TITLE

CLINICAL PRACTICE GUIDELINES ON THE MANAGEMENT OF RESISTANT TUBERCULOSIS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR) AND THE SPANISH SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (SEIMC).

SUMMARY

The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) have deemed it necessary to prepare Clinical Practice Guidelines (CPG) on the management of people affected by tuberculosis (TB) resistant to drugs with activity against *Mycobacterium tuberculosis*; these are aimed at health professionals dedicated to the care and accompaniment of these patients, and other professionals interested in increasing their knowledge about this disease. The main objective is to draw up clinical practice guidelines on the management of people affected by TB resistant to the most relevant drugs for its treatment, particularly rifampicin, isoniazid, fluoroquinolones, bedaquiline, and linezolid, as well as resistance combinations. These clinical practice guidelines count on the collaboration of professionals from different fields involved in the care of people affected by TB with resistance to anti-TB drugs, and include the latest updates of the SEPAR regulations for the diagnosis and treatment of drug-resistant TB from 2017 and 2020 as the starting point. The methodology included asking relevant clinical questions based on PICO methodology, a literature search focusing on each question, and a systematic and comprehensive evaluation of the evidence, with a summary of this evidence for each question. Finally, recommendations were developed and the level of evidence and the strength of each recommendation for each question were measured. Of the recommendations made, it is worth highlighting the high quality of the existing evidence for the use of nucleic acid amplification techniques (rapid genotypic tests) as initial tests for the detection of the *Mycobacterium tuberculosis* genome and rifampicin resistance in people with presumptive signs or symptoms of pulmonary TB; and for the use of an oral combination of anti-TB drugs based on bedaquiline, delamanid (pretomanid), and linezolid, with conditional fluoroquinolone supplementation (conditioned by fluoroquinolone resistance) for six months for the treatment of people affected by pulmonary multidrug-resistant tuberculosis (MDR-TB). We also recommend directly observed therapy (DOT) or video-observed treatment for the treatment of people affected by DR-TB. The document has been presented and subjected to a period of review by the members of the societies, participants in the guidelines, and has been reviewed by a community group of people affected by previous TB.

KEYWORDS

Bedaquiline; Delamanid; Pretomanid Ethambutol; Guidelines; Isoniazid; Levofloxacin; Linezolid; Moxifloxacin; *Mycobacterium tuberculosis*; Pyrazinamide; Recommendations; Resistance; Rifampicin; Tuberculosis; Multidrug-resistant tuberculosis; Resistant tuberculosis; MDR-TB; RR-TB

ABBREVIATIONS

B: Bedaquiline.
BSL: Biosafety Level.
BPaL: bedaquiline, pretomanid, linezolid.
BPaLC: bedaquiline, pretomanid, linezolid, clofazimine.
BPaLM: bedaquiline, pretomanid, linezolid, moxifloxacin.
CDC: Centre for Disease Control and Prevention.
CLSI: Clinical and Laboratory Standards Institute.
CNE: National Centre for Epidemiology.
COVID-19: COronaVIrus Disease 2019.
CPG: Clinical Practice Guideline.
D: Delamanid.
DNA: Deoxyribonucleic acid.
DOT: Directly observed therapy.
DR: Drug-resistant or resistant to antituberculosis drugs.
DR-TB: TB caused by a strain of *M. tuberculosis* resistant to any of the antituberculosis drugs.
DST: Drug susceptibility test.
E: Ethambutol.
ECDC: European Centre for Disease Prevention and Control.
ESTC: European Union Standards for Tuberculosis Care.
EU/EEA: European Union and European Economic Area.
FQs: Fluoroquinolones.
GeSIDA: AIDS Study Group-SEIMC.
GRADE: Group Reading Assessment and Diagnostic Evaluation.
H: Isoniazid.
HIV: Human Immunodeficiency Virus.
HR: Hazard ratio.
L: Linezolid.
LTI: Latent TB infection.
M: Moxifloxacin.
MDR: Multidrug-resistant.
MGIT: Mycobacterial Growth Indicator Tube.
MIC: Minimum inhibitory concentration.
MDR-TB: TB caused by a strain of *M. tuberculosis* resistant to at least isoniazid and rifampicin.
MS: Multi-susceptible.
MTB: *Mycobacterium tuberculosis.*
MTBC: *Mycobacterium tuberculosis* complex.
NAAT: Nucleic Acid Amplification Techniques.
P: Pretomanid.
PAS: Para-aminosalicylic acid.
PCR: Polymerase chain reaction.
PICO: Patient, Intervention, Comparison, and Outcome.
PII-TB&MNT: Integrated Research Program on Tuberculosis and Non-Tuberculous Mycobacteria.
PPV: Positive Predictive Value.

preXDR-TB: TB caused by a strain of *M. tuberculosis* resistant to isoniazid, rifampicin, and a fluoroquinolone.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses.

R: Rifampicin.

RENAVE: National Epidemiological Surveillance Network.

RR: Resistance to rifampicin.

RR-TB: TB caused by a strain of M. tuberculosis resistant to rifampicin.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

SEIMC: Spanish Society of Infectious Diseases and Clinical Microbiology.

SEPAR: Spanish Society of Pneumology and Thoracic Surgery.

TB: Tuberculosis.

VOT: Video Observed Treatment (telematically).

WHO: World Health Organization.

XDR: Extensively drug-resistant.

XDR-TB: TB caused by a strain of *M. tuberculosis* resistant to isoniazid, rifampicin, a fluoroquinolone, and bedaquiline or linezolid.

Z: Pyrazinamide.

1. INTRODUCTION AND RATIONALE

Tuberculosis (TB) is caused by the *Mycobacterium tuberculosis* complex (MTBC). The disease continues to be a global health problem, being the leading infectious cause of death in the world.(1) Despite the efforts made in recent years to control the disease, and the good overall results, the advent of the COVID-19 pandemic has weakened TB control systems and has led to an increase in TB cases, as well as deaths, worldwide.(2)

One of the problems that make it difficult to control the disease is the emergence of *Mycobacterium tuberculosis* (MTB) strains resistant to drugs (DR) commonly used for its treatment. Isoniazid-resistant TB, rifampicin-resistant TB (RR-TB), and multidrug-resistant TB (MDR-TB), i.e., resistant to at least isoniazid and rifampicin, have been associated with poorer treatment outcomes and increased mortality. To date, the treatments available for DR-TB cases lacked high-quality evidence, resulting in adverse events that required discontinuation of treatment in a significant number of people affected by TB. In addition, long treatment periods increased the likelihood that people affected by TB would miss follow-ups.(3,4) Fortunately, in recent years, new anti-MTB drugs have emerged that have facilitated the creation of shorter, safer, better-tolerated, and more effective treatment regimens for people affected by DR-TB.

In Spain, the incidence of DR-TB is low and generally associated with people with previous TB treatments or from areas with a high incidence of DR-TB. Many professionals in our environment are not familiar with the accompaniment of people affected by DR-TB. However, the disease poses a significant risk to public health. The treatment of DR-TB is changing rapidly, which requires regular updating, as well as dissemination of the latest developments among the professionals involved. The latest recommendations of the Plan for the Prevention and Control of Tuberculosis in Spain are from 2019 and do not include the latest published news.(5) The updates of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) regulations of 2017 and 2020, already incorporate some of the advances of recent years.(6)

For all the above, we believe it is necessary to have guidelines that direct the management of people affected by DR-TB.

Rationale of the need for clinical practice guidelines in DR-TB

DR-TB treatments were very long, complicated to administer, and frequently produced adverse events, many of them serious, making adherence difficult. As a result, treatment success rates at the programmatic level were well below those achieved for multi-susceptible (MS)-TB. In recent years, there has been a breakthrough in the management of DR-TB, with the advent of new treatment regimens based on repositioned or new drugs. Even so, the management of DR-TB poses many uncertainties, is complex, and requires the participation of specialists with experience in this field. The available evidence has increased considerably, and its reading and critical analysis are of vital importance to be able to make recommendations adapted to the characteristics of people affected by DR-TB, as well as to the context of

our healthcare setting. In 2020, an update of the SEPAR recommendations for the diagnosis and treatment of DR-TB was published and serves as the starting point for the current document.(6) The current Clinical Practice Guidelines (CPG), developed with a high-quality systematic methodology and critical analysis of the evidence, will help all healthcare professionals and people affected by MDR-TB, and will provide insights into the rationale, level of evidence, and strength of the recommendation behind each of the recommendations.

Clinical Aspects Covered

The CPG addresses the management of people affected by DR-TB and covers epidemiological, microbiological, and clinical aspects. The DR-TB considered in this guideline is isoniazid-resistant TB, RR-TB, MDR-TB, pre-extensively resistant TB (preXDR-TB), and extensively resistant TB (XDR-TB).

Who is it for?

The CPG is aimed at health professionals who treat, and care for people affected by DR-TB, as well as other non-health professionals who help in the accompaniment of people affected by TB. The guidelines are not intended to be a support document for people affected by TB, given the abundance of technical concepts and use of scientific language; however, we encourage anyone interested to consult them.

Objectives of the Document

This CPG aims to evaluate the available evidence on the management of people affected by DR-TB and to offer recommendations that can help to better manage these people.

2. METHODS

General methodology of the document

The preparation of the CPG has been carried out in accordance with the standards of the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) and *Group Reading Assessment and Diagnostic Evaluation* (GRADE) Evidence to decision methodology.(7–10) The working group identified 14 key questions included in the document, ten of which are PICO questions (Patient, Intervention, Comparison, and Outcome) and four refer to complementary questions that facilitate the understanding of the recommendations made in the guidelines, and serve to place its content in context. The questions were formulated by the coordinators of the document, and submitted to review by all the authors, collaborators, and reviewers of the document. Each question was assigned to a minimum of two collaborators and was coordinated by a member of the guide's coordinating committee. A non-systematic literature search was conducted in the PUBMED search engine for the sections included in the introduction and the supplementary questions not subject to PICO methodology. To answer the PICO questions, a systematic literature search was conducted using the PUBMED, MEDLINE, SCOPUS, and COCHRANE search engines; the search strategy used to answer each question is available in the supplementary material (question reports). Relevant articles were selected according to the following stratification: high-quality clinical trials (randomised, blinded, and controlled), other clinical trials (non-controlled, non-blinded, or non-randomised), multicentre prospective studies, other prospective studies, multicentre retrospective studies, other retrospective studies, and case series. If the number of high-quality studies was sufficient to form a quality recommendation, we did not review lesser-quality articles. We included systematic reviews of the literature and other relevant consensus documents and conducted a manual search of the references of the selected articles. No material from the grey literature was included. The selection of the most relevant articles was carried out by at least two independent authors. Discordances were resolved by agreement between the two. Subsequently, data extraction was performed via a standardised data extraction questionnaire, to finally proceed to an evaluation of the evidence, a summary of the evidence, and reasoned recommendations according to the GRADE system of level of evidence and strength of the recommendation.(8) The risk of bias in each study was assessed using an adapted tool.(11–13) The level of evidence and strength of the recommendation were adjusted according to the likelihood of relevant biases in the included studies. The final reports for each question are available in the supplementary material. Paediatric TB has not been addressed in this document. To consult the recommendations on the treatment of TB in children, we suggest referring to the updated documents of the Spanish Paediatric Society.(14)

The coordinators and collaborators agreed on a preliminary version, which was published on the SEPAR and Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) websites and submitted to a public review process. The CPG was also evaluated by the Scientific Committee of the participating scientific societies. All authors have approved the content of the document and the final recommendations.

3. SUPPLEMENTARY AND PICO QUESTIONS

Supplementary question 1: What is the epidemiological situation of resistant TB globally and in Spain?

Internationally, the World Health Organization (WHO) publishes TB resistance data, in the form of genotypic RR-TB identified via molecular tests. Xpert MTB/RIF is the most widely used test, following the recommendation regarding its **implementation** in 2010. It should be noted that most cases of RR-TB are also resistant to isoniazid, so it is used as a marker of MDR-TB.(15) Other institutions, such as the Institute for Health Metrics and Evaluation of the University of Washington (through the *Global Burden of Disease* study), also reports on the global estimation of MDR-TB. The different reports contain minimal discrepancies.(16,17) The WHO estimates that, in 2022, there were around 410,000 (uncertainty range 370,000-450,000) new cases of RR-TB, which represents a decrease of 8.9% compared with 2021; however, the irruption of the SARS-CoV-2 pandemic in RR-TB reporting, continuity of care, and dynamic systems must be taken into account. Figure 1 shows the absolute number of people diagnosed with RR-TB globally by year. The proportion of RR-TB cases in relation to new TB cases was 3.3% in 2022, and 17% for previously treated cases. Notably, just three countries accounted for 42% of the estimated global number of people who developed RR-TB in 2022: India (27%), the Philippines (7.5%), and the Russian Federation (7.5%). Countries with an RR-TB ratio above 50% among previously treated people are the Russian Federation, several countries in Eastern Europe, and Central Asia. In 2022, only 175,650 people diagnosed with RR-TB were able to access adequate treatment, representing only 43% of the estimated cases for that year; and only 73% of bacteriologically confirmed TB cases were tested for rifampicin resistance.(1)

There are no up-to-date data on the global prevalence of isoniazid monoresistance, although, in 2018, the WHO estimated that around 8% of TB cases were monoresistant to this drug (and rifampicin-susceptible).(18) Other studies estimated that this prevalence was higher, in the order of 12-16%.(19,20)

In 2022, the estimated number of cases of preXDR-TB was 27,075.(1) In the European region, 33.4% of RR-TB cases were classified, at least, as preXDR-TB, and the proportion of XDR-TB cases was 11.2% of the preXDR-TB cases. There are no quality global data on the incidence of XDR-TB. Nevertheless, there is accumulating evidence of an increase in cases of resistance to linezolid or bedaquiline.(21,22) For example, one study reported 15% bedaquiline resistance in a cohort of people affected by MDR-TB in Moldova. (23)

In Spain, DR-TB data are available through the reports of the National TB Control Plan and the National Epidemiological Surveillance Network (RENAVE) system. The data are collected by the Autonomous

Communities and are transferred and centralised in the National Centre for Epidemiology (CNE). Information regarding the total number of people affected by DR-TB is not disaggregated, so it is difficult to know the number of people affected by isoniazid-resistant TB, RR/MDR-TB, preXDR-TB, and XDR-TB independently. On the other hand, there is an underreporting of the results of anti-TB susceptibility data, so the percentage of people affected by DR-TB over the total is inferred from the total data available with susceptibility studies. In addition, the definitions of preXDR-TB and XDR-TB were modified in 2020, making it difficult to compare historical results with current data. However, this setback is not particularly relevant due to the low number of people affected by preXDR-TB or XDR-TB, regardless of the definition applied. The percentage of MDR-TB between 2015-2021 in Spain ranged from 1.1-4.9% of all TB cases. However, in recent years, it has ranged between 2-2.5%, with significant variations by geographical area, and with incidence rates highly dependent on aggregate cases or outbreaks given the low annual number of people diagnosed. These percentages increase by 1-1.5 percentage points if only TB with rifampicin monoresistance is considered. Table 1 shows the epidemiology of DR-TB in Spain, distributed annually between 2012-2021.(24) An epidemiological study conducted by the National Mycobacterial Laboratory Network Study Group over a 20-year period reported a total of 834 people affected by MDR-TB, corresponding to an average of 41 people affected by MDR-TB per year (5.7% of whom had XDR-TB). The most frequent characteristics associated with a person with MDR-TB were being male, between 15-34 years old, born outside Spain, and presenting smear-positive pulmonary TB.(25)

Information on people affected by isoniazid-resistant TB is not published in the RENAVE reports. However, data published by the Department of Health of the Government of Catalonia between 2005-2021 reported a percentage of people affected by isoniazid-resistant TB of approximately 6.2-7.9% of the total cases diagnosed annually.(26) Other data, from a national survey of sentinel hospitals, showed that 6.4% of people affected by TB have isoniazid resistance. This percentage increases to 18% if the person had received previous anti-TB treatment, with differences depending on the person's place of birth (migrant 29.2% vs. autochthonous 10.8%). In addition, this study reported 2.7% of people affected by RR-TB and 2.3% with MDR-TB.(27)

Supplementary question 2: What are the current definitions of MDR, preXDR, and XDR-TB?

Table 2 shows the historical evolution of the definitions of multidrug resistance in TB.

As can be seen, the definitions of multidrug-resistant TB have been modified over the years, and there may be different definitions depending on the promoting organisms. For the development of these guidelines, we have used the most recent WHO definitions, which are those most internationally accepted, and those used in our national surveillance system:

- MDR-TB: TB caused by *M. tuberculosis* strains with resistance (phenotypic and/or genotypic) to at least isoniazid and rifampicin.
- preXDR-TB: TB caused by *M. tuberculosis* strains that meet the definition of MDR-TB, adding resistance to a fluoroquinolone (levofloxacin or moxifloxacin)
- XDR-TB: TB caused by *M. tuberculosis* strains that meet the definition of MDR-TB with resistance to a fluoroquinolone, and at least one other group A drug (currently, bedaquiline or linezolid).

Alternatively, the term RR-TB is defined as TB caused by *M. tuberculosis* strains that have demonstrated resistance to rifampicin, usually by molecular testing, and for which resistance to other first-line drugs is not normally available or there is susceptibility to these drugs. This term is often used when molecular tests are available that only detect rifampicin resistance, in the *rpoB* gene, and is often used as an indicator of MDR-TB as in most cases people affected by RR-TB have associated isoniazid resistance.

We are aware that the definition of preXDR-TB is highly volatile and, with the extensive use of bedaquiline and linezolid, it is possible that resistance to these group A drugs appears, without an associated resistance to fluoroquinolones. On the other hand, new or existing drugs will likely be incorporated into group A in the near future, and the definitions of pre-XDR and XDR-TB will be modified in the coming years.

The term "totally drug-resistant"-TB (TDR-TB) does not have a clear definition, and its use is discouraged by the WHO, as *in vitro* susceptibility testing for some second-line drugs presents limitations regarding consensus, reproducibility, and correlation with clinical response.

Supplementary question 3: What are the possible outcomes of MDR-TB treatment?

The WHO programmatic outcome definitions launched in 2013, and subsequently updated in December 2014 and January 2020, were modified in 2021 to adapt them to the new reality of TB management. The new 2021 proposal has common definitions for susceptible TB and DR-TB, to facilitate monitoring and surveillance, as well as facilitate comparability across regions.(28)

The definitions are as follows:

- Cured: A person with pulmonary TB confirmed bacteriologically at the start of treatment, as recommended by the national program, with evidence of bacteriological response and no evidence of failure. The bacteriological response is defined as microbiological conversion to negative of the culture without subsequent reversion to positive. These terms signify the following:

    - Bacteriological conversion: the presence of two consecutive negative cultures or smears, taken on two occasions at least seven days apart, are available.
    - Bacteriological reversion: the presence of two positive cultures at least seven days apart, after previous bacteriological conversion or in patients with no previous bacteriological confirmation of TB.
- Treatment completed: A person with TB who completed treatment as recommended by the national programme, yet does not meet the definition of cured or treatment failure.
- Treatment success: This is the sum of cured and treatment completed.
- Treatment failure: A person with TB whose treatment needs to be terminated prematurely or permanently modified to a new treatment regimen or strategy. Reasons for the change include:
    - Absence of clinical or bacteriological response.
    - Adverse events caused by anti-TB drugs.
    - Evidence of additional resistance to drugs from their treatment regimen.
- Lost to follow-up: A person with TB who does not start treatment or whose treatment is interrupted for more than two consecutive months without medical justification.
- Not evaluated: A person with TB for whom no treatment outcome is assigned. This includes patients who have been “transferred out” to another treatment unit and whose treatment outcome is unknown. It does not include a person with TB lost to follow-up.
- Died: Death from any cause before starting or during the course of treatment. A distinction is made between the cause of death related to TB and another cause not related to TB.

In addition, a new definition has been added that allows relapse-free cure to be assessed sometime after treatment has ended and thus ensure efficacy.

- Sustained treatment success: applies to a person with TB assessed at six and 12 months after successful treatment, who is still alive and TB-free. If there is a new episode, it would include recurrence, which in turn can be divided into relapse and reinfection; relapse being a new episode of TB with the same strain as the previous episode (endogenous reactivation), while reinfection constitutes a new episode of TB with a new strain (exogenous reinfection).

As far as possible, attempts have been made to use the latest version of the definitions to analyse the impact of the interventions.

Supplementary question 4: Which are the anti-tuberculosis drugs used in DR-TB and how are they classified?

The current WHO classification separates the drugs used in DR-TB into three groups: A, B, & C (Table 3).

Based on current scientific evidence, it is difficult to know the efficacy of each drug individually as studies compare regimens with several drugs, and few studies compare optimised regimens with and without the same drug to infer the efficacy attributable to a specific drug. The expert panel proposes a classification based on proven evidence of combinations, prioritising those oral drugs that have a better balance between efficacy and safety. Thus, the panel suggests the following classification of drugs with anti-MTB activity for the treatment of people affected by MDR-TB (see Table 4). Table 5 shows the recommended doses for the main drugs used in the treatment of MDR-TB.

