

Concept Note

Dose optimization of rifampicin, isoniazid, pyrazinamide and ethambutol in the treatment of drug-susceptible tuberculosis

1. Background

Rifampicin, isoniazid, pyrazinamide and ethambutol are essential TB drugs and medicines in the standard first-line treatment of drug-susceptible TB. They are in the adult and children WHO Model Lists of Essential Medicines (1) both as an oral single dose formulation or part of the fixed-dose combinations .

The recommended dose of rifampicin for treatment of TB in adults, 10 mg/kg (8-12 mg) once daily with a maximum daily dose capped at 600 mg (2) and a range of 10-20 mg/kg in paediatric patients, also with a maximum at 600 mg/day, (3) was introduced back in 1971, when rifampicin was approved by the US FDA, based on pharmacokinetic, toxicity, and cost considerations at the time (49 years ago). This development followed several clinical trials where regimens containing rifampicin were shown to be very effective and when combined with pyrazinamide allowed reduction of treatment duration for drug-susceptible TB to 6 months. Most of these trials used rifampicin at a single daily dose of 600 mg, without however, providing detailed reasoning for this specific dose selection. Rifampicin was considered a second-line drug in the early 1970s and was prohibitively expensive for wide use since its cost as a single drug formulation was many times higher than the cost of the first line regimen used at the time (streptomycin, isoniazid and PAS). Not only were the production costs high, the drug suffered from low production and availability issues. Since then, the situation has changed dramatically vis-a-vis the cost, availability, production capacity and treatment policies. Currently, rifampicin is a first-line TB agent, produced by many generic manufacturers at affordable costs and is readily and widely available.

A published literature review (4) made an attempt to investigate the historical data and understand the rationale for rifampicin dose selection. The review assessed the three most prominent factors believed to have influenced dose selection in the last century - pharmacokinetics, toxicity and cost. It postulated that cost considerations had an unequally high weight and therefore swayed the decision towards the lowest end of possible dosing options. The literature review also discovered a significant body of historical data and contemporary evidence that challenges previous thinking on rifampicin pharmacokinetics and toxicity. The understanding of rifampicin activity has also changed with the development of the science of pharmacokinetics/pharmacodynamics (PK/PD). (5, 6) According to newly established models, concentrations of rifampicin achieved at the site of pulmonary infection are described as very low when 10mg/kg dosing is used. It has also been highlighted that *in vitro*, animal, and early bactericidal activity studies suggest that the 600-mg once daily dose is at the lower end of the dose-response curve even for patients weighing 50 kg (at start or during treatment), therefore delivering suboptimal concentrations for patients above 50 kg. (4) There are also some studies that highlight particular risks with rifampicin dosing in corpulent TB patients. (7) Both toxicity studies and clinical experience using rifampicin for treatment of other diseases showed no increased toxicity or tolerability problems when daily doses used were two or three times higher than currently recommended. (8-11) PK studies

have shown low rifampicin exposures in children with malnutrition and in the very young, with modelling studies suggesting poor outcomes in these paediatric populations. (12-15) The paper by Boeree et al. postulated that the increased doses of rifampicin, as part of the first-line TB regimen or in combination with other drugs, may even contribute to potential shortening of the regimen duration. (16)

The recommended normal dose of isoniazid for the treatment of drug-susceptible TB is between 4-6mg/kg/day while “high” dose (most commonly 10-15mg/kg/day) is used for treatment of patients with a specific type of isoniazid-resistant TB (with the presence of *inhA* mutation only). In the host, isoniazid is metabolized by N-terminal acetyltransferase 2 (NAT2), and a mutation in the NAT2 genotype leads to substantial differences in isoniazid metabolism, and individuals are classified as either “slow” or “fast” acetylators. In both slow and fast acetylators, a daily isoniazid dose of 5 mg/kg for drug-susceptible TB can achieve the target levels in adults and higher doses would only predispose to toxicity. (17) In the presence of the *inhA* mutation, the same dose may suffice in slow acetylators but fast acetylators may require a higher dose (e.g. 15mg/kg/day) to reach the threshold. In settings like China where the majority of the population are fast acetylators, a higher dose needs to be considered, so long as the medicine is tolerated. (18) In children the currently recommended daily dose of isoniazid is 7-15 mg/kg/day, with the lower range expected to provide adequate levels in the majority of children, except in children below two years of age and fast acetylators to whom the higher range applies. (19)

