

Rifampicin Mono-Resistant Tuberculosis—A Review of an Uncommon But Growing Challenge for Global Tuberculosis Control

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Tuberculosis (TB) remains the leading cause of death by an infectious pathogen worldwide, and drug-resistant TB is a critical and rising obstacle to global control efforts. Most scientific studies and global TB efforts have focused on multidrug-resistant TB (MDR-TB), meaning isolates resistant to both isoniazid (INH) and rifampicin (RIF). Newer diagnostic tests are resulting in an increasing awareness of RIF-resistant TB in addition to MDR disease. To date, RIF resistance has been assumed to be synonymous with MDR-TB, but this approach may expose TB patients with RIF mono-resistance disease to unnecessarily long and toxic treatment regimens. We review what is currently known about RIF mono-resistant TB, its history and epidemiology, mechanisms of RIF resistance, available diagnostic techniques, treatment outcomes reported globally, and future directions for combatting this disease.

Keywords. tuberculosis; rifampicin mono-resistant tuberculosis.

INTRODUCTION

Despite almost 30 years of global public health efforts, tuberculosis (TB) remains the leading cause of death by an infectious pathogen worldwide [1]. Global TB control efforts have been stymied in part by the emergence of drug-resistant TB; managing this patient population is more complex, challenging, and costly than treating individuals with drug-sensitive TB. Much of the research on drug-resistant TB to date has focused on multidrug-resistant TB (MDR-TB), defined as *Mycobacterium tuberculosis* isolates resistant to at least isoniazid (INH) and rifampicin (RIF). MDR-TB patients require longer treatments with more costly therapies than patients with drug-sensitive disease and have higher treatment failure and mortality rates [2–6]. Recent work has demonstrated that INH resistance is also associated with poorer treatment outcomes than drug-sensitive TB [7–11]. Although RIF and INH resistance often occur concurrently such as in

MDR-TB strains, resistance to each of these agents arises independently from each other, and resistance to 1 agent can occur without resistance to the other.

In December 2010, the World Health Organization (WHO) recommended the Xpert MTB/RIF assay as a first-line diagnostic test for TB [12]. The expansion of diagnostic tests that enable the rapid recognition of RIF resistance has raised awareness of the existence of patients with rifampicin mono-resistant TB (RR-TB), which previously had been considered uncommon. In 2014, only 1.1% of TB patients worldwide were believed to harbor RIF resistance without concomitant INH resistance [13]. Of the ~558 000 incident MDR/RR-TB patients in 2017, just over 100 000 had RR-TB [1]. Limited evidence suggests that the prevalence of RR-TB is increasing and is associated with increased morbidity and poorer outcomes compared with drug-sensitive TB [9, 14, 15].

International guidelines generally recommend using individualized MDR-TB treatment regimens for patients with RR-TB [16–18]. However, MDR-TB treatment regimens may expose rifampin mono-resistant TB patients to unnecessarily long and toxic therapies while excluding the possible benefits of an INH-containing regimen [19]. We review the available epidemiology and treatment outcome data associated with RR-TB to inform the current state of knowledge and to highlight key needs for further research in the optimal management of patients with RR-TB.

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HISTORY & EPIDEMIOLOGY

Mycobacterium tuberculosis has long been recognized as a human pathogen, with evidence of its emergence dating as far back as 70 000 years [20]. After the initial use of streptomycin as anti-TB therapy, resistance during monotherapy was quickly recognized, and a subsequent trial demonstrated the benefits of combination antimicrobial therapy for TB treatment outcomes and the prevention of drug resistance emerging during treatment [21]. It was not until the 1950s and 1960s that INH and RIF became recognized as anti-TB therapies, respectively [22], with the latter transforming the future of tuberculosis treatment. The addition of RIF to treatment regimens formed the basis for the modern-day, short-course oral treatment still in use today [23].

