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CANADIAN TUBERCULOSIS STANDARDS—8TH EDITION

Chapter 6: Tuberculosis preventive treatment in adults

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KEY POINTS

For tuberculosis preventive treatment (TPT):

- Either once-weekly rifapentine and isoniazid for 3 months (3HP), or daily rifampin for 4 months (4R) is recommended.
- When rifamycin based regimens cannot be used because they are not tolerated, not feasible or are contraindicated, the 9-month daily isoniazid regimen (9H) is the preferred option.
- When the 9H regimen cannot be used, the six-month daily isoniazid regimen (6H) is recommended.
- Evaluate for interactions between patients' baseline medications and the prospective TPT regimen through an up-to-date drug decision support tool prior to treatment initiation.

1. Introduction

As Canada moves toward the elimination of tuberculosis (TB), the treatment of latent tuberculosis infection (LTBI), referred to as tuberculosis preventive treatment (TPT), is paramount. The vast majority of people who have LTBI will not develop active TB disease; on average, 5%-10% of those who are infected will develop TB during their lifetime.[1,2] The efficacy of isoniazid (INH) monotherapy for TPT was established in the 1960s.[3] This landmark randomized controlled trial (RCT) established mono-INH regimens as the standard for TPT that have been used for the last 50 years. In fact, all subsequent completed RCTs on TPTs have used mono-INH as the standard of care. However, TPT with mono-INH has significant limitations, due to the lengthy treatment and risk of severe adverse events, particularly hepatoxicity. The previous Canadian TB guidelines[4] for TPT recommended 9H as the first-line treatment. Significant changes have occurred since those standards were published in 2013, including the introduction of shorter rifamycin-based TPT.

2. Indications for treatment

The decision to initiate TPT should be individualized and should employ shared decision making between the patient and health care provider. However, in a low TB-burden country like Canada, targeted screening of individuals at increased risk of progression is recommended, with the supposition that treatment will be offered if the screening test is positive (see Chapter 4: Diagnosis of Tuberculosis Infection). The development of active TB disease occurs with greatest frequency in the first 2 years after infection. In fact, 50% of the total lifetime risk of reactivation is estimated to occur in that period.[5,6]

For all individuals being considered for TPT, it is essential to rule out active TB disease prior to starting any TPT regimen. If TPT is declined, then the patient should be advised of active TB symptoms and told to seek medical attention if these occur. A period of formal observation can be considered for high-risk patients who decline treatment.

3. TB preventive treatment regimens

3.1. First line regimens

The following 2 regimens are considered equivalent in terms of safety and efficacy, although they have not been directly compared in an RCT. The choice between regimens should be tailored to the patient's specific circumstances, considering factors such as patient preference, pill burden/number of doses, potential for adverse effects and cost. Local healthcare resources and capacity to ensure high likelihood of completion of treatment should also be considered when deciding on which regimen to use.

3.1.1. Rifapentine and isoniazid once weekly for three months (3HP)

The 3HP (Rifapentine and INH once weekly for three months) regimen, when given as directly observed preventive therapy (DOPT) has been shown to be noninferior to self-administered (SAT) 9H in preventing TB in large RCTs

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in both children (age 2 to 17) and adults.[7,8] Furthermore, recent network meta-analyses confirm efficacy, reduced hepatotoxicity[9,10] and improved completion in comparison to longer INH-based regimens.[9] Since the publication of the network meta-analysis, one of the largest cohorts assembled to study 3HP in routine healthcare settings in the US demonstrated a completion rate of 87.2% (2867/3288) via DOPT.[11] The risk of hepatotoxicity is significantly reduced with 3HP compared to 9H,[7,9,12] although the regimen can cause an influenza-like syndrome. For the most part, this is mild and short lived and usually does not result in discontinuation of treatment. Severe events such as syncope and hypotension that resulted in hospitalization have been reported in rare instances (0.1%); however, no long-term sequelae attributable to the regimen have been reported.[13,14] Pyridoxine (Vitamin B6) 50 mg should be given at each dose to minimize the risk of neuropathy.