Summary of findings:

BEDAQUILINE

Bedaquiline works by inhibiting adenosine 5'-tryptophan, which limits the capacity of MTB to produce energy. Bedaquiline was initially shown to improve efficacy, measured as sputum conversion at 120 weeks after treatment initiation, when supplementing optimised treatment regimens for people affected by MDR-TB.(29) In addition, a 2018 meta-analysis found that the use of bedaquiline in people affected by MDR-TB increased treatment efficacy and reduced mortality.(30) Recently, several studies and clinical trials have been published in which the combination of bedaquiline with other drugs, mainly pretomanid, linezolid, and fluoroquinolones, obtained high percentages of treatment success with a good safety profile.(31–33)

DELAMANID and PRETOMANID

Both drugs inhibit the formation of mycolic acids, which are essential for cell wall synthesis. In addition, activation of pretomanid generates three inactive but stable metabolites, as well as reactive nitrogen species that affect the respiratory chain of the bacterium.(34) The efficacy of delamanid has been studied in combination with an optimised regimen, showing a higher percentage of people with sputum conversion at two months compared with the same optimised regimen plus placebo.(35) The use of delamanid in combination with levofloxacin, clofazimine, and pyrazinamide has also been evaluated in a clinical trial, with non-inferiority observed compared with a standard regimen.(36) Likewise, there is extensive information from prospective studies and clinical trials where the combination of delamanid and bedaquiline ensures shorter culture negativisation times in lung samples and high cured rates with reduced rates of serious adverse events, and little risk of corrected QT prolongation.(37)

The efficacy of pretomanid has been proven in combination with moxifloxacin and pyrazinamide in people affected by MDR-TB infection.(38) In the same way, pretomanid has been evaluated in combination with linezolid, bedaquiline, and moxifloxacin, demonstrating high efficacy and a good safety profile.(31–33)

There are clinical trials that demonstrate a good therapeutic response with the combination of bedaquiline and delamanid, which also show a good risk-benefit ratio for patients with disseminated disease.(37,39)

LINEZOLID / TEDIZOLID

The activity of linezolid and tedizolid is due to protein synthesis inhibition by binding to the 50S ribosomal subunit. As mentioned above, linezolid has been evaluated in combination with different drug regimens, showing high efficacy (31–33). The safety profile depends on the dose at which it is used, with a high percentage of people developing side effects (mainly peripheral neuropathy and myelotoxicity) when used at doses of 1200 mg per day. The safety profile is substantially improved by decreasing drug doses to 600 mg per day, without penalising efficacy.(31) The meta-analysis of individual patients published in 2018, which served as the basis for the classification of anti-TB drugs proposed in the WHO guidelines, showed that the use of linezolid was associated with greater treatment success and lower mortality.(30)

On the other hand, tedizolid has good *in vitro* activity against MTB strains, both susceptible and resistant to rifampicin. The combination with moxifloxacin, as well as with bedaquiline and pretomanid, has been shown to have a high sterilising power *in vitro* and in murine models.(40–47) Clinical experience is limited to a few successful clinical cases in which linezolid could not be used.(48,49) However, it has not yet been evaluated in clinical trials. Given that it presents activity similar, at least, to linezolid, it could be considered an alternative to other oxazolidinones in cases where its use is limited by interactions or adverse secondary events.

FLUOROQUINOLONES: LEVOFLOXACIN AND MOXIFLOXACIN

Fluoroquinolones inhibit bacterial DNA synthesis by inhibiting enzymes such as topoisomerases. Both moxifloxacin and levofloxacin exhibit potent bactericidal activity against MTB strains.(50) Like bedaquiline and linezolid, both levofloxacin and moxifloxacin showed increased efficacy and decreased mortality in the meta-analysis published in 2018. (30) In principle, both drugs are equally effective and there appear to be no differences in their bactericidal capacity,(51) although recent regimens that have shown great efficacy in the treatment of MDR-TB have more frequently used moxifloxacin regimens.(31–33)

CLOFAZIMINE

Clofazimine inhibits bacterial DNA synthesis by binding to RNA polymerase. Clofazimine has been evaluated in multiple treatment regimens in people affected by MDR-TB infection and has formed part of the combination of long classic regimens.(52,53) However, there is little evidence of the benefit of clofazimine in shortened, oral regimens. In the TB-PRACTECAL clinical trial, the regimen combining bedaquiline, pretomanid, and linezolid with clofazimine was not evaluated in the second phase of treatment efficacy, even though a high percentage of sputum culture negativisation was observed two months after initiating treatment. In the meta-analysis published in 2018, clofazimine use was associated with an increase in treatment success, although no association with decreased mortality was observed.(30) Additionally, the use of clofazimine in combination with a standard treatment regimen in MDR-TB demonstrated greater treatment success than the non-clofazimine treatment regimen in a randomised clinical trial.(54)

AMINOGLYCOSIDES (AND CAPREOMYCIN)

Aminoglycosides are bactericidal and act by interfering with protein synthesis in bacteria. They bind to the 30S ribosomal subunit of the bacterium, thereby inhibiting protein synthesis and causing damage to the bacterial cell wall, leading to the death of bacterial cells.(55) Until 2017, aminoglycosides were part of the WHO-recommended regimens of choice for the treatment of MDR-TB, (56,57) and have formed part of both long regimens and the first short regimens, the latter demonstrating high efficacy.(58)

However, in the meta-analysis published in 2018, both kanamycin and capreomycin were associated with lower treatment success and only amikacin was associated with increased efficacy in MDR-TB, without being associated with a decrease in mortality.(30) This limited evidence, associated with the adverse side effects of long-term use, has led to amikacin currently being recommended only in cases where no other oral treatment option exists. Of all the aminoglycosides available, amikacin would be the treatment of choice for people affected by TB.

CYCLOSERINE / TERIZIDONE

Cycloserine has been widely used in long regimens for the treatment of MDR-TB. A prospective study showed that an optimised regimen for the treatment of MDR-TB with the addition of cycloserine had higher success rates compared with the addition of terizidone. However, cycloserine can have significant side effects, such as neurotoxicity, psychiatric disorders, and gastrointestinal symptoms, which require close monitoring during treatment. In addition, cycloserine resistance has also been described in certain MTB strains; therefore, it is important to consider the organism’s susceptibility to this drug before administration.(59) This was observed in a meta-analysis published in 2018, where the use of cycloserine was associated with an increased treatment success rate when susceptibility to this drug was demonstrated.(30)

CARBAPENEMS

Carbapenems, such as imipenem, meropenem, and faropenem, are used as part of second-line therapy to treat MDR-TB when other medications are not effective. There are conflicting results on the bactericidal activity of ertapenem.(60) As a general rule, the activity of carbapenems against MTB is enhanced when combined with clavulanic acid.(61) The combination of imipenem with relebactam has shown promising preliminary results. They are bactericidal and act by inhibiting the synthesis of the bacterial cell wall. They bind to enzymes called penicillin-binding proteins, which are responsible for cell wall formation, and block their activity, leading to the weakening and eventual death of MTB.(62) Classically, their intravenous bioavailability limited their use, despite the good bactericidal activity, so they were relegated to personalised treatments of people affected by preXDR or XDR-TB.(63) Nevertheless, we now have oral carbapenems, such as faropenem, which have synergistic activity with other drugs *in vitro* and in animal models.(64–68) Faropenem has been tested in a clinical trial, replacing ethambutol for two months in an adult population, with promising results and a good safety profile.(69) Other predictive studies have calculated the optimal clinical dose to maximise its efficacy.(70)

PYRAZINAMIDE

Pyrazinamide is one of the first-line drugs recommended by the WHO for the treatment of TB. Its action is sterilising and acts mainly against bacteria in the latent phase. Pyrazinamide is the pyrazinoic acid (POA) prodrug that inhibits the synthesis of coenzyme A by binding to aspartate decarboxylase (PanD). Its bactericidal action is due to the interruption of energy metabolism, especially at low pH, and the death of bacterial cells.(71) However, evidence on the efficacy of pyrazinamide in MDR-TB treatment is limited. Several studies have shown conflicting results as to its effectiveness, and the variability in response to treatment may be due to differences in the specific resistance of MTB strains.(72)

ISONIAZID AT HIGH DOSES

Isoniazid is one of the first-line drugs recommended by the WHO for the treatment of MDR-TB. Isoniazid is bactericidal and acts by inhibiting the bacterial cell wall synthesis of MTB. Isoniazid is a prodrug that requires the catalase-peroxidase system to be transformed into its active form. The active form of isoniazid interferes with an enzyme called enoyl-ACP reductase, which is essential for the synthesis of mycolic acids, an important component of the bacterial cell wall. By inhibiting this enzyme, isoniazid weakens the bacterial cell wall and contributes to the death of bacterial cells.(52) Resistance to isoniazid is mainly caused by mutations in the *inhA* gene, which encodes the enzyme enoyl-ACP reductase and confers low-level resistance, and the *katG* gene, which encodes the catalase-peroxidase system for the transformation of the prodrug and confers a high level of resistance. In cases where isoniazid resistance is secondary to

mutations in the *inhA* gene, high-dose isoniazid may be effective in the treatment of MDR-TB. In fact, high-dose isoniazid has been widely used in MDR-TB treatment regimens.(52,73) A retrospective study showed that the use of isoniazid at high doses had greater treatment success.(74) However, since drugs with full activity against RR-resistant MTB strains are now available, high-dose isoniazid is considered a drug for restricted use in special situations, where few bactericidal drugs are available and resistance is demonstrated to be of a low level (e.g., secondary to mutations in the *inhA* gene).

ETHAMBUTOL

Ethambutol acts by inhibiting the synthesis of the MTB cell wall. The drug is thought to affect the enzyme called arabinosyltransferase, which is responsible for the formation of the arabinogalactan layer in the bacterial cell wall. By interfering with this enzyme, ethambutol alters the structure of the bacterial cell wall and contributes to the death of bacterial cells.(20) It has been widely used in patients with MDR-TB, however, its role is unclear and should be added only if there is susceptibility to it and other alternatives with a better risk-benefit profile are not available.

CEFTAZIDIME AVIBACTAM

Ceftazidime is a third-generation cephalosporin that inhibits cell wall peptidoglycan synthesis by binding to penicillin-binding proteins; avibactam is a beta-lactamase inhibitor. The combination of ceftazidime-avibactam has been seen to have bactericidal and sterilising capacity against MTB in *in vitro* models, however, there are no *in vivo* model studies.(75)

PAS (para-aminosalicylic acid)

PAS is a bacteriostatic drug, whose mechanism of action is not well understood, although it is known to inhibit the synthesis of folic acid. It has been widely used in the treatment of MDR-TB; however, it is frequently related to the development of digestive intolerance, which has limited its use. A meta-analysis published in 2018 found that the use of PAS was not associated with greater treatment success in susceptible strains, and, in resistant strains, PAS was associated with a worse prognosis.(30) The use of PAS has also been seen to be associated with an increase in the incidence of adverse events that condition treatment discontinuation in a high percentage of people.(76) For these reasons, we believe that there are other drugs with a better balance between efficacy and safety, which signifies that, in these guidelines, the use of PAS for the treatment of MDR-TB is not recommended.

Rationale for the recommendation: The classification of anti-TB drugs involves equating drugs with different pharmacokinetic characteristics, safety profiles, and bactericidal and sterilising efficacies within

the same group, which may reduce the singularities of each drug and favour the combination of drugs lacking evidence. However, the expert panel understands that, at the programmatic level, and when access to expert staff is not available, it facilitates the choice of combinations with a high probability of success.

The classification is based on the existing evidence of the efficacy and safety of each of the drugs in specific combinations, knowing that regimens based on unproven combinations do not have sufficient evidence regarding their efficacy. They also do not have a defined treatment time, so the duration of treatment must be based on the patient's clinical evolution and experiences with similar combinations; always bearing in mind that the greater the number of sterilising drugs, the more likely it is that the treatment time can be reduced. Thus, the classification of drugs is useful for the development of treatment regimens under special situations and aids decision-making, but the composition of a treatment regimen, its duration, and the follow-up of the person is more complex than the simple choice of drugs according to the classification table.

The drug classification chosen for these guidelines is based on current WHO recommendations and the latest SEPAR regulations, but applying an additional evidence criterion on safety that aids decision-making.

PICO question 5: What are the main diagnostic tools for drug-resistant tuberculosis?

Recommendation: We recommend performing some of the nucleic acid amplification techniques (NAAT) recommended by the WHO for the detection of the MTB genome, and, at least, the simultaneous detection of genotypic rifampicin resistance in initial respiratory specimens from people with symptoms or presumptive signs of pulmonary TB (strong recommendation, moderate quality of evidence). Rapid molecular tests for resistance to other anti-TB drugs or sequencing technologies can provide rapid and reliable information on resistance to other anti-TB drugs (conditional recommendation, low quality of evidence). We recommend performing NAAT on samples of extrapulmonary origin rather than not performing them (conditional recommendation, low quality of evidence).

We recommend performing mycobacterial culture in respiratory samples from people with presumptive symptoms or signs of pulmonary TB rather than not doing so (strong recommendation, high quality of evidence). We recommend using cultures in liquid (preferably) and solid media for all clinical samples from people with presumptive symptoms or signs of pulmonary TB rather than using only one media (conditional recommendation, low quality of evidence). We recommend performing a mycobacterial culture of extrapulmonary samples rather than not doing so (strong recommendation, low quality of evidence).

We recommend performing smear tests, versus not performing them, in all people affected by presumptive pulmonary (or extrapulmonary) TB, especially to facilitate the follow-up of people affected by TB and to design the contact study (strong recommendation, moderate quality of evidence). Negative results do not exclude pulmonary (or extrapulmonary) TB. The performance of at least three smear tests on three different samples is recommended to improve sensitivity. The use of concentrated respiratory specimens and fluorescence microscopy is recommended (strong recommendation, moderate quality of evidence).

Summary of findings: Molecular biology tests or NAAT are very useful tools for the identification of MTB and the detection of resistance to anti-TB drugs. There are different molecular tests with different technologies and performance. The WHO recommends the use of those tests that meet minimum requirements for clinical use on direct sputum samples. Three meta-analyses have been identified that assess the performance of NAAT in the diagnosis of TB and anti-TB drug resistance. In the former, NAAT are assessed based on smear test results. In smear-positive respiratory samples, NAAT sensitivity and specificity were 96% and 85%, respectively. Most studies used culture as the gold standard, when the smear test was negative, the sensitivity and specificity were 66% and 98%, respectively.(77) The second meta-analysis demonstrated a sensitivity of 85% and specificity of 97% overall.(78) A third meta-analysis stratified NAAT results taking into account the smear test and the degree of clinical presumption of TB. This study showed that a positive result is useful if there is a high clinical presumption, however, a negative result does not rule out active TB.(79) Other studies support the use of these techniques for the detection and identification of MTB in respiratory and extrapulmonary samples. Results are obtained quickly and the sensitivity is higher than that of the smear test.(80–84) Studies comparing the latest version of Xpert, Xpert® Ultra, with the previous NAAT, Xpert® MTB/RIF, concluded that both afford accurate results and have a high predictive value that justifies the initiation of anti-TB treatment.(85) In a study that retrospectively analysed the results of 1706 samples sent to the laboratory between 2016-2022 for an MTBC study, they evaluated Ziehl-Neelsen (ZN) staining, culture (BACTEC Mycobacterial Growth Indicator Tube (MGIT) and Löwenstein Jensen automated system), and NAAT. Culture was positive in 48 (2.8%) samples, polymerase chain reaction (PCR) in 40 (2.3%), and ZN staining in 32 (1.9%), concluding that culture obtained greater sensitivity, although the introduction of molecular methods to obtain rapid and accurate results in TB diagnosis and to detect drug resistance was important.(86) There are also published studies that support the use of Xpert® Ultra in the paediatric population and areas of high disease prevalence. (87,88). Nevertheless, these tests are not suitable as biomarkers of cure and, therefore, should not be used to monitor the clinical course of people affected by TB, nor to make therapeutic decisions.(89,90)

Mycobacterial culture is still considered the gold standard; it can take up to 6-8 weeks to generate a result. Culture is more relevant in paucibacillary TB (mainly incipient, paediatric, and extrapulmonary TB). Molecular tests can also be used on positive isolates from cultures for the rapid identification and detection

of genotypic resistance. Phenotypic resistance testing is recommended in the first MTB-positive isolate, or in the event of presumed resistance amplification during treatment. A meta-analysis comparing two liquid medium culture methods with solid medium cultures found that both liquid medium culture methods were more sensitive (88% and 90%) than the solid culture method (76%), and also had a shorter time to detection (13.2 and 15.2 days for liquid medium culture versus 25.8 days for the solid culture method).(91) The specificity of the three methods exceeded 99%. Liquid culture medium has a higher contamination rate than solid culture medium due to the growth of different bacteria (4%–9% in the meta-analysis). Smear tests and cultures are the microbiological tools used to monitor the effectiveness of treatment. They are not closely related to the risk of recurrence after treatment ends, however, they are good markers of treatment failure.(92) In extrapulmonary TB, culture has low sensitivity, a positive result confirms extrapulmonary TB, while a negative result does not exclude the disease.(93,94)

Performing three smear tests allows the diagnosis of pulmonary TB with a sensitivity of approximately 70% when culture is the gold standard. Three smear tests are performed because the sensitivity increases with each sample. The sensitivity of the first sample is 53.8%, and increases by an average of 11.1% when a second sample is obtained; obtaining a third sample increases sensitivity by an average of only 2%–5%. By concentrating the samples, the average increase in sensitivity is 18% (using culture as the gold standard). The use of fluorescence microscopy is 10% more sensitive than conventional microscopy.(95,96) The specificity of microscopy is relatively high (≥90%), however, the positive predictive value (PPV) varies (70%–90%) depending on the prevalence of TB versus non-tuberculous mycobacterial disease.(97–99). Smear tests recognise acid-fast bacilli but do not identify MTB.

Rationale for the recommendation: In the case of a person with presumptive TB, we recommend obtaining the clinical samples that are considered appropriate. One of the diagnostic tools that we recommend for TB diagnosis is the smear test using fluorophore (Auramine-O/Auramine-rhodamine) and/or ZN staining. However, this test has a low detection limit (5000-10000 bacilli/ml) and is largely dependent on the quality of the sample and the experience of the observer. Smear tests do not identify the species or provide information on the resistance pattern. There are automatic counting methods of acid-fast bacilli with a sensitivity of 97% and a specificity of 86%.(100) Microscopy is a fast, inexpensive, and technically simple test. The recommendation is strong because the quality of the evidence provided moderate confidence in the characteristics of the test. The desirable consequences of a smear test (i.e., early presumptive diagnosis, initiation of treatment, and possibly less transmission) outweigh the undesirable consequences (i.e., cost, burden, and effects of false results) in the vast majority of people affected by presumptive TB.

The conditional qualification for culturing samples from people affected by presumptive TB applies to the different yields of liquid and solid cultures in each sample type. Liquid culture should be performed on all

sample types, as culture is the gold standard for the microbiological diagnosis of TB disease. Cultures in liquid medium are very sensitive and highly specific but they have the disadvantage of the possibility of contamination. Solid cultures are less sensitive and results are obtained later; however, some MTBC isolates are only detected in this medium. Performing both types of culture is likely to improve sensitivity. Recovered isolates should be identified in accordance with the Clinical and Laboratory Standards Institute (CLSI) and the *American Society for Microbiology*, Manual of Clinical Microbiology.(101,102)

NAAT have the advantage of high throughput and very short response times that allow rapid clinical decisions to be made in respiratory samples, although there is increasingly more information regarding extrapulmonary samples.(103) NAAT are an adjunct to smear tests and culture. On the other hand, they provide information on genotypic resistance to rifampicin with high sensitivity, and isoniazid and, in addition, the detection of genotypic mutations that determine resistance to other anti-TB drugs yields good results. (104) In people with positive smear tests, NAAT produce less than 4% of false-negative results, allowing MTBC infection to be ruled out in most cases. In people with a negative sputum smear, the result should be evaluated according to the pre-test probability of having TB. If the presumption of TB is intermediate or high, a positive NAAT result can be used to initiate anti-TB treatment; however, false-negative results are common enough that a negative NAAT does not exclude pulmonary TB. The recommendation is strong because the quality of the evidence is moderate as there is sufficient evidence that the desirable consequences of performing NAAT (i.e., rapidly diagnosing TB disease and initiating treatment), rather than not performing them, outweigh the undesirable consequences (i.e., cost, false positives and results leading to unnecessary treatment, and false negatives with results that provide false reassurance) in the vast majority of cases. Nonetheless, the quality of the evidence in terms of interpretation based on smear tests and clinical presumption has also been classified as high. On the other hand, it should be noted that microbiological tests are complementary examinations and do not replace clinical diagnosis, especially in situations where there is a low burden of disease.(105) The cost-effectiveness of NAAT is improved if they are performed on successive samples from a person with presumptive TB. (106) In extrapulmonary TB, a positive NAAT result may reinforce the diagnosis of TB in the face of a high presumption of extrapulmonary TB. A negative NAAT result, however, should be considered with caution and cannot be used to exclude TB.

PICO Question 6: What is the usefulness of molecular (genotypic) testing in the diagnosis of rifampicin-resistant tuberculosis and for the other drugs used in the treatment of drug-resistant tuberculosis?

Recommendation: We recommend the use of the NAAT suggested by the WHO as an initial test for the detection of the MTB genome and, at least, the simultaneous detection of genotypic resistance to rifampicin in an initial respiratory sample from people affected by presumptive TB (strong recommendation, moderate quality of evidence). We recommend NAAT capable of detecting resistance to other anti-TB

drugs, especially isoniazid, regardless of the outcome of rifampicin resistance in initial respiratory specimens (conditional recommendation, low quality of evidence). We recommend NAAT with the capacity to detect resistance to other anti-TB drugs, especially fluoroquinolones, in people affected by RR-TB or MDR-TB, to help design the treatment regimen (conditional recommendation, moderate quality of evidence). We recommend the use of sequencing technologies that can provide a complete individual profile of anti-TB drug resistance (conditional recommendation, low quality of evidence). We recommend performing NAAT on samples of extrapulmonary origin rather than not performing them (conditional recommendation, low quality of evidence).