Preclinical and clinical evidence (based on culture conversion data) suggests that the current dose of pyrazinamide in standard use is not optimised (e.g. 20-30mg/kg/day). (20-23) For children the pyrazinamide dosing was determined at 35 mg/kg (30-40 mg/kg range) in the 2014 WHO guidance. (19) The recommended dose of ethambutol is between 15-25mg/kg/day for adults and children. Increasing the dose of pyrazinamide or ethambutol could probably improve effectiveness in certain patients but is expected to increase toxicity to unacceptable levels if this is applied in all patients. (18) New evidence is needed to consider possible dose optimization options for the first-line TB medicines as part of the multi-drug regimen. It is important to note that the current dosing of individual drugs in widely available first-line FDCs cannot achieve the target levels suggested by PK/PD data by simply doubling or tripling the number of pills given daily. This could lead to toxicities. Evidence on the optimal dosing of the first-line TB drugs is being gathered currently through advanced PK/PD studies and clinical trials or is being synthesized by systematic reviews. (24, 25) Systematic reviews of efficacy and safety that are related to the optimal dose of the first-line TB medicines would be instrumental in assessing appropriate risk-to-benefit ratio for the drugs. The evidence, when it becomes sufficiently available, is likely to lead to multiple changes in TB treatment policies, clinical practices and manufacturing standards for these medicines.

2. Recent WHO consultations and decisions made on optimizing dose of the first-line TB medicines

- WHO convened a PK/PD consultation in April 2017 when dosing of rifampicin, isoniazid and pyrazinamide was discussed. At this meeting it was concluded that a full review of evidence on the optimal dose of the medicines, in terms of efficacy and safety, would be important once more data become available, especially for rifampicin: “While a change to WHO policy on the currently recommended weight-based dosing of rifampicin would

require additional trial evidence, the point was made that a higher rifampicin dose may be needed to achieve therapeutic concentrations, particularly in younger children, underweight adults, patients with TB meningitis and immunocompromised HIV-infected TB-patients.” (18)

- In response to the findings of the PK/PD consultation, in June 2017 the TB STAG supported a continued exploration of PK/PD data on drug dosage before any increase of dose is contemplated for a regimen that achieves a relapse free cure in the vast majority of TB patients who adhere to treatment. Some argued that measured levels of individual drugs are less important than the combined action of multiple agents given together even if individual exposures are suboptimal, and that patient outcome data are critical to any change in current dosage regimens.
- Following the PK/PD consultation, the decision was made by WHO to remove the cap on the maximum daily dose of 600mg of rifampicin in the WHO guidelines on the treatment of drug-susceptible TB and patient care: 2017. (26) Removing the 600mg dose “ceiling” in the guidance allows the dose of rifampicin to be achieved in all patients with drug-susceptible TB, especially patients in the higher body-weight bands, when taking the WHO-recommended standard 6-month treatment regimen (2HRZE/4HR) (see also Table below). Since there is no longer a cap on the daily maximum dose of rifampicin per day, adults in the higher body-weight bands (e.g. over 70kg) may be dosed as per current recommended range in terms of the mg/kg body weight per day. The WHO PK/PD report (2018) identified situations where case by case increments in rifampicin dose could be considered based on direct patient data, although more evidence is still needed. (18)

Table 1. Change in adult dosing of rifampicin in the WHO treatment guideline 2017 update

Previously recommended dosing of rifampicin	Optimised dosing of rifampicin
10 mg/kg (8-12 mg) once daily, maximum daily dose 600 mg	10 mg/kg (8-12 mg) once daily

- Further WHO/MTB internal discussions and consultation with PK/PD experts have been held since 2017 and a suggested next step is an assessment of available evidence that could support possible dose optimization of the first-line TB medicines.

3. Issues that need to be addressed to further optimize rifampicin dose

- There are concerns about low exposure to the first-line TB medicines with recommended dosages, and this remains a topical subject of discussion in the TB PK/PD community. The major issues are the potentially suboptimal dosage in some specific sub-groups of TB patients such as children, patients with TB meningitis (27), extensive cavitary disease (28), HIV infection or diabetes mellitus. A contemporary body of available data may lend itself to provide a basis for dose modifications in these particular patient groups.
- More patient data are needed to understand if the added benefit of optimising blood levels of the drugs is justified against the balance of any significant increase in toxicity. A substantial contributor to unfavourable outcomes in the current first-line treatment

regimens is loss to follow up, which could potentially be worsened if adverse events increase with higher dosage.

- The formal WHO policy decision to increase the weight-based dosing of first-line TB medicines requires additional evidence (including from trials which assess different patient outcomes), appropriate systematic reviews and potentially also a GRADE-based evidence assessment.
- Any changes to the actual dose of the first-line TB medicines would require a series of articulated actions to communicate widely the rationale for the change, and to assist countries and partners to update the international and national treatment and diagnostic guidelines. It will also require new fixed-dose combinations (FDCs) or other interim solutions which permit an appropriate dosing of all the component drugs and which have proven bioequivalence and bioavailability, without increasing adverse events.
- The future perspective, taking into account the objectives of several ongoing clinical trials¹³ will also need to consider contribution of dose increases to shortening the first-line regimen below the currently recommended 6 months of the first-line TB treatment.¹

4. Objective of the concept note

The results of clinical trials investigating possible shortening of the duration of first-line treatment by increasing the dose of rifampicin and other first-line TB medicines are not expected to be available in 2020-21. However, the evidence on the optimal dosage of the medicines in children, patients with TB meningitis, patients with extensive cavitory disease, HIV infection or diabetes has become available recently. An assessment of currently available evidence on optimal dosing of the first-line TB medicines in all TB patients and in these particular patient groups is urgently needed to consider whether the current evidence is sufficient for any dosing changes. Therefore, the purpose of this concept note is to focus on the work required for dosing optimization of rifampicin, isoniazid, pyrazinamide and ethambutol in the treatment of drug-susceptible TB. This is the top priority in the optimal use of the medicines to achieve the best treatment outcomes in patients who receive first-line TB treatment, particularly paediatric TB patients and all patients with TB meningitis, extensive cavitory disease, HIV infection or diabetes.

