralement un terrain de comorbidités. Les douleurs articulaires, les nausées,

les vomissements, l'ototoxicité, les événements gastro-intestinaux, la dépression, les démangeaisons, l'hypothyroïdie, les vertiges, les problèmes rénaux et hépatiques, nombreux sont les EI couramment associés au traitement de la TB-MR avec une incidence de l'ordre de 20 à 90 %.(53,54) Une surveillance étroite et une gestion appropriée de ces EI est donc indispensable afin d'assurer un succès du traitement, une bonne gestion des cas graves et optimiser la prise en charge, réduire les interruptions précoces du traitement et par conséquent empêcher le développement de nouvelles souches de résistance.

La réalisation de cette thèse fait suite au constat qu'au Cameroun il n'existe à notre connaissance aucune donnée permettant d'estimer le profil de sécurité des médicaments utilisés pour la prise en charge de la TB-MR. En effet, on note de manière générale une sous notification des EI de ces médicaments pourtant réputés très toxiques.

A titre illustratif, en septembre 2023, seules trois notifications relatives aux EI secondaires à l'utilisation des antituberculeux étaient enregistrés dans la base de données de pharmacovigilance de l'OMS, Vigibase. De plus, il n'existe aucune autre base de données ou système de surveillance permettant une revue des EI liés au traitement de la TB-MR au niveau national.

C'est fort de ces constats que dans le cadre de nos travaux de thèse, nous sommes intéressés à l'évaluation du profil de sécurité des antituberculeux utilisés pour la prise en charge de la TB-MR au Cameroun. A cet effet, lesdits travaux se sont déroulés en deux phases distinctes pour un total de trois études réalisées.

Au cours de la première phase, nous avons réalisé deux études rétrospectives couvrant la période 2017-2019. Lesdites études ont été menées au niveau du centre de diagnostic et de traitement de la TB de l'hôpital Jamot de Yaoundé qui prend en charge 2/3 des cas de la TB-MR du pays.

La première étude visait à déterminer l'incidence des EI liés aux traitements de la TB-MR, à évaluer leur sévérité et enfin, à identifier les effets indésirables conduisant à l'arrêt du traitement ou à la modification du schéma thérapeutique. A l'issue de cette étude faite dans une cohorte de 107 patients, nous avons constaté une forte incidence des EI avec 89.7% de patients ayant manifestés au moins un EI. Des problèmes d'ototoxicité attribués aux aminosides étaient très fréquents (65.4%) et constituaient le principal problème de sécurité, en particulier au cours des premiers mois de traitement.

Afin d'établir un potentiel lien entre la survenue des EI observés et les pratiques d'utilisation des médicaments, nous avons mené une deuxième étude dont les principaux objectifs étaient d'évaluer le respect des recommandations de l'OMS relatives à la prise en charge de la TB-MR, la persistance au programme et la persistance à la thérapie initiale lors de chaque phase.

Les résultats de cette étude ont montré que la plupart des patients TB-MR étaient traités conformément au régime de traitement court et standardisé recommandé par l'OMS pendant la période de notre étude. Les prescriptions des médecins respectaient dans la plupart des cas les recommandations de l'OMS et la persistance au traitement était bonne. Toutefois, cette dernière n'a cessé de diminuer au cours de la période de suivi. Presque tous les changements de médicaments ou les modifications de doses ont eu lieu pendant la phase intensive, tandis que la plupart des abandons de traitement ont été observés pendant la phase continue. En outre, nous avons remarqué que la persistance du traitement était affectée par l'apparition d'effets indésirables qui ont conduit à un changement de médicaments, à des modifications de dose et, souvent, à l'arrêt du traitement.

En juin 2020, l'OMS a publié de nouvelles directives relatives au traitement de la TB-MR dans lesquelles les aminoglycosides, identifiés dans nos études précédentes comme principale cause des problèmes d'ototoxicité ont été remplacés par la bédaquiline pendant la phase intensive.