Summary of findings: Within the END TB 2035 strategy, it is stressed that the rapid detection of drug resistance and early initiation of appropriate treatment are essential for TB prevention and care. This is why fast and accurate techniques are necessary, both for genome detection and drug susceptibility, which is why the WHO-recommended rapid diagnostic molecular tests must be made available to all people with signs or symptoms of the disease. International TB management protocols recommend molecular testing for RR; the National Expert Group recommends performing a molecular test for rifampicin resistance. The updated WHO guidelines highlight the importance of genotypic susceptibility testing before treatment initiation, especially for those drugs with WHO-recommended rapid molecular tests available (such as rifampicin, isoniazid, and fluoroquinolones).(103,107)

In recent years, different commercial molecular tools have been developed that allow the detection of genotypic resistance to rifampicin, isoniazid, fluoroquinolones, ethionamide, and amikacin.(108–111) To detect drug resistance, the microbiology laboratory should have genotypic and phenotypic tests for rifampicin, isoniazid, aminoglycosides, ethambutol, and fluoroquinolones (Table 6), and phenotypic susceptibility tests for drugs recommended in MDR-TB regimens (bedaquiline, linezolid, clofazimine, pyrazinamide, and delamanid).

Susceptibility studies using rapid molecular techniques can be performed through hybridisation techniques or by RT-PCR. Several systematic reviews with meta-analyses of hybridisation tests (111–113) detected rifampicin resistance with sensitivities and specificities greater than 97% and 98%, respectively, when the conventional phenotypic susceptibility study was used as the Gold Standard. Another study showed that the accuracy of the Xpert® MTB/RIF for the detection of rifampicin resistance increased slightly with repeated samples.(112) In the latest version (Xpert® MTB/RIF Ultra), the sensitivity and specificity for the detection of rifampicin resistance are similar to those found with Xpert® MTB/RIF.(85) Despite the high yield, the PPV in populations with a low prevalence of drug resistance is low, and some experts recommend its use, especially in populations with a high pretest probability of a positive result for resistance to anti-TB drugs.(107,113–115) Features that increase the likelihood of having RR-TB include having been treated for TB in the past, being born or having lived for at least one year in a country with a high primary prevalence of MDR-TB (≥2%), having had contact with a person with transmissible MDR-TB, low socioeconomic status, positive sputum smear at diagnosis, presence of pulmonary cavity, chronic

obstructive pulmonary disease, HIV infection, infection with the Beijing MTB strain, age over 40 years, and alcohol abuse.(113,116–120) The role of these techniques in children and extrapulmonary TB is not yet well defined, however, they seem to improve the diagnostic performance and reduce the time to treatment initiation. Some NAAT can detect genotypic resistance to other anti-TB drugs, e.g., a test capable of detecting resistance to isoniazid achieved a sensitivity and specificity of 84% and 99%, respectively, using the phenotypic susceptibility study as the reference technique. However, a meta-analysis of a subset of studies evaluating a more current version of the test found a sensitivity close to 90%. In contrast to rifampicin resistance, isoniazid resistance in our environment is higher, so the PPV of the test improves the results of NAAT that detect rifampicin resistance. (116,121)

Rationale for the recommendation: Performing a phenotypic susceptibility study based on the culture of the first MTB isolate from people affected by TB is recommended. The culture-based phenotypic susceptibility study is now considered the gold standard.(101)

Drug susceptibility testing is important because people with MTB strains with minimum inhibitory concentrations (MIC) considered resistant have worse outcomes if they are treated with regimens that include the resistant drugs in the selected treatment regimen. People affected by DR-TB treated with drugs defined as susceptible in phenotypic susceptibility tests have greater treatment success.(122) Unfortunately, the isolation of the MTB strain in culture, necessary to perform the phenotypic susceptibility study, can take at least two weeks. Rapid molecular tests (genotypic tests) address this limitation and can provide results in less than 24 hours, reducing the time to obtain results. Despite having a lower sensitivity than phenotypic tests, they can help personalise the treatment of people affected by TB and avoid the prescription of ineffective drugs, although it should be noted that they are an adjunct and not a replacement for culture. Nevertheless, their results must be interpreted by qualified personnel since false positives and false negatives can lead to incorrect clinical decisions that pose a risk to the safety of people affected by TB and/or an extra cost to the health system. In most cases, rifampicin resistance is due to a mutation in the *rpoB* gene, which explains why the test for genotypic resistance to this drug is so robust, consistent, and reproducible with sensitivities and specificities greater than 97%, and with false negative and positive results in less than 3% of cases. In addition, its detection generally implies simultaneous resistance to isoniazid which, therefore, implies a modification of the clinical management. Thus, in our setting, the recommendation of performing a molecular test to identify MTB and detect rifampicin resistance would be conditional in the general population but strong in the population with a higher risk of presenting rifampicin resistance mutations, i.e., when the PPV of the test is higher.

On the other hand, molecular tests for isoniazid resistance have a sensitivity of 90% and a specificity of 99%, which indicates that false negative results occur in at least 10% of cases. Thus, this test would be useful to confirm isoniazid resistance, however, a negative result would not definitively rule it out.

The use of molecular tests for the detection of genotypic resistance to other drugs would be justified in people diagnosed with MDR-TB, especially if the drug to be tested is to be included in the treatment regimen of the person with TB. Currently, there are commercial molecular tests that can detect genotypic resistance to second-line drugs; these include the study of genotypic mutations that determine resistance to fluoroquinolones, aminoglycosides, ethionamide, ethambutol, and recently also linezolid. This would be particularly justified in the case of fluoroquinolones and linezolid, where a positive result confirms the presence of resistance but a negative result does not preclude that the phenotypic resistance detection study may be positive. Ideally, it would be advisable to sequence positive isolates or direct samples to obtain more in-depth information on genotypic resistance to anti-TB drugs. In our setting, molecular tests should be complemented by phenotypic susceptibility studies.

PICO Question 7: Is there a standardised methodology for conducting phenotypic studies of resistance to anti-tuberculosis drugs?

Recommendation: In everyone with presumptive symptoms or signs of pulmonary and extrapulmonary TB, an effort proportionate to the clinical context should be made to obtain a sample suitable for microbiological study (strong recommendation, moderate quality of evidence). All MTB-positive isolates in our setting must have a phenotypic study of resistance to isoniazid and rifampicin (strong recommendation, high quality of evidence). Additionally, all MTB-positive isolates in our setting must have a phenotypic study for pyrazinamide and ethambutol (conditional recommendation, low quality of evidence). In those with RR/MDR-TB, the phenotypic resistance study should be extended to fluoroquinolones, linezolid, bedaquiline, pretomanid/delamanid, clofazimine, and amikacin (conditional recommendation, very low quality of evidence). Testing for phenotypic resistance to other drugs must be carried out by consensus between a physician expert in the treatment of people affected by TB and a microbiologist with experience in mycobacteria. The recommended methods are the modified proportions method in solid medium (Löwenstein-Jensen, 21 days) and the modified proportions method in liquid medium (Middlebrook, 7-14 days). The critical concentrations established by consensus for the different drugs with the Mycobacterial Growth Indicator Tube (MGIT) are isoniazid 0.1 µg/ml, rifampicin 0.5 µg/ml, amikacin 1-1.5 µg/ml, ethambutol 5 µg/ml, levofloxacin 1 µg/ml, moxifloxacin 0.25 µg/ml, clofazimine 1 µg/ml, bedaquiline 0.25 µg/ml, delamanid 0.06 µg/ml, and pretomanid <2 µg/ml (conditional recommendation, low quality of evidence). Alternatively, the economical and standardised method of 96-well plate microdilution can be used.

Summary of findings: There are no high-quality studies analysing clinical results based on different critical drug concentrations. Most of the information comes from expert opinion or expert consensus. Retrospective studies or case reports have reported that participants exhibiting failure in antibiotic regimens develop an increased critical concentration that leads to worse clinical outcomes. In the case of

rifampicin and isoniazid, there is extensive clinical experience and prospective and retrospective studies that associate critical concentrations with poorer treatment outcomes. In 2018, the *European Union Standards for Tuberculosis Care* (ESTC) document was published.(123) The purpose of this document was to provide public health experts, medical personnel, and health programs with a structured set of evidence-based standards outlining the minimum requirements to ensure optimal treatment, prevention, and control of TB. Standard No. 2 states that at least two sputum samples should be collected, whenever possible, from anyone with presumptive pulmonary TB for microscopic study and another sample for a rapid test to identify *M. tuberculosis* and drug resistance via an internationally recommended molecular (rapid) analysis. In addition, the sample should be sent to a laboratory with quality assurance for culture in liquid medium and, if the result is positive, for a drug susceptibility test (DST). From a microbiological point of view in Europe, the *European Centre for Disease Prevention and Control* (ECDC) in the document *Technical Report Handbook on Tuberculosis Laboratory Diagnostic Methods in the European Union – Updated* 2022, in point 7 covers *Phenotypic susceptibility testing to anti-tuberculous agents for Mycobacterium tuberculosis complex*, which specifies how and under what circumstances a phenotypic DST of resistance to anti-TB drugs should be performed.(124) In the case of *M. tuberculosis*, there are direct and indirect methods to test resistance to different anti-TB drugs. Drug susceptibility tests are usually performed on MTBC cultures (indirect testing) but they can also be carried out on samples containing acid-fast bacilli that are known to belong to MTBC (direct test). Results are obtained faster for direct testing; however, there is a lower success rate due to possible contamination. Phenotypic methods are technically complicated and difficult to interpret, and their accuracy is influenced by the prevalence of resistant strains and their level of resistance.(104) All laboratories performing drug susceptibility testing are additionally required to participate in an external quality control program. The most commonly used methods in Europe include the modified proportions method on solid Löwenstein-Jensen medium (21 days) and the modified proportions method in liquid Middlebrook media, with the commercial MGIT 960 (Becton Dickinson) system using Middlebrook 7H9 medium (7-14 days) being the most widely used in Europe. There is an alternative method, 96-well plate microdilution, which allows up to 12 drugs to be tested and at a lower cost, for which a document has been published with the standardised technical and methodological characteristics that ensure future approval for clinical use by the WHO.(125) The proposed methods, both direct and indirect, should be carried out in laboratories with a BSL3 safety level since their risk level is C. The manual published by the WHO makes special reference to the study of antibiotics used in the treatment of DR-TB.(126) Based on these guidelines, the WHO recommends that national programmes establish a phenotypic drug susceptibility test (DST) for those drugs that have reproducible and reliable methods available, i.e., bedaquiline, clofazimine, delamanid, fluoroquinolones, isoniazid, linezolid, rifampicin, and amikacin. In the European Union and the European Economic Area (EU/EEA), susceptibility to ethambutol is considered reliable when performed in quality-assured laboratories and similarly, susceptibility to pyrazinamide should be performed with automated methods based on growth in a liquid medium. The critical concentrations of many first-choice drugs in the presence of MDR-TB (bedaquiline, clofazimine,

delamanid, linezolid, and fluoroquinolones) have been established and published by the WHO.(127)

Rationale for the recommendation: Currently, there are international guidelines that standardise the cut-off points for critical concentrations, facilitating the comparability of results. In this guide, given the lack of quality data in the literature, we will rely on internationally accepted recommendations. Given the epidemiological context and the infrastructure available in our country, we believe that performing a phenotypic DST is recommendable in the first isolated diagnosis of a person / individual with TB.

PICO Question 8: Which drug combinations and treatment durations safely improve the outcomes of people affected by isoniazid-monoresistant tuberculosis and people affected by rifampicin-monoresistant tuberculosis?

Recommendation:

1. *Recommendation on isoniazid monoresistance*

In people affected by rifampicin-susceptible pulmonary TB (and the anti-TB drugs recommended in this regimen) and confirmed isoniazid resistance, i.e., isoniazid monoresistance, treatment with rifampicin, ethambutol, pyrazinamide, and a fluoroquinolone for six months is recommended (conditional recommendation, low quality of evidence). The fluoroquinolones recommended by this study group are levofloxacin or moxifloxacin. The expert group considers that treatment based on rifampicin, pyrazinamide, and a fluoroquinolone, if susceptibility to rifampicin and fluoroquinolones is confirmed, could also obtain similar favourable results to treatment with ethambutol, thus limiting adverse events (conditional recommendation, low quality of evidence).

Several considerations should be taken into account when implementing this recommendation. If isoniazid-monoresistant TB is confirmed by genotypic or phenotypic testing prior to initiating treatment, starting with the regimen of rifampicin, ethambutol, pyrazinamide, and fluoroquinolone is advisable. We recommend having a phenotypic or genotypic susceptibility test for fluoroquinolones before initiating this regimen (strong recommendation, moderate quality of evidence). If isoniazid-monoresistant TB is confirmed after starting treatment with an isoniazid, rifampicin, pyrazinamide, and ethambutol-based regimen, and resistance to rifampicin and fluoroquinolones has been definitively ruled out, we recommend starting a regimen with rifampicin, ethambutol, pyrazinamide, and fluoroquinolone for six months or up to six months if the person has received at least four months of fluoroquinolones. If fluoroquinolones cannot be used, we recommend using a regimen based on rifampicin, pyrazinamide, and ethambutol for six to nine months (conditional recommendation, low quality of evidence).

2. *Recommendation on rifampicin monoresistance*

We recommend that people affected by rifampicin-monoresistant TB be managed like people affected by MDR-TB (see PICO question 9) (conditional recommendation, very low quality of evidence).

Summary of findings:

1. *Summary of isoniazid monoresistance findings*

Twelve publications were reviewed, three of which were meta-analyses, (128–130) three CPGs, (6,130,131), one review(132), and five observational studies, three of which presented results using first-line drugs (133–135) and two that analysed the differences when a fluoroquinolone was added to the treatment (136,137). In a sample of 44 patients treated with two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months of isoniazid and rifampicin, Nolan et al.,(134) reported that no treatment failure occurred in any patient; however, 4% experienced a relapse within the two-year follow-up. Kim et al., (135) in an observational study with a small sample size in which first-line drugs were used in 6, 9, and 12-month regimens, therapeutic failure and the appearance of acquired resistance to rifampicin were observed in 8% of cases, most of them in the 12-month regimens. Nevertheless, Gegia et al., (129) in a meta-analysis including 19 cohort studies and 33 randomised trials, conducted between January 2008 and March 2015 with a sample of 3744 patients with isoniazid-monoresistant TB, found that treatment with first-line drugs was associated with a higher rate of failure and relapse (15% versus 3.6%), and acquired resistance (4% versus 0.6%) compared with patients with MS-TB. It should be noted that these differences were not seen in those patients who underwent a nine-month regimen with rifampicin, pyrazinamide, and ethambutol; due to which SEPAR, in its latest recommendations,(6) advised to continue considering the nine-month regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol. This meta-analysis had several limitations, among them, the large number of therapeutic regimens compared, making it difficult to analyse aspects such as the time of administration of each drug, final outcome definitions, and the length and thoroughness of follow-up were not homogeneous among the studies.

A meta-analysis that included 23 studies,(128) mostly observational, with an analysable sample of 5418 patients, compared treatment results between six-month regimens that included isoniazid, rifampicin, ethambutol, and pyrazinamide, with others of longer duration, and analysed whether the results could be improved by adding a fluoroquinolone or streptomycin. Regarding treatment duration, they found that a six-month regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide had a similar probability of success to when treatment was extended beyond six months. Subsequent analyses showed that there were no significant differences in final outcomes between patients receiving six months of rifampicin, pyrazinamide, and ethambutol and those who maintained it for more than six months; on the other hand, shortening the treatment time with pyrazinamide to three months was associated with a worse response.

Adding fluoroquinolones to the six-month regimens with isoniazid, rifampicin, pyrazinamide, and ethambutol resulted in higher treatment success rates (OR: 2.8; 95% CI: 1.1-7.3) and reduced mortality (OR: 0.4; 95% CI: 0.2-1.1) compared with patients treated without fluoroquinolones. The rate of acquired rifampicin resistance was also reduced (OR: 0.10; 95% CI: 0.01-1.2): 0.5% (1/221) with the regimen including fluoroquinolones versus 3.8% (44/1160) in those without fluoroquinolones; although in both cases statistical significance was not reached. The analysis also showed that the addition of streptomycin (up to three months) to an isoniazid, rifampicin, pyrazinamide, and ethambutol regimen with less than four months of pyrazinamide decreased the likelihood of treatment success (OR: 0.4; 95% CI: 0.2-0.7); there were no data on the use of other injectable drugs (kanamycin, amikacin, capreomycin). However, it is important to highlight the inherent limitations of the design of the studies analysed, which do not allow for the control of all confounding factors. For example, it is possible that there was a greater number of cases with severe disease in the group of patients who underwent treatment regimens longer than six months; in addition, the small number of patients with cavitary disease and smear test persistence do not allow definitive conclusions to be drawn from this group of patients.

Based on the results of this meta-analysis, the WHO recommended the addition of levofloxacin to the six-month regimen of rifampicin, pyrazinamide, and ethambutol for the treatment of isoniazid-monoresistant TB.(58) Previous observational studies also demonstrated that the association of a fluoroquinolone increases the treatment success rate, reaching 60-90%, and reduces the percentage of treatment failure, which did not exceed 1%.(132) However, recent series, all observational, did not find a significant benefit with this association. In a study carried out by Min et al. on a sample of 318 patients, the addition of fluoroquinolone only exhibited a beneficial effect in those patients under a therapeutic regimen lasting longer than six months, in order to reduce the length of pyrazinamide use.(136) Wilson et al.,(137) in another series of 198 patients with a high percentage of genotypic resistance tests, in most of which low-grade resistance to isoniazid was detected, no differences in treatment outcomes were found between those using only first-line drugs and those adding a fluoroquinolone; although differences were observed according to the degree of resistance, patients with a high-grade isoniazid mutation (*KatG*) used fluoroquinolones more frequently. Another study with 656 patients, found no difference between the addition or absence of fluoroquinolones in 12-month regimens based on rifamycins, nor according to the mutation detected in the genotypic study.(131)

Regarding which fluoroquinolone to use, there is more experience with levofloxacin than with moxifloxacin, however, both have been widely used in the treatment of MDR-TB with good results.(58) Moxifloxacin forms part of the first shortened TB treatment.(138) In addition, when moxifloxacin replaces isoniazid in the intensive phase, better study negativisation results are obtained, although these results are not statistically significant.(139) A meta-analysis comparing the antituberculous activity of different fluoroquinolones in pulmonary TB found that moxifloxacin, together with conventional treatment, was

superior to conventional treatment regarding time to sputum negativisation and the treatment success rate, whereas levofloxacin was superior only when analysing treatment success rates. Nevertheless, levofloxacin had a better safety profile.(140) In patients with MDR-TB, treatment success rates obtained with moxifloxacin and levofloxacin (750 mg daily) were similar in at least one clinical trial.(141) In the WHO MDR-TB treatment guidelines, both drugs are among the key drugs for treatment.(58) The favourable pharmacokinetic profile of moxifloxacin, together with its capacity to penetrate alveolar macrophages and epithelial lining fluid, make it a very attractive drug, although its penetration into hypoxic environments is marginal, unlike rifampicin.(142,143) Moxifloxacin has a synergistic effect with rifampicin but the pharmacokinetics of the former may be altered by rifampicin, although the clinical significance of this phenomenon is unknown.(144,145) The optimal dose of moxifloxacin for TB treatment when associated with rifampicin is unknown; on the one hand, *in vitro* studies suggested that moxifloxacin doses of 800 mg per day have optimal potency to eliminate fast-growing bacteria and prevent the emergence of resistance. On the other hand, plasma moxifloxacin levels are highly variable when administered at doses of 400 mg. Thus, the optimal bactericidal and sterilising dose may differ between patients, so it is advisable to monitor drug concentrations in people at high risk of low exposure to anti-TB drugs. Plasma levofloxacin levels are less affected by rifampicin and there is no clear contraindication to the use of levofloxacin with antiretroviral agents.(146,147)

2. *Summary of rifampicin monoresistance findings*

A retrospective study conducted in South Africa observed that 22.7% of isolates with rifampicin resistance, detected by molecular methods, had monoresistance to rifampicin and susceptibility to isoniazid in the phenotype study. In addition, these isolates were associated with mutations in the low-level *rpoB* gene.(148) Rifampicin monoresistance has significant consequences in terms of mortality;(149) a review of cases in the United States between 1998-2014 observed higher mortality in people affected by rifampicin-monoresistant TB with a relative risk of 1.4 (95%CI 1.04-1.8).(150)

Currently, international guidelines recommend that people affected by rifampicin-monoresistant TB be treated with the same therapeutic regimens as people affected by MDR-TB. However, some retrospective publications also found that personalised treatments achieve good results.(151) We reviewed eight publications that included people affected by documented RR-TB. Five publications were retrospective observational cohort studies,(152–156) one was an observational study of prospective cohorts,(157) one a longitudinal study of pharmacokinetics (158), and one conducted a cross-sectional prevalence study and retrospective case-controls.(159) Two of these papers analysed the results regarding the use of different pharmacological regimens. Studies that used bedaquiline-based regimens for at least nine months presented good efficacy results, finding no differences between participants with MDR-TB and rifampicin monoresistance. On the other hand, some had very few experiences with isoniazid, pyrazinamide,

ethambutol, and fluoroquinolones with good results.(156) In another study, which included people affected by MS-TB who were unable to use rifampicin due to adverse events and people affected by rifampicin-monoresistant TB, they found that regimens of between 12-14 months with first-line anti-TB treatment and fluoroquinolone had good cure outcomes.(155) However, the consequences of extrapolating these results to people affected by rifampicin-monoresistant TB are unknown

The studies reviewed include at least 29 participants with rifampicin-monoresistant TB and HIV co-infection.(155,156,160–162) In these studies, co-infection *per se* did not appear to be associated with an increased risk of treatment failure, however, delays in initiating antiretroviral therapy did. Two of these studies also suggested that people living with HIV could be treated with first-line drugs by replacing rifampicin with fluoroquinolones.(155,162)

Rationale for the recommendation:

1. *Rationale for the recommendation on isoniazid monoresistance treatment*

Recommendations to guide the treatment of isoniazid monoresistance are based on observational studies, and high-quality clinical trial data are scarce. Also, the meta-analyses used as the basis for recent recommendations by the WHO were included. People affected by isoniazid-monoresistant TB have a higher chance of treatment success when they are treated with fluoroquinolones for at least three months. There is no consensus on which fluoroquinolone should be prioritised, nor on dosage, but based on the literature, the expert panel suggests levofloxacin 750 mg per day and moxifloxacin 400 mg per day as options with equivalent or similar efficacy. People taking moxifloxacin are likely to benefit from its synergy with rifampicin, its high bactericidal potential, and its intracellular activity, whereas levofloxacin interacts poorly with rifampicin and has a more favourable safety profile. The duration of treatment, provided it is carried out with the recommended drugs, can be limited to six months, treatment prolongation in general does not provide a clear clinical benefit. Despite the scant evidence, the expert panel advocate caution and to follow international recommendations, and recommends that all treatment be carried out with four drugs (rifampicin, ethambutol, pyrazinamide, and fluoroquinolone). However, some authors of the guidelines consider that the withdrawal of ethambutol would not limit the efficacy, while it would reduce the toxicity associated with the regimen. Performing the maintenance phase with rifampicin and moxifloxacin alone is not sustained by sufficient evidence for it to be recommended. In people with known isoniazid resistance, when the participant is already in intensive phase treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol, we recommend withdrawing isoniazid and replacing it with fluoroquinolones. These people could end the treatment six months after initiation, provided that they complete between three to four months of treatment with fluoroquinolones, according to the results of the meta-analysis of Fregonese et al.(128) When fluoroquinolone cannot be used due to drug hypersensitivity or a high risk of adverse events, a six-month treatment with rifampicin, pyrazinamide, and ethambutol is recommended. Many studies included isoniazid in the treatment of people affected by isoniazid-

monoresistant TB, however, this is due to the fact that, in many centres, it is difficult to obtain treatment separately or it involves administering a very large number of tablets; therefore, combined tablets were used that included rifampicin, isoniazid, pyrazinamide, and ethambutol, adjusted to weight. The expert group considers that, in our setting, it is not justified to expose the participant to the toxicity derived from isoniazid, thus the use of isoniazid should be avoided whenever possible. If people affected by TB have polyresistance, i.e., resistance to isoniazid and pyrazinamide, ethambutol, or fluoroquinolones, we recommend consulting with a TB expert and personalising both the combination of drugs and the duration of treatment.