The future work to look at the increased dosing of medicines for shortening the regimen below 6 months falls beyond the scope of this concept note.

A series of systematic reviews is a first step to synthesize available evidence, leading to a wider consultation with relevant experts in the field to advise WHO on any necessary policy decisions. As PK data linked to treatment outcomes in the paediatric population are expected to be limited, an additional individual patient data meta-analysis may be needed following these reviews.

¹ Results of the following trials will be helpful: <https://www.newtbdrugs.org/pipeline/trials/rifashort>; <https://clinicaltrials.gov/ct2/show/NCT01392911>; and <https://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-016-0597-3>.

5. Plan of actions

a) Conducting a systematic review

A review of the landscape of current evidence on the most effective dosing of rifampicin, isoniazid, pyrazinamide and ethambutol to be commissioned by qualified and independent consultants or research groups.

A suggested question, based on the PK/PD Task Force discussion in November 2017, for the evidence review is provided below in the Population, Intervention, Comparator, Outcomes (PICO) format (Table 2):

In patients on combination regimens for drug-susceptible TB, does a higher dose of the first-line TB medicines (listed in table below) than currently recommended doses safely increase the likelihood of treatment success and reduce the unfavourable treatment outcomes?

Table 2. The question presented in the PICO format

Population	Intervention	Comparator	Outcome
Patients receiving treatment with rifampicin, isoniazid, pyrazinamide or ethambutol in combination regimens for treatment of drug-susceptible TB <i>Stratified by:</i> • New, previously treated • Daily, intermittent dosing • Regimen combinations • Pulmonary, severe EPTB (e.g. TB meningitis) • Extensive disease • Adults, children* • Weight-bands • Nutritional status • Genetic status (e.g. fast/slow acetylators for isoniazid) • Comorbidities: HIV, diabetes and others	1) Rifampicin increased dose 2) Isoniazid increased dose 3) Pyrazinamide increased dose 4) Ethambutol increased dose	1) Rifampicin at currently recommended dose 2) Isoniazid at currently recommended dose 3) Pyrazinamide at currently recommended dose 4) Ethambutol at currently recommended dose	• Treatment success • Failure • Relapse • Death • Adverse events

** In children, stratification by age, nutritional status, severity of disease, and HIV status is required.*

The quality of evidence will need to be graded for RCTs or observational studies. If no direct evidence is forthcoming to summarize what other elements exist to suggest systematic under-dosing (PK/PD studies, tissue concentrations, modelling) then the consultants should summarise the date(s) by when study results are expected that could inform a change of dosage regimens.

In addition, as the level of exposures (low/high) to medicines place patients at risk for treatment failure or toxicity, and patient's specific covariates influence exposures at any given dose, it is required to record whether exposure-response data are available in the papers being reviewed - although these data may not be available in every treatment study and normally available in studies that are not explicitly examining treatment outcome. These data should be collated in a spreadsheet or database into which the quantitative variables of interest are extracted. These data will help address and acknowledge the relationship between exposure and response while the main analyses are restricted to dose. Actions that need to be taken:

- i. develop terms of reference for a systematic review/landscape analysis for evidence on the PICO question.
- ii. get further input on the TORs from external experts.
- iii. Develop a request for proposals and select an appropriate and unconflicted expert or expert group to conduct the systematic review.
- iv. The selected review group or individual develops the protocol for systematic for review and agreement with WHO team.
- v. The group proceeds with systematic review
- vi. WHO team reviews the results of the systematic review and decide on whether the consultation meeting will be required.

b) Consultation meeting (if needed)

If the review indicates that the current evidence is sufficient to make changes to recommended dosing, then a broader expert group will be convened to discuss the next steps on dosage revision. This group should include other stakeholders (e.g. NTP managers, donors, manufacturers).

c) Timeline

- a. Concept note and TOR development and internal consultation: May – June 2020.
- b. Seek further input on the concept note and TORs from external experts: July 2020.
- c. Publish request for proposals: July - August 2020 (4-week range for accepting proposals).
- d. Selection and contracting of the systematic reviewer/team: September 2020.
- e. Systematic review period: 1 October – 31 December 2020 (number of working days to be indicated during this period).
- f. Consultation meeting (if needed): March/April 2021.

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