Administration of 3HP should generally be given by DOPT, since administration by SAT is associated with a lower completion rate when compared to DOPT as shown in an RCT comparing these two ways of administering the regimen (SAT's completion rate was 74%, vs 87% for DOPT). However, a preplanned subgroup analysis in the same study demonstrated that SAT was non-inferior to DOPT in the US sites.[15] The Centers for Disease Control and Prevention (CDC)[16] and World Health Organization (WHO)[2] guidelines consider 3HP given by SAT as an acceptable option; it should be noted, however, that the original efficacy trial[7] was based on 3HP given by DOPT.

The 3HP regimen has consistently been found to be cost-effective compared to INH monotherapy.[17–19] Within the Canadian context, when analyzed in an Arctic setting, 3HP was both more effective and cost-saving compared to the previous standard of care (DOPT with 9H twice weekly).[20]

Potential disadvantages of 3HP include a high pill burden, the risk of drug-drug interactions and the influenza-like syndrome. In Canada, 300 mg rifapentine tablets are available, reducing the number of pills to be taken weekly to 7. A rifapentine 300 mg/INH 300 mg fixed dose combination tablet is expected to become available in 2022, which should further reduce pill burden.[2]

At present, Health Canada has not approved the use of rifapentine. However, the federal government has issued an urgent public health need regulation which allows front-line practitioners to access rifapentine for TPT anywhere in Canada. 3HP is currently the standard of care in Nunavut, and standard operating procedures for 3HP can be obtained from the Government of Nunavut.

3.1.2. Rifampin self-administered daily for 4 months (4R)

The 4R regimen — rifampin self-administered daily for 4 months — is only given SAT; this has been shown to be noninferior in preventing TB to SAT 9H in large RCTs in both children (age 6 months to 17) and adults.[21] The risk of grade 3-4 adverse events (all types and hepatotoxicity) was also significantly lower with 4R compared to 9H among adults.[21–23] In the trial in children, there were no grade 3-4 adverse events with either 4R or 9H.[22] Network meta-analyses also support efficacy, reduced hepatotoxicity and improved completion of this regimen compared to longer INH-based regimens in all patients.[9,10]

The 4R regimen is more cost-effective than 9H in a variety of different settings, including high-income countries such as Canada.[24] Potential disadvantages of 4R include the risk of drug-drug interactions (as with 3HP), as well as the longer duration and greater number of doses compared to 3HP. At present, there is limited evidence of safety and efficacy in human immunodeficiency virus (HIV) patients, particularly those using newer antiretroviral treatments.[25]

Recommendation

- **We strongly recommend either once-weekly rifapentine and isoniazid for 3 months (3HP) or daily rifampin for 4 months (4R) for tuberculosis preventive treatment** (*good evidence*).

3.1.3. Drug-drug interactions

All rifamycin-based regimens have important drug-drug interactions because rifamycins are inducers of hepatic metabolizing enzymes, including cytochrome P450 enzymes, which can result in increased elimination of many other medications. Some of the important categories of interacting medications include many antihypertensives, anticoagulants, antifungal drugs, methadone, some immunosuppressive agents, hormonal contraceptives, antiretrovirals and others. These medications may need to be adjusted, stopped or changed to an alternate medication during TPT. In the case of oral contraception, an alternative form of contraception such as a barrier contraceptive or an intrauterine device should be used during treatment. Practitioners can check for drug-drug interactions with Lexicomp and Micromedex, the two main professional-level tools for doing so. Both are widely used (license required).

Good practice statement

- **Interactions between patients' baseline medications and the prospective tuberculosis preventive treatment regimen should be considered through an up-to-date drug decision support tool prior to treatment initiation.**

3.2. Alternative TPT regimens in Canada

If both first-line regimens are not tolerated, not feasible or contraindicated, the following regimens can be considered as alternatives. Regimens are listed in order of preference.

