Canadian Journal of Respiratory, Critical Care, and Sleep Medicine

Revue canadienne des soins respiratoires et critiques et de la médecine du sommeil

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ucts20

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To cite this article: James C. Johnston, Ryan Cooper & Dick Menzies (2022) Chapter 5: Treatment of tuberculosis disease, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6:sup1, 66-76, DOI: 10.1080/24745332.2022.2036504

To link to this article: https://doi.org/10.1080/24745332.2022.2036504

Published online: 25 Mar 2022.

CANADIAN JOURNAL OF RESPIRATORY, CRITICAL CARE, AND SLEEP MEDICINE
2022, VOL. 6, NO. S1, 66–76
https://doi.org/10.1080/24745332.2022.2036504

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CANADIAN TUBERCULOSIS STANDARDS—8TH EDITION

Chapter 5: Treatment of tuberculosis disease

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KEY POINTS

- Treatment of drug-susceptible tuberculosis (TB) disease should include 2 effective drugs at all times, and at least 3 effective drugs in the intensive phase (ie, first 2 months of therapy).
- Most patients with TB disease should be initiated on a regimen of isoniazid, rifampin, pyrazinamide and ethambutol until results of genotypic or phenotypic drug susceptibility are available. Therapy should be given daily for the first 2 months, then daily when feasible.
- Meaningful and culturally appropriate patient engagement, education and support are critical for achieving successful TB treatment.
- TB clinicians and programs should provide comprehensive, patient-centred care that uses incentives and enablers to ensure optimal treatment adherence.
- All jurisdictions should have capacity to provide daily, in-person, supportive care for people with TB. Support should be tailored to individual needs and may include directly observed therapy.
- Regardless of insurance coverage or immigration documentation, people with active TB should be provided with TB medications and appropriate treatment support free of charge.
- People at high risk for TB recurrence should be monitored for signs/symptoms of TB recurrence during the first 12-24 months post-therapy.
- Pulmonary function testing should be performed in all people completing therapy for pulmonary TB, given the high incidence of respiratory disease in people with TB.
- TB programs should ensure that people with TB are linked to a stable primary care provider before the end of TB treatment.

1. Fundamentals of treatment of TB disease

1.1. Objectives of treatment of TB disease

There are four objectives in treating TB disease:

1. Achieving rapid killing of TB bacilli to produce rapid improvement in clinical condition, prevent TB-related morbidity and death and prevent further transmission;
2. preventing the emergence or worsening of drug resistance;
3. preventing relapse of disease and achieving long-lasting cure; and
4. optimizing long-term health by ensuring linkage to care for treatment of co-morbidities, and helping mitigate social and economic vulnerability.

These objectives should be addressed through comprehensive, patient-centred care and targeted drug therapy.

1.2. Principles of drug therapy in TB disease

1.2.1. First-line drug therapy

Drug therapy for TB disease is given in 2 phases: the *intensive phase* and *continuation phase*. In the intensive phase, 3 or 4 effective drugs are used in combination to rapidly kill TB organisms and prevent the selection of drug-resistant organisms. In treatment of drug-susceptible disease, the intensive phase should last 2 months; during this time, TB drugs should be dosed daily (Table 1).[1,2] In the continuation phase, a minimum of 2 effective drugs are used, and treatment duration varies depending on the drug regimen, adherence and risk of relapse. In this second phase, there is an option for intermittent (thrice weekly) therapy in select circumstances under directly observed therapy, or DOT (defined here as the direct observation of a person ingesting TB medications) (Table 1), but daily dosing is preferred when possible.[2–4]

1.2.2. Rationale for multidrug therapy

Patients with TB disease are infected with a large number of TB bacilli, with up to 10^{10} bacilli in people with cavitary pulmonary disease.[5,6] Mutations conferring resistance to any particular drug appear to occur spontaneously at a very low but constant rate. The rate of spontaneous resistance to isoniazid (INH) and rifampin is estimated to be 4×10^{-6} and 3×10^{-8}, respectively, with the rate of spontaneous mutation to both drugs estimated to be as low as 1×10^{-15}.[6,7] In people with drug-susceptible TB disease, particularly those with a high bacillary burden, the presence of small numbers of TB bacilli with spontaneously occurring resistance to

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Table 1. Recommended drug doses for daily and intermittent therapy in adolescents and adults.