C'est ainsi que pendant la seconde phase de notre thèse qui a couvert la période 2021 – 2023, nous avons voulu connaître l'impact de ce changement de traitement sur le profil de sécurité et la persistance au traitement TB-MR. Compte tenu du faible nombre de patients sous ce traitement mais aussi du fait que les problèmes de sécurité et d'utilisation des médicaments survenaient plus pendant les premiers mois, cette étude a porté uniquement sur la phase intensive.

Pour ce qui est du profil de sécurité, les résultats de cette étude ont montré que l'ototoxicité n'était plus un problème observé et que la persistance au traitement initial s'était fortement améliorée. Ainsi, nos résultats pourraient servir comme preuve de la valeur ajoutée des nouvelles recommandations de l'OMS. Entre-temps, cette étude a soulevé de nouvelles inquiétudes quant à la sécurité de la bédaquiline, qui pourrait augmenter le risque de toxicité cardiovasculaire, en particulier lorsqu'elle est associée à la clofazimine, et à la moxifloxacine également connus comme médicaments pouvant prolonger l'intervalle QT.

Par ailleurs, si aucun changement de médicaments ou de dose relatif aux EI n'a été observé, il faut noter que des erreurs systématiques ont été constatés sur les doses prescrites à certaines catégories de patients. Il s'agit notamment de la prescription d'une dose de 400mg de moxifloxacine chez tous les patients pesant plus de 39 kg au lieu de doses supérieures, et d'une dose 100 mg de clofazimine au lieu d'une dose de 50 mg chez les patients pesant moins de 40 kg. Il convient donc de souligner que l'utilisation non conforme de médicaments pendant le traitement de la TB-MR demeure un problème auquel le personnel médical du Cameroun doit s'attaquer, car cela pourrait réduire l'efficacité attendue, augmenter la toxicité des médicaments ou même, contribuer au développement de résistances aux antituberculeux.

En sommes, les résultats de cette thèse sont utiles pour mieux comprendre le profil de sécurité du traitement de la TB-MR et pourraient être utilisés pour améliorer la prise en charge des patients. Le site de notre étude rassemblant 2/3 des patients TB-MR du pays, nos résultats

pourraient être considérés comme représentatifs et à cet effet, attesteraient d'une forte association des effets indésirables au traitement de la TB-MR au Cameroun. La disparition des problèmes d'audition qui étaient fréquents chez plus de la moitié des patients pendant la période 2017-2019 sonne comme une confirmation du lien de causalité de cet effet indésirable à la prise des aminoglycosides voir plus, comme une justification du nouveau régime de traitement proposé par l'OMS en 2020. Si une étroite surveillance de l'audiogramme semble ne plus être d'actualité pour les patients TB-MR utilisant le nouveau régime standardisé, il convient de mettre en place un dispositif efficace de suivi de la cardiotoxicité à travers une réalisation systématique et périodique d'un électrocardiogramme (ECG). Compte tenu de la cherté de cet examen et la gratuité du traitement TB-MR, des dispositions doivent être prises pour garantir également une accessibilité des patients à cet examen qui peut permettre de prévenir des morts subites évitables. Les erreurs médicamenteuses observées et relatives aux prescriptions des mauvaises doses de médicaments attestent d'une insuffisante appropriation des protocoles de prise en charge par les médecins traitants soulignant ainsi un besoin de sensibilisation et de renforcement des capacités de ces derniers. En perspective, nos résultats mettent en exergue l'importance de la mise en place d'une pharmacovigilance active permettant de continuellement collecter les informations sur la sécurité des antituberculeux. Cette surveillance active passe notamment par la mise en place d'un système actif de contrôle et de gestion de l'innocuité des médicaments antituberculeux (aDSM) recommandé par l'OMS.(24) D'autres approches actives tel que la mise en place d'un registre national des patients TB-MR, la considération des sites TB-MR comme sites sentinelles de surveillance des EI ou encore la mise en place d'un système de notification ciblés des effets indésirables des antituberculeux dans le PNLT sont envisageables. En fin, la création d'une unité de pharmacovigilance au sein du PNLT et un renforcement de la collaboration avec les services de vigilances du Ministère de la Santé

Publique seront des atouts dans le processus de renforcement de la surveillance de la sécurité des antituberculeux.

