

## A perspective of *Mycobacterium Tuberculosis* resistance on patients with retreat in Madagascar

Harison Michel TIARAY<sup>\*,†,1</sup>, Kiady RAVAHATRA<sup>2</sup>, Jobeline RAJAOARIFETRA<sup>3</sup>, Oninala Fenitra RAKOTONDRASOA<sup>4</sup>, Iantsotiana Davidson RAKOTONDRABE<sup>5</sup>, Marie odette RASOAFARANIRINA<sup>6</sup>, Anjara Mihaja NANDIMBINIAINA<sup>7</sup>, Jocelyn Rakotomizao<sup>8</sup>, Rakotoson Joelson Lovaniaina<sup>9</sup>, ANDRIANASOLO Radonirina Lazaso<sup>10</sup>, RAHARIMANANA Rondro Nirina<sup>11</sup>

<sup>1</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>2</sup>Department of pneumonology, Tertiary hospital of Fenoarivo, Antananarivo, Madagascar

<sup>3</sup>Department of pneumonology, Tertiary hospital of Tamatave, Antananarivo Madagascar

<sup>4</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>5</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>6</sup>Department of pneumonology, Tertiary hospital of Tamatave, Antananarivo Madagascar

<sup>7</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>8</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>9</sup>Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>10</sup>Departement of Infectious deasese, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

<sup>11</sup>Department of pneumonology, Tertiary hospital of Fenoarivo, Antananarivo, Madagascar

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### ABSTRACT

**Introduction:** Despite advances in diagnostic and therapeutic way, drug-resistant tuberculosis is an increasingly worrying threat. Several studies suggest that one of the risk factors for carrying resistant *Mycobacterium tuberculosis* is the history of anti-tuberculosis treatment. The objective of our study is to describe the Resistance Profile of Mycobacterium Tuberculosis of patients in retreatment in Madagascar. **Methods:** This is a descriptive and retrospective study, carried out from January 2014 to September 2018 (45 months). All the cases of re-treatment recorded in the database of the National Tuberculosis Control Program in Madagascar were included in the study. **Results:** We gathered 1456 cases, the average age was 40 years, there was a male predominance (sex ratio of 2.32). In the 1302 cases where the category was specified, there was a predominance of relapse (76.57%). According to the culture, the incidence of rifampicin resistance was 05.36% (78/1456) including 83.33% of cases of multi-resistant tuberculosis (MDR-TB) (65/78). The incidence of isoniazid monoresistance was 05.49% (80/1456). Carrying MDR-TB is much more important for patients who have failed (69.43%). The GeneXpert *mtb*/RIF enabled us to detect more cases of Rifampicine monoresistance (97 cases). **Conclusion:** cases of retreatment is a real source of the emergence of MDR-TB in Madagascar, especially cases of failure and relapse. Which is consistent with the data in the literature. The treatment effectiveness of new cases must be maximum to prevent these cases of retreatment.

\*Corresponding author.

†Email: [tiarayharison@yahoo.fr](mailto:tiarayharison@yahoo.fr).

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## 1 INTRODUCTION

Tuberculosis is an infectious communicable disease caused by the microorganism of the *Mycobacterium tuberculosis complex* or Koch's bacillus. Man is the only reservoir of *Mycobacterium tuberculosis*. It particularly affects the lungs, but it can also reach other organs of the body, giving extrapulmonary tuberculosis [1].

Despite advances in diagnostic and therapeutic methods, drug-resistant tuberculosis is an increasingly worrying threat. In 2016, there were 600,000 new cases of rifampicin resistance, including 490,000 cases of multidrug-resistant tuberculosis (MDR-TB), i.e. *Mycobacterium tuberculosis*, which is resistant to both isoniazid and rifampicin, two major first-line anti-tuberculosis drugs.

Several studies suggest that one of the risk factors for carrying resistant *Mycobacterium tuberculosis* is the history of anti-tuberculosis treatment, cases of failure to the World Health Organization (WHO) category I schemes, cases of relapse and cases of dropped out of anti-tuberculosis treatment [2-4].

Before 2019, the National Tuberculosis Control Program (NTP) of Madagascar adopts the WHO category II scheme (2SRHEZ / 1RHEZ / 5RHE) for retreatment cases. Given the risks compared to carrying TBMR for these cases and taking into account the recommendation of the WHO, the National tuberculosis programme (NTP) in Madagascar revised the treatment protocol for retreatment cases in 2019, based on the use of the technique of molecular biology (GenEXpert *mtb*/RIF).

It is in this way that we carried out this study. the objective is to describe the resistance profile of *Mycobacterium Tuberculosis* on the patients in retreatment in Madagascar before the period of 2019 in order to appreciate the reality on the carrying of resistance among these newly diagnosed reprocessing cases.