	Daily		Thrice weekly	
	By weight	Maximum[a]	By weight	Maximum[a]
Isoniazid	5mg/kg	300 mg	15 mg/kg	900mg
Rifampin	10mg/kg	no max[b]	10 mg/kg	no max[b]
Pyrazinamide	25mg/kg	2000 mg	30-40 mg/kg	4000 mg
Ethambutol	15mg/kg	1600 mg	25-40 mg/kg	2400 mg

Abbreviations: TB, tuberculosis.
[a]Dosing based on body weight for people with body mass index (BMI) 18.5-30. In people with BMI >30 or <18.5 consider dosing based on ideal body weight and consider therapeutic drug monitoring if available.[1]
[b]This represents a change from previous Canadian TB Standard dosing recommendations, based on an evidence review performed by the WHO Pharmacokinetics and Pharmacodynamics Task Force.[2,27]

each first line drug is likely, while simultaneous resistance to 2 drugs is less likely and 3 drugs is highly unlikely.[5,6]

Based on the aforementioned reasoning and extensive randomized controlled trial experience, it is recommended that at least 2 effective drugs be used at all times in treatment of TB disease.[6,8] A drug is considered effective when susceptibility of the Mycobacterium tuberculosis (*M. tuberculosis*) strain has been confirmed by drug susceptibility testing (DST). If DST results are pending, then more drugs are required to ensure receipt of at least 2 drugs that are likely to be effective. This reinforces the importance of microbiologic confirmation of TB disease and the use of DST to guide treatment.

1.3. Drugs used in First-Line therapy

Isoniazid, rifampin, pyrazinamide and ethambutol are classified as first-line drugs in Canada; these drugs are effective when used in combination, can be taken orally and have well-known safety profiles[9] with extensive randomized controlled trial data to support their use.[6,8]

Isoniazid (INH) is a cornerstone of modern TB therapy, with powerful early bactericidal activity, meaning that it is highly effective in rapid killing of bacteria in the first few days of therapy.[10] This is an important drug in achieving the aforementioned Objective 1. It is also effective in preventing drug resistance, but its ability to prevent relapse is inferior to rifampin. INH is commonly associated with asymptomatic increases in hepatic aminotransferases and bilirubin (10-22%) and associated with clinical hepatitis, but rarely acute hepatic necrosis, which can be fatal.[9] Peripheral neuropathy is a common adverse effect, so pyridoxine is often given to reduce INH-related peripheral neuropathy.[11] Other adverse events include gastrointestinal (GI) symptoms (often associated with hepatitis), rash and neurologic and hematologic adverse events.[9]

Rifampin (RMP) is the most commonly used rifamycin, a class of medications that also includes rifabutin and rifapentine.[12] RMP is the most important first-line TB drug, with good bactericidal activity (Objective 1), prevention of drug resistance (Objective 2) and prevention of relapse (Objective 3). If RMP (or another rifamycin) is not given for the full duration of six months, then therapy should be extended in consultation with a TB expert. If a rifamycin is not given at all, then therapy should be extended to 12-18 months (see Chapter 8: Drug-resistant Tuberculosis). RMP is notable for its frequent drug-drug interactions through induction of the p450 enzyme (CYP3A4) system and p-glycoprotein efflux transporters (see Chapter 10: Treatment of Active Tuberculosis in Special Populations). Common adverse events include orange discolouration of body fluids, rash and urticaria. Less common adverse events include hematologic effects, GI symptoms and hepatotoxicity.[9,13] In June 2017, a World Health Organization (WHO) panel reviewed pharmacokinetic/pharmacodynamics data on RMP, along with the original rationale for the 600 mg dose ceiling, and recommended a dose of 10 mg/kg body weight per day with no ceiling. More recently, RMP has been noted to contain levels of nitrosamine impurities in excess of acceptable limits proposed by the United States Food and Drug Administration and Health Canada.[14] Despite this, RMP continues to be recommended as a first-line drug due to its critical importance in TB treatment and the lack of convincing evidence of harm from the detected nitrosamine levels.

Pyrazinamide (PZA) has significant sterilizing effect and appears to provide most benefit when part of a multidrug regimen in the first 2 months of therapy (Objective 1). PZA offers minimal protection against drug resistance and does not provide benefit (ie, no effect on relapse rates) when used in the continuation phase with isoniazid and rifampin.[15] If PZA is not given for the first 2 months, the total duration of therapy should be at least 9 months. PZA is commonly associated with hepatotoxicity and rash, and less commonly associated with acute gout, GI symptoms and hematologic effects.[9]

Ethambutol (EMB) inhibits growth of *M. tuberculosis*. It is the least effective of the first-line drugs for bactericidal activity (Objective 1) and prevention of relapse (Objective 3), but it is a well-tolerated companion drug that effectively prevents drug resistance (Objective 2). EMB is added to the initial phase of therapy until DST is available. In people with TB that is fully susceptible to all first-line drugs, EMB can be discontinued. If DST is not available and drug-resistant disease is not suspected, EMB should be continued throughout treatment. EMB is associated with optic neuropathy, which presents with decreased visual acuity and/or colour vision changes.[16] Rare adverse effects include rash, hematologic effects, GI upset and neurologic effects.[9]