3.2.1. Isoniazid daily for nine months (9H)

The efficacy of INH has been established in a variety of populations (both HIV-positive and-negative) and settings.[3,26–28] The recommended duration of nine months is based on a reanalysis of data from trials among Alaskan Inuit.[29] Disadvantages of this regimen include: the longer

duration, with lower rate of treatment completion compared to 3HP and 4 R,[9] and greater adverse effects, particularly hepatotoxicity, which in rare circumstances (<0.1%) can result in a liver transplant or death.[30–32] The risk of INH-associated hepatotoxicity increases with older age.[25,33–37] We suggest pyridoxine (Vitamin B6) 25 mg daily given at each dose to minimize the risk of neuropathy.

Recommendation

- **We strongly recommend that, when rifamycin-based regimens cannot be used because they are not tolerated, not feasible, or are contraindicated, the 9-month daily isoniazid regimen (9H) for tuberculosis preventive treatment be used** (*good evidence*).

3.2.2. Isoniazid daily for six months (6H)

6H might be required when 9H is considered if a patient is unwilling or unable to complete more than 6 months of therapy. This regimen has demonstrated efficacy in preventing active TB compared to placebo in RCTs and network meta-analyses RCTs.[9,10,38,39] Nonetheless, efficacy in these trials was modest (65-67%),[38,39] providing a rationale for extending treatment to 9 months whenever possible. However, 6H likely carries a lower risk of hepatotoxicity compared to longer durations of INH monotherapy,[39] results in better completion rates.[9]

Recommendation

- **We strongly recommend that, when the 9-month isoniazid regimen (9H) cannot be used, the 6-month daily isoniazid regimen (6H) for tuberculosis preventive treatment be used** (*good evidence*).

3.3. Other TPT regimens

The regimens described in the following sections are not recommended for general use in Canada but can be considered when other alternatives are not viable.

3.3.1. Twice-weekly isoniazid for nine months

Twice-weekly INH has been evaluated in 2 small trials, both in HIV-infected individuals and both using a 6-month regimen.[40,41] Both studies demonstrated a significant reduction in active TB compared to placebo.[40,41] In another trial among young children with HIV, up to 24 months of thrice-weekly INH showed similar efficacy compared to daily INH and improved efficacy compared to placebo.[42] However, power was limited because the trial was stopped early as a result of a very high rate of active TB in the placebo arm.[42] Recent observational studies in Iqaluit, Nunavut, have shown relatively high rates of completion among patients treated with 9 months of twice-weekly INH by DOT. Although this regimen showed a trend toward lower completion compared to 3HP, the difference was not statistically significant.[43,44]

Twice-weekly INH is not a preferred TPT regimen but can be considered when other regimens are not feasible. The CDC continues to support its use (see Table 1) as an alternate regimen.[16]

Good practice statement

- **Given the uncertainty regarding treatment efficacy and the relatively increased importance of each dose compared to daily regimens, twice-weekly isoniazid regimens should be given via DOT over a 9-month duration.**

3.3.2. Isoniazid and rifampin daily for three months (3HR)

Although small, trials comparing 3 or 4 months of INH and rifampin to 6 or 12 months of INH have found a similar incidence of active TB in both HIV-uninfected[45–48] and HIV-infected populations[38,49] and network meta-analyses support efficacy compared to placebo.[9,10] Adverse events, including drug discontinuations and hepatotoxicity, have been similar with 6 or 12 months INH or 3-4HR in HIV-uninfected populations,[45,48] whereas drug discontinuations have been higher in those taking 3-4HR in some studies in HIV-infected populations.[38,49]

Thus, the 3HR regimen does not confer any advantage in terms of efficacy, safety or treatment completion in comparison to the mono-INH regimens that are now recommended as second-line regimens. Furthermore, the 3HR regimen also carries the same risk of drug-drug interactions as 4 R and 3HP. Given this, we suggest that the role of this regimen for TPT in Canada is very limited.