2. *Rationale for the recommendation on rifampicin monoresistance treatment*

There is very little evidence available in the literature and there are no quality clinical trials that evaluate rifampicin monoresistance in a differentiated manner; therefore, the available evidence derives from trials with participants with RR-TB (without isoniazid resistance confirmation) or from participants with MDR-TB. The first treatment option should be to use a treatment regimen based on bedaquiline, pretomanid/delamanid, linezolid, and fluoroquinolones. If this regimen cannot be used, we recommend consulting a TB Unit with experience in the management of DR-TB.

HIV co-infection does not alter the recommended treatment of RR-TB. However, drug interactions and the addition of adverse events must be considered when designing the antiretroviral regimen. In pregnant women, we recommend using the treatment recommended for people affected by MDR-TB.

PICO Question 9: How many drugs, which drug combination and treatment duration safely (percentage of grade 3 or higher adverse effects) improve (treatment success rate) the final outcomes of people affected by MDR-TB?

Recommendation:

We recommend that the management and follow-up of people affected by RR/MDR-TB be carried out by specialist TB units with experience in the management of people affected by DR-TB (conditional recommendation, very low quality of evidence).

In people over 14 years of age with pulmonary RR-TB, with no information on isoniazid resistance, or with pulmonary MDR-TB, with genotypic or phenotypic susceptibility to fluoroquinolones, we recommend treatment with bedaquiline, linezolid, pretomanid, and moxifloxacin (BPaLM) for six months (strong recommendation, high quality of evidence). We recommend replacing pretomanid with delamanid if the former is not available maintaining the same treatment duration (strong recommendation, moderate quality of evidence).

In people affected by extrapulmonary MDR-TB, the recommendation is to follow the same regimens as for pulmonary RR/MDR-TB (conditional recommendation, very low quality of evidence). In people affected by MDR-TB with bone or central nervous system (CNS) involvement, we recommend consulting with an experienced specialist TB Unit (conditional recommendation, very low quality of evidence). In general, people with disseminated, osteoarticular, or CNS TB may benefit from longer treatment (conditional recommendation, very low quality of evidence).

We recommend the use of the same shortened treatment regimens in pregnant women with RR/MDR-TB (conditional recommendation, very low quality of evidence). There is little information on the use of pretomanid in pregnant women and people younger than 14 years. However, delamanid has safety and efficacy data in these populations, so we recommend prioritising its use (conditional recommendation, very low quality of evidence).

If the proposed regimens cannot be used, treatment should be personalised according to allergies, interactions, safety profile, type of TB, and DST, using, if possible, an effective and safe oral drug combination for 9-12 months (conditional recommendation, very low quality of evidence). In the case of injectable drugs, we recommend that their use should be as short as possible, preferably less than eight weeks, with a total treatment duration of between 9-12 months, which can be reduced to six months if a combination containing bedaquiline is used together with the injectable drug (conditional recommendation, low quality of evidence).

In people affected by RR/MDR-TB living with HIV, we recommend applying the same regimens and durations as in people affected by RR/MDR-TB without HIV, as long as there are no additive interactions or adverse events, at least in people with CD4 ≥50 cells/μL (strong recommendation, moderate quality of evidence). Otherwise, the treatment regimen should be personalised (conditional recommendation, low quality of evidence). The recommendation is to start antiretroviral therapy within the first two weeks after initiating anti-TB therapy, especially in those with CD4 <50 cells/μL (strong recommendation, high quality of evidence). In the case of tuberculous meningitis, delaying the initiation of antiretroviral therapy at least four weeks after the start of anti-TB treatment is recommended due to the risk of complications associated with immune reconstitution syndrome, choosing the optimal time depending on the patient's clinical situation (conditional recommendation, moderate quality of evidence).

Summary of findings:

Classically, the treatment of RR/MDR-TB has consisted of prolonged regimens, with a total duration of between 18 and 24 months, divided into two phases. First, an intensive phase, lasting about six to eight months with at least five drugs including an injectable aminoglycoside, followed by a continuation or maintenance phase of 12 to 16 months, with all drugs administered orally.(163) These prolonged regimens

are poorly tolerated and have a high dropout rate, with cure rates of 70% or even less, depending on the pattern of resistance to second-line drugs.(164) In 2010, a new shortened treatment regimen emerged with a total duration of 9 to 11 months, based on fluoroquinolones, with an intensive phase of four to six months including an injectable aminoglycoside, and a maintenance phase of five months (Bangladesh regimen). This regimen demonstrated good efficacy in cohort studies with a relapse-free cure rate of 87.9%.(52) These favourable results, together with the interest in reducing the treatment duration for RR/MDR-TB, motivated numerous initiatives to assess the efficacy of new shortened treatments.

Twelve clinical trials evaluating different treatment regimens for people affected by RR/MDR-TB were reviewed. Each clinical trial contained a different treatment regimen and the comparators were also different, so the main findings of each study are summarised. Since several clinical trials have evaluated different short and oral regimens with high efficacy and a low percentage of side effects, the expert panel decided to summarise the clinical trial findings in a logical order. Given that pretomanid is not available in Spain, prospective and retrospective observational studies on the use of bedaquiline and delamanid in combination have also been reviewed to obtain safety and efficacy information on a regimen based on bedaquiline, delamanid, linezolid, and fluoroquinolones (moxifloxacin).

Summarised below are the clinical trials evaluating different regimens, both oral and injectable, with durations ranging from 6 to 18 months.

STREAM (57) was a phase 3, non-inferiority clinical trial involving adults with pulmonary RR-TB, with no evidence of resistance to fluoroquinolones and aminoglycosides determined by NAAT, specifically a line-probe assay. A 2:1 randomisation was performed placing 253 participants in the experimental regimen and 130 in the control arm. The experimental treatment (short treatment) consisted of a regimen based on optimised doses of moxifloxacin (up to 800 mg), clofazimine, ethambutol, and pyrazinamide, supplemented with kanamycin, isoniazid and prothionamide during the first 16 weeks, with the possibility of extending to 20-24 weeks in slow responders. The total treatment duration was 9-11 months. The control arm received treatment based on the 2011 WHO guidelines with a duration of 20 months. The primary objective was treatment success 30 months after randomisation, defined as sputum negativity at 30 months with a previous negative sputum, and no intercurrent positive sputum or unfavourable episode outcomes. A 10% upper limit of the 95% confidence interval was used to determine non-inferiority. Participants were recruited in Ethiopia, Mongolia, South Africa, and Vietnam. In the control arm, bedaquiline, delamanid, or linezolid could be used if resistance, intolerance, or aminoglycoside toxicity was observed. Four hundred and twenty-four participants were randomised, and 383 were included in the modified intention-to-treat analysis. A successful result was achieved in 79.8% of the participants in the control arm and 78.8% in the experimental group, a difference of 1% (95%CI -7.5 to 9.5), fulfilling the established limit of non-inferiority. A total of 45.5% of control group participants and 48.2% of the

experimental arm experienced grade 3 or higher adverse events. QTc prolongation occurred in 11% of participants in the experimental arm and 6.4% in the control arm. A total of 8.5% of participants in the control arm and 6.4% in the experimental arm died; 3.3% of participants in the control arm and 2.3% in the experimental arm acquired resistance to fluoroquinolones or aminoglycosides. This study demonstrated that a nine-month treatment regimen can be as effective as longer treatments; however, the percentage of serious adverse events remained very high. There were more unfavourable outcomes regarding bacteriological failure or relapse in the experimental group (10.6% vs. 5.6%), however, this is mitigated by the higher proportion of subjects lost to follow-up in the standard 18-24-month regimen (0.4% vs. 2.4%). Subsequent observational cohort studies carried out in different countries (China, Guinea Conakry, Sierra Leone, and Kyrgyzstan) have shown that short regimens that include an injectable in the intensive phase were significantly associated with a higher percentage of favourable outcomes compared with the long injectable treatments recommended by the WHO at this time.(165–169) Two of these studies reported an even higher percentage of sputum negativisation with the shortened regimen.(165,167)

MDR-END (36) was a multicentre, randomised, 1:1, open-label, phase 2/3, non-inferiority clinical trial with block randomisation and stratification for diabetes and cavitation at the time of inclusion. Twelve hospitals in South Korea participated. The study aimed to compare the treatment success rate 24 months after randomisation. The 2014 WHO outcome guidelines were followed. Non-inferiority was defined if the lower limit of the 97.5%CI of the inter-group difference was greater than -10%. Adults with pulmonary RR-TB and fluoroquinolone susceptibility were included. Participants were randomised into two treatment arms, an experimental arm based on treatment with delamanid, linezolid, levofloxacin, and pyrazinamide for nine months and a control arm that received treatment with injectables for 20-24 months according to WHO guidelines. In case of failure or toxicity, the injectable treatment could be modified to bedaquiline, delamanid, or linezolid, following WHO recommendations. A total of 214 participants were included, of whom 168 (75%) were included in the modified intention-to-treat analysis. At 24 months post-randomisation, 60 (70.6%) participants in the control group and 54 (75%) in the experimental arm were considered successful outcomes (4.4% inter-group difference; 97.5%CI -9.5%); therefore, the non-inferiority criterion was met. No differences in safety were observed between the two groups. At the time of publication, this was the first all-oral treatment regimen tested in a delamanid-containing MDR-TB clinical trial to present non-inferiority to the considerably longer conventional treatment regimen. The results suggested that short oral treatments (nine months) based on new anti-TB drugs (e.g., bedaquiline and/or pretomanid/delamanid), and including linezolid and fluoroquinolones, are as effective and safe as long treatments with injectable drugs.

The NExT Study (170) was a 1:1, randomised, controlled phase II clinical trial in adults aged 18 years and older, with pulmonary MDR-TB/RR without resistance to fluoroquinolones or aminoglycosides. The study was conducted in South Africa. Participants in the experimental group received treatment based on

bedaquiline, linezolid, levofloxacin, pyrazinamide, terizidone or ethionamide, or high doses of isoniazid for six to nine months. In the standard arm, treatment duration was 18-20 months with five to six drugs (including an injectable): kanamycin, moxifloxacin, clofazimine, pyrazinamide, terizidone or ethionamide, or high doses of isoniazid. The primary aim was a successful outcome, defined based on 2014 WHO guidelines, 24 months after randomisation. A total of 111 participants were randomised, of whom 93 were included in the modified intention-to-treat analysis (49 in the experimental arm and 44 in the control arm). The clinical trial was suspended prematurely when bedaquiline became available for prescription in South Africa. Participants in the experimental arm were 2.2 times more likely to have a successful outcome than those in the control arm (51% vs. 22.7%; $p<0.01$). In addition, culture conversion was significantly better in the experimental arm (Hazard Ratio (HR) 2.6, 95%CI 1.4-4.9). Treatment modifications due to adverse events were more frequent in the control than in the experimental arm (65.9% vs. 34.7%), and these were mainly due to hearing loss secondary to injectable treatment in the control group, and neuropathy secondary to linezolid treatment in the experimental group. Grade 3 or higher adverse events, however, were more frequent in the experimental than in the control arm (55.4% vs. 32.7%; $p<0.01$). The data suggested that a short treatment (six to nine months), including the three drugs designated by the WHO as group A (bedaquiline, fluoroquinolones, linezolid) and two others from groups B/C, in an oral-only regimen has better results in terms of cure (treatment success) and relapse rate than regimens of nine months or longer that include (or are based on) an injectable drug. This represents a paradigm shift in establishing the duration of MDR-TB treatment. However, 25% of unfavourable outcomes suggest that there is an opportunity to improve these regimens. Both regimens were associated with considerable toxicity, indicating the need to discover oxazolidinones less toxic than linezolid and to avoid the use of injectables.

The TB-PRACTECAL clinical trial (33) was an open-label, phase IIb-III, multicentre (South Africa, Belarus, and Uzbekistan), randomised, controlled, non-inferiority trial in subjects 15 years of age or older with pulmonary RR-TB. It aimed to compare the safety and efficacy of three 24-week experimental regimens (1. bedaquiline, pretomanid, linezolid, moxifloxacin, 2. bedaquiline, pretomanid, linezolid and clofazimine, 3. bedaquiline, pretomanid and linezolid) vs. a control group receiving standard treatment according to each country's national guidelines for 9 to 20 months. It was an adaptive clinical trial, divided into two phases. In the first phase, the early sterilising capacity was evaluated eight weeks after randomisation of the experimental treatments. In the second phase, the most successful experimental arm was compared with the control group. Endpoint assessment was performed 72 weeks after randomisation and was defined by the percentage of unsuccessful outcomes. The margin of non-inferiority was 12%. The clinical trial was terminated before the end of the recruitment marked by the sample size. In the intention-to-treat analysis, 11% of participants in the experimental arm and 48% in the control arm had unsuccessful outcomes (risk difference 37%; 96.6%CI -53 to -22%). In addition, the percentage of culture negativisation at 12 weeks was higher in those treated with the BPaLM regimen, although there were no significant

differences with those who received the standard regimen. The incidence of grade 3 or higher adverse events was lower in the experimental group than in the control group. The study concluded that a 24-week oral treatment based on bedaquiline, pretomanid, linezolid, and moxifloxacin is safe and effective for the treatment of people affected by pulmonary RR-TB. These favourable results with the shortened regimens, which also had a good safety profile, led the WHO to recommend the six-month BPaLM regimen in its latest 2022 guidelines as the first choice for the treatment of RR-TB/MR, followed by the short nine-month all-oral drug regimen for those in whom quinolone resistance was excluded.(58)

Another clinical trial evaluating the combination of the results at eight weeks of a regimen consisting of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide for MS-TB and MDR-TB obtained good results with an acceptable safety profile.

The ZeNix trial (31) was a randomised, partially blinded study that included patients over 14 years of age from South Africa, Georgia, Moldova, and Russia, diagnosed with pulmonary RR/preXDR/XDR-TB. Participants were randomised to receive bedaquiline and pretomanid for 26 weeks, supplemented with linezolid, at different doses and duration (1200 mg for 26 weeks vs. 1200 mg for 9 weeks vs. 600 mg for 26 weeks vs. 600 mg for 9 weeks). Randomisation was stratified according to HIV infection status and type of resistance. HIV-infected people with >100 CD4+/mL were included. The study objective in the modified intention-to-treat analysis was the incidence of unfavourable outcomes, defined as treatment failure or relapse (clinical or bacteriological) 26 weeks after treatment completion. A total of 181 participants were included, 88% with preXDR/XDR-TB. Participants who received bedaquiline, pretomanid, and linezolid at doses of 1200 mg for 26 weeks, 1200 mg for 9 weeks, 600 mg for 26 weeks, and 600 mg for 9 weeks had a treatment success rate of 93%, 89%, 91%, and 84%, respectively. The treatment with linezolid had to be modified or discontinued in 51%, 30%, 13%, and 13% of participants, respectively. This trial showed favourable cure rates with three anti-TB drugs (bedaquiline, pretomanid, and linezolid), of between 84-93%, in patients with different degrees of MDR, preXDR, and XDR-TB who had not responded to other regimens or who had to discontinue them due to adverse effects. In addition, the linezolid dose of 600 mg over 26 weeks was shown to offer the best risk/benefit profile. Nonetheless, the sample size limited the precision of the estimated treatment effect. The lack of a control group with standard WHO treatment implies the absence of a comparator with demonstrated efficacy; however, the efficacy data obtained corroborated and were consistent with those of the NixTB study.(171). In that study, a six-month regimen (which could be extended to nine months in cases of MTB-positive sputum culture at week 16), comprising bedaquiline, pretomanid, and linezolid, was evaluated in patients with preXDR-TB or MDR-TB, who had failed previous regimens. They achieved a success rate of 90% (83%-95%) six months after the end of treatment. Other combinations based on bedaquiline, pretomanid, moxifloxacin, and pyrazinamide also had good early sterilising activity, especially if the strains were susceptible to pyrazinamide.(172)

The STREAM-2 clinical trial (53) was a phase 3 non-inferiority study conducted in 13 hospitals in seven countries, in people affected by RR-TB aged 15 years or older without resistance to fluoroquinolones or aminoglycosides. Participants were randomised to a) the Bangladeshi short regimen (control group) — nine-month regimen with kanamycin, moxifloxacin, clofazimine, ethambutol, pyrazinamide, high-dose isoniazid, and prothionamide for four months, followed by five months of moxifloxacin, clofazimine, ethambutol, and pyrazinamide; b) a long regimen based on the 2011 WHO recommendations; c) a nine-month oral regimen based on levofloxacin, clofazimine, ethambutol, pyrazinamide, and bedaquiline with an intensive phase supplemented with isoniazid and prothionamide for 16 weeks; and d) to a six-month regimen based on levofloxacin, clofazimine, pyrazinamide, bedaquiline, supplemented with kanamycin and isoniazid at high doses for eight weeks. The primary endpoint was a successful outcome, defined as a negative culture without a prior unsuccessful outcome (death, bacteriological failure, recurrence, or treatment modification) at 76 weeks. The non-inferiority criterion was met if the lower limit of the 95%CI was less than 10% in both the intention-to-treat and per-protocol analyses. A total of 588 participants were randomised, of whom 517 were included in the intention-to-treat analysis. Participants in the nine-month oral treatment and the six-month shortened treatment with high-dose injectables and isoniazid supplementation had better cure rates than the control treatment (oral 83% vs. control 71%, risk difference 11%; 95%CI 2.9-19%; six months 91% vs. control 69%, risk difference 22.2%; 95%CI 13.1-31.2%) with a similar or even more favourable safety profile. Follow-up in this study was 18 months from the start of treatment, and the proportion of people with negative culture and no relapses 18 months after treatment initiation was considered as the treatment success rate. Based on this study, we can conclude that a nine-month regimen with bedaquiline, levofloxacin, clofazimine, ethambutol, pyrazinamide, high-dose isoniazid, and prothionamide for four months, followed by five months of bedaquiline, levofloxacin, clofazimine, ethambutol, and pyrazinamide is more effective and less toxic than a nine-month regimen with kanamycin, moxifloxacin, clofazimine, ethambutol, pyrazinamide, high-dose isoniazid, and prothionamide for four months, followed by five months of moxifloxacin, clofazimine, ethambutol, and pyrazinamide. On the other hand, a six-month treatment based on the described regimen is also superior to the control treatment. Thus, treatment with a potent sterilising combination for six to nine months can improve the success rates of treatments that include injectable drugs for periods > three months.