Mots clés : pharmacovigilance, santé publique, TB-MR, sécurité des médicaments, effets indésirables.

Titre : Sécurité des antituberculeux utilisés pour la prise en charge de la Tuberculose Multirésistante.

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ANNEXES

Annexe 1. Scientific articles, oral communications and others Pharmacovigilance work

Scientific articles

- 1- Mpoh MM, Deli V, Daniel TT, Salvo F. Safety of antituberculosis agents used for multidrug-resistant tuberculosis among patients attending the Jamot Hospital of Yaounde, Cameroon. *Int J Mycobacteriol* 2023;12:168-74.
- 2- HIRMA KT, Mbwe MM, Tchokomeni H et al. Drug Safety Monitoring in Health Programs of Cameroon. *J Pharmacovigil.* 2022 ; 10(9)
- 3- MBWE MM, Deli V, Daniel TT, Salvo F. Multidrug-resistant tuberculosis in Cameroon: respect of WHO recommendations and treatment persistence (submitted to publication)
- 4- MBWE MM, Deli V, Daniel TT, Salvo F. bedaquiline all oral standard treatment regimen: assessment of safety and drug utilization (to be finalized)

Others publications and oral communications

- 1- Impact of the pharmacist in setting up a pharmacovigilance system in hospitals. cameroon pharmaceutical studies exhibition. May 2019
- 2- Alima NC, Mbwe MM et al. Drug-induced toxidermia secondary to antimalarial drugs: a case report. Poster and oral communication. Pharma expo Cameroon 2023
- 3- Mbwe MM, Alima NC; Impact médico-économique d'une mauvaise prise en charge des patients en pharmacie. Poster and oral communication. Pharma expo Cameroon 2023
- 4- Mbwe Mpoh Maurice. Place de la pharmacie dans la couverture santé universelle. Communication orale. Pharma expo Cameroon 2023

Others pharmacovigilance work

- 1- European Programme in Pharmacovigilance and Pharmacoepidemiology. Academic advisor of master year 1 student on her research project related to Misuse of drugs during the pandemic of COVID-19 in Brazil; 2021
- 2- Specialized committee of pharmacovigilance; Causality assessment of individual case safety report submitted to the vigilance service, evaluation of PSUR, February 2023
- 3- Specialized committee of pharmacovigilance; Causality assessment of individual case safety report submitted to the vigilance service, May 2023
- 4- Specialized committee of pharmacovigilance; Causality assessment of individual case safety report submitted to the vigilance service, September 2023
- 5- Support the Ministry of Public Health on the elaboration and validation of the Cameroonian National strategic plan of pharmacovigilance 2024-2026, January - April 2023.
- 6- Support the Ministry of Public Health on the reviewing and validation of the pharmacovigilance organizational structure 2024-2026, January-April 2023.
- 7- Support the Ministry of Public Health on the elaboration and validation of the Pharmacovigilance digital transformation and integration plan June-August 2023.
- 8- Support the Ministry of Public Health on the elaboration and validation of pharmacovigilance Communication Plan August-October 2023.
- 9- Support the Ministry of Public Health on the elaboration and validation of pharmacovigilance training plan November 2023.
- 10- Support the Ministry of Public Health on the elaboration and validation of SOPs of core pharmacovigilance activities.
- 11- Support the Ministry of Public Health on the elaboration of roles and responsibilities of pharmacovigilance stakeholders.
- 12- Publication of drug safety information through social media and web site of the Cameroon drug safety association, our pharmacovigilance network created in 2019.
- 13- Publication of the first issue of VIGIDOR, a Cameroon drug safety magazine or newsletter. June