3.4. TPT regimens requiring further evidence

3.4.1. Rifapentine and isoniazid daily for one month (1HP)

The 1HP regimen given daily has been shown to be noninferior to self-administered 9H in a large RCT in HIV patients in Africa.[50] The applicability of this regimen in low-burden settings is still unknown, given that the regimen was provided to participants regardless of results from the tuberculin skin test or interferon-gamma release assay (although in a subgroup analysis in patients with confirmed LTBI, 1HP was noninferior to 9H). To date, there have been no studies published looking at this regimen in the HIV-negative population, although a clinical trial is ongoing.[51] Nonetheless, the WHO has recommended this regimen regardless of HIV status.[2]

Good practice statement

- **Until further evidence is published in patients without human immunodeficiency virus who have confirmed latent TB infection in low TB-burden settings, isoniazid daily for 1 month (1HP) should not be used for tuberculosis preventive treatment in Canada.**

Table 1. **Summary of recommended treatment regimens for latent tuberculosis infection.**

Regimen	Duration	Dose	Frequency	Common adverse effects
First-line regimens				
Rifapentine and isoniazid (3HP)	3 months (12 doses)	Isoniazid: 15 mg/kg Maximum: 900 mg Rifapentine: 10-14.0 kg: 300 mg 14.1-25.0 kg: 450 mg 25.1-32.0 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50.0 kg: 900 mg Maximum: 900 mg	Once weekly	Flu-like reactions, drug interactions
Rifampin (4 R)	4 months (120 doses)	10mg/kg Maximum: 600 mg	Daily	Rash, drug interactions
Second-line regimen				
Isoniazid (9H)	9 months (270 doses)	5mg/kg Maximum: 300 mg	Daily	Hepatoxicity, peripheral neuropathy
Alternative regimens				
Isoniazid (6H)	6 months (180 doses)	5mg/kg Maximum: 300 mg	Daily	Hepatoxicity, peripheral neuropathy
Intermittent isoniazid for 9 months	9 months (78 doses)	15mg/kg Maximum: 900 mg	Twice weekly	Hepatoxicity, peripheral neuropathy
Isoniazid and rifampin (3HR)	3 months (90 doses)	Isoniazid: 5mg/kg Maximum: 300 mg Rifampin: 10mg/kg Maximum: 600 mg	Daily	Hepatoxicity, peripheral neuropathy, drug interactions

4. TB Preventive treatment in select populations

4.1. Contacts of a Drug-Resistant TB case

In a systematic review using 5 comparator studies, treatment of multidrug-resistant (MDR) latent TB infection did suggest effectiveness in the prevention of progression to MDR-TB disease among contacts of a person with MDR-TB disease.[52] However, an observational study found a lower rate of progression to TB disease among MDR contacts taking 12 months of a fluoroquinolone with or without ethambutol or ethionamide, compared to those refusing treatment.[53] Trials to assess levofloxacin as a TPT for MDR-TB contacts are ongoing to determine if this approach is indeed effective.[54,55] At present, there is insufficient evidence to make a recommendation regarding TPT for contacts of fluoroquinolone-resistant MDR cases. However, a trial of delamanid for high-risk MDR-TB contacts is ongoing and may inform future recommendations.[56]

Recommendation

- **We conditionally recommend, for contacts of an index TB patient who is known to have an isolate resistant to both rifampin and isoniazid (MDR-TB), levofloxacin or moxifloxacin for six-to-nine months if the source case is fluoroquinolone-sensitive** *(poor evidence)*.

Good practice statements

- **For contacts of an index TB patient who is known to have an isoniazid mono-resistant isolate, we suggest 4 months of daily rifampin (4R).**
- **For contacts of an index TB patient who is known to have a rifampin mono-resistant isolate, we suggest 9 months of isoniazid (9H).**
- **All patients with latent tuberculosis infection who are contacts of a person with MDR-TB should be followed for 2 years to ensure that they do not develop disease.**

4.2. Persons being treated for organ transplant or HIV infection

Transplant patients and patients on direct oral anticoagulants are unlikely to be good candidates for either of the rifamycins, given the drug-drug interactions.