In a non-randomised clinical trial conducted in China, participants with MDR-TB received personalised oral treatment, based on availability, interactions, and DST, with at least four to five drugs for 9-12 months. A total of 103 participants were included, 53% received treatment based on linezolid, fluoroquinolones, clofazimine, cycloserine, and pyrazinamide, and 34% received treatment based on bedaquiline, linezolid, fluoroquinolones, cycloserine, and pyrazinamide. Therefore, two short 9-12-month regimens, both oral, were compared, one with bedaquiline and the other without. The study showed sputum conversion rates at two months of 83.1%, and at four months of 94.4%, and the treatment success rate was 97.6% (only

available in 41 participants who had already completed treatment). The results of sputum negativisation and treatment success were similar in bedaquiline-containing vs. non-bedaquiline-containing treatment regimens, and also in cases caused by fluoroquinolone-susceptible MTBs vs. fluoroquinolone-resistant MTBs.(173)

Other trials evaluated long-term (18 months) oral regimens, with a six-month intensive phase and a 12-month continuation phase. The two regimens used consisted of 1) bedaquiline, levofloxacin, linezolid, cycloserine, clofazimine vs. 2) bedaquiline, levofloxacin, linezolid, cycloserine, and prothionamide. In both regimens, bedaquiline was only maintained for six months. A total of 68 participants with MDR-TB were included, with 34 participants per group. It is noteworthy that there was a statistically significant difference in the percentage of people who successfully completed treatment (82% vs. 56%) in favour of the clofazimine group and the percentage of adverse effects was higher in the clofazimine group (44% vs. 18%). The treatment regimens were highly effective, however, the proposed duration is excessive, as other clinical trials show that durations between 6-12 months are sufficient.(174)

Some clinical trials compared different regimens that included injectables, however, the expert panel considers that, since there are oral guidelines with demonstrated efficacy for the treatment of people affected by MDR-TB, the use of injectables should be left exclusively for situations in which these regimens cannot be used.(165)

An observational study compared efficacy measured as sputum conversion at two and six months after initiation of delamanid supplementation in a three-drug treatment regimen (at least two WHO group A drugs) in people affected by MDR-TB. The six-month sputum conversion rate was 81.3% when supplemented with delamanid and 88.7% without supplementation, with a relative risk of sputum conversion (delamanid supplementation vs. no supplementation) in the intention-to-treat analysis of 0.94 (95%CI 0.84-1.02). According to this study, the use of a fourth drug in an active regimen does not afford a benefit in sputum sterilisation.(175)

Another prospective study conducted in Georgia evaluated the efficacy of treatments based on bedaquiline or delamanid plus other accompanying drugs—mainly linezolid, clofazimine, cycloserine, and fluoroquinolone—with a median of four drugs per person. Adjusted sputum conversion rates at six months were 96% for people with bedaquiline and 72% for those with delamanid (p<0.01), as well as lower resistance acquisition during treatment.(176)

At least three recent systematic reviews examined the role of bedaquiline and delamanid-based regimens in the treatment of MDR-TB with a sputum conversion rate at six months of between 63-94%. The pooled estimate of treatment success was 73% (95%CI 64-81%). In addition, the risk of QTc prolongation was

7.8% (95%CI 4.1-11.6%) with a cardiac event rate of 0.8%. This treatment appears to be an effective alternative, with a low rate of serious cardiac events.(37,177,178)

A multicentre cohort (endTB *Observational Study*) of people affected by RR-TB treated with regimens designed according to WHO recommendations containing delamanid and/or bedaquiline, analysed a total of 1109 people affected by RR-TB, 63% with regimens containing bedaquiline, 27% with delamanid, and 10% with both drugs.(179) A total of 85% of participants had sputum conversion at six months and 5% of people were lost to follow-up. However, they did not provide detailed information by type of treatment. The participants with the lowest likelihood of conversion were those with HIV, cavitary disease, and high bacillary load. The drugs most frequently associated with sputum conversion were linezolid, clofazimine, fluoroquinolones, and cycloserine.(180) Another study with this cohort showed that adverse events attributed to bedaquiline or delamanid were less frequent and severe than those caused by linezolid or any of the injectable drugs.(181)

A systematic review of the use of a delamanid regimen in people affected by RR-TB showed an aggregate success rate of 80.9% (72.6-87.2%), and a success rate of 75.2% if delamanid was combined with bedaquiline.(182)

Real-life data under implementation conditions also demonstrated that bedaquiline-based short oral treatment regimens of 9-12 months, replacing injectable therapy in people affected by RR-TB for at least three months, achieved higher cure rates than injectable treatment-based regimens.(152)

Another prospective observational study found that the concomitant use of bedaquiline and delamanid, generally associated with linezolid and clofazimine, in people affected by MDR-TB (74.2% with fluoroquinolone resistance) achieved a treatment success rate of 78%.(183)

We have considered people living with HIV and pregnant women as special groups. Children are not the subject of this guideline as there are other documents that deal with this topic. On the other hand, there is no information on people with non-HIV immunosuppression, liver cirrhosis, and chronic renal failure with MDR-TB.

People living with HIV participated in the different clinical trials as long as they had CD4 levels above 50-100 cells/μL, with similar efficacy and toxicity results; therefore, MDR-TB regimens can be used in people living with HIV.(184)

There are no specific trials on the treatment of MDR-TB in HIV-infected populations, thus the available information comes from the subgroup analysis of studies in the general population. The MDR-END study

did not include participants with HIV infection. In the Next Study, 55% of participants had HIV infection and a median CD4 score of 158 cells/μL, finding no difference in this subgroup with the six-month shortened oral treatment versus standard treatment. The STREAM-2 study included participants with HIV infection, finding that oral treatment had greater efficacy than standard treatment in this population subgroup, attributable to a greater need for early switching from anti-TB treatment due to side effects. This highlights the importance of considering the increased risk of side effects and interactions in this population group. The most relevant clinical trials of oral regimens for MDR-TB with BPaL or BPaLM regimens included participants with HIV infection (with CD4 > 50 cells/μL), finding no differences in this population group. In the Nix-TB study, there were no significant differences in the efficacy or toxicity of the BPaL regimen in HIV-infected patients (51% of the sample, all on antiretroviral therapy and CD4 ≥ 50 cells/μL, median 343 cells/μL). The Zenix study included 20% of participants with HIV infection (all on antiretroviral therapy and CD4 ≥ 100 cells/μL), finding no difference in the results of the BPaL regimen in this subgroup. The TB-PRACTECAL study also included a significant percentage of HIV-infected participants with CD4 counts ≥ 100 cells/μL, finding no differences in efficacy for the BPaLM regimen. Based on previous results, there is no information against the use of the same bedaquiline-based short oral regimens for the treatment of MDR-TB in people living with HIV, at least in patients with CD4 ≥ 50 cells/μL. Furthermore, there is no information on the efficacy and safety of short oral regimens for the treatment of MDR-TB in patients with HIV and CD4 infection < 50 cells/μL. In these patients, the worse immunological situation could negatively influence the evolution; however, the initial results of the studies analysed suggest that the new treatment regimens in this subpopulation should have a superior result to the previously recommended treatments. Nevertheless, it will be important to closely monitor and adjust the treatment duration based on clinical, radiological, and microbiological improvement, as well as assess the possible interactions and influence of immune reconstitution on the final probability of a favourable outcome. Until more information becomes available, when implementing short oral regimens in patients with CD4 < 50 cells/μL, the need for longer treatments should be considered and the evolution and risk of relapse should be closely monitored after completion.

As a rule, and although there are no specific studies on the choice of antiretroviral therapy in patients with HIV and MDR-TB infection, the considerations for selecting the initial antiretroviral therapy do not differ between patients with or without TB. However, the risk of specific side effects and drug interactions should be specifically considered. The absence of rifampicin in the MDR-TB treatment regimen significantly reduces the risk of drug interactions. Overall, currently recommended antiretroviral treatment regimens (based on integrase inhibitors or doravirine) do not have significant interactions with the BPaLM regimen. Patients treated with regimens based on protease inhibitors, efavirenz, or rilpivirine may present significant interactions and/or risk of QT prolongation with bedaquiline, pretomanid, delamanid, or fluoroquinolones and, therefore, alternative regimens or close monitoring should be considered. Regardless, it is advisable to always assess potential drug interactions associated with antiretroviral treatment (see https://www.hiv-

druginteractions.org/).

The timing of antiretroviral treatment initiation should be individualised based on the general clinical situation, immunological status, and tolerance of anti-TB treatment, striking a careful balance between the risk of AIDS-related events and complications associated with untreated HIV infection, versus the risk of side effects, drug interactions, and immune reconstitution syndrome of early antiretroviral treatment initiation. Information on the timing of antiretroviral treatment initiation derives from studies on first-line drug-susceptible pulmonary TB.(92,185,186) In these studies, early treatment (during anti-TB treatment) showed a reduction in mortality and AIDS-related events in all immunological groups but especially in those with a lower count (< 50 cells/μL). This benefit did not reduce the rate of anti-TB treatment success, nor did it increase the risk of recurrence or serious secondary events that require treatment to be discontinued. However, it did come at the cost of an increased risk of immune reconstitution syndrome. Despite the absence of specific information regarding MDR-TB, we believe that the management of these patients should not be different from that of the population with HIV infection and TB susceptible to first-line drugs. Generally, antiretroviral therapy should be started during TB treatment and as soon as possible, bearing in mind that simultaneous initiation with anti-TB treatment may make it difficult to identify the drug responsible in the event of side effects, hinder adherence, and increase the risk of immune reconstitution syndrome, which may complicate management or confuse a possible poor evolution. In people with CD4 < 50 cells/μL, information from previous studies showed that treatment initiation within the first two weeks of starting anti-TB treatment may reduce the risk of AIDS events and death, independent of an increased risk of immune reconstitution syndrome. In people with CD4 ≥ 50 cells/μL, we recommend initiating antiretroviral therapy within the first eight weeks of initiating anti-TB treatment. As for TB of the CNS, the risk of immune reconstitution syndrome with potentially serious consequences should be considered, so regardless of the CD4 count, delaying treatment by eight weeks from the start of anti-TB treatment is recommended; although, in people with CD4 < 50 cells/μl, an earlier initiation within the first two to eight weeks with close monitoring could be considered.

The management of HIV infection is beyond the scope of these guidelines. For more information, consult the updated recommendations for antiretroviral treatment and opportunistic infections of the AIDS-SEIMC Study Group (GeSIDA) (187) or the European guidelines.(188)

There is very little information available on the use of the new drugs in pregnant women with MDR-TB; clinical trials systematically exclude pregnant women. The safety profile of pretomanid in pregnant women is unknown, although teratogenicity has not been observed in animal models, so no recommendation can be made for or against its use in this population or lactating women.

A recent publication analysed 43 pregnant women with MDR-TB treated with bedaquiline and/or

delamanid, 98% of whom had a successful outcome. Of the 31 women who continued with the pregnancy, 81% gave birth to children without malformations, and 68% had babies with a normal weight.(189) Other experiences also showed an acceptable safety and efficacy profile for linezolid, levofloxacin, clofazimine, cycloserine, delamanid and bedaquiline.(190,191) From this information, it can be deduced that treatment with new anti-TB drugs can improve treatment success without producing a high proportion of serious adverse events in women or their children. Aminoglycosides and ethionamide/prothionamide are not recommended in pregnant women.(192) Another small longitudinal study in RR-TB assessed bedaquiline exposure in pregnant women, breast milk, and neonates. It included 13 women with different resistance patterns: RR-TB by NAAT=6, MDR-TB=3, PreXDR-TB=2, XDR-TB=1, and one unknown case. Only six completed the postpartum follow-up: RR-TB=2, MDR-TB=2, PreXDR-TB=0, XDR-TB=1, and the unknown case. They observed that bedaquiline levels were 50% lower in the plasma of pregnant women compared with the usual pharmacokinetics of non-pregnant women. However, sample extraction was not very rigorous as regards the last bedaquiline dose, therefore, the results should be assessed with caution. Plasma levels similar to those of their mothers were observed in breastfed infants (samples taken up to seven weeks postpartum), while lower levels were noted in those who were not breastfeeding. High levels of bedaquiline in breast milk could account for this difference.(158) On the other hand, isoniazid, ethambutol, and pyrazinamide have a long history as a treatment in pregnant women with TB. Fluoroquinolones cross the human placenta and are found in the amniotic fluid at low concentrations. The prenatal use of fluoroquinolone may be associated with abdominal wall defects or bone malformations,(193–196) however, other studies have not shown an increased risk.(197,198,198–200) MDR-TB treatment during the first trimester has been associated with increased complications during pregnancy and childbirth, compared with women who start treatment in the second or third trimester.(160) However, these results were prior to the establishment of the new treatment regimens, so the risk to the mother and baby of not initiating effective treatment as soon as the diagnosis is made should be carefully assessed.

There is very little evidence regarding which regimen should be used in immunocompromised people affected by MDR-TB and whether the new short regimens might be as effective as in non-immunocompromised people. There are retrospective cohorts of transplant recipients with MDR-TB, in which treatment regimens were personalised to their resistance profile and possible drug interactions, observing a high number of side effects.(201,202) The expert panel recommends that, in cases of MDR-TB in people with non-HIV immunosuppression, both the treatment regimen and duration should be individualised, taking into account possible drug interactions, safety profiles, and the clinical, microbiological, and radiological evolution of each patient.

There is little or no evidence available on the use of single or combination drugs for the treatment of MDR-TB in patients with renal impairment, especially for delamanid and pretomanid. In a systematic review of

treatment outcomes in people affected by MDR-TB on haemodialysis,(203) in the conclusions, the authors comment that a guide for drug dosage is necessary to reduce the adverse effects, which are increased in this type of patients. An article published by Park et al.,(204) described the favourable outcomes of bedaquiline-based therapy in two people affected by MDR-TB on haemodialysis. Due to their safety profile, group A drugs (bedaquiline, fluoroquinolones, and linezolid) can be used in patients with chronic kidney disease, monitoring adverse effects, particularly QTc prolongation. Regarding the addition of drugs from other groups to complete an individualised regimen, ethambutol requires dose adjustment and the use of aminoglycosides or pyrazinamide is not recommended. In patients with end-stage chronic kidney disease, drugs from groups A, B, and C may be administered at usual doses after haemodialysis to prevent accumulation and decrease the toxicity risk. There are no data on the pharmacokinetic behaviour of delamanid and pretomanid in haemodialysis patients.

The evidence available in people with liver disease originates from the safety data of different clinical trials and cohort studies. The hepatotoxicity associated with short oral regimens is lower than that found with treatments used in MS-TB. Due to its greater capacity to induce hepatotoxicity and the eventual associated severity, the first drug not recommended for patients with chronic liver disease is pyrazinamide. Also, high doses of isoniazid cannot be used in these patients. In an article by Lee et al.,(205) conducted in a cohort of 299 patients with chronic liver disease, drug-induced toxicity during MDR-TB treatment occurred most frequently in alcoholic liver disease and HBV or HCV-infected patients. In this regard, S Tunesi (206) and ID Olaru (207), in their respective Letters to the Editor, reported that MDR-TB and hepatitis C can be treated at the same time with direct-acting antivirals, although it is unclear when to start hepatitis treatment. Regimens based on bedaquiline and/or delamanid or pretomanid may be used in the treatment of MDR-TB in patients with chronic liver disease. Close monitoring of the hepatic profile is advised in people at increased risk of hepatic toxicity.

Rationale for recommendation: In people affected by RR/MDR-TB with or without HIV infection, treatment with shortened regimens consisting of bedaquiline, linezolid, delamanid or pretomanid supplemented with fluoroquinolones (levofloxacin/moxifloxacin) for six months has demonstrated high efficacy and an adequate safety profile. The highest quality clinical trials were conducted with pretomanid, nevertheless, we believe that the evidence from observational studies is sufficient to recommend replacing pretomanid with delamanid without posing a risk to people affected by TB, as well as achieving similar treatment success rates. The same fluoroquinolone-free regimen has also been shown to be effective (although with somewhat lower success rates), and should be considered in people affected by MDR-TB with fluoroquinolone resistance. The addition of clofazimine to this regimen may improve success rates and reduce resistance amplification, at the cost of increasing adverse events, including skin pigmentation, which may have adverse social implications in some communities. The dosage of bedaquiline used in clinical trials was different, therefore, the expert panel cannot opt for any of them, and recommends using

the one that best suits the conditions of the person with TB and that *a priori* ensures better adherence. Also, we must be aware that there is still a percentage of people who fail with this regimen and, likely, people affected by RR/MDR-TB with high bacillary load or extensive pulmonary involvement could benefit from extending treatment duration, especially those with delayed sputum negativisation. There are other promising regimens, such as combinations of bedaquiline, moxifloxacin/levofloxacin, and pretomanid/delamanid, with or without pyrazinamide, particularly in people affected by pyrazinamide-susceptible MDR-TB. Clofazimine has been studied extensively in clinical trials of long regimens with injectables and nine-month oral treatment regimens and may be a recommended alternative to establishing different treatment regimens if previously recommended regimens cannot be used. In situations where the recommended regimens cannot be used, we recommend personalisation of the treatment regimen by an expert group and close monitoring of people for early detection of adverse events or treatment failures. The total duration of treatment, in these cases, will be defined by the combination selected; although, generally, in pulmonary TB, it is not justified to carry out treatment for longer than 9-12 months. Injectable treatments have been shown to have a powerful bactericidal and sterilising activity, however, their high toxicity, as well as the severity of adverse events, relegate these drugs to residual use, and as a last resort when no other effective and safe oral alternative is available. The duration for injectable drugs should be limited as much as possible (whenever possible, limited to three to four months of induction phase treatment, or eight weeks if treatment is combined with bedaquiline), and ototoxicity and nephrotoxicity should be closely monitored. On the other hand, special populations are not included in clinical trials, so it is difficult to support the above recommendations with evidence. The combination of drugs and the treatment duration in the case of people affected by RR/MDR-TB with disseminated involvement, CNS, or osteoarticular TB has not been studied in clinical trials, so the recommendations are extrapolated from pulmonary RR/MDR-TB or MS-TB data.

PICO Question 10: How many drugs, which drug combination and treatment duration safely improve the final result for people affected by preXDR-TB or XDR-TB?

Recommendation:

We recommend that the management and follow-up of people affected by preXDR/XDR-TB be carried out by specialist TB Units with experience in the management of people affected by DR-TB (conditional recommendation, very low quality of evidence).

In people over 14 years of age with pulmonary preXDR-TB, we recommend oral treatment with a three-drug regimen consisting of bedaquiline, linezolid, and pretomanid for six months (strong recommendation, high quality of evidence). If there are contraindications or non-availability of pretomanid, the recommendations are: 1) replace pretomanid with delamanid (fairly similar activity) and continue with a three-drug regimen (strong recommendation, moderate quality of evidence); 2) use a four-drug regimen

(bedaquiline, linezolid, delamanid, and clofazimine) (strong recommendation, moderate quality of evidence). The duration of treatment is not modified if it is decided to supplement treatment with clofazimine and replace pretomanid with delamanid, or simply substitute pretomanid with delamanid (strong recommendation, moderate quality of evidence). We recommend extending treatment with the same regimen beyond six months if sputum culture at 16 weeks is still positive (conditional recommendation, low quality of evidence).

In adults with pulmonary preXDR/XDR-TB who are not candidates for treatment with the above regimens (due to drug intolerance, drug interactions, safety profile of the regimen, susceptibility study, or amplification of resistance during treatment), we recommend personalising treatment with drugs with expected or documented activity in the susceptibility study. We recommend at least four to five drugs, prioritising oral treatment regimens over injectable drugs (conditional recommendation, low quality of evidence). If an all-oral treatment regimen can be constituted, these four-five selected drugs should include as many drugs as possible with potent sterilising activity, such as bedaquiline, delamanid/pretomanid, linezolid, or clofazimine, and should be maintained throughout the course of treatment. The recommended treatment duration in these cases is between 9-20 months. Durations nearing nine months generally have comparable success rates and lower rates of adverse events compared with durations nearing 20 months (conditional recommendation, low quality of evidence). If the treatment regimen includes an injectable drug and bedaquiline, the duration of the injectable drug may be limited to eight weeks. If the treatment regimen includes an injectable drug but bedaquiline cannot be used, the recommendation is to maintain the injectable treatment for as short a time as possible. The duration of the injectable drug may be guided by the negativisation of sputum cultures and the appearance of adverse events and normally does not exceed three months. Once the injectable drug has been withdrawn, we recommend maintaining at least three to four oral drugs until the end of treatment (conditional recommendation, low quality of evidence).

In people affected by extrapulmonary preXDR/XDR-TB, the same regimens as for pulmonary preXDR/XDR-TB are recommended (conditional recommendation, very low quality of evidence). In people affected by preXDR/XDR-TB with bone or CNS involvement, we recommend consulting with an experienced specialist TB Unit (conditional recommendation, very low quality of evidence). In general, people with disseminated, osteoarticular, or CNS TB may benefit from longer treatment duration (conditional recommendation, very low quality of evidence).

We recommend the use of the same shortened treatment regimens in pregnant women with pre-XDR/XDR-TB (conditional recommendation, very low quality of evidence). There is little information on the use of pretomanid in pregnant women and people younger than 14 years. However, there are safety and efficacy data for delamanid in this population, so we recommend prioritising its use (conditional recommendation, very low quality of evidence).

In people affected by preXDR/XDR-TB living with HIV, we recommend applying the same regimens as in people affected by preXDR/XDR-TB without HIV, provided that there are no additive interactions or adverse events, at least in those with CD4 ≥ 50 cells/μL (strong recommendation, moderate quality of evidence). Otherwise, the treatment regimen should be personalised (strong recommendation, low quality of evidence). It is recommended that antiretroviral therapy begin within the first two weeks after initiating anti-TB therapy, especially in those with CD4 < 50 cells/μL (strong recommendation, high quality of evidence). In the case of tuberculous meningitis, delaying the initiation of antiretroviral therapy at least four weeks after the start of anti-TB treatment is recommended due to the risk of complications associated with immune reconstitution syndrome, choosing the optimal time depending on the patient's clinical situation (conditional recommendation, moderate quality of evidence).

Summary of findings: Three clinical trials included people affected by PreXDR-TB within the study population (Zenix, NixTB, TB-PRACTECAL), with treatment success rates between 80-90% with regimens of at least three drugs, including Bedaquiline, Pretomanid, and Linezolid.

Nix-TB (32) was an open-label, uncontrolled study that included 109 participants with RR/MDR-TB, of whom 65% had resistance to fluoroquinolone and to an injectable. Participants were assigned to a single treatment arm with a treatment regimen with three oral drugs bedaquiline, pretomanid, and linezolid (BPaL) for 26 weeks. In this study, 90% of participants had favourable outcomes six months after completion of treatment (clinical and bacteriological resolution). There were no significant differences in efficacy between the fluoroquinolone and injectable resistance groups, nor in HIV-infected patients (51% of the sample, all on antiretroviral therapy and CD4 ≥ 50 cells/μL). Adverse events were common, especially peripheral neuropathy (81%) and myelosuppression (48%), attributable to the high doses of linezolid used, nonetheless, all participants with favourable evolutions were able to complete the treatment regimen with dose adjustments or temporary interruptions.

