World Health Organization

Co-administration of treatment for drug-resistant tuberculosis and hepatitis C

Rapid Communication

March 2024

Background

Tuberculosis (TB) remains a threat to global public health and the world's second leading cause of death from a single infectious agent, after coronavirus disease (COVID-19). More than 10 million people continue to fall ill with TB every year (1).

Globally, an estimated 410 000 people (95% UI: 370 000– 450 000) developed multidrug-[1]or rifampicin-resistant tuberculosis (MDR/RR-TB) in 2022. There have been steady improvements in the treatment success rate for people diagnosed with MDR/RR-TB, but it remains alarmingly low. Globally in 2020, the treatment success rate was 63%, up from 60% in 2019 and 50% in 2012. MDR/RR-TB treatment poses many challenges, which are further exacerbated for those with pre-existing liver disease due to the potential hepatotoxicity of some anti-TB medicines, which may increase the risk of drug-induced liver injury.

There is a substantial overlap in the epidemiology of chronic hepatitis C (HCV) and TB due to common risk factors, for example, injection drug use, homelessness, or incarceration. Chronic viral hepatitis C or B may negatively impact tuberculosis treatment by increasing the risk of tuberculosis drug-related hepatotoxicity and thus affecting drug choices. This, in turn, may reduce tuberculosis treatment success. The global HCV antibody seroprevalence in TB patients has been estimated to be 10.4%, surpassing the general population's average of 1.4%. Moreover, studies among TB patients who inject illicit drugs show an HCV prevalence of 92.5% (95% CI 80.8–99.0) (2).

Curative short-course (12 to 24 weeks) oral direct-acting antivirals (DAAs) have transformed the landscape of HCV treatment, with high rates of cure - more than 90% of patients attain a sustained virologic response (SVR), indicating virus clearance, alongside an excellent safety profile and high tolerability. Known drug-drug-interactions with rifamycins preclude co-administration of DAAs in the context of drug-susceptible TB [few or no interactions are anticipated to occur with drugs for MDR/RR-TB treatment] (3). However, relatively little is known about how to manage chronic HCV infection among MDR-TB patients, and national policies and practices vary, highlighting the need for global guidance. Despite the limited direct evidence, concomitant therapy for HCV and MDR/RR-TB seems feasible and potentially beneficial for patients with co-infection. To address this need, WHO commissioned a systematic review of the literature on the co-administration of treatment for drug-resistant TB and hepatitis C. The results of this systematic review highlighted that published evidence on this subject is minimal (4).

To address this knowledge gap, the WHO's Global Tuberculosis Programme (WHO/GTB) initiated a public call to collect 'expert evidence' from individual experts in various countries. Expert evidence has been defined as the observations or experience obtained from a person who is knowledgeable about or skilful in a particular area (5). This approach can be considered under certain circumstances if published direct evidence is exceptionally scarce. ''Expert evidence'' can be considered in the same way as case reports or case series are used within the GRADE framework as if systematic and transparent methods are used for its collection and the description of the evidence minimizes interpretation of the extent to which it does or does not support a conclusion.

An independent GDG assessed the results of this expert evidence using the Grading of

[1] Defined as combined resistance to rifampicin and isoniazid, the two most important anti-TB medicines.

Recommendations Assessment, Development and Evaluation GRADE process in November 2023 (6). Detailed recommendations based on this analysis will be presented in a 2024 update of the WHO consolidated tuberculosis treatment guidelines.

This rapid communication aims to inform NTPs and other stakeholders about the key implications for the co-administration of treatment for drug-resistant tuberculosis and hepatitis C, facilitating seamless integration and planning at the country level.

Key updates

Expert evidence

Obtaining findings from expert evidence on treatment strategies for patients co-infected with HCV and MDR/RR-TB:

- Sixteen respondents (expert clinicians) from 9 countries participated in gathering the expert evidence.
- Outcomes were reported for 135 patients who received MDR & HCV treatment co-administration and 439 patients who received MDR treatment first and HCV treatment after completion of TB treatment.
- Eight respondents contributed data from both cohorts for comparative analysis.
- The other eight respondents contributed data only for the intervention or comparator cohorts for descriptive analysis.

The overall certainty of evidence was very low, with the estimates of effects based on outcome data from recall or records obtained from the experts.

Key findings

The evidence suggested that the co-administration of MDR-TB and HCV treatments, compared to MDR-TB treatment alone with a delay in HCV treatment, may lead to an increase in MDR-TB treatment success, fewer cases of MDR-TB treatment failure, fewer losses to follow-up, and a slight decrease in the number of deaths. The potential benefit of adherence support for HCV treatment while on MDR/RR-TB treatment was also recognized (5).

The concomitant treatment for HCV and MDR/RR-TB was considered feasible, and the overall benefits are likely to outweigh the potential harms.

Summary

The evidence suggests that patients with confirmed MDR/RR-TB and hepatitis C stand to benefit from co-administration of relevant therapies under programmatic conditions. It's important to note that patients suffering from MDR/RR-TB can undergo treatment with either shorter or longer all-oral regimens concurrently with hepatitis C treatment.

- Co-administration of both MDR-TB and HCV treatments is favoured for better outcomes and cost-effectiveness over delaying HCV treatment until after MDR/RR-TB treatment completion. This applies to all patients with confirmed MDR/RR-TB and HCV.
- In patients co-infected with drug-resistant TB and HCV, co-administration of HCV and MDR/RR-TB treatment may yield better treatment outcomes compared to delaying

HCV treatment until after completing MDR/RR-TB treatment.

- Administering both treatment regimens for HCV and MDR/RR-TB should be guided by knowledge and considerations regarding potential drug-drug interactions and patient preferences. The unavailability of HCV treatment should not delay the initiation of MDR treatment.
- Treatment delivery should adhere to WHO-recommended standards, including patient-centred care and support, active drug safety monitoring and management, and regular patient monitoring.

Next steps

- The new edition of WHO consolidated guidelines on the treatment of TB and drug-resistant will include updated recommendations and detailed results of the evidence review that guided the analysis.
- The new edition of WHO consolidated guidelines will be accompanied by an update of the Operational Handbook on Tuberculosis: Module 4: treatment, with further details on patient selection, regimen design, subgroup considerations, drug-drug interactions, and programmatic monitoring and evaluation.

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