In some instances, Rifabutin has been used for TPT because it comes from the family of rifamycins. There is, however, no evidence to support this approach and the drug-drug interactions would have to be carefully considered.

Rifamycin-containing TPT appears safer and at least as effective as INH regimens in preventing TB disease and TB-related death among people living with HIV.[57] The HIV population that is on antiretrovirals such as protease inhibitors or nevirapine is also subject to significant drug-drug interactions.[58] We suggest that an HIV specialist be involved in deciding the optimal TPT, given its dependence on the antiretroviral regimen. However, efavirenz is safe when used concomitantly with rifampin or rifapentine and dose adjustment is not required.[59,60] These drugs are also safe to use with dolutegravir, although the dose of dolutegravir should **be** doubled when used with rifampin (but not rifapentine).[61,62] The combination of rifapentine and raltegravir also appears to be safe.[63] Patients receiving antiretrovirals for Hepatitis C can also have significant drug-drug interactions with the rifamycins.

Good practice statements

- **Transplant candidates should receive latent tuberculosis infection testing and tuberculosis preventive treatment (if testing is positive) prior to transplantation.**
- **In transplant patients receiving latent tuberculosis infection treatment post-transplant, we suggest 9 months of isoniazid (9H) or an alternate non-rifamycin-containing regimen, due to the risk of rejection from altered drug pharmacodynamics with rifamycins.**

4.3. Pregnant and breastfeeding patients

Data regarding the use of most LTBI treatment regimens during pregnancy are limited, with the majority of data available for INH monotherapy. Observational data have suggested a possible increased risk of INH-induced hepatotoxicity during pregnancy and the first three months postpartum.[64] Furthermore, a recent RCT of 28 weeks of INH preventive therapy in pregnant and postpartum patients with HIV who were on antiretroviral therapy showed an increased risk of adverse pregnancy outcomes in those receiving INH.[65] No data have been published regarding rifampin for TPT during pregnancy. However, rifampin is considered safe during pregnancy for treatment of active TB disease, suggesting safety for TPT as well. Only limited data are available for 3HP. Notably, an analysis of the subgroup of 126 pregnant patients in two large trials showed rates of adverse pregnancy outcomes similar to background rates and no increased risk in 3HP vs 9H.[66]

The potential risk of TPT must be weighed against the risk of progression to active TB. Some observational data suggest an increase in the risk of active TB disease in the postpartum period, and possibly during pregnancy,[67] although this finding is not consistent across studies.[68] The potential risk of TPT must be weighed against the risk of progression to active TB.

INH and rifampin are excreted in breast milk in small quantities, well below the usual therapeutic neonatal dose, and are unlikely to pose a substantive risk to infants.[69] The US Red Book recommends against pyridoxine for breastfed infants who are not on INH, but whose mother is taking INH.[70] The extent of rifapentine excretion in breastmilk and the safety of exposure in breastfed infants has not been determined.

Recommendation

- **We conditionally recommend that, if tuberculosis preventive treatment is given during pregnancy, 4 months of daily rifampin (4R) is the preferred option. Isoniazid-based regimens should be avoided until 3 months postpartum in all but exceptional circumstances (eg, a contact of a rifampin-resistant TB case who has a very high reactivation risk)** (*poor evidence*).

Good practice statements

- **In pregnant patients, we suggest that tuberculosis preventive treatment should generally be deferred until after delivery unless the risk of reactivation is very high (eg, for recent close contacts of a person with active TB, people on immunosuppressants and/or people living with HIV).**
- **Once weekly rifapentine and isoniazid for 3 months should generally be avoided during pregnancy and in breastfeeding mothers until more data are available.**
- **Supplemental vitamin B6 is not required for breastfed infants whose mother is taking isoniazid but who are not taking isoniazid themselves.**