Pyridoxine (vitamin B6) should routinely be added to INH in people at risk of peripheral neuropathy, including people with diabetes, chronic kidney disease, human immunodeficiency virus (HIV) malnutrition, seizure disorder or

a history of substance misuse, as well as pregnant or breastfeeding women.[11,17] Some clinicians and programs add pyridoxine in all active TB regimens for adults. In people who develop peripheral neuropathy, B6 dose is often escalated to 100 mg daily. At doses exceeding 100 mg daily, however, there is concern over reduced INH efficacy.[11,18]

Fluoroquinolones (moxifloxacin, levofloxacin) are often used as alternative agents when a person has an adverse reaction requiring cessation of a first-line drug.[19,20] Moxifloxacin is also part of the recently reported four-month drug regimen for drug-susceptible TB (discussed in the following section on Standard Regimen) and is a core component of INH-resistant and multidrug-resistant TB regimens.[21] Fluoroquinolones are generally safe and well tolerated. Common adverse events include nausea, headache, diarrhea, insomnia, dizziness and constipation. Less common, but more significant, side effects include tendinopathy, QT prolongation and transaminitis, with severe hepatitis being rare.[22] When starting fluoroquinolones in drug-susceptible TB, ensure that fluoroquinolone susceptibility testing is performed, as isolated fluoroquinolone resistance can be present in otherwise-drug-susceptible disease.

Rifabutin has similar activity to RMP *in vitro* against *M. tuberculosis*, but causes much less upregulation of the cytochrome p450 system, resulting in fewer drug-drug interactions. Rifabutin is commonly used as a substitute for RMP in people living with HIV and solid organ transplant recipients, and when multiple drug interactions exist.[23] The side-effect profile is similar to RMP, but hematological toxicity (particularly neutropenia) and uveitis are more common with this drug.

Rifapentine has a longer half-life than RMP and is a component of the recently reported 4-month regimen.[21] The side-effect profile of rifapentine is similar to RMP, except that hypersensitivity reactions appear to be more common.[24] Recently, rifapentine has been noted to contain levels of nitrosamine impurities in excess of acceptable intake limits outlined by the United States Food and Drug Administration and Health Canada.[14] As of July 2021, rifapentine is included on Canada's List of Access to Drugs in Exceptional Circumstances to address urgent public health needs not managed by other therapies.[25]

2. Therapeutic regimens for drug susceptible disease

2.1. Standard regimen

The standard six-month TB treatment regimen described in Table 2 was established through a series of clinical trials from the 1960s-1980s.[6,8] Extensive clinical trial data support this regimen and TB programs have considerable experience in using and adapting this regimen in populations with TB disease. For this reason, it remains the recommended TB regimen for TB disease susceptible to first-line medications.[2,26]

Recently, a new four-month regimen composed of daily rifapentine, INH, PZA and moxifloxacin was compared to the standard 6-month regimen in a randomized, multinational phase 3 trial in people with pulmonary TB susceptible to INH, RMP and fluoroquinolones.[21] The 4-month regimen was statistically non-inferior to the standard six-month regimen, but rates of failure and relapse were higher with this regimen. Notably, in per protocol 95% analysis (which removed participants who did not complete 95% of treatment doses unless the reasons for incomplete treatment were death or treatment failure), the rate of unfavourable outcome was 5.8% in participants taking the four-month regimen versus 2.7% in participants taking the control (standard 6-month) regimen. Given these findings, concerns have been raised by the WHO regarding implementation in programmatic settings.[26] Nonetheless, the WHO Global TB Programme Guidelines Development Group reviewed the study data for the four-month regimen, and supported its use as a possible alternative to the standard 6-month regimen.[26] More outcome data, including data from programmatic settings, would be required, however, to recommend this regimen routinely.

Table 2. Recommended treatment regimens for known or suspected drug-susceptible pulmonary TB.