Epidemiologic estimates of RR-TB prevalence are difficult to discern, as until recently widespread testing for RIF resistance was not available. The introduction of the Xpert MTB/RIF assay as a first-line diagnostic test for TB has substantially expanded testing for RIF resistance. However, early generations of the Xpert assay did not include INH resistance testing, making it impossible to distinguish RR- from MDR-TB without additional laboratory testing. Therefore, few studies have been published demonstrating the prevalence of rifampicin-resistant, isoniazid-susceptible *M. tuberculosis* [9, 14, 24–28].

Evidence from South Africa suggests that rates of RR-TB may be higher than previously estimated and increasing. One retrospective study in Cape Town noted that the total number of RR-TB cases more than tripled between 2004 and 2008, from 31 to 98 cases [24]. Another study performed in the Western Cape Province found that RR-TB was becoming increasingly encountered, more so in HIV-infected and HIV-exposed, noninfected children in the region (50% of RR-TB patients were HIV infected, and another 22% were HIV exposed) [25]. A retrospective review of MTB-positive sputum cultures from 16 748 patients in KwaZulu-Natal between 2007 and 2009 found that the proportion of RR-TB ranged from a low of 7.3% to a high of 10.0% (overall estimate 8.8%) using culture-based phenotype drug susceptibility testing (DST) [27]. Most recently, among 88 559 *M. tuberculosis* cultures with DST results in KwaZulu-Natal between 2011 and 2014, 18 352 (20.7%) were RIF resistant and 19 190 (21.7%) were INH resistant. The proportion of RR-TB cases increased from 15.3% in 2011 to 21.4% in 2014, similar to increases seen for INH mono-resistant and MDR disease [26].

Estimates of RR-TB prevalence in other parts of the world are highly varied. Among TB cases reported to the US Centers for Disease Control and Prevention between 1998 and 2014 and excluding cases from California, 359/126 431 (0.28%) had primary RR-TB [15]. A study by Bai et al. [28] in Korea found that among 8840 new TB cases diagnosed between 1994 and 2004, 266 cases (3.0%) had RIF resistance, with approximately

one-fifth of these having mono-resistance only. A retrospective cohort analysis in France found 39 patients with RR TB between 2005 and 2010, ~0.12% of all TB cases identified [14]. In a study of 11 467 new cases of TB in Shandong, China, the presence of RIF resistance increased from 1.97% in 2004 to 5.77% in 2018. INH resistance declined during this same period [29]. In Germany, RIF resistance without INH resistance accounted for only 0.3% (87/26 228) of all TB cases with DST results between 2008 and 2017, with no increase over time. Among the 3324 TB isolates with resistance to any first-line antimycobacterial agent, 634 (19.3%) were RIF resistant alone or in combination with other agents [30]. In a systematic review of 2552 newly diagnosed TB cases in Iran, 156 (5.5%) had resistance to RIF. Among the RIF-resistant cases, 52 (33.3%) were susceptible to INH [31].

MECHANISMS OF RESISTANCE

RIF halts DNA-directed RNA synthesis by interacting with the β -subunit of RNA polymerase [32, 33]. Several mechanisms of resistance to rifampicin have been demonstrated, with mutations in the *rpoB* gene being the most common in *M. tuberculosis* isolates. In 95% of strains, this mutation is located in an 81-base-pair region named the RIF resistance-determining region (RRDR) [34, 35]. Within this 81-bp region, mutations specifically within codons 516, 526, and 531 are responsible for up to 90% of RIF-resistant strains [36, 37].

An efflux pump mechanism is thought to be responsible for the ~5% of RIF-resistant *M. tuberculosis* strains with no mutations in the RRDR [38]. A study conducted by Pang et al. (2013) of *M. tuberculosis* strains without *rpoB* gene mutations found that efflux pumps contribute to RIF resistance in RIF-mono-resistant isolates. Through transcription-level analysis, the authors showed 3 efflux pumps to be involved in exporting RIF from the cell: Rv0783, Rv2936, and Rv0933 [39].