4.4. Older patients

The risk of toxicity, particularly hepatotoxicity from INH, increases with age.[25,33–37] However, a large RCT has not found a similar pattern with 4R.[25,71] It is unclear whether there is an increase in adverse events in older patients taking 3HP. Of note, a Chinese trial of 3HP vs a twice-weekly two-month regiment of INH and rifapentine in patients aged 50-69 was stopped early due to a high rate of adverse events in both study arms (1.1% rate of severe adverse events in the 3HP arm).[72] Furthermore, a large Taiwanese study of older patients with poorly controlled diabetes revealed a similar rate of severe adverse events in 3HP vs 9H but a higher rate of mild adverse events with 3HP.[73] However, a large American observational study suggested a lower rate of adverse events with 3HP vs 4R in patients over 50 years,[74]

Good practice statements

- **A carefully weighing of individual risks and benefits when considering TB preventive treatment in older patients, should be undertaken, considering the potential toxicity of treatment as well as both the risk of reactivation and the risk of a poor outcome if active TB develops; age alone should not be the determining factor in declining to offer tuberculosis preventive treatment.**
- **In older patients, 4 months of daily rifampin or once-weekly rifapentine and isoniazid for 3 months remain the preferred TB preventive treatment regimens.**

4.5. Patients with end-stage renal disease

Patients with LTBI who are also on dialysis are at increased risk for progression to TB disease and thus may receive increased benefit from TPT.[75] However, they are also at increased risk of treatment-related adverse events.[76,77] As such, close monitoring is suggested in this patient group. Dose adjustment based on renal function is not required for INH, rifampin or rifapentine.

4.6. Patients with prior documented TB infection and/or disease who are re-exposed to a smear-positive active case

There are no tests available to determine if a patient has been re-infected with latent infection following exposure to a smear-positive active case. Studies primarily from the pretreatment era suggest that prior TB infection provides

approximately 80% protection against development of disease following re-exposure.[78,79] However, it is still uncertain whether greater intensity or duration of exposure may overcome this protective effect. This may be of particular relevance in high-TB-incidence communities, where repeated or high-intensity exposure is more likely. Further, immunocompromised people, such as people living with HIV, are likely to derive less protective benefit from prior infection.

Recommendation

- **We conditionally recommend that retreatment with tuberculosis preventive treatment is usually not necessary unless the exposed person is at elevated risk of progression to TB disease** (*poor evidence).*

5. Directly-observed versus self-administered treatment

The 4R regimen is given as SAT. The 3HP regimen was originally studied as DOPT. While all regimens can be given as SAT, DOT may be useful in short regimens, since each dose becomes that much more important. A study looking at 3HP SAT versus DOT resulted in fewer people completing 3HP in the SAT group compared to the DOT group across all sites and countries; in the prespecified subgroup of American study sites, DOT was noninferior to SAT. Using virtual approaches for DOT may reduce the time and resources required to carry it out. Although the relative benefit of virtual (synchronous or asynchronous) vs in-person DOT has not definitively been established, small observational studies suggest favorable rates of treatment completion when administering 3HP with virtual DOT compared to SAT.[80,81] Potential advantages and disadvantages of DOT are listed in Table 2.

5.1. Baseline testing and monitoring

Suggested evaluation prior to and during TPT are outlined below. Although differing follow-up strategies have not been compared in RCTs, these recommendations are based on the protocols of large RCTs in which moderate rates of adverse events have been observed.[7,21]

Pretreatment evaluation

It is critical to exclude active TB prior to initiation of TPT in order to avoid undertreatment of TB disease, with subsequent development of drug resistance. At a minimum, the initial assessment should include a clinical assessment and chest x-ray. If abnormalities are detected, then TPT should be deferred until negative mycobacterial sputum culture results have been obtained. Patients' baseline medications should be determined and evaluation for potential drug-drug interactions between these and proposed TPT regimens examined (see drug-drug interactions section, above). Evaluation of potential risk factors and barriers for non-completion, as well as patient understanding, is also important to ensure successful completion. We suggest baseline testing for all patients undergoing TPT, including complete blood count, alanine aminotransferase, bilirubin, as well as hepatitis B and C and HIV serologies.