## 2 METHODOLOGY

This is a retrospective and descriptive study, carried out over a period of three years and nine months (45 months) from January 01, 2014 to September 30, 2018. We included in the study all the cases of tuberculosis in retreatment from the active line of the National Tuberculosis Control Program in Madagascar during the fixed study period. were excluded from the study, all patients with incomplete information making interpretation of treatment outcomes impracticable.

The cases of retreatment or cases to be retreated are:

- failures: these are the patients who are "positive on bacilloscopic examination of sputum" at the end of the 5th month or at any time between the end of the 5th month and the date of the end of the treatment (which lasts 6 months for new cases)

- relapses: these are patients previously treated for active tuberculosis, "declared cured" or "treatment completed" at the end of treatment and in whom we again find "a positive bacilloscopy"

- recoveries: these are patients "lost to follow-up for 2 months or more" and who return with "a positive bacilloscopy". To be classified in this category of patients; the person must have had at least 1 month of treatment.

After completing a survey form, We collected data from the database of the National Tuberculosis Control Program in Madagascar. The data collected was then entered and processed using Microsoft office Excel<sup>®</sup> 2007 software and Microsoft office Word<sup>®</sup> 2007.

Patient confidentiality was respected and no information revealing their identity is present in this study to ensure anonymity. The data is secure to avoid any problem of information disclosure. To carry out this study, authorization was requested from the Director of the National Tuberculosis Control Program in Madagascar.

## 3 RESULTS

During the study period, we found 2,375 cases of retreatment tuberculosis recorded on the NTP database. Nine hundred and nineteen files were excluded before an incomplete file. In total, we retained 1 456 reprocessing cases during the study period. The average age of the patients was 40 years with extremes ranging from 15 to 86 years. There was a male predominance (69.92% of the male gender and 30.08% of the female gender) with a sex ratio of 2.32. Figure I shows the distribution of retreatment cases according to patient categories. For the GenXpert *Mtb* / RIF test, the proportion of cases of resistance to Rifampicin was 06.66%(97 cases among the 1456 cases of retreatment). Regarding culture and antibiogram, we found 78 cases of resistance to Rifampicin among which 65 cases were also resistant to Isoniazid (Table I). Fourteen cases were monoresistant to rifampicin and 80 cases were monoresistant to Isoniazide (Table II).

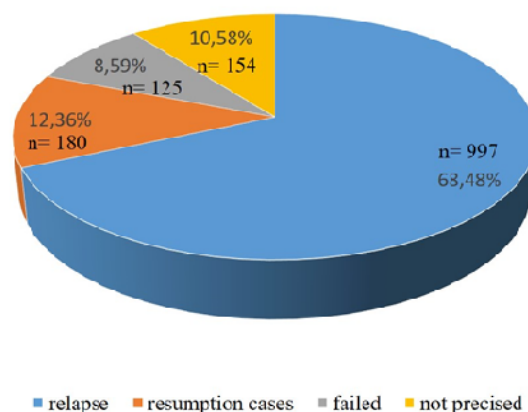


Figure 1. Distribution of re-treatment cases by category

**Table 1. Distribution of MDR-TB cases among Rifampicin resistant tuberculosis**

Type	RR		RH percentage (%)
	numbers (n=78)	numbers (n=65)	
Relapse	41	33	80,49
Dropped out of treatment	09	05	55,56
Failed	28	27	96,43
Total	78	65	83,33

RR : Rifampicin Resistant RH: Rifampicin and Isoniazide resistant

**Table 2. resistance profile of re-treatments cases**

Rifampicine monoresistant tuberculosis n(%)	Isoniazide monoresistant tuberculosis n(%)	Multi drug resistant tuberculosis n(%)
14 (0,90)	80 (5,49)	65(4,46)

#### 4 DISCUSSION

Retreatment is a risk factor for resistance of *Mycobacterium tuberculosis* to anti-tuberculosis treatments [5]. For our study, we could note that the huge majority of retreatment cases were relapse cases (76.57%) followed by dropped out of treatment cases (13.82%) and finally failure cases (9.61%). Our result was consistent with that of Ottmani SE et al, who found this predominance of relapse cases among re-treatments [6]. The distribution of retreatment cases varies from region to region. The causes are different and multifactorial. Some authors explain that the fluctuation in the epidemiology of retreatment cases is partly related to the patient attitudes (especially perception of the disease and compliance), the contribution of the private health sector in the fight against TB (identification / diagnosis of TB cases), the availability of anti-TB treatments outside the national circuit (importance of illicit markets for anti-TB drugs), the level of prevalence of HIV infection in the region and finally the prevalence of MDR-TB in the population [6].