	Initial phase (first two months)	Continuation phase
Suspected drug susceptible[a]		
Preferred regimen	**INH**[b] **RMP PZA EMB**[c] **daily**[d]	**INH RMP EMB daily for 4 months**
Alternative regimen[e]	INH RMP EMB daily	INH RMP EMB daily for 7 months
Alternative regimen[f]	INH RMP PZA EMB daily	INH RMP EMB 3x per week[g] for 4 months
Alternative regimen[f]	INH RMP EMB daily	INH RMP EMB 3x per week[g] for 7 months
Known drug susceptible		
Preferred regimen	**INH RMP PZA daily**[d]	**INH RMP daily for 4 months**
Alternative regimen[e]	INH RMP EMB daily	INH RMP daily for 7 months
Alternative regimen[f]	INH RMP PZA daily	INH RMP 3x per week[g] for 4 months
Alternative regimen[e,f]	INH RMP EMB daily	INH RMP 3x per week[g] for 7 months

Abbreviations: TB, tuberculosis; INH, isoniazid; RMP, rifampin; PZA, pyrazinamide; EMB, ethambutol; DOT, directly observed therapy.
[a]INH: isoniazid, RMP: rifampin, PZA: pyrazinamide, EMB: ethambutol.
[b]No known risk factors for drug resistance and culture pending or culture not performed.
[c]Add Pyridoxine 25-50mg/day for all people taking isoniazid at risk of peripheral neuropathy.
[d]In both four-drug regimens here, EMB can be discontinued if strain is confirmed drug susceptible on culture.
[e]Daily defined as 7 days/week or minimum 5 days/week with DOT.
[f]For use when PZA is not indicated or two months of PZA therapy is not completed.
[g]DOT required with all intermittent regimens.

Recommendation

- **We strongly recommend that standard therapy for patients with drug-sensitive pulmonary TB disease or expected drug-sensitive pulmonary TB (with pending drug susceptibility testing results) include isoniazid, rifampin, pyrazinamide and ethambutol for the first 2 months followed by isoniazid and rifampin for 4 more months** (*good evidence*).

2.2. Prolonging the continuation phase

An individual-patient-data meta-analysis of randomized controlled trials in people with drug-susceptible pulmonary TB on standard first-line therapy reported a TB relapse rate of 5.6%.[28] Presence of cavitary disease on baseline x-ray *and* smear or culture positivity at 2 months increased the relapse rate to >10%. This is consistent with previous studies demonstrating an increased risk of relapse in people with extensive disease or cavitary disease and persistent sputum positivity at 2 months.[28–30] In a separate meta-analysis, the relapse rate in people receiving RMP-containing regimens for 8 months or more was <1%.[4] Despite the lack of direct randomized controlled trial data to support extension of therapy, we believe that extension of therapy is warranted in this population. Other factors to consider when deciding to prolong therapy include HIV status, diabetes mellitus, medical immune suppression, male sex, active smoking history and being <90% below ideal body weight (see Chapter 10: Treatment of Active Tuberculosis in Special Populations).[1]

Recommendation

- **We conditionally recommend, in people with drug-susceptible pulmonary TB and risk factors for relapse (i.e., extensive disease OR baseline cavitary disease on x-ray *and* smear or culture positive sputum at two months), extension of the continuation phase to seven months for a total of nine months of TB drug therapy** (*poor evidence*)**.**

2.3. Intermittent therapy

Intermittent therapy (ie, regimens that include doses taken 3 times per week) should only be used in combination with DOT.[1,2] If therapy is self-administered, intermittent therapy should not be used, and drugs should be administered daily. Findings from a recent systematic review and meta-analysis of randomized controlled trials of people receiving standard first-line therapy demonstrated higher rates of failure, relapse and acquired drug resistance in people taking medications thrice weekly throughout therapy, including during the intensive phase.[3] For intermittent therapy in the continuation phase, twice-weekly therapy was associated with higher rates of failure and relapse. Thrice-weekly intermittent therapy in the continuation phase was associated with a non-significant increase in relapse in pooled analysis, which was not demonstrated in the meta-regression results.[3]

Recommendations

- **We strongly recommend *against* rifampin-containing regimens given thrice weekly throughout therapy, as they are associated with higher rates of failure, relapse and acquired drug resistance** (*good evidence*).
- **We strongly recommend *against* rifampin-containing regimens given daily in the intensive phase then twice weekly in the continuation phase, as they are associated with higher rates of failure and likely relapse** (*good evidence*).
- **We conditionally recommend that thrice-weekly therapy be used in the continuation phase if daily therapy is not feasible, and the person is not living with HIV. Directly observed therapy must be used with this regimen and it may be associated with higher rates of relapse** (*poor evidence*).

2.4. Fixed-dose combination

Fixed-dose combination (FDC) tablets containing 2 or more first-line drugs have been on the WHO essential medication list for more than 30 years, and the WHO continues to recommend their use. In theory, these formulations should prevent monotherapy and reduce the pill burden of TB therapy. Unfortunately, however, 2 systematic reviews from 2013 and 2016 that pooled data from 15 and 13 randomized controlled trials respectively, demonstrated a trend toward higher rates of relapse in people receiving FDC tablets compared with single-drug formulations. The 2013 systematic review and meta-analysis also demonstrated a trend toward higher risk of failure or relapse in people taking FDC tablets, and demonstrated no benefit on acquired drug resistance, 2-month culture conversion, adverse drug reactions, adherence rates or patient satisfaction.[31,32]

Recommendation

- **We strongly recommend against the routine use of fixed dose combination tablets in adults** (*good evidence*).

