Case Report: Therapeutic Threshold for Rifampicin-Resistant Tuberculosis in a Patient from Maputo, Mozambique

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Abstract. We present a case of a patient in Mozambique, who initiated treatment for rifampicin-resistant tuberculosis (RR-TB) without proof of resistance. For this patient, we estimated the probability of RR-TB using likelihood ratios of clinical arguments. The probability of RR-TB in Mozambique, positive HIV status, and treatment failure after a first treatment and after retreatment were included as confirming arguments, and a rapid molecular test showing rifampicin susceptibility as excluding argument. The therapeutic threshold to start treatment for RR-TB is unknown, but probably lower than 47% and should be calculated to guide clinical decisions.

INTRODUCTION

Rollout of rapid molecular tests to detect rifampicin (RIF) resistance (RR) has likely led to a decrease in empirical treatment for RIF-resistant tuberculosis (RR-TB). Most RR-conferring mutations are situated in the rifampicin resistance determining region (RRDR), targeted by rapid molecular tests such as Xpert\textsuperscript{a} Mycobacterium tuberculosis (MTB)/RIF and Xpert\textsuperscript{b} MTB/RIF Ultra (Xpert MTB/RIF, Cepheid, Sunnyvale, CA) and line-probe assays (LPAs; GenoType\textsuperscript{c} MTBDRsl and GenoType\textsuperscript{d} MTBDRs, HAIN Lifescience, Nehren, Germany).\textsuperscript{4,5} Both tests report on the detection of MTB and of RIF. When diagnosis of RR-TB depends on such tests, RR-TB patients with mutations outside of the RRDR may be repeatedly treated with first-line regimens, mostly without success.\textsuperscript{4,6}

The probability of disease required to treat a patient, or the therapeutic threshold, with equipoise between treating and not treating, has not yet been estimated for RR-TB. Current guidelines recommend all TB patients should be tested for RIF.\textsuperscript{7} The sensitivity and specificity of Xpert MTB/RIF to detect RIF are 96% and 98%, respectively.\textsuperscript{11} In case of Xpert MTB+/RIF− (MTB detected, RIF not detected), first-line treatment is recommended.\textsuperscript{8} In patients with a very high probability of RR-TB, treatment can be started regardless of test results, based on clinical decision-making. We determined this probability for a Mozambican patient when clinicians started RR-TB treatment without bacteriological proof of RR.

Mozambique is a high TB- and RR-TB–burden country. An estimated 3.7% of new, 20% of previously treated patients, and 80% of patients with repetitive first-line treatment failure have RR-TB.\textsuperscript{11} Drug susceptibility testing (DST) by Xpert MTB/RIF is recommended for all TB patients. Health facilities without Xpert MTB/RIF send sputum samples to a nearby facility and manage TB patients based on smear microscopy while waiting for results. In the capital Maputo, DST beyond RIF is carried out at the Central Hospital for retreatment, treatment failure, or suspected RR-TB cases.

Likelihood ratios (LRs) were calculated for clinical arguments and Xpert MTB/RIF results for one patient, using probabilities and odds ratios from the literature. The confirming power is the positive LR or the number of times a positive test result is more likely in a diseased versus a non-diseased person. The excluding power is the inverse of a negative LR or the number of times more likely a negative test result is in a non-diseased versus a diseased person. Excluding and confirming powers are not directly influenced by disease prevalence.\textsuperscript{12}

\begin{align*}
\text{excluding power} &= \frac{\text{sensitivity}}{1 - \text{sensitivity}} \\
\text{confirming power} &= \frac{\text{specificity}}{1 - \text{specificity}}
\end{align*}

The estimated probability of RR-TB in Mozambique was converted to odds and multiplied by the LRs of confirming arguments before testing. That result was multiplied with the excluding power of Xpert MTB+/RIF−. After accounting for all arguments, the probability of RR-TB and its variation were estimated. Uncertainty intervals (UIs) were constructed for log-odds, odds, and probabilities at each step by selecting the relevant quantiles from 1,000 independent estimates calculated based on random draws from the relevant power and probability distributions. R version 3.5.2 was used for analysis.\textsuperscript{13} (Supplemental File 1: detailed methodology).

In a clinical setting, the power of arguments can be estimated based on clinical expertise (e.g., strong) or rounded up or down to obtain integer numbers and then categorized. Such intuitive approximation of an LR can be converted to a log-odds scale (Table 1).\textsuperscript{14} The patient was informed about the purpose of this study and signed consent.

CASE STUDY

The patient was a 40-year-old woman from rural southern Mozambique. In 2012, she was diagnosed with HIV and started first-line antiretroviral therapy (lamivudine, tenofovir, and efavirenz). She reported having a TB diagnosis and TB treatment at least twice: in 2014 for 6 months (RIF, isoniazid, ethambutol, pyrazinamide) and later for 8 months with the same drugs strengthened with 2 months of streptomycin. She interrupted the last regimen as her clinical presentation worsened. We considered at least two episodes of treatment failure.

In May 2018, the patient presented with productive cough, thoracic pain, wasting, no fever, normal blood pressure, a respiratory rate of 23 counts per minute, wheezing, and a
positive sputum smear microscopy with high bacillary load. She had no known RR-TB contacts. Despite Xpert MTB/RIF showing MTB+/RIF−, an RR-TB treatment containing levofloxacin, capreomycin, ethionamide, cycloserine, pyrazinamide, and ethambutol was started. In June 2018, LPA DST showed RR to levofloxacin, ethionamide, and isoniazid, and confirmed RIF susceptibility. Treatment was modified to contain bedaquiline, delamanid, clofazimine, linezolid, and para-aminosalicylic acid. The patient had smear conversion and negative cultures from month 5. The detailed clinical history and chest X-ray are available as Supplemental Files 2 and 3.