Patient education

Prior to starting TPT (all regimens), patients should be counseled that on average 5-10% of those who are infected will develop TB during their lifetime and that half of those people will develop TB within the first two years of infection. Key risk factors could also increase the risk of reactivation considerably (see Chapter 4: Diagnosis of Tuberculosis Infection). They should be counseled that taking all doses of the TPT will reduce this risk significantly, thus preventing the development of active TB disease. Patients should also be informed about possible adverse events associated with TPT that can occur but are rare. They should be told to contact the clinic should they develop possible adverse events. If prompt evaluation of such events by a health care provider is not possible or if symptoms are severe then the patient should stop their treatment medication. The British Columbia Center for Disease Control (BCCDC) provides a website with basic information regarding latent TB infection, including patient handouts in a variety of languages.[82]

Evaluation during treatment

Evaluation at the end of the first month of treatment provides an opportunity to assess medication tolerability and to encourage adherence, since adherence to treatment in the first month strongly predicts treatment completion.[83] In general, monthly clinical assessments should be continued for the duration of treatment. However, in patients at low risk of adverse events and likely to complete treatment, the interval between visits may be extended.

Table 2. Potential advantages and disadvantages of providing latent tuberculosis infection treatment as directly-observed therapy (DOT).

Potential advantages of DOT	Potential disadvantages of DOT
Allows for patients to ask questions to providers with each dose	Requires substantial additional healthcare worker time
Allows providers more frequent opportunities to detect potential adverse effects and to detect them earlier, which may enhance safety	Less convenient for patients
Increases treatment completion rates	Less flexibility in timing of doses
Ensures treatment is going according to plan, including that bloodwork and follow-up visits are arranged and attended	Patients may perceive DOT as an infringement on their autonomy
Allows the team to offer incentives and enablers when barriers are identified, so that patients can better adhere to the treatment	
Allows for an opportunity for the healthcare team to identify others who might need testing in the patient's environment	

As part of evaluation after one month of treatment, ALT (a blood test for liver function) and bilirubin should be performed (all regimens). In patients on TPT regimens including a rifamycin, a complete blood count should also be performed at this time. Patients taking 4R or 3HP do not require further laboratory monitoring during treatment unless the patient has an abnormal test result, develops symptoms suggesting an adverse event or has risk factors for hepatotoxicity (history of previous drug-induced hepatitis, current cirrhosis or chronic active hepatitis of any cause, hepatitis C, hepatitis B with abnormal transaminases). This approach is justified given that the risk of hepatotoxicity with these regimens is much lower than for isoniazid monotherapy[7,21] For patients on regimens other than 3HP or 4R, monthly monitoring of ALT and bilirubin should also be performed among patients with risk factors for hepatoxicity. In patients without such risk factors, the benefit of ALT and bilirubin monitoring is uncertain but should be considered.

6. Management of adverse events

TPT can be associated with a wide variety of adverse events (common adverse effects for each regimen are noted in Table 1). In general, mild to moderate adverse events (i.e., those not interfering with, or only modestly interfering with, instrumental activities of daily living, also known as Grade-1 and Grade-2 adverse events) should result in greater monitoring but do not necessarily require stopping therapy. However, severe adverse events that interfere with normal daily activity, including the ability to go to work (Grade 3) or any life-threatening or disabling adverse event (Grade 4) should lead to a pause in treatment until recovery or permanent discontinuation. A change to an alternative regimen should be considered once the patient has recovered. Detailed approaches to the management of specific adverse events have been published elsewhere.[2,21]

Evidence is lacking regarding the best approach to manage interruptions in TPT. However, the WHO has provided recommendations based on expert opinion.[2,84]

7. Future regimens

In addition to the 1HP regimen noted in section 3.4.1., several short duration TPTs are undergoing study and may be available for future use. These include six weeks of daily rifapentine[51] and high dose rifampin for two months.[85] The quest to continue to shorten TPT while maintaining efficacy and reducing side effects is at the forefront of TB research.

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