More recently in 2015, Li and colleagues studied efflux pump gene expression in RIF-mono-resistant *M. tuberculosis* isolates in order to identify specific genes involved in this mechanism. PCR amplification and DNA sequencing of the *rpoB* gene from 16 RIF-mono-resistant *M. tuberculosis* clinical isolates from adult pulmonary TB patients was performed; 15 of 16 were shown to have mutations within the RRDR of *rpoB*. Half of the RIF-mono-resistant isolates with *rpoB* mutations overexpressed 1 or 2 of the following putative efflux pump genes: *Rv2333*, *drvB*, *drvC*, *Rv0842*, *bacA*, and *efpA*. The authors noted that the level of RIF resistance varied independently of the *rpoB* gene mutations, indicating that the 6 efflux pump genes may also play a role in RIF resistance [40].

Additionally, *rpoB* gene mutations outside the RRDR that confer RIF resistance have been described. An *rpoB* Ile491Phe mutation accounted for 30% of the MDR-TB isolates identified in a survey of TB drug resistance in eSwatini (formerly

known as Swaziland) in 2009 [41]. Of concern, currently available commercial diagnostic tests for RIF resistance including the BACTEC mycobacteria growth indicator tube (MGIT) 960 automated detection system (BD, Franklin Lakes, NJ, USA) do not routinely detect this mechanism, increasing the likelihood of inadequate treatment regimens with worse outcomes and possible amplified drug resistance [42].

CURRENT DIAGNOSTIC TECHNIQUES

In the past decade, there have been several advances in TB diagnostics and drug resistance testing. Molecular diagnostic methods for mutations in the *rpoB* gene region have revolutionized TB diagnostics and facilitated rapid molecular detection of RIF resistance [43–47].

In 2008, the WHO recommended the line probe assay (LPA) based on reverse hybridization of DNA for MDR-TB detection [48]. LPA-based assays capable of detecting resistance to multiple anti-TB agents including RIF, INH, ethambutol, fluoroquinolones, and injectable antimicrobials now exist, but their use tends to be limited to reference laboratories with the necessary technical expertise [49]. In 2010, the WHO endorsed the introduction of the Xpert MTB/RIF nucleic acid amplification test (NAAT; Cepheid, Inc.) for TB diagnosis. This was a particularly historic change in the TB diagnostics world, as it provided an automated and rapid point-of-care method to detect both active pulmonary TB and RIF resistance. In high-burden settings, Xpert MTB/RIF assays are used as a surrogate marker for multidrug resistance without directly testing for isoniazid resistance in the first line of testing [50–52].

Both LPA and Xpert MTB/RIF assays show strong diagnostic performance (95%–98% sensitivity) when compared with phenotypic DST [53, 54]. Per WHO guidelines, LPA results can usually be reported within 2–3 days. In contrast, the Xpert MTB/RIF assay can report results within 3 hours, depending on the exact timing of receiving a sample and reporting the result [55]. High sensitivity (98%) of the Xpert MTB/RIF test has been reported in smear-positive samples. In smear-negative specimens, the detection rate is lower (72.5% to 76.9%) [56], and its accuracy for detecting RIF resistance can vary by region, depending on the variation of circulating TB strains within that area [53, 57].

CURRENT GUIDELINES AND RECOMMENDATIONS

The WHO Global Tuberculosis Programme has published several guidelines over the past 2 decades addressing the emergence of drug-resistant TB. The first guidelines, published in 1996, recognized the dire impact drug-resistant strains could have on global TB control, defined MDR-TB as *M. tuberculosis* resistant to at least INH and RIF, and provided treatment recommendations [58]. These guidelines described a treatment regimen for INH-mono-resistant TB and defined any isolate

with RIF resistance as “MDR-TB.” Subsequent WHO guidelines published in 2014, 2016, and 2018 have specifically mentioned RIF-mono-resistant TB; however, treatment recommendations remained the same as for MDR-TB, with no deviations [59–61].