To explore safer doses of Linezolid in the BPaL regimen without compromising its efficacy, the ZeNix study was designed (31), a clinical trial in patients with unresponsive RR/MDR-TB or with side effects to the previous second-line regimen, or resistance to fluoroquinolones and/or an injectable drug. In this study, participants were treated with a regimen based on bedaquiline, pretomanid, and linezolid and randomised 1:1:1:1 to four different dosages of linezolid (1200 mg/day 24 weeks, 1200 mg/day 9 weeks, 600 mg/day 24 weeks and 600 mg/day 9 weeks). The primary objective of the study was the incidence of unfavourable outcomes in the intention-to-treat analysis, defined as treatment failure or clinical or bacteriological recurrence 26 weeks after completing treatment. The study included 181 participants, comprising 75 (41%) with fluoroquinolone resistance and at least one injectable drug, 85 (47%) with resistance to fluoroquinolone or an injectable drug, 145 (80%) without HIV infection, and 112 (62%) with cavitated

pneumonia. Participants had favourable outcomes in 84-93% of cases, an incidence of peripheral neuropathy in 13-38%, myelotoxicity in 2-22%, and 13-51% required a dose change or discontinuation of linezolid. The linezolid regimen with the best balance between efficacy and safety was 600 mg/day for 26 weeks. Success rates in this study, even in the worst-case group (600 mg/day 9 weeks) were comparable to those in the Nix-TB study and higher than those previously described for preXDR- and XDR-TB. An estimated 86.2% of participants had an adverse event, however, serious adverse events occurred in just 6.1%. The expected duration of treatment was 26 weeks, with the option to extend the treatment to 39 weeks if uncontrolled disease was presumed between weeks 16 and 26 of treatment (persistent sputum positivity and/or clinical and/or radiological progression attributable to TB). The only study participant who required treatment extension was in the linezolid 9-week 600 mg/day group.

In the TB-PRACTECAL study (33), the modified intention-to-treat analysis at 72 weeks of follow-up after randomisation demonstrated that 89% of participants in the BPaLM group had favourable outcomes compared with 52% with standard treatment. The study was not designed for participants with preXDR-TB; however, fluoroquinolone resistance was not an exclusion criterion and 20.1% of participants with fluoroquinolone resistance were included, with no differences found in this subgroup, supporting the use of the BPaL regimen in patients with preXDR-TB. This study also included a considerable number of participants with risk factors for poor outcomes, such as HIV infection (10.3%) or cavitary disease (29%), with no differences found in these groups. The incidence of side effects (≥ grade 3 or serious adverse events) was also higher in the standard treatment group than in the BPaLM group (59% vs. 19%).

Meanwhile, the BEAT-India trial (208), a prospective, open-label, single-arm study, explored the four-drug regimen with bedaquiline, delamanid, linezolid (600 mg daily), and clofazimine (100 or 200 mg depending on the participant's weight) for 24 weeks in patients with RR/MDR-TB with fluoroquinolone and/or injectable resistance. Treatment could be extended up to a total of 36 weeks if cultures at week 16 remained positive. Patients with HIV infection were specifically excluded. Finally, 153 participants (95.8% with fluoroquinolone resistance) were included, of whom 139 (91%) had a favourable outcome at the end of treatment, defined by bacteriological (two negative cultures four weeks apart), clinical (improvement of symptoms and signs), and radiological success. The most common side effects were skin alterations in 59% of participants (especially hyperpigmentation), 52% of participants developed myelopathy (especially anaemia), and 42% peripheral neuropathy. Of the participants who continued the follow-up at 48 weeks after completion of treatment, 131 maintained a favourable outcome, with resolution of most adverse events. Only seven participants needed to extend the treatment.

Finally, based on the similarity of action between pretomanid and delamanid (209), and with the evidence of prospective programmatic studies in which delamanid was used as a substitute for pretomanid, in cases where there is no possibility of using pretomanid (non-availability, or no evidence of its use in certain

population groups such as pregnant women or children under 14 years of age), this could be replaced by delamanid. This constitutes the bedaquiline, delamanid, linezolid, regimen supplemented with moxifloxacin, or clofazimine in the case of non-use of fluoroquinolones due to resistance, serious adverse events, or drug interactions. This would apply especially to pregnant women and children under 14 years of age, a population group in which the safety profile and efficacy of regimens based on pretomanid are unknown; in contrast, there is information on the safety and efficacy of delamanid in this population.(189–192)

Participants with preXDR/XDR-TB on personalised bedaquiline or delamanid-based regimens have a high probability of experiencing an adverse event, with 12.3% of people on bedaquiline-based regimens experiencing serious adverse events versus 14.3% of those on a delamanid-based regimen.(210)

As for XDR-TB, the working group found no evidence regarding the number of drugs required to treat patients with the current definition of XDR-TB. Given the lack of evidence, this working group has collected information on treatment regimens used for the old definition of XDR-TB, which could be applied to people affected by TB according to the new definition. Most of the information comes from observational studies or clinical trials focused on RR/MDR-TB, whose treatment could be tailored to people affected by XDR-TB. The largest study was a meta-analysis of individual data adjusted for risk factors. This study included information from 12030 patients with RR/MDR-TB with the aim of analysing the relationship between the number of drugs, duration of treatment, and drug composition of the regimen. The chosen outcomes were treatment success and death.(30) The results of this extensive meta-analysis were used to develop the latest WHO RR/MDR-TB treatment recommendations.(58) This study targeted RR/MDR-TB and many participants lacked information for the expanded DST, however, at least 16.8% of participants had documented resistance to ofloxacin and 3.5% to levofloxacin/moxifloxacin. Linezolid resistance was studied in a small number of participants, and there was no study of bedaquiline resistance, so the results would not be directly applicable to the current definition of XDR-TB. In this meta-analysis, 61% of participants had treatment success (defined as completed treatment or cured), 8% failed or recurred, 14% died, and the remainder were lost to follow-up or had unknown outcomes. Based on this study, the optimal number of effective drugs was obtained with the use of five presumably effective drugs in the intensive phase (defined as the period of treatment with an injectable drug or the drug that replaced it), and four drugs in the continuation phase (defined as the period of treatment without an injectable drug). Overall, there was a higher probability of treatment success in participants with a longer intensive phase (between six and eight months), with a total duration of 18-20 months, a total duration of the intensive phase since negativisation of the sputum culture of five to seven months, and a treatment duration after sputum culture conversion of 15-18 months. However, this study did not make extensive use of the new, highly bactericidal and sterilising anti-TB drugs, while abusing excessively long treatments based on previous recommendations. Participants with HIV infection had high mortality but 51% were not receiving

antiretroviral treatment.

Finally, a recent prospective observational study gathered information, between 2015 and 2018, from patients who had received oral treatment regimens for MDR-TB including at least four potentially active drugs, confirmed by susceptibility study and/or absence of prior treatment with that drug for more than one month.(211) Of the 759 participants included, 80% had favourable outcomes, regardless of fluoroquinolone resistance. The population had risk factors for poor prognosis; of the participants, 21.7% had HIV infection, 44.5% had a BMI < 18.5, 44.5% received previous treatment with second-line drugs, and significant disease extension (67.6% bilateral involvement and 52.8% cavitary). When focusing on patients who received regimens that would be useful for the current definition of XDR-TB, those who received a median of five drugs, with a linezolid or bedaquiline-based regimen, supplemented with four drugs selected from clofazimine, cycloserine, ethambutol, delamanid, pyrazinamide, and PAS for an average of approximately 20 months, had a treatment success rate of 72.1%. Between 80-90% of the participants required some change from the initial treatment, most of them three months after treatment initiation. Even with the limitations of an observational study and the absence of a comparator group, these regimens of five-four oral drugs exhibited higher success rates than those previously described for people affected by preXDR- and XDR-TB. These conclusions were refuted by another prospective study, which emulated the demands of clinical trials and obtained a treatment success rate of 85% with bedaquiline and a total of four active drugs. The treatment duration in this study was 18-20 months but no differences were observed between participants receiving six months of bedaquiline and those who received longer treatment.(212)

Systematic reviews of the usefulness of pretomanid and linezolid in the treatment of DR-TB were assessed.(213,214)

There is no evidence on the best combination of drugs for treating people affected by XDR-TB. The lack of molecular testing for bedaquiline and linezolid limits the identification of people affected by XDR-TB. Currently, diagnosis can only be made at the clinical level with phenotypic susceptibility or DSTs Evidence was drawn either from studies analysing a combination of drugs potentially useful for these patients or from studies conducted using previous definitions of XDR-TB, although many of the treatments used included bedaquiline and/or linezolid. Sometimes, people affected by XDR-TB need to use injectable or intravenous drugs to be able to complete a minimum of three to four active drugs; in these cases, the use of carbapenems (meropenem-clavulanic acid, imipenem, relebactam, amikacin, and even new-generation cephalosporin) could be considered.(30,75)(184)

Rationale for recommendation: There is scant evidence available to make a recommendation. The available studies mainly include participants with RR/MDR-TB, some of whom have susceptibility studies

showing resistance to fluoroquinolones; however, there is no information on resistance to bedaquiline or linezolid. Therefore, it has been decided to extrapolate the information from regimens that can be used in participants with MDR/preXDR/XDR-TB. People affected by pulmonary preXDR-TB could be treated with bedaquiline, pretomanid/delamanid, and linezolid, which could be supplemented with clofazimine for six months or longer in special situations. This achieves treatment success rates greater than 85-90%, which is close to the data obtained for MS-TB. The safety profile of this regimen is acceptable, adverse events are generally tolerable, and reversible with dose modification and temporary or permanent discontinuation of the suspect drug. The recommended dose of linezolid in these cases is 600 mg administered for the entire treatment duration (26 weeks), thus reducing the incidence and severity of myelotoxicity and neuropathy. QTc monitoring is especially relevant in people receiving the combination of bedaquiline with pretomanid/delamanid, although its use is usually not associated with clinically significant cardiac events, and prolongations are reversible with temporary treatment interruption.

People living with HIV (with CD4 levels ≥ 50 cells/μL) have shown similar results, so they can be used in this population. Drug interactions must be carefully reviewed (online tool: https://www.hiv-druginteractions.org/). As a rule, current regimens based on integrase inhibitors or doravirine do not exhibit significant interactions with the bedaquiline, pretomanid, and linezolid regimen. People under treatment with regimens based on protease inhibitors, efavirenz, or rilpivirine may have significant interactions and/or risk of QT prolongation with bedaquiline, pretomanid, or delamanid, therefore, a personalised treatment regimen for both diseases should be instituted.

Extrapulmonary preXDR-TB and special populations will require treatment personalisation; however, the above-recommended regimen should be used whenever possible. In situations where penetration into a specific compartment must be ensured, the pharmacodynamics of the drugs should be considered, among other factors, when developing the treatment regimen. As mentioned above, people with liver or kidney failure, extrapulmonary disease, pregnancy, or breastfeeding were excluded from these studies, thus we cannot provide specific recommendations in this regard, although whenever possible, the treatment regimen recommended in this section should be used.

Regarding the non-discriminated use of pretomanid/delamanid proposed in these guidelines, it must be mentioned that pretomanid has high-quality evidence derived from clinical trials, while delamanid has more experience in programmatic use and *real-world data*. Currently, there are no comparative studies between the two drugs; the available preclinical information suggests a similar efficacy in case the substitution of pretomanid by delamanid is necessary due to lack of availability, side effects, or interactions. Therefore, in situations where pretomanid cannot be used, it could be replaced by delamanid.

As previously discussed, there are no data on treatment regimens in people affected by XDR-TB according

to the current definition. The management of these patients is extremely complex and presents a high risk of failure as, by definition, it implies resistance to drugs with greater bactericidal and sterilising potency, in addition to the fact that they are generally people with long-term illness who present more severe forms of TB. These patients require an individualised regimen designed according to the drug susceptibility study, availability, interactions, type of TB, and tolerance, ideally always with the participation of experts in its management. In people affected by XDR-TB, the studies afford favourable results, higher than 70%, but the management of people requires close follow-up and frequent treatment modifications, with median treatment durations of approximately 18-20 months. The aforementioned studies included people with advanced disease and comorbidities that confer a poor prognosis, including people living with HIV, therefore, the recommendation can be extended to this population. Nevertheless, as is the case with MDR-TB, there are no data on people affected by XDR-TB and liver or kidney disease, TB with extrapulmonary involvement, and pregnant or breastfeeding women, among others. A limitation of most of these studies is that drugs regarded as effective are considered equivalent, when the bactericidal and sterilising activity may vary significantly between them. At the same time, in some studies, the regimens used were designed following previous recommendations corresponding to the 2019 WHO treatment guidelines, so it is possible that some treatment regimens were oversized in terms of the number of drugs and treatment duration. On the other hand, some studies excluded people affected by pre-XDR/XDR-TB who were treated with three or fewer drugs, thus it would not reflect the spectrum of all people affected by pre-XDR/XDR-TB. Treatment personalisation, therefore, should always be guided by a committee of experts in TB treatment. Based on WHO recommendations and the latest published cohort studies, we recommend a long treatment regimen (9-20 months) with at least four to five active drugs (provided bedaquiline or linezolid can be used, supplemented with pretomanid/delamanid, plus two or three other oral drugs). Treatment can probably be simplified once the patient presents sputum conversion and clinical improvement, also, attention should be paid to the tolerance and bactericidal and sterilising activity of the drugs. In the case of including an injectable treatment to complete the regimen, this should be discontinued as soon as possible. If the regimen includes bedaquiline, eight weeks of treatment with injectable drugs is probably sufficient, otherwise, the duration of the injectable drug will have to be individualised, which is usually between four and eight months. The use of all-oral regimens has enormous advantages in terms of administration route and safety profiles over injectable regimens. Bedaquiline has been approved for six-month treatment, however, there is already experience with longer uses. It should be highlighted that there likely is no specific answer to the number of most effective drugs and treatment duration for XDR-TB, rather that the answer to both questions depends on the bactericidal and sterilising potency of the drugs included, as well as the bacillary load of the person with TB. The efficacy of an individual drug may differ from its efficacy in combination with other drugs, as many have synergistic effects in combination and, therefore, we should consider specific drug combinations rather than individual drugs. We cannot rule out that the use of drugs with greater bactericidal and sterilising potency and a higher barrier to resistance may have greater or equal therapeutic success by combining a smaller number of drugs and for a shorter

time than the current recommendations based on available studies. Certain combinations of four active drugs with high sterilising and bactericidal potency, such as bedaquiline or linezolid, clofazimine, cycloserine, and delamanid/pretomanid, for a sufficient period, probably less than 20 months, may be effective for the treatment of XDR-TB with fewer side effects and discontinuations, especially in patients with limited disease, low bacillary load, and without associated risk factors for poor outcomes.

The duration of treatment regimens, as discussed above, should be closely linked to the treatment combination used. Generally, the main guidelines and observational studies available remain cautious and recommend treatments with durations between 18-20 months, with intensive phases of six to eight months, and 15-17 months from the negative sputum culture. However, evidence from recent trials and other observational studies confirm that treatments lasting between 9-20 months could maintain the same efficacy while reducing toxicity. As far as possible, a fully oral treatment should be established, modifying the number of drugs according to the evolution of the people affected by TB, withdrawing the less active drugs when there is a significant decrease in the bacillary load and clinical improvement. The initial recommendations suggested ending bedaquiline at six months, however, currently, both bedaquiline and delamanid tend to be used for more than six months.

PICO Question 11. In what situations would surgical treatment be indicated in patients with DR-TB?

Recommendation: Adjuvant surgical therapy to improve prognosis is not recommended in people affected by pulmonary MDR /preXDR/XDR-TB (strong recommendation, low level of evidence). Surgery could be associated with the recommended pharmacological treatment to improve the cure and prognosis of people affected by DR-TB in situations where localised lesions are present and a persistent clinical, microbiological, and/or radiological lack of response is demonstrated, despite optimised treatment by a TB Unit with experience in the management of people affected by DR-TB (conditional recommendation, very low level of evidence).

Summary of findings: There are no randomised controlled studies evaluating the role of surgery in cases of DR-TB. The evidence comes from observational studies, meta-analyses with systematic reviews, and meta-analyses of individual patient data, so the quality of the evidence is very low. A meta-analysis of individual data analysed 26 studies with a total of 6431 patients with MDR-TB; Surgery was used in 18 of these studies with 478 patients undergoing surgery. The surgical techniques used were pneumonectomy in 117 patients, lobectomy or segmentectomy in 229, and in 132 the extent of the resection was not specified. In general, patients who underwent surgery had more extensive disease and received longer pharmacological treatments and more effective drugs in the intensive phase of therapy than non-surgical patients in the same centres or those enrolled in non-surgical studies. Partial surgical resection was associated with improved treatment success (aOR 3.0), except for pneumonectomy. Treatment success

was more likely if surgery was performed after culture negativisation than before (aOR 2.6), although this is quite logical since the bacillary load had been significantly reduced. The explanations for these findings may be related to the low mortality of people who underwent partial resection; likewise, it may be that people who underwent surgery were in better condition, although this seems unlikely if the characteristics of the patients are analysed. It is not clear why the mortality of pneumonectomised patients was higher than that of patients undergoing partial resections (8.5% vs. 2.2%), although this could be due to the greater number of lobes affected, greater bacillary load, and poorer response to antibiotic therapy, all of which generate a worse prognosis. Some of the limitations of this study refer to unknown confounding factors such as the respiratory functional status before surgery or the difference between patients lost to follow-up (much higher in non-surgical patients).(215) Finally, it should be noted that the studies included in this meta-analysis were published between 1970 and 2008, periods in which the management and prognosis of patients with MDR-TB differed substantially from today's situation, and the pharmacopoeia was limited to drugs that are not very sterilising and toxic, so it is difficult to extrapolate these findings to the present time. In 2016, a systematic review was published that included a meta-analysis evaluating the role of surgery as an add-on therapy to drug treatment in people affected by MDR-TB.(216) After reviewing 1203 bibliographic citations, 20 articles were included in the final analysis, with an inclusion period spanning between 1990 and 2015. Six articles were systematic reviews or meta-analyses and 14 were research articles, of which two were prospective studies and 12 were retrospective. Of these 14 articles, eight included people affected by XDR-TB and 12 included people living with HIV. Only four observational studies and one meta-analysis specified the surgical technique used. All meta-analyses studied included observational studies, and three of them analysed individual patient data.

The analysis of the 14 main research studies returned a relevant result: 81.9% of patients who underwent surgery achieved favourable results (cured or treatment completed) compared with 59.7% of those who did not undergo surgery, with an OR of 2.62, and moderate heterogeneity in the populations. A sensitivity analysis was performed with studies that included cure as the final outcome, also finding a favourable effect in people who underwent surgery compared with those who did not (75.2% vs. 54.9%, OR 3.03). Lost to follow-up and treatment failure were lower in the surgical group (p=0.01 in both cases). The methodological problems of the analysed papers include numerous biases and provide an extremely low certainty of the evidence. In addition, most of these studies predate the availability of new, highly effective DR-TB treatment regimens.

Another systematic review with meta-analysis was published in 2017 by Roh et al.(217) After reviewing 2960 studies, published in English between 1981 and 2015, which included patients with MDR-TB and XDR-TB treated with anti-TB drugs and surgery, the final meta-analysis was narrowed down to just six articles, with a total of 331 patients recruited in Asia, America, and Europe. This study concluded that lung resection combined with pharmacological treatment did not provide benefits in terms of survival compared

with patients treated with drugs alone. The review had several limitations, including the heterogeneity of the studies and the absence of clear criteria for selecting who should be treated with additional surgery. The first limitation was reflected in the fact that patients who underwent surgery could have a better functional status, while those who did not undergo surgery could have worse general conditions. Regarding the second limitation, each participating centre had its own criteria and variables for selecting surgical patients. Obviously, these biases limit the validity of the results of this publication. In addition, these results contradicted the other meta-analysis reviewed, adding a bias in the direction of the results.

The study published in 2019 by Krasnov et al. aimed to delve into more modern techniques for lung collapse in people affected by MDR-TB and XDR-TB who also had HIV infection.(218) The study design was an open-label randomised study that included patients with advanced MDR-TB who had been treated with second-line drugs related to their resistance patterns for at least 12 months before entering the study. All patients had positive smear tests, no microbiological conversion within the last six months, and were being treated with at least five drugs. A total of 102 patients (recruited in Russia between 2008 and 2014) were included, of whom 49 were treated with an endobronchial valve endoscopically placed in the most affected lobar bronchus destroyed by the original tuberculous cavity, with no major complications appearing in the medium term. A cured case was considered one with completed treatment, with no evidence of failure, and with three or more negative cultures obtained at least 30 days after the intervention. The results showed culture negativisation three months after the intervention in 95.9% of the patients who received the valve compared with 37.7% in the control group (p<0.0001), and cavity closure in 67.3% compared with 20.7% (RR 2.72). In the three-year follow-up, 80.5% of patients in the first group were considered cured compared with 25% in the control group (RR 3.44). The authors concluded that insertion of an endobronchial valve results in faster bacteriological conversion and cavity collapse in MDR-TB patients, with minimal and reversible complications. From this study, it can be highlighted that people with persistent treatment failure were included. The same authors conducted another study included in the same publication, with the same methodological design but with patients with different clinical characteristics. It included 125 patients of the same geographical origin, selected between 2013 and 2017, with pulmonary TB and HIV infection. Sixty-eight people received an endobronchial valve while 57 constituted the control group. All patients had destructive forms of the disease and a positive smear or culture despite correct treatment; 69.2% of the intervention group and 59.6% of the control group had MDR-TB. Again, the group that received the endobronchial valve achieved bacteriological conversion in 75% of its members, compared with 42% of the control group (OR 4.13). Despite immunosuppression, cavity collapse occurred in 55.9% and 28.1%, respectively (OR 3.25). This last sub-study raises some ethical doubts since some of the people included had susceptible TB with HIV co-infection, and it is well established that under adequate treatment and follow-up, the cure rate of these people is very high. Surgical intervention would therefore not be indicated for this subgroup of people. It should be remembered that endobronchial valve placement is not without short- and long-term complications. Finally, the same

authors also published their experience with a less-invasive osteoplastic thoracoplasty technique in people with contraindications for lung resection, followed by endobronchial valve implantation. Four hundred and fourteen patients were recruited in Russia between 2007 and 2013, 191 in the intervention group and 223 in the control group; all had advanced TB, with 43 people in the intervention group and 61 people in the control group having bilateral cavities. Other clinical characteristics of both groups were the presence of positive smears (93.7% vs. 92.8%), MDR-TB (88.9% vs. 86.1%), and XDR-TB (64.7% vs. 56.7%). A total of 196 minimally invasive thoracoplasties were performed in the intervention group and 238 conventional thoracoplasties in the control group. Subsequent endobronchial valve implantation to improve the effectiveness of surgical collapse was carried out in 163 patients from the first group and 191 from the second. The results one year after surgery showed a bacteriological conversion rate of 80.4% in people with minimally invasive thoracoplasty compared with 69.3% of those with conventional thoracoplasty (OR 1.84); cavity collapse was also more frequent in the first group (OR 2.13). As expected, associated surgical complications such as transfusion requirements, infections, and respiratory failure were more frequently associated with conventional thoracoplasty.