2.5. Interactions of TB medications with other drugs

Significant interactions may occur between TB medications and other medications (see Chapter 10: Treatment of Active Tuberculosis in Special Populations for information on common drug-drug interactions in TB treatment). The most important TB drug for interactions with other medications is RMP. Most drug interactions can be managed by adjusting the dose of the concomitant medication, based on serum drug concentrations (eg, phenytoin), or by monitoring clinical effect (eg, INR for warfarin) or by substituting drugs (eg, anti-retroviral regimens). It is important to monitor these interactions early in therapy (ie, within 1-to-2 weeks of starting RMP). In some patients, the drug interactions are not manageable and could result in serious adverse consequences (eg, RMP in transplant recipients). It is also important to note that drug-drug interactions will cease within about 2 weeks after RMP is stopped, leading to potential adverse

consequences if dosing of other medications is not reassessed (eg, increased clinical effect of methadone or warfarin after withdrawal of RMP).

2.6. Treatment intensification strategies

Some clinicians add or substitute a fluoroquinolone during the intensive phase in people with extensive disease, in an effort to improve treatment response or enhance sputum clearance.[20] This practice may result in more rapid sputum clearance but not does appear to improve end-of-treatment outcomes and may be associated with a higher rate of adverse events.[19,20] In addition, high-dose, RMP-based regimens are often used in people with extensive or disseminated TB disease. There is no evidence to support improved long-term clinical outcomes with this strategy.[33]

Recommendation

- **We conditionally recommend *against* routine treatment intensification with fluoroquinolones or high-dose rifampin in people with extensive or disseminated TB** (*poor evidence*).

2.7. Adjunctive use of corticosteroids

Before using adjunctive corticosteroids in TB therapy, we recommend consulting with a TB expert. For use of corticosteroids in TB meningitis and TB pericarditis, see Chapter 7: Extra-pulmonary Tuberculosis. For use of steroids in people with HIV, see Chapter 10: Treatment of Active Tuberculosis in Special Populations.

2.8. Tuberculosis in special populations

See Chapter 10: Treatment of Active Tuberculosis in Special Populations for discussion and recommendations on TB treatment in special populations, including elderly populations; people living with HIV, liver disease or kidney disease; solid organ transplant recipients; people taking TNF inhibitors); people with drug and alcohol use disorders or who smoke; and women who are pregnant or breastfeeding.

3. Patient support during therapy

Treatment of TB requires multiple drugs, often with adverse effects, and frequently requires airborne isolation for several weeks. Meaningful and culturally appropriate engagement, education and support are critical for achieving successful TB treatment.

Meaningful engagement with a person with TB may include:

- an understanding of the social and historical forces that put a person at risk for TB, and may impact their healthcare engagement and trust in health care providers, including potential for bias and discrimination from health care workers and the healthcare system (see Chapter 12: An Introductory Guide to Tuberculosis Care… Serving Indigenous Peoples and Chapter 13: Tuberculosis Surveillance and Tuberculosis Infection Testing and Treatment in Migrants);
- education and counseling to improve treatment literacy;[34]
- use of professional interpreters in the patient's language of choice (preferably professional interpreters rather than family and friends);[35]
- use of appropriate, non-stigmatizing and person-centred language;[36]
- review of information and comprehension at return visits; and
- use of incentives and treatment supports, when appropriate.[37]

3.1. Adherence support through incentives and enablers

Poor adherence to prescribed TB treatment is a common cause of treatment failure and relapse.[29]

Adherence is optimized when TB medications are delivered as part of a comprehensive, patient-centred program that promotes patient understanding and removes barriers to adherence, rather than a focus on adherence to pharmacologic therapy alone.[1,37] Incentives and enablers can also help mitigate any social and economic marginalization a person may be experiencing. Early linkage with a social worker, along with early engagement with appropriate governmental and community organizations, is recommended when treating people from marginalized populations.

Examples of incentives and enablers that can be used include:[1,37–40]

- peer counseling;
- patient reminders and following up on missed appointments;
- integration into primary or specialty care (eg, HIV care, dialysis, mental health services, methadone delivery);
- financial supports, including stipends, personal products, coupons and gift cards;
- social assistance for housing and to gain access to or funding of healthcare services;
- assistance with transportation and childcare;
- reminder systems for appointments;
- field or home visits;
- blister packing medications;
- video directly observed therapy.