The most recent WHO guidelines on drug-resistant tuberculosis treatment continue to recommend identical treatment regimens for RR- and MDR-TB. These recommendations include an option for a shorter regimen (9–12 months) in patients who have not been previously treated for more than 1 month with second-line medicines used in the regimen. For patients requiring a longer duration, a regimen ranging from 15–20 months is sufficient, unless there is additional resistance to second-line agents [62]. This guidance is similar to their recommendations in previous recent years.

In contrast to the WHO guidelines, the 2019 joint American Thoracic Society (ATS), US Centers for Disease Control and Prevention (CDC), European Respiratory Society (ERS), and Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for drug-resistant TB treatment specifically do not address management of RIF resistance in the absence of INH resistance [63]. Other institutional bodies, including the United Kingdom National Institute for Health and Care Excellence and the European Union Standards for Tuberculosis Care, have followed the WHO recommendations for treating RR-TB similarly to MDR disease.

Previous joint ATS/CDC/IDSA TB guidelines did suggest an alternative treatment regimen to MDR-TB for RIF mono-resistance, outlining a 9-month regimen consisting of INH, pyrazinamide, and streptomycin. An all-oral regimen consisting of INH, pyrazinamide, and ethambutol for 12 months was recommended if using an injectable agent was not feasible. The guidelines also suggested the addition of a fluoroquinolone in patients with more extensive disease. In contrast, the recommendations for MDR-TB treatment were a fluoroquinolone, pyrazinamide, ethambutol, and an injectable agent, +/- an alternative agent, for 18–24 months’ duration [64, 65].

Because of the low incidence of MDR-TB and the availability of reliable DST in the United States, the Curry International Tuberculosis Center and the California Department of Health recommend a tailored RR-TB treatment approach consisting of INH, ethambutol, and a fluoroquinolone daily for 12–18 months, supplemented with pyrazinamide for a minimum of 2 months during the intensive phase [66].

TREATMENT OUTCOMES

Compared with INH mono-resistant TB and MDR-TB patients, data on RR-TB treatment outcomes are limited. These data suggest that patients with RR-TB are more likely to have poorer outcomes compared with patients with drug-susceptible TB. In a prospective cohort study of 1039 culture-positive TB patients in Lima, Peru, 24 (2%) were confirmed as having RIF

mono-resistance. RR-TB patients were more likely to have HIV co-infection (adjusted odds ratio, 9.43; 95% CI, 1.9–47.8) or die (8.3% vs 1.4%; $P = .004$) than patients with drug-susceptible TB [9]. A retrospective cohort analysis of 42 582 cases from the California Department of Public Health TB Registry over a 16-year period (1993–2008) identified 178 (0.4%) RR-TB cases. There were 3469 (8.1%) cases with INH mono-resistance, and 635 patients (1.5%) had MDR-TB. In a multivariate analysis controlling for HIV co-infection and other covariates, RR-TB cases were twice as likely to die as patients with drug-susceptible TB (relative risk, 1.94; 95% CI, 1.40–2.69) [67]. In a retrospective cohort analysis of 39 patients with RR-TB in France, only 20 (51%) had documented treatment success (clinical cure). Of the 30 cases where treatment outcomes were assessed, 3 RR-TB patients died, 3 had relapse of disease, and 4 were lost to follow-up [14].

A retrospective study from South Korea compared treatment outcomes in patients with RR-TB and those with pan-susceptible TB who did not receive RIF because of an adverse event. Forty-four RR-TB patients and 29 pan-susceptible TB patients intolerant of RIF were identified between 1999 and 2013. RR-TB patients were younger, had more alcohol use, more often had a history of TB, and had radiologically more severe disease compared with the RIF-intolerant TB group. Treatment success rates were not significantly different (87.2% and 80.0% in the RR-TB and RIF-intolerant TB groups, respectively; $P = .586$). However, the RR-TB patients had a longer average duration of therapy (453 days vs 371 days; $P = .011$) compared with RIF-intolerant pan-susceptible TB patients [68]. In a study of 545 patients with DR-TB treated in the Netherlands between 2005 and 2015, MDR disease, but not RIF mono- or poly-resistance, was associated with worse treatment outcomes [69].