In 2021, Vashakidze et al. published a retrospective study of patients treated between 2008 and 2012 in Tbilisi, Georgia.(219) It included 408 patients with MDR-TB and XDR-TB, of whom 299 had been treated with drugs alone (not including bedaquiline, delamanid, pretomanid, or linezolid) and 109 with combination therapy with drugs and surgery. Criteria for surgical referral included therapeutic failure, high probability of failure or relapse, disease complications, localised cavity, and adequate lung function. The first group comprised older patients, with higher smoking and alcohol consumption, more cases with hepatitis C, and more bilateral involvement; the surgical group consisted of more cases with XDR-TB (28% vs. 15%). The most used surgical techniques were lobectomy (47%) and segmentectomy (36%). The results showed a higher percentage of people with treatment completion and cure in the surgical group than in the non-surgical group (76% vs. 41%; RR 1.9). After adjusting for multiple factors, the association between surgical resection and favourable outcomes remained (RR 1.6), which was also observed in secondary models that excluded patients with bilateral disease and those who had received less than six months of treatment. This study had relevant limitations as it was a retrospective study with an evident bias in the selection of participants. As we previously mentioned, this study also preceded the emergence of new, highly effective regimens.

Rationale for recommendation: In the pre-antibiotic era, surgical treatment was frequently used in the management of TB. The advent of highly effective anti-TB drugs relegated surgical treatment to specific situations with poor response to pharmacological treatment, or to the management of complications (massive haemoptysis secondary to giant cavitations, among others). With the emergence of antibiotic resistance, we have returned to situations in which people affected by active TB did not have effective drug treatment; so surgical treatment by experienced surgeons was again used to improve treatment

success rates for people affected by TB with limited drug treatment options. However, the emergence of new drugs or the repositioning of others has led to highly effective treatments becoming available to people affected by DR-TB, relegating adjuvant surgical treatment to a last-resort and marginal option in the treatment of DR-TB. If used, minimally invasive techniques, supplemented with lung collapse through endobronchial valves, are prioritised over other techniques.

Thus, adjuvant surgical treatment in people affected by DR-TB is not recommended, except in special situations in which there is evidence of failure with pharmacological treatment, no other alternative treatment can be resorted to without risk to the lives of people affected by TB, there are localised lesions that can be managed surgically, and the person has an acceptable respiratory reserve.

PICO Question 12. How often and which complementary tests should be performed during clinical follow-up in people affected by DR-TB depending on the combination of treatment drugs?

Recommendation: Monitoring of the microbiological response to treatment with monthly smear tests and sputum culture is recommended in people affected by MDR-TB with lung involvement (conditional recommendation, very low quality of evidence). Sputum culture has a higher sensitivity than smear tests in detecting failure or relapse (strong recommendation, moderate quality of evidence). Serial periodical chest x-ray studies are recommended, or earlier if there is evidence of clinical worsening (conditional recommendation, very low quality of evidence).

Clinical monitoring and monthly follow-up with blood counts and renal and hepatic biochemistry are recommended (conditional recommendation, low quality of evidence). An electrocardiogram with corrected QT measurement at baseline is recommended 15 days after the start of treatment and monthly thereafter in those receiving drugs with the potential to prolong QT, i.e., bedaquiline, fluoroquinolones, delamanid / pretomanid, and clofazimine (conditional recommendation, low quality of evidence). Frequent ophthalmologic monitoring is recommended for people receiving treatment with ethambutol and/or linezolid (conditional recommendation, low quality of evidence). A psychiatric assessment prior to cycloserine administration is recommended, as well as monitoring for the appearance of psychiatric symptoms during follow-up (conditional recommendation, low quality of evidence). Thyroid profile monitoring is recommended in people being treated with ethionamide/prothionamide and/or PAS (conditional recommendation, low quality of evidence). Routine testing of therapeutic levels of the drugs for DR-TB treatment is not recommended; however, they may be useful in specific cases to monitor therapeutic ranges and limit the appearance of toxicity, particularly with amikacin and linezolid (conditional recommendation, low quality of evidence). The recommendation is to educate people on DR-TB treatment so that they can identify adverse events early and contact their medical team quickly (conditional recommendation, low quality of evidence).

Monitoring of people affected by DR-TB is recommended according to Table 7 (conditional recommendation, low quality of evidence).

Summary of findings: The evidence available to analyse the usefulness of culture and smear tests, as well as the optimal frequency of their performance during the follow-up of people with treated MDR-TB, was obtained from a subset of individual patient data that South Africa's fight against TB plan shared with the WHO for the update of the TB management guidelines (unpublished data).(58) The sub-analysis was performed on a population of 3762 people from a cohort with a total of 26522 participants. This study compared (i) the performance of the two methods (smear test and sputum culture) in terms of sensitivity/specificity, and (ii) culture testing once a month versus every two months to assess the minimum frequency of testing needed to avoid unnecessary delays in treatment modifications. The focus of the analysis was to compare the performance of the two tests in terms of predicting treatment failure or relapse.

The main findings of the analysis were that monthly culture had a higher sensitivity than monthly smear tests (0.93 vs. 0.51) but slightly lower specificity (0.97 vs. 0.99). Likewise, the sensitivity of monthly culture was much higher than when performed every two months (0.93 vs. 0.73) but with a slightly lower specificity (0.97 vs. 0.98). Monthly culture increases the number of participants detected with a true positive bacteriological result by 13 per 1000 patients and compared with smear test alone. Conversely, it is estimated that monthly culture leads to 17 per 1000 more false-positive results for treatment failure, implying that treatment may be prolonged in the case of missed false positives or true negatives. The results of these cultures are necessary for the final classification of the treatment result. The second source of evidence was a meta-analysis of 5410 individual data (913 with treatment failure) from 12 observational studies measuring delay in the detection of treatment failure.(220) The study included HIV patients and patients from all continents. The study observed a greater delay in detecting treatment failure if follow-up was performed with bi-monthly smear tests (nine-month delay), followed by monthly smear tests (seven-month delay), and bi-monthly culture (two-month delay). The implications of a delay in detecting treatment failure are longer hospitalisations and isolations, as well as increased exposure to ineffective drugs with a high potential for adverse events. However, the quality of the meta-analysis was very low, due to the high heterogeneity of the studies, as well as the low retention of participants in the included observational studies.

There are no clinical trials nor other quality data sources addressing complementary tests and their frequency for the management of adverse events and follow-up of people affected by TB. Most of the information comes from follow-up protocols derived from clinical trials, as well as the balance between the frequency, intensity, and availability of tests for early detection of adverse events. The frequency of adverse effects in people on MDR-TB treatment is very high, with data ranging between 71-60% for

treatment regimens that include injectable drugs and 74% for new oral treatment regimens.(221) However, the severity of adverse events and long-term sequelae, as well as treatment discontinuation, are usually higher in treatment regimens that include injectable drugs.(170,222) Serious adverse events are detected in 22-36% of patients with delamanid treatments (36,223) and 26-34% of treatments involving bedaquiline.(170,224) The TB-PRACTECAL study also included safety among its objectives, finding that serious adverse events were higher in classic treatments with injectables (59%) compared with oral treatments based on bedaquiline, pretomanid, linezolid, and moxifloxacin (19%), or bedaquiline, pretomanid and linezolid (22%).(33) There are studies that correlate the adverse effects associated with linezolid with trough levels and AUC24.(225)

A meta-analysis using individualised data from 9,178 patients found that the drugs associated with the greatest side effects are injectables (10% discontinuation of treatment) and linezolid (14% discontinuation). These treatment interruptions were reduced with moxifloxacin to 2.3%, bedaquiline to 1.7%, and clofazimine to 1.6%. Another observational study corroborated these results with slightly higher percentages.(76) Unfortunately, there are no studies that identified the optimal frequency or the most cost-effective approach for monitoring adverse reactions related to each drug. The most common adverse events associated with the drugs used to treat people affected by MDR-TB were as follows. Bedaquiline produces QTc prolongation corrected by the Fridericia formula in 2.5-24% of people, hepatotoxicity in 16%, and diarrhoea and nausea in 9%.(226–228). It should be noted that most studies analysed excluded patients with a baseline QTc >450 msec. Adverse events associated with linezolid are dose-dependent. If 1200 mg per day is used, adverse events in the form of polyneuropathy may occur in up to 80% of people, and myelotoxicity in 49%.(32) At doses of 600 mg per day, anaemia presents in 30-40% of people, thrombocytopenia in 14-30%, and neutropenia in 1-10%, while peripheral neuropathy is reduced to 30% and optic neuropathy to 2.5%.(31,229,230) Regarding delamanid, gastrointestinal adverse events were observed in 27%, hypomagnesemia in 6%, and QTc prolongation in 5% of exposed persons.(223) Fluoroquinolones, on the other hand, can cause arthralgia in 11%, tendinopathy in 1%, and QTc prolongation in 1%.(231) Finally, injectable drugs were responsible for nephrotoxicity in 8%, ototoxicity in 3-15%, and hydroelectrolyte alterations in 19%. The first two adverse events are irreversible, and people experience scant improvement after withdrawal of treatment. (39) Hyperpigmentation and gastrointestinal intolerance are present in 14% and 47% of people taking clofazimine, respectively.(165) Cycloserine is responsible for psychiatric disorders and skin reactions in exposed people.(232) Finally, ethionamide is responsible for gastrointestinal complications, hepatotoxicity, hypothyroidism, and neurological toxicity. A prospective observational study in India of people living with HIV found that more than 50% of patients on ethionamide or PAS treatment developed hypothyroidism.(233)

Regarding the potential risk of QTc prolongation in people exposed to drugs with the potential to lengthen QTc, a recent meta-analysis of 25 studies, including data from 591 patients with delamanid, found QTc

prolongation in 2.4% vs. 12.8% in 685 patients with delamanid and bedaquiline combined.(182) A recent randomised placebo trial adding delamanid to standard treatment showed a minimal non-significant increase in adverse effects, with a low rate of QTc prolongation (5% vs. 2.5%).(36) On the other hand, a meta-analysis including 1447 patients from eight studies concluded that adding moxifloxacin to standard treatment or treatment with levofloxacin does not increase the number of side effects (gastrointestinal, hepatotoxicity, or skin abnormalities).(232) Another randomised trial found no increased risk of adverse events when adding clofazimine to bedaquiline, with QT prolongation >500 in 3% of participants;(174) data very similar to those of the STREAM-2 study combining moxifloxacin, bedaquiline, and clofazimine.(53)

Rationale for the recommendation: The decision to propose monthly monitoring of treatment efficacy is based on the possibility of the early detection of treatment failures, which allows treatment to be optimised while reducing disease transmission in the community.

As there are no quality data on the most efficient way to monitor people on MDR-TB treatment, it is difficult to make an evidence-based recommendation. In this guide, we have ventured to make suggestions based on the information available in trial monitoring protocols, as well as the frequency, intensity, and reversibility of adverse events. We believe that the proposed recommendations maintain proportionality between the regularity of controls and the risk of late detection of an adverse event. Regardless, we believe that it is essential to train and involve people in their treatment so that they can identify adverse events early and thus quickly contact their treating team. It is also vitally important that people under treatment for MDR-TB have a quick and easy mechanism to access a high-quality consultation to resolve doubts related to adverse events. The type and frequency of the complementary tests and clinical visits for monitoring adverse events will ultimately have to be agreed upon with the people affected by MDR-TB, based on numerous factors related to the risk of developing adverse events and the person's social context. There are no data on how to proceed in people affected by HIV and pregnant women, therefore, no specific recommendations can be made. Thus, how, and how often monitoring is carried out will have to be individualised according to the specific risk of each person. Tables 7 and 8 show the most frequent adverse events and a proposal for the follow-up of people affected by MDR-TB according to the drugs used.

PICO Question 13. Does face-to-face follow-up, compared to telematics, improve final outcomes and reduce adverse events in people affected by DR-TB?

Recommendation: Individualising the type of follow-up according to the possibilities of the healthcare centre, as well as the preferences and risk factors of the person affected by TB is recommended (conditional recommendation, very low quality of evidence). We recommend directly observed therapy (DOT) in people affected by DR-TB (conditional recommendation, very low quality of evidence). The panel considers that telematic follow-up, using video-observed treatment (VOT), results in adherence and cure

outcomes similar to DOT in people affected by TB (conditional recommendation, moderate quality of evidence).

Summary of findings: We reviewed 10 publications that analysed face-to-face follow-up and various telematic follow-up options in people affected by TB under treatment, regardless of resistance. Of the total number of publications reviewed, two were systematic reviews with meta-analyses, two were systematic reviews, and six were prospective randomised studies. Given the nature of the intervention, all studies were at risk of observational and measurement bias as they cannot be blinded, however, we have several clinical trials comparing different interventions.

One of the published systematic reviews compared face-to-face versus telematic follow-up of TB treatment. The study selected 16 randomised trials with 9789 participants globally.(234) The study, however, covered very heterogeneous situations ranging from latent TB prophylaxis to the treatment of people affected by MDR-TB in very different settings with unequal access to technological advances (study period 2012-2020). It could only conclude that, in general, telematic monitoring decreased the number of doses missed, however, it did not find an improvement in the negativisation of cultures or treatment success. It did not assess the effect on the frequency of adverse events or their management.

Another review, which included 2481 participants, also confirmed that VOT increases adherence as well as bacteriological resolution, although there was a great deal of heterogeneity between studies.(235) On the other hand, these studies cannot be extrapolated to the general population given the different contexts in which they were carried out.

Two recent randomised controlled studies directly compared face-to-face monitoring with telematic monitoring using VOT (236) and a wirelessly controlled adherence system (237) in Moldova and California, respectively. Both studies included a questionnaire on quality of life, satisfaction, and preferences regarding monitoring techniques. Both studies agreed that the telematic technique increased the number of doses observed and that people affected by TB preferred digital over face-to-face monitoring. The sample size, however, did not allow us to extract significant differences in terms of treatment success, nor did it address the issue of the management of side effects.

In New York, a study of the non-inferiority of VOT versus directly observed face-to-face treatment was specifically designed. This study did not include people affected by MDR-TB.(238) The study was completed by 173 patients performing a crossover of the two techniques. VOT reached non-inferiority with a higher number of complete doses 89.8% (95%CI, 87.5%-92.1%) compared with the directly observed face-to-face treatment 87.2% (95%CI, 84.6%-89.9%). Doses that could be monitored over the weekend by deferred VOT were not counted since the monitors only made direct observations on weekdays,

however, VOT could be counted on a deferred basis. In this study, people affected by TB mostly preferred digital follow-up (84%), with no differences between synchronous and asynchronous VOT. Adverse events were not analysed in this study. Another study conducted in the United States obtained similar results.(239)

Another randomised study of 405 people compared VOT vs. DOT in China, excluding people affected by DR-TB. The study showed that VOT significantly decreased the time-dose ratio as well as the total cost. Furthermore, VOT was clearly superior in terms of the overall satisfaction of people affected by TB at follow-up, although, again, it did not modify the cure rate. Adverse events were also not monitored in this study.(240)
Another study compared VOT seven days a week vs. DOT on weekdays, with a higher compliance rate in patients with VOT: 79% in this arm compared with 45% in the DOT arm. In this case, there was evidence of a higher rate of adverse events in the VOT arm, although it was assumed to be secondary to the systematic process of information gathering.(241)

Another follow-up model was conducted via a call centre in Thailand. In this study, similar adherence was observed compared to DOT; however, people preferred the latter option since there were significant limitations due to poor telephone signal, problems with batteries, and the advanced age of the participants.(242)

We do not have any studies comparing telematic monitoring of DR-TB treatment side effects versus face-to-face follow-up. We can only infer that digital technology facilitates continuous contact with the person and adherence to treatment. Asynchronous or delayed VOT allows treatment to be monitored every day of the week but may reduce contact with healthcare personnel and lose the proximity that facilitates the detection of adverse effects. On the other hand, there are implantable sensors that could be useful for detecting adverse effects, such as the appearance of QTc prolongation, changes in gastric pH, etc. The availability of the procedures will determine the best strategy for the follow-up of people affected by MDR-TB.(243)

Alternatively, other studies analysed community-based versus hospital-based treatment supervision in MDR-TB. The points in favour of the first strategy were convenience for the person with TB, greater adherence to treatment, and lower healthcare expenditure. A meta-analysis with a sample size of 3344 participants found that the rate of treatment failure in people on community-supervised treatment was 6.5% vs. 18.8% in hospitalised people. The sub-analysis of the data detected the following factors related to greater treatment success: age (younger age, higher success rates), people with a negative HIV test, prolonged treatment (>18 months), and appropriate treatment regimens.(244)

Based on all of this evidence, the CDC recommended the use of VOT during TB treatment and equated it

to the use of DOT. (245) On the other hand, economic impact studies indicated that VOT is less expensive, and saves time for healthcare professionals and people affected by TB.(246,247)

Rationale for the recommendation: The follow-up of people affected by TB can be carried out with different formats or typologies. Follow-up is important as it allows us to check the clinical progress of the patient, carry out complementary tests to confirm efficacy, monitor adverse effects and adherence, and motivate people to complete treatment correctly. The current alternatives for monitoring adherence and adverse events are 1) anamnesis during the face-to-face visit of self-administered doses and adverse events, 2) DOT (in health institutions or the community) and control of adverse events, 3) treatment observed through synchronous or asynchronous video with the possibility of monitoring adverse events. DOTs are expensive, involve a large logistical deployment, and are not available in all healthcare settings. Based on the studies analysed, VOT and DOT afford similar results in terms of adherence and final treatment outcomes. VOT could be an alternative in our setting, furthermore, it is more economical and time-saving for health professionals and people affected by TB. Self-administered treatment and face-to-face follow-up in clinics also obtain similar adherence and cure results; however, a careful evaluation of poor adherence factors should be conducted as not all people affected by TB are candidates for the same follow-up formats. People with risk factors for poor adherence or with treatment regimens that include injectable drugs should undergo a DOT.

The main limitations of these studies reside in the heterogeneity of the populations and the absence of experience with people affected by MDR-TB. The reviewed studies quantified adherence (number of doses taken) but the vast majority could not demonstrate an improvement in the final outcome or adverse effects. Another point to consider is the low statistical power of the studies and the lack of recent studies. Given the nature of the intervention, all studies were at risk of observational and measurement bias as they could not be blinded. However, the effect of telematic monitoring is not inferior, and in some cases superior, to DOT. Generally, telematic follow-up is better accepted by people affected by TB, and is less expensive than a directly observed system, so it could be a high-value and cost-effective alternative in TB programs. In addition, technological advances have permitted a large part of the population with TB in our setting to have technological devices that allow the use of this type of telematic monitoring.

PICO Question 14. Should contacts of people affected by RR/MDR/preXDR/XDR-TB be offered treatment for latent tuberculosis infection? Which drug or combinations of drugs safely reduce the development of active TB in high-risk contacts of people affected by RR/MDR/preXDR/XDR-TB?

Recommendation: In people who have had contact with a person with RR/MDR-TB and are at risk of progression to active TB, we recommend the administration of an effective and safe strategy to reduce the risk of progression to RR/MDR-TB, such as a fluoroquinolone (levofloxacin or moxifloxacin) for six months

if the index case is affected by TB that is susceptible to fluoroquinolones (conditional recommendation, low quality of evidence). If the index case is affected by TB that is resistant to fluoroquinolones, treatment with delamanid during six months could be preferentially considered, alternatively, treatment with linezolid could be implemented (conditional recommendation, very low quality of evidence). Another alternative would be to design a personalised treatment based on the DST of the index case (conditional recommendation, very low quality of evidence).

If treatment is not administered to people at risk of progression, we recommend regular close monitoring for at least two years to detect early TB (conditional recommendation, very low quality of evidence).

Summary of findings: There are no quality data to support a high-quality recommendation. The available data originate from retrospective or prospective studies with interventions without a control group.