Good practice statements

- **The decision by a care provider to initiate treatment of TB disease implies a commitment to ensuring that a person with TB completes their TB therapy safely and with minimal interruption. This is best done by providing a comprehensive, patient-centred treatment program, which may include incentives and enablers.**
- **People with TB disease should be provided all medications and services required to successfully complete TB therapy free of charge, regardless of their insurance coverage or residency status in Canada.**

3.2. Use of directly observed therapy

Since publication of the 2013 TB standards, at least five systematic reviews have examined the effectiveness of DOT compared with self-administered therapy (SAT) in drug-susceptible TB treatment, although no new high-quality randomized controlled trials have been published.[37,41–44] Four systematic reviews analyzed the same five or six studies that compared outcomes of DOT and SAT[45–50], while 1 lower-quality systematic review included several additional studies that did not directly compare DOT to SAT.[44] Overall, 3 of the 4 high-quality systematic reviews found no significant difference when comparing pooled outcomes of treatment success from randomized control trials comparing DOT to SAT.[41–43] In these studies, DOT was usually clinic-based, while the SAT arms usually still received significant adherence support from providers in the form of frequent clinical follow-up and adherence monitoring. The fourth high-quality systematic review had somewhat inconsistent findings, demonstrating that SAT had lower rates of both adherence and cure, but no change in treatment completion, mortality, failure, loss to follow-up or acquired drug resistance.[37]

In addition, systematic reviews of observational studies have reported improved treatment outcomes with DOT in people living with HIV and people with multidrug-resistant TB, with limited data examining other populations at risk for adverse outcomes.[37,51] Existing data highlight the need for DOT, at minimum, in populations at higher risk for adverse outcomes from TB therapy. People with risk factors for non-adherence, people with TB with significant morbidity and people with infectious drug-resistant disease should be considered for DOT. Individual risk factors for adverse outcomes may include: people with multidrug-resistant TB, people living with HIV, people experiencing TB treatment failure or relapse, people with substance use or mental health disorders, people experiencing homelessness or unstable housing and people with suspected or known non-adherence to TB therapy.

The decision to use DOT, and the type of DOT, should be made in collaboration with the patient to ensure that autonomy and trust are maintained. One approach to increase patient autonomy is community-based DOT, where DOT services are decentralized, and people can remain in their homes, schools or workplaces while receiving DOT rather than traveling to healthcare facilities. A recent systematic review of randomized controlled trials and observational studies comparing community-based DOT to clinic-based DOT demonstrated that community-based DOT increased the pooled odds of successful treatment outcome significantly in both randomized control trials and observational studies.[52]

Virtual DOT (VDOT) through video-enabled devices such as smartphones and computers has emerged as a cost-effective way to deliver DOT that may improve patient autonomy. VDOT has shown promise in randomized controlled trials of high-risk populations,[40] and remains an active area of investigation. VDOT may be considered an acceptable alternative to DOT in some settings, and should be considered an option within the larger program of supportive care for people with TB disease. VDOT should be accompanied by in-person support and DOT when required, and within the framework of monitoring and evaluation.

Recommendations

- **We strongly recommend that all jurisdictions provide the capacity to deliver daily, in-person, supportive care for people with TB disease. Daily support should be individualized, and may include directly observed therapy** (*good evidence*).
- **We strongly recommend that, if directly observed therapy (DOT) is used, community-based DOT be performed rather than clinic-based DOT** (*good evidence*).

4. Investigations at treatment start and follow-up

The following recommendations for routine follow-up in standard first-line therapy are based on expert opinion for treatment of drug-susceptible pulmonary TB, and may vary from region to region. We recommend that routine follow-up be performed at least monthly to assess adherence and response to therapy, and to detect adverse events. Follow-up should be performed in-person whenever possible. Response to therapy should be gauged by clinical, radiologic, laboratory and microbiologic response. More frequent and intensive investigations may be required in some situations. The following investigations should be undertaken at start of treatment and during follow-up.

Clinical

- Start of treatment: Physical examination, weight, visual acuity, colour vision testing
- Follow-up: Weight, repeat vision testing monthly while on EMB
- Follow-up should also assess adherence, detect adverse events, assess response to therapy and discuss any barriers to successful TB care (including social and financial)

Radiology

- Start of treatment: chest x-ray at diagnosis (if not already done as part of diagnostic process)
- Follow-up: chest x-rays at two months and at the end of therapy

Laboratory

- Start of treatment: complete blood count (CBC) with differential, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), bilirubin, creatinine, HIV serology, hepatitis B virus serology, hepatitis C virus serology, hemoglobin A1C
- Follow-up: CBC, creatinine, AST or ALT, bilirubin, all monthly

Microbiology

- Routine monitoring of sputum twice monthly until conversion to smear negative, then again at 2 months and one month before planned end of therapy. If sputum remains culture positive at 2 months, repeat sputum cultures should be performed monthly until culture conversion is confirmed

- Sputum induction not required if unable to produce sputum and smear negative
- Repeat DST if sputum culture is positive at 3 months

5. Hospitalization

Although frequently diagnosed in hospital, TB is largely managed in the outpatient setting. With the high proportion of people with TB also having advanced age or co-morbidities, however, complex disease is common, and may require management in hospital. People with TB requiring hospitalization should be admitted to institutions with adequate airborne isolation rooms and with providers experienced in TB management (see Chapter 14: Prevention and Control of Tuberculosis Transmission in Healthcare Settings).