Stagg and colleagues [70] undertook a systematic review and meta-analysis of randomized controlled trials to evaluate treatment regimens for RR-TB, but found only 3 studies collectively reporting outcomes for only 9 patients with RIF-mono-resistant isolates [71–73].

FUTURE DIRECTIONS

There is a clear need for further studies and surveillance systems to better estimate the prevalence and incidence of RIF-resistant, INH-susceptible TB. While the widespread use of Xpert has been a major milestone in TB diagnostics, there are limitations in its utility, specifically in managing RR-TB. Automated rapid diagnostic tests for the direct detection of *M. tuberculosis complex* with INH and/or RIF resistance from sputum samples have been developed [74]. Their utility and cost-effectiveness in routine clinical practice need to be determined, but modalities that identify INH resistance will aid in more rapidly distinguishing between RR-TB and MDR-TB, with potentially significant treatment implications. Additionally, there is a need

for more routine use of sophisticated diagnostics in order to recognize RR-TB strains that do not contain RRDR mutations. With the greater usage of next-generation sequencing technologies in microbiology, the routine use of whole-genome sequencing (WGS) for *M. tuberculosis* isolates has become more plausible and, in particular, has been shown to have high sensitivity and specificity specifically for the detection of RIF and INH resistance [75, 76]. Further consideration should also be given to more rapid and cost-effective ways to perform DST on second-line agents once a patient has been identified as having RIF-resistant TB. Second-line DST can ensure a more effective regimen has been chosen, thereby also reducing further RR-TB transmission [77].

Additionally, more robust data from trials regarding the most effective treatment regimens (both drugs and duration of therapy) for RR-TB remain needed, particularly in high-risk areas of RR-TB and MDR-TB endemicity such as South Africa, Peru, Korea, and India. As with MDR-TB, effective treatment outcomes with shorter, less toxic, and less complex regimens are needed for this patient group. Novel laboratory-based approaches for identifying more effective, shorter TB treatment regimens have been developed, and data from mouse models suggest that RIF-free regimens could be effective for DS- and DR-TB [78].

Finally, as we look to the future of managing these patients, other key areas for investigating include optimizing the pharmacokinetics/pharmacodynamics of existing antituberculous agents and the development of new antimicrobials with novel mechanisms of action. Using medications such as verapamil and chlorpromazine, shown to act as efflux pump blockers, may also prove clinically useful in treating this disease [40]. Increased attention should be paid to the field of nonantimicrobial interventions to combat antimicrobial drug resistance, and funding for basic and clinical research in these areas is sorely needed.

Though the scope of this review has focused largely on studies involving TB-endemic countries, it should be noted that in low-incidence TB countries, in particular, rigorous data for incidence and treatment outcomes of RR-TB remain sparse. This is largely because the incidence of drug-resistant TB in such regions is low. However, there is a continued need for studies in these regions, and there is an increased need for provider awareness. Some drugs becoming part of commonly used regimens for MDR-TB treatment in high-incidence countries, such as bedaquiline, remain more last resort treatment options in many low-incidence countries. Further exploration of using such newer agents in low-TB incidence countries should be considered.

CONCLUSIONS

Drug resistance remains a major barrier to winning the global fight against TB. For more than 50 years, RIF has been the

cornerstone of effective TB treatment. With the spread of genomic-based rapid diagnostic tests for TB worldwide, there is growing awareness of the magnitude of RIF resistance complicating TB control efforts. Increased research and policy analysis are needed to understand the magnitude of the problem and to develop effective, less toxic, and less costly treatments for RR-TB. These include treatments with shorter overall durations of therapy, reduced pill burdens, and reduced rates of adverse events, to name a few benefits. In addition, and also of paramount importance, better identification and treatment of RR-TB may reduce the progression of further drug resistance, which still greatly contributes to the obstacle of meeting the WHO End TB Strategy Goals by 2035 [79].

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