Among the cases of retreatment, we found an incidence of 05.36% (78/1456 cases) of resistance to rifampicin of which 83.33% were associated with resistance to isoniazid (MDR-TB) giving a prevalence of 4.46%. Studies in the literature have shown that the level of resistance carrying varies from one region to another [7-9]. There are many explanations that could be behind these variations (patient compliance, weak health system, etc.). This underlines the importance for each country to examine the local epidemic, the specificities of each region in order to take the best strategy for the care of their respective patients. Hence the importance of anti-tuberculosis resistance surveillance activities in Madagascar, which should be strengthened, not only in terms of resources but also in terms of the coverage of sites that can contribute to this surveillance.

Since years, in our countries where anti-tuberculosis susceptibility testing has not been done routinely for retreatment; WHO recommends a probabilistic treatment (category II regimen) using for the first 2 months a combination chemotherapy combining Streptomycin, Ethambutol,

Rifampicin, Isoniazid and finally Pyrazinamide followed by one month without streptomycin and finally 5 months without streptomycin and pyrazinamide (2SERHZ / 1ERHZ / 5ERH) [10]. This was still the case for Madagascar before 2018. According to studies, this treatment offers an average treatment success rate which is around 50-60% for patients who fail and relapse [11]. It is important to know for the follow-up of the cohort the future of these cases of retreatment, more particularly the therapeutic outcomes (healing, failure, dropped out of treatment and death)

In these studies, Ragonnet R et al found that the failure to diagnose RR monoresistance at the very start of category II treatment would be among the main causes of the emergence of MDR-TB among cases of retreatment [12]. Other studies have shown that the long-term use of Rifampicin (more than 4 months) increases the risk of developing resistance to this molecule, especially if compliance is incorrect [13]. This underlines the importance of carrying out sensitivity tests such as the GeneXpert *Mtb* / RIF in all cases of retreatment to guide the choice of the subsequent therapeutic regimen. The need to identify resistance as quickly as possible for retreatment cases is currently accepted by all, as well as the contribution of molecular biology for this detection [60]. One study reported that prescribing anti-tuberculosis drugs with sensitivity testing tripled the success rate in the category II regimen compared to the standardized empirical strategy within category I regimen failures [61].

As for monoresistance to Isoniazid was 05.49% for our study. In some countries, isoniazid resistance can be as high as 12% in previously treated TB patients, but it can vary from region to region [62,63]. Isoniazid monoresistance is a known predictor of a bad outcome from this WHO Category II regimen. It predisposes to failure or relapse after 2 years of WHO category I treatment (ie the regimen for new cases) [65,66].

In our study, the prevalence of MDR-TB was 4.20%. For cases of relapse and failure of our study; the proportion of multidrug-resistant cases was 80.49% and 96.43% respectively. In other words, according to our result, failure cases could be a more important predictor of multidrug resistance than other cases of retreatment (relapse, recovery). This finding has already been discussed by other authors [69-71].

Despite these results, our study presents some limitation: The retrospective nature which does not allow us to control all the data even those which are relevant for the study. Some important information such as HIV status, HIV infection, diabetes, etc. known to have an impact on the outcome of TB treatment were not available in the NTP database.

A revision of the content of the database is desirable or even necessary for Madagascar in order to better analyze the data of the cohorts of tuberculosis patients.

#### Conclusion

The prevalence of MDR-TB is still low in Madagascar. Cases of retreatment is a real source of the emergence of MDR-TB, especially cases of failure and relapse. Which is consistent with the data in the literature. The treatment effectiveness of new cases must be maximum to prevent these cases of retreatment.

**Conflicts of interest:** The authors declared no conflicts of interest.

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## AUTHOR BIOGRAPHY

**Harison Michel TIARAY** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**Kiady RAVAHATRA** Department of pneumonology, Tertiary hospital of Fenoarivo, Antananarivo, Madagascar

**Jobeline RAJAOARIFETRA** Department of pneumonology, Tertiary hospital of Tamatave, Antananarivo Madagascar

**Oninala Fenitra RAKOTONDRASOA** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**Iantsotiana Davidson RAKOTONDRABE** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**Marie odette RASOAFARANIRINA** Department of pneumonology, Tertiary hospital of Tamatave, Antananarivo Madagascar

**Anjara Mihaja NANDIMBINIAINA** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**Jocelyn Rakotomizao** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**Rakotoson Joelson Lovaniaina** Department of pneumonology, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**ANDRIANASOLO Radonirina Lazaso** Departement of Infectious deasese, Tertiary hospital of Joseph Raseta Befelantanana, Antananarivo Madagascar

**RAHARIMANANA Rondro Nirina** Department of pneumonology, Tertiary hospital of Fenoarivo, Antananarivo, Madagascar