5.1. Indications for hospitalization

- Investigation and treatment of symptoms and signs of severe or life-threatening TB disease (eg, life-threatening hemoptysis, cachexia/malnutrition)
- Severe and morbid forms of TB, such as TB meningitis, cerebral TB, TB pericarditis
- Establishment of an acceptable drug regimen in patients with significant/severe drug-related adverse events or known/suspected multidrug-resistant disease
- Drug desensitization
- Management of co-morbid medical conditions whether related or unrelated to TB diagnosis (eg, heart failure, respiratory failure or recent solid organ transplantation)
- Institution of airborne isolation if this cannot be achieved in the outpatient setting
- Involuntary admission when all other measures are unsuccessful (should be an extremely rare event and performed as a last resort in consultation with public health authorities)

6. Therapeutic drug monitoring

There are clinical situations in which monitoring of serum concentrations of TB drugs may be helpful. Currently, no laboratory in Canada offers this service, and serum samples must be sent to Florida Infectious Disease Pharmacokinetics Laboratory (https://idpl.pharmacy.ufl.edu/) or National Jewish Health in Colorado (http://www.nationaljewish.org). Information about timing of blood draws, processing and shipping of samples is available from the websites of these laboratories.

Evidence to support the safety and efficacy of therapeutic drug monitoring (TDM) is limited. A systematic review and meta-analysis of therapeutic drug monitoring in first-line TB therapy, published in 2016, identified 41 studies that reported 2-hour, post-dose drug concentrations and 12 of them that tied these to clinical outcomes. A high proportion of people had INH (43%; 95% CI:32-55) and RMP (67%; 95% CI:60-74) levels below established thresholds, although full pharmacokinetic data sampling was limited, and there were insufficient data linking low drug levels to treatment outcomes.[53]

Recommendation

- **We conditionally recommend therapeutic drug monitoring for people with TB disease who also have risk factors for altered drug absorption (eg, HIV, diabetes), altered metabolism and excretion (eg, advanced liver and chronic kidney disease), disseminated TB and/or significant over- or underweight status (ie, BMI >30 or <18.5)** (*poor evidence*).

7. Management of treatment interruptions

Interruptions are common in treatment of TB disease. Generally speaking, treatment interruptions are more concerning in people with extensive disease (eg, smear positive, cavitary or disseminated disease) and in people with advanced immune suppression (eg, untreated HIV). Treatment interruptions are also more concerning during the intensive phase, when uninterrupted treatment is needed to achieve a rapid reduction in bacillary burden. Reinstituting therapy after treatment interruption should be performed in consultation with the patient and a TB expert. Table 3 is based on expert guidance and modified from existing guidelines and protocols.[1,54]

8. Follow-up and monitoring post-treatment

People treated for TB disease have high rates of morbidity and mortality after treatment.[28,55–58] This is likely related to the high proportion of people with preexisting morbidities, the social and economic marginalization of many TB patients and the direct consequences of TB disease itself. Management of post-TB morbidity is an active area of research, and new international post-TB treatment guidelines are currently under development.

8.1. Tuberculosis recurrence

People treated for active TB remain at high risk for recurrent TB (relapse or reinfection), particularly in the first 2 years post-treatment.[28,29] TB recurrence is associated with worse morbidity, mortality and acquired drug resistance, along

Table 3. Management of treatment interruptions in first line therapy.

Treatment phase	Total length of interruption	Approach
Intensive phase	<14 days	Continue therapy to complete intensive phase within three months
	≥14 days	Restart therapy
Continuation phase	<2 months	Continue therapy to complete treatment
	≥2 months and ≥80% of medications taken	Continue therapy to complete treatment
	≥2 months and <80% of medications taken	Restart therapy from start of intensive phase

with the renewed potential for transmission of infection to contacts. In a recent systematic review examining TB recurrence in low-incidence regions, the pooled recurrence rate was 1.47 (95% CI: 0.87-2.46) per 100 person years, with 83% of people with recurrence experiencing relapse.[59] This TB incidence rate exceeds the TB incidence rate in many people receiving TB screening and treatment for latent TB in Canada (see Chapter 6: Tuberculosis Preventive Treatment in Adults). People at high risk of TB recurrence may include people with extensive or disseminated disease, cavitary *and* smear or culture positive disease, drug-resistant disease, people with immune suppressing co-morbidities, people with a history of treatment interruptions, non-adherence or an atypical treatment regimen.