After including all arguments, the estimated probability of RR-RB in this patient was 46.6% (95% UI: 25.0–72.0; Table 2, Figure 1). An alternative starting point was a pretest probability of RR-TB in retreatment cases in Mozambique of 20% (95% CI: 5.2–40). When including the probability of HIV of 36%, assuming the same HIV prevalence in new and retreatment TB cases, the probability of RR-TB increases to 24.0% (95% UI: 8.1–54.2) among HIV-positive patients with a TB history.11,15

### Table 1

| Rounded power* | Strength | Steps on the log-odds scale† |
|---------------|----------|-----------------------------|
| 60–200        | Very strong | 2                           |
| 20–50         | Strong     | 1.5                         |
| 6–15          | Good       | 1                           |
| 2–5           | Weak       | 0.5                         |
| 1             | Useless    | 0                           |

* Confiming or excluding power can range between 0 and infinity. The power is rarely 200 or more, whereas power lower than 1 means the test is useless or should have its outcomes reversed.

† If confirming power, add the respective number of steps, if excluding power, subtract steps (unit in log₁₀ odds).

### Table 2

| Argument | Available data | Odds of RR-TB | Probability of RR-TB | Reference |
|----------|----------------|---------------|----------------------|-----------|
| 1 Newly diagnosed TB patient in Mozambique | Prevalence of RR-TB in Mozambique: 3.7% (95% CI: 2.5–5.2) | 0.038 | 3.7% (95% CI: 2.5–5.2) | 11 |
| 2 HIV positive | OR of RR-TB in HIV-positive patients: 1.49 (95% CI: 0.73–3.06) | 0.049 | 4.6% (95% UI: 2.5–8.7) | 24 |
| 3 Treatment failure after a first treatment | OR of initial RR-TB in retreatment cases (after treatment failure of a first treatment): 7.24 (95% CI: 4.06–12.89) | 0.246 | 19.8% (95% UI: 9.0–36.7) | 24 |
| 4 Treatment failure after retreatment | Probability of acquiring RR-TB during a first TB treatment (if no initial RR-TB) that resulted in treatment failure: 28.6% (95% CI: 8.4–58.1) | 0.745 | 42.7% (95% UI: 24.0–67.8) | 6 |
| 5 Xpert MTB+/RIF− | Likelihood ratio of retreatment failure in patients with RR-TB acquired during first treatment (before starting retreatment): 19.1 (95% CI: 15.2–24.1) | 14.152 | 93.4% (95% UI: 85.4–97.5) | 6 |

OR = odds ratio; TB = tuberculosis; RR-TB = rifampicin-resistant tuberculosis; UI = uncertainty interval; Xpert MTB+/RIF− = Xpert Mycobacterium tuberculosis detected/isoniazid resistance not detected.

* Pretest probability.
† Posttest probability.

### Discussion

We estimated the probability of RR-TB in an HIV-positive TB patient with retreatment failure and a susceptible RIF-DST result in Mozambique at 46.6% (95% UI: 25.0–72.0). At this probability, RR-TB treatment was started without delay. We illustrated the use of the log-odds scale to facilitate the process of clinical decision-making.

Because of its high sensitivity and specificity,10 Xpert MTB+/RIF− (MTB detected, RIF detected), has a strong confirming power (approximately 50), whereas Xpert MTB+/RIF− has a lower, but still strong excluding power. However, RIF-DST can miss RR-TB if mutations happened outside of the RRDR.5,16,17 In Eswatini, 38/125 (30%) of RR strains were not detected by Xpert MTB/RIF.3 In South Africa, 37/249 (15%) samples identified as RS by Xpert MTB/RIF were reclassified as RR after sequencing.4 These patients could be wrongly treated for RS-TB, have worse treatment outcomes, and silently spread RR-TB.6 In Rwanda, when RIF-DST was not available or results delayed, RR treatment initiation based on clinical decision-making reduced mortality.18 In patients with a high pretest probability of RR-TB, Xpert MTB+/RIF− is unlikely to lower the posttest probability below the therapeutic threshold, justifying empirical treatment.7

These scenarios, common in low-resource settings, show why establishment of a therapeutic threshold for RR-TB is important. The therapeutic threshold for pulmonary RS-TB in Rwanda was 2.6%, rising to 12% when including regret factors such as treatment-related cost and morbidity.8,19 In our case, the therapeutic threshold is not equipoise between treating and not treating, but between treating for RS-TB or RR-TB. Compared with RS-TB, RR-TB treatment is longer, more toxic, and expensive, but disease-related mortality and morbidity is also higher.11 These regret factors should be considered when calculating the RR-TB threshold.20 Clinical
The probability of RR-TB in HIV-positive retreatment cases estimated as alternative starting point (24%) approached the estimate of the pretest probability of RR-TB in first treatment failure cases (20%) because of initial RR-TB in HIV-positive patients, but was lower than the estimated 43% for a HIV-positive case with treatment failure, with a large UI. This could be explained by the fact that patients with a TB history include patients with treatment failure and those with reinfection.  

The therapeutic threshold is yet unknown for RR-TB, but probably less than 47%. Establishing this threshold can guide clinical decision-making. Attributing confirming and excluding power to clinical arguments on a log-odds scale can help to rationalize the process.

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