A cross-sectional study evaluating children under five years of age who were contacts of people affected by MDR-TB showed that 44.7% of children had latent tuberculosis infection (LTI). Of these, 14.7% had prevalent TB.(248) Similar results were published in studies from other parts of the world.(249–260) All these studies showed that, in the paediatric population, the risk of LTI, or prevalent TB, after family contact is very high and would justify the development of strategies aimed at slowing the progression to TB after a risk contact. Children younger than five years of age, malnourished, without BCG vaccination, and infected with HIV, are at increased risk of having prevalent TB. In addition, the risk of LTI or prevalent TB is similar to that found in contacts of index cases of MS-TB.(261–265)

Prospective studies evaluating incident TB and the effect of receiving prophylactic treatment, or LTI treatment, generally showed a benefit in the group of participants who received preventive treatment. The incident TB in the different studies showed a range of 0-5% after different follow-up times.(252,256,257,263,266–268) In the few studies where preventive treatment was given, the incident cases decreased when compared with no treatment.(269–271). The first studies with regimens based on ofloxacin and pyrazinamide for six months had very high dropout rates.(272,273) The same was true for the combination of levofloxacin and pyrazinamide.(274,275) With the use of other treatments and the optimisation of follow-ups, treatment adherence rates have improved substantially; in some studies it is even beyond 90%.(276,277) The treatments used in the studies analysed varied between personalised treatments based on the DST of the index case, or programmatic treatments for all contacts.(248,251,251,254,276,278–285) When treatments were used for which the index case was resistant, efficacy was drastically reduced, with incident TB rates similar to no treatment.(286,287) None of these treatments, however, are free of toxicity, and in some studies, between 20-30% of participants experienced toxicities that required treatment to be discontinued or modified.(284) The type of toxicity and its frequency depends on the treatment regimen selected. On the other hand, the acceptance of preventive

treatment by guardians of children under 15 years of age is high, between 79-89%.(288,289) The findings described were corroborated by a recent systematic review of the literature and meta-analysis reporting a relative risk of 0.34 (95%CI 0.16-0.72) in those who were contacts of people affected by MDR-TB and received treatment for LTI. In addition, the risk was lower if the treatment was adapted to the resistance profile of the index case. The discontinuation rate was 6.5%, and 22.9% of people suffered adverse events.(290) Theoretical cost-effectiveness models showed that treatment with fluoroquinolones is cost-effective, especially in children under five years of age or people living with HIV infection.(291,292) Recently, the WHO published a rapid communication recommending treatment of LTI. A six-month regimen with levofloxacin is recommended for the treatment of LTI in contacts of people affected by RR/MDR-TB.(293)

Rationale: Based on the high percentage of risk contacts who develop the disease over the years following contact, we believe that the administration of a strategy that decreases the risk of developing TB is warranted. It had been argued that resistant strains of *M. tuberculosis* might be less virulent or contagious than wild-type strains because of the toll on fitness derived from this new evolutionary advantage. However, studies showed that the percentages of infected contacts, prevalent TB, and the development of tuberculous disease after contact are maintained and are similar to those of susceptible TB. The acquisition of infection and risk of developing the disease are based on well-known factors, such as the bacillary load of the index case, the type and duration of contact, and factors regarding the contact such as age, immune system competence, and nutritional status, among others.

It is important to emphasise that the quality of the evidence is very low and that there are no quality trials to support the recommendation. Furthermore, there are inconsistencies between some studies and a lack of precision. However, the experience derived from susceptible TB and the impact of the treatment of LTI make the strategy of studying and treating risk contacts highly advisable, especially in children and immunocompromised people, where the acceptability and understanding of the treatment are high.

Currently, there are no randomised clinical trials comparing drugs or combinations of drugs for preventing the progression to TB in people infected after exposure to an MTB resistant to rifampicin and isoniazid. At least three clinical trials (TB-CHAMP, VQUIN, and PHOENIX) are now in the home stretch, and we are likely to have results in the coming months.

Some studies have analysed treatment with different drugs or combinations of drugs in patients with LTI, presumably due to the MDR-TB strain, in a non-randomised manner. Encouraging results were presented, although there was a high degree of heterogeneity and sometimes inconsistency in these results. The studies evaluated various treatment regimens, including quinolones (levofloxacin, moxifloxacin, ofloxacin, or ciprofloxacin) associated or not with ethambutol, ethionamide, or pyrazinamide; isoniazid (at different

doses) alone or in combination with ethambutol, ethionamide, pyrazinamide, or quinolone; delamanid; and linezolid in combination with cycloserine. Our recommendation is based on the opinion of the expert panel and the extrapolation, on the one hand, of data on the sterilising potential of drugs, and on the other hand, of information on the combination and duration of existing treatment regimens for LTI used in people exposed to a susceptible MTB. The proposed guidelines are not based on solid evidence and are likely, therefore, to vary in the coming months. Children under 15 years of age, and especially those under five years of age, as well as the immunocompromised population, have an increased risk of progression to TB after close contact, therefore, the intervention would be especially indicated in this population. The choice of treatment should be determined by the resistance profile of the index case, drug interactions, allergies, and risk of serious adverse events. If the index case is susceptible to fluoroquinolones, preventive treatment with fluoroquinolones (levofloxacin or moxifloxacin) for six months, whether supplemented with ethambutol or not, could be an effective and safe treatment. In the case of fluoroquinolone resistance, one option may be delamanid supplemented or not with reduced doses of linezolid for six months, or linezolid for six months. There is no evidence to support this suggestion, nevertheless, the expert panel believes that the benefit of preventing the development of TB outweighs the risks associated with administering treatment, especially in people at high risk of developing the disease.

If treatment is not administered to people at risk of progression, we recommend regular close monitoring for at least two years in order to detect incipient TB early and, therefore, have a greater chance of cure, a lower risk of long-term sequelae, and less dissemination in the community.

CONCLUSIONS

The CPG on DR-TB management is the joint effort of professionals with extensive experience in TB management. These guidelines present the recommendations agreed upon by SEIMC and SEPAR. The content of this guideline was drawn up by and correspond to both scientific societies. This guideline updates the 2017 and 2020 SEPAR guidelines. The purpose of these recommendations is to share knowledge with all professionals and facilitate the correct management of this disease. Due to the constant evolution of DR-TB treatment, the current guidelines will be reviewed periodically, particularly when relevant and clinically interesting developments arise.

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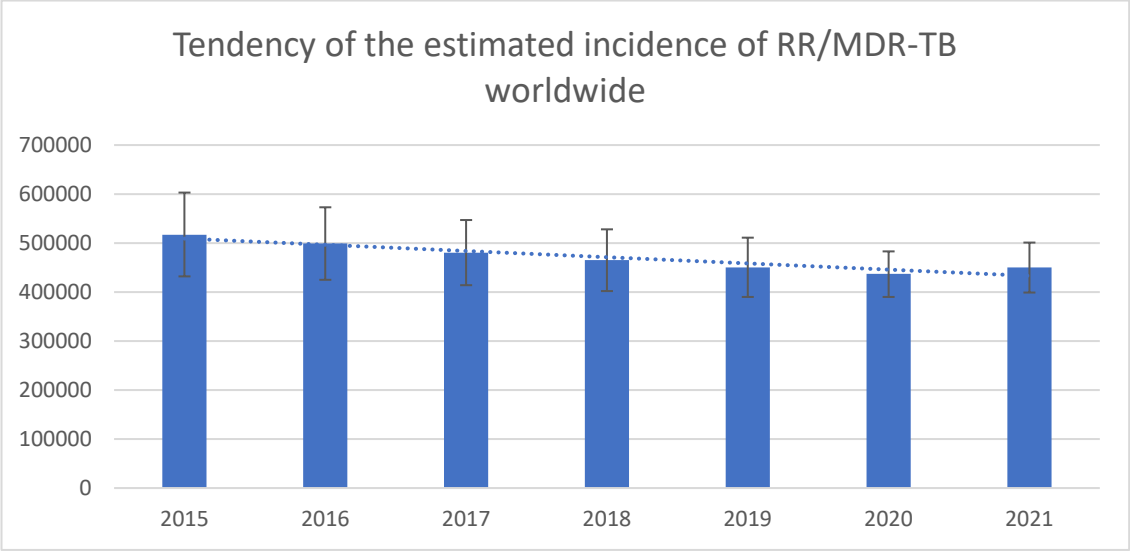
FIGURES & TABLES

Figure 1. The absolute number and confidence levels of people diagnosed with rifampicin-resistant tuberculosis worldwide.



Source: Global Tuberculosis Reports from World Health Organization.

Table 1. Epidemiology of drug-resistant tuberculosis in Spain distributed annually between 2019-2022. Monitoring indicators of the Plan for the Prevention and Control of tuberculosis in Spain.

Year	TB Cases Reported	MDR-TB Cases Reported	Percentage of MDR-TB cases	MDR-TB Case Notification Rate (per 100000 population)
2019	4421	39	0.9	0.074
2020	3681	29	0.8	0.06
2021	3603	58	1.6	0.12
2022	3675	33	0.9	0.38

MDR: multidrug-resistant; TB: tuberculosis

Table 2. History of tuberculosis resistance categories

Reference	Year	MDR	pre-XDR	XDR
Fox (294)	1957	Resistance to at least 2 out of 3: streptomycin, isoniazid, PAS.		
Toman K (295)	1979	Resistance to at least streptomycin and isoniazid.		
WHO (296)	1996	Resistance to at least isoniazid and rifampicin.		
WHO, CDC (297)	2006, March	Resistance to at least isoniazid and rifampicin.		Resistance to isoniazid, rifampicin and 3 classes of the 6 second-line drugs (aminoglycosides, polypeptides (capreomycin), fluoroquinolones, thionamides, cycloserine, and PAS)
WHO (298)	2006, October	Resistance to at least isoniazid and rifampicin.		Resistance to isoniazid and rifampicin, with added resistance to fluoroquinolones and at least one second-line injectable (amikacin, kanamycin, or capreomycin).
WHO (299)	2021	Resistance to isoniazid and rifampicin.	Fulfils the definition of RR/MDR plus resistance to a fluoroquinolone.	Fulfils the definition of RR/MDR being more resistant to fluoroquinolones and resistance to at least one other WHO group A drug (bedaquiline or linezolid).
CDC (300)	2022	Resistance to isoniazid and rifampicin.	Resistance to isoniazid, rifampicin, and a fluoroquinolone.	Resistance to isoniazid, rifampicin, a fluoroquinolone, and a second-line injectable; or resistant to isoniazid, rifampicin, a fluoroquinolone, and bedaquiline or linezolid

CDC: *Center for Disease Control*; MDR, multidrug-resistant; PAS, para-aminosalicylic acid; ; XDR, extensively drug-resistant; preXDR TB, TB caused by a strain of *M. tuberculosis* resistant to isoniazid, rifampicin, and a fluoroquinolone; WHO, World Health Organization.

Table 3. WHO Classification of the drugs for formulating treatment for people with tuberculosis caused by a strain of *M. tuberculosis* resistant to some drugs used to treat drug-susceptible tuberculosis.

GROUP	DRUG
A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
B	Clofazimine
	Cycloserine or terizidone
C	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem-cilastatin or meropenem
	Amikacin or streptomycin
	Ethionamide or prothionamide
	Para-aminosalicylic acid (PAS)

Table 4. Expert panel classification of drugs for formulating treatment for people affected with tuberculosis caused by a strain of *M. tuberculosis* resistant to some drugs used to treat drug-susceptible tuberculosis.

GROUP		DRUGS
1	Oral drugs shown to be effective in combination and have a low proportion of adverse events that require treatment modification. Use preferably in the order proposed.	Levofloxacin / Moxifloxacin Bedaquiline Delamanid/ Pretomanid Linezolid / Tedizolid$ Clofazimine
2	Drugs shown to be effective in combination and that either must be administered parenterally, or have an intermediate/high proportion of adverse events that require treatment modification. Use preferably in the order proposed.	Imipenem / Meropenem (+Clavulanic acid) Amikacin Cycloserine / Terizidone
3	Oral drugs with limited efficacy and with a low/moderate proportion of adverse events requiring treatment modification.	Pyrazinamide Isoniazid at high doses Ethambutol
4	Oral drugs that could be effective, but with insufficient evidence and with a low proportion of adverse events that require treatment modification.	Faropenem
5	Intravenous drugs that could be effective but lack evidence, and with insufficient reporting of adverse events in extended treatments.	Ceftazidime avibactam

$In those who do not tolerate linezolid, or it cannot be administered due to interactions, tedizolid could be an alternative.

Table 5. Recommended doses of drugs used in the treatment tuberculosis caused by a strain of M. tuberculosis resistant to some drugs used to treat drug-susceptible tuberculosis.

Drug	**Route**	**Daily Dose**
Levofloxacin	Oral, IV	15-20 mg/kg/day, once daily (750-1500 mg/day)
Moxifloxacin	Oral, IV	7.5-10 mg/kg/day, once daily Usual dose: 400 mg Max dose: 600-800 mg/day, especially when combined with an enzyme inducer (e.g., rifampicin)
Bedaquiline	Oral	400 mg/day 14 days, then 200 mg 3 times a week Alternative, 200 mg/day 8 weeks, followed by 100 mg/day 18 weeks
Pretomanid	Oral	200 mg/day
Delamanid	Oral	>30-50 kg: 50 mg/12 h >50 kg: 100 mg/12 h
Linezolid	Oral, IV	600 (300-1200) mg/day*
Tedizolid	Oral, IV	200 mg/day
Clofazimine	Oral	100-200 mg/day
Imipenem-cilastatin	IV	1 g 3-4 times/day or 1-1.5 g/12 h
Meropenem	IV	1 g 3-4 times/day or 1.5-2 g/12 h
Clavulanic acid (+ carbapenem)	Oral, IV	125-250 mg 2-3 times/day (administer 30 min before carbapenem drugs)
Amikacin	IM, IV	15-20 mg/kg Max: 1000 mg
Cycloserine / Terizidone	Oral	15 mg/kg/day, once daily (250-1000 mg/day)
Pyrazinamide	Oral	20 - 30 mg/kg If < 50 kg: max. 1.5 g; 50 – 75 kg: max. 2 g; > 75 kg: max. 2.5 g
Isoniazid (high doses)	Oral, IV, IM	15-20 mg/kg/day
Ethambutol	Oral, IV	15-25 mg/kg/day Max. 2 g/day
Faropenem	Oral, IV	200-300 mg/8 h
Ceftazidime-avibactam	IV	2/0.5 g/8 h

IV: intravenous; IM: intramuscular; Kg: Kilograms; g: grams; mg, milligrams; DR-TB: Drug-resistant tuberculosis; h: hours.

*We recommend the use of a linezolid dose of 600 mg per day (better efficacy-safety ratio). Higher doses have a higher bactericidal potential but also a high rate of adverse events that require treatment discontinuation. Doses of 300 mg per day have been shown to be effective with a good safety profile but the available evidence is inferior.

Table 6. Genes with mutations associated with resistance. Source: "MTBC WHO 2023 Mutation Catalogue" (only group 1 and group 2 mutations are shown)

DRUG	GENE	
	Group 1	Group 2
Isoniazid	***inhA*** *(Low-Level Resistance),* ***katG*** *(High-Level Resistance),* *fabG1, furA, ahpC*	*dnaA, Rv0010c, mshA, hadA, ndh, glpK*
Rifampicin	***rpoB****	*nusG, rpoC, lpqB, mtrB, mtrA rpoA, glpK*
Ethambutol	***embB,*** *embA, afta, embC, ubiA*	*embR, Rv2477c, Rv2752c, glpK, aftB*
Pyrazinamide	*pncA, clpC1, panD*	*Rv1258c, rpsA, sigE, PPE35, Rv3236c*
Fluoroquinolones**	***gyrA, gyrB***	*Rv1129c, Rv2477c, Rv2752c, glpK*
Bedaquiline***	*mmpL5, mmpS5, Rv0678, pepQ, atpE*	*lpqB, mtrB, mtrA*
Linezolid	*rplC, rrl*	*tsnR*
Clofazimine	*mmpL5, mmpS5, pepQ*	*fgd1, fbiC, Rv2983, fbiA, fbiB*
Delamanid	*ddn, fgd1, fbiC, fbiA, fbiB*	*ndh*
Amikacin	***rrs****, eis, whiB7*	*ccsA, bacA, Rv2477c, whiB6*
Streptomycin	*rpsL, rrs, whiB7, gid*	*bacA, Rv2477c, glpK*
Ethionamide****	*inhA****, fabG1****, ethA, mshA,*	*Rv0565c, ndh, Rv3083, ethR*
Kanamycin	*rrs, eis, whiB7*	*ccsA, bacA, Rv2477c, whiB6*
Capreomycin	*rrs, tlyA*	*ccsA, rrl, bacA, Rv2680, Rv2681, whiB6*

Genes in **bold** have more evidence and their correlation with phenotypic resistance is usually greater than 80%.

Mutations are stratified into five groups according to the amount and quality of evidence available to support a statistically significant association. Group 1: associated with resistance. Group 2: associated with interim resistance. Group 3: Uncertain meaning. Group 4: Not associated with interim-resistance. Group 5: not associated with resistance. This table shows that Group 1 and Group 2 variants should be interpreted as clinically relevant markers of phenotypic resistance.

*Resistance to rifampicin is mediated by the *rpoB* gene in >95% of cases and its presence is associated with isoniazid resistance. Therefore, it is considered an indirect marker of MDR-TB.

** Mutations in *gyrA* and *gyrB* confer cross-resistance to levofloxacin and moxifloxacin. *GyrA* mutations at positions Gly88Cys, Asp94Asn, Asp94Gly, Asp94His, and Asp94Tyr confer high-level resistance to moxifloxacin. All other mutations in *gyrA* and *gyrB* confer low-level resistance to moxifloxacin.

*** Mutations in *Rv0678* and *pepQ* confer cross-resistance to bedaquiline and clofazimine.

**** Mutations in *inhA* and *fabG1* confer cross-resistance to ethionamide and isoniazid.

Table 7. Monitoring proposal for people affected by RR/MDR-TB under treatment.

Procedures‡	Baseline study	Months of treatment					
		1	2	3	4	5	6*
Complete Clinical Evaluation	X	X	X	X	X	X	X
Weight Management	X	X	X	X	X	X	X
Visual acuity and colour vision assessment**	X	X	X	X	X	X	X
Evaluation of possible symptoms/signs of peripheral neuropathy$	X	X	X	X	X	X	X
Hemogram	X	X	X	X			X
Fasting blood glucose	X	X	X	X	X	X	X
Creatinine and ionogram	X	X	X	X	X	X	X
Liver Function Tests	X	X	X	X	X	X	X
Thyroid hormones$$	X		X		X		X
HIV and Viral Hepatitis Testing	X						
Pregnancy test (women of childbearing age).	X						
Chest X-ray	X			X			X
Nucleic acid amplification test (MTBC identification and genotypic resistance study)	X						
Sputum smear†	X	X	X	X	X	X	X
Sputum culture	X	X	X	X	X	X	X
Drug Susceptibility Testing††	X						
Electrocardiogram¥	X	X	X	X	X	X	X

MTBC; *Mycobacterium tuberculosis* complex; HIV: Human immunodeficiency virus.

‡ In people affected by extrapulmonary TB, microbiological follow-up should be determined according to clinical criteria. The frequency of all procedures can be customised according to medical criteria.
* For treatments longer than six months, we recommend monthly evaluations starting at the sixth month.
** Special attention should be paid to people treated with ethambutol or linezolid.
$ Special care in people treated with linezolid.
$$ Only if treated with ethionamide or prothionamide.
† We recommend a smear test every 1-2 weeks until negativisation to guide isolation indications. Subsequently, we recommend monthly check-ups.
†† In case of persistence of a positive smear test two months after the start of treatment, consider repeating the drug susceptibility test. In case of sustained positivity of the culture, after its negativisation, consider repeating the drug susceptibility test.
An ECG should be performed 15 days after starting treatment in people with drugs that prolong QT (bedaquiline, fluoroquinolones, delamanid /pretomanid, clofazimine), then we recommend ECG one month after the start of treatment, and monthly thereafter.

Table 8. Most common adverse events of drugs used in the treatment of multidrug-resistant tuberculosis.

Drug	Adverse Events	Management of Adverse Events
Bedaquiline	QTc Prolongation corrected by the Fridericia formula 2.5-24%, Hepatotoxicity 16%, and diarrhoea and nausea (9% each)	Monitoring with baseline ECG, 2 weeks, and monthly ECG. Regular monitoring of basic biochemistry including kidney and liver function.
Linezolid	Toxicity is dose-dependent. At the 1200 mg/day dose, these adverse effects are greater, reaching 80% for polyneuropathy and 49% for anaemia. The 600 mg/day dose is associated with anaemia in 30-40% of cases, thrombocytopenia in 14%-30%, and neutropenia in 1-10% of participants. Peripheral neuropathy at this dose reaches up to 30% in some studies and optic neuropathy 2.5%	Haematology (myelosuppression): complete blood counts every 2 to 4 weeks. Systematically evaluate symptoms and clinical signs consistent with peripheral neuropathy. There is no clear recommendation for the routine use of EMG.
Levofloxacin and Moxifloxacin	Arthralgia 11%, tendinopathy 1% (increases in the elderly with renal insufficiency or if concomitant use with steroids) QT prolongation 1%	Monitoring with baseline ECG, 2 weeks, and monthly ECG. Signs of tendonitis should be checked at each visit. Patients should be informed about the risk of tendon rupture. Caution in patients with aortic aneurysms, monitoring is not currently recommended.
Clofazimine	Skin pigmentation alterations 14%, gastrointestinal intolerance (1-47%)	Prolonged QT interval monitoring if used with other drugs with potential cardiotoxicity. Skin pigmentation is common but does not involve interruption of treatment and is reversible
Cycloserine Terizidone	Psychiatric disorders 1%, skin reactions	Monitoring of symptoms related to psychiatric disorders and CNS toxicity, including seizures, depression, psychosis, and suicidal ideation, is recommended
Delamanid	Gastrointestinal adverse effects 27%, hypomagnesemia 6%, and QT prolongation 5%	Monitoring with baseline ECG, 2 weeks, and monthly ECG. Monthly ionogram control.
Injectable Aminoglycosides	Nephrotoxicity 7.4%, ear disturbances 3-15%, hydroelectrolyte disturbance 19%	Monthly renal function check and audiometry, although this should be adapted to the baseline risk.
Ethionamide Prothionamide	Gastrointestinal intolerance, hepatotoxicity, hypothyroidism, neurological toxicity	Monitoring with ionogram, renal function, and thyroid hormones

CNS: Central Nervious System; ECG: Electrocardiogram; EMG: Electromyography