Understanding the timing of recurrence is important to inform follow-up. A review of 15 tuberculosis treatment trials from 1970-1983 involving RMP and that contained regimens for drug-susceptible TB found that 78% of recurrences occurred within six months of therapy and 91% within 12 months.[60] Some programs perform routine post-treatment surveillance to ensure timely diagnosis of TB recurrence. Routine monitoring may include regular review of symptoms or chest x-rays in the 12-24 months post-TB treatment. A recent post-hoc analysis of systematic review data demonstrated a non-significant increase in the diagnosis of recurrent TB in people with active follow-up with chest x-rays compared with passive follow-up (L. Otero, personal communication).[59]

Recommendation

- **We conditionally recommend that people with a high risk for TB recurrence post-treatment should be monitored for signs/symptoms of TB recurrence during the first 12-24 months post-therapy. This may include use of symptom review and radiological or microbiological testing** (*poor evidence*).

8.2. Post-TB treatment follow-up

After completion of TB therapy, TB survivors have approximately three times the mortality of age- and sex-matched controls. The causes of death in TB survivors appear to be similar to the general population.[55,61] This highlights the importance of linkage with primary care for management of new and pre-existing comorbidities during and following TB treatment.

8.3. Post-TB lung disease

Post-TB lung disease is a term that encompasses diverse chronic lung disease and respiratory pathologies experienced by TB patients after treatment for TB disease.[57,62,63] TB survivors have high rates of airway disease, including chronic obstructive pulmonary disease (COPD), bronchiectasis and airway stenosis[57,62,63] and also experience higher rates of restrictive lung disease.[63] Infectious pulmonary complications also occur at a higher rate, including chronic aspergillus lung disease and non-tuberculous mycobacterial disease.[63]

Post-TB lung disease is diverse in presentation and likely under-appreciated by clinicians. To date, there is a lack of prospective data to support evidence-based recommendations on appropriate screening and treatment interventions, but research is rapidly evolving in this area. All patients should be evaluated for respiratory disease during TB therapy, including a focused history and physical examination. Pulmonary function testing is recommended for all people completing therapy for pulmonary TB, given the high incidence of pulmonary function abnormalities in this population.[62,64] In areas with limited access to a pulmonary function laboratory, spirometry can be performed as an acceptable first-line test.

Recommendation

- **We conditionally recommend that pulmonary function testing be performed on all people at the end of treatment for pulmonary TB, or within six months of completing treatment** (*poor evidence*).

8.4. Non-Respiratory disease post TB

TB survivors experience higher rates of cardiovascular disease, malignancy, mood disorders, smoking and alcohol use disorder, in addition to the well-documented infectious and immunosuppressive comorbidities placing people at risk of TB.[61,65–67] Efforts should be made to address comorbidities as part of comprehensive care during TB therapy, in collaboration with primary care and allied health care providers. After TB treatment, at minimum, people should be linked with a stable primary-care provider to ensure continuity of care and optimal treatment of preexisting co-morbidities. Until further evidence emerges specific to TB populations, it seems prudent to perform age-based health screening according to primary care guidelines in TB survivors.

Good practice statement

- **TB programs should ensure that people completing TB therapy are linked to a primary care provider to ensure that co-morbidities are promptly identified and managed as per existing guidelines.**

Disclosure statement

The CTS TB Standards editors and authors declared potential conflicts of interest at the time of appointment and these were updated throughout the process in accordance with the CTS Conflict of Interest Disclosure Policy. Individual member conflict of interest statements are posted on the CTS website.

Funding

The 8th edition Canadian Tuberculosis Standards are jointly funded by the Canadian Thoracic Society (CTS) and the Public Health Agency of Canada, edited by the CTS and published by the CTS in collaboration with AMMI Canada. However, it is important to note that the clinical recommendations in the Standards are those of the CTS. The

CTS TB Standards editors and authors are accountable to the CTS CRGC and the CTS Board of Directors. The CTS TB Standards editors and authors are functionally and editorially independent from any funding sources and did not receive any direct funding from external sources.

The CTS receives unrestricted grants which are combined into a central operating account to facilitate the knowledge translation activities of the CTS Assemblies and its guideline and standards panels. No corporate funders played any role in the collection, review, analysis or interpretation of the scientific literature or in any decisions regarding the recommendations presented in this document.

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