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CANADIAN TUBERCULOSIS STANDARDS—8TH EDITION

Chapter 10: Treatment of active tuberculosis in special populations

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KEY POINTS

- The management of tuberculosis (TB) in people with medical co-morbidities, substance-use disorders, advanced age or pregnancy is challenging; consultation with a TB expert is recommended.
- Adverse events and treatment interruption are more common in these special populations; close monitoring and additional support is often needed.
- Given alterations in TB-drug pharmacokinetics and the potential for severe drug-drug interactions in patients with medical co-morbidities, we recommend consultation with an experienced pharmacist.
- TB disease and its treatment have important implications for the management of co-morbid conditions; close collaboration with medical specialists and allied health professionals is often required.
- The prolonged course of TB treatment is a useful opportunity to screen for co-morbidity and to facilitate referral and linkage into care.

1. Introduction

Medical co-morbidities, substance use-disorders, advanced age and pregnancy can complicate management of TB.[1,2] Alterations in immunologic control of TB infection may increase the risk of reactivation and lead to more severe forms of TB disease.[1] Co-morbidity may also lead to slower TB treatment response and higher rates of TB relapse.[1] As a result, extension of TB treatment duration is sometimes required to optimize TB treatment outcomes.

These special populations may also differ in absorption, metabolism and clearance of TB drugs. Thus, special attention to dosing of TB medications is needed and, in some groups, therapeutic drug monitoring is recommended.[3] Increased susceptibility to adverse events in some groups may mandate closer monitoring and support, including for drug-drug interactions and overlapping toxicities.

Finally, there is often a lack of comparative clinical data directly relevant to these special populations, as these groups are often excluded from clinical trials due to concerns over harm.

Given these challenges and limitations in the clinical data, consultation with a TB specialist and an experienced pharmacist is strongly recommended. Furthermore, it is important to initiate close collaboration with the patient's medical and allied health care team throughout the TB treatment course.

Here we review additional considerations in TB management of special populations. For each population we will review the impact on epidemiology, clinical presentation, treatment outcomes and management.

2. People with human immunodeficiency virus

Human immunodeficiency virus (HIV) infection increases the risk of TB disease nearly 100-fold.[4,5] Among people with HIV and *M. tuberculosis* coinfection, the annual risk of active TB may be as high as 10 per 100 person years.[5,6] Antiretroviral therapy (ART) reduces the incidence of active TB substantially, although the incidence remains higher than in people without HIV infection, even after normal CD4+ lymphocyte counts are attained.[7,8]

The predominant immunologic effect of HIV is to reduce cell-mediated immune function. By reducing the number of T-helper cells, macrophage activation and granuloma formation is impaired, compromising the immunologic containment of latent and new TB infections.[9]

HIV also alters the clinical and radiologic features of TB, which are partly determined by the host response.[10] Extra-pulmonary and disseminated forms of TB are more common in people with HIV infection, especially in those with CD4+ lymphocyte counts below 50×106/L, while cavitary lung disease and sputum smear-positive disease is less common.[11] This atypical presentation can contribute to diagnostic delay.

HIV infection also affects TB treatment outcomes. Treatment failure with acquired rifampin mono-resistance has been observed with intermittent treatment regimens in

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people with HIV, particularly among people with CD4 counts <100 × 106/L.[12,13] TB recurrence is also more common among people with HIV.[14] When molecular techniques have been used to distinguish between relapse and reinfection in communities with high levels of ongoing transmission, however, the rates of relapse with the original strain have been similar.[15,16] Mortality is higher among people with both HIV and TB and correlates with the degree of immune suppression.[17] With appropriate anti-TB therapy and timely initiation of ART, however, the difference in outcomes can be attenuated.[16]

There are several special considerations in the management of TB and HIV co-infection, including TB drug malabsorption, potential for profound drug-drug interactions and the avoidance of immune reconstitution inflammatory syndrome.

Recommendation

- **We strongly recommend that, due to the profound impact of human immunodeficiency virus (HIV) on patient survival and TB treatment outcomes, all patients with TB be screened for HIV infection** (*good evidence*).

Good practice statement

- **Treatment of TB in people with human immunodeficiency virus (HIV) should be guided by a physician with expertise in the management of both diseases or in close collaboration with a physician expert in HIV care. Consultation with an expert pharmacist is also advised**.

2.1. TB therapy in people with HIV

The anti-TB regimen choice and duration is the same for people with HIV as for those without HIV, except for the selective use of rifabutin in place of rifampin when necessary to achieve compatibility with the ART regimen (see Table 1).[16,18–24]

Daily administration of TB drugs throughout the treatment course is recommended, as intermittent therapy is associated with worse treatment outcomes, including treatment failure, relapse and acquired drug resistance.[16,25] Treatment duration is not extended on the basis of HIV co-infection alone. However, in the uncommon scenario where a patient declines to take ART, TB treatment should be extended to 9 months.[16,21]

Several studies have found that a substantial proportion of people with both HIV and TB infection have low serum concentrations of anti-tuberculous agents.[26–31] This is thought to be due to a combination of factors, including drug interactions with ART and decreased absorption related to gastrointestinal dysfunction associated with HIV infection.[32] Low serum drug concentrations have been linked to slower response to TB treatment[21,29,33,34] and acquired rifamycin resistance.[35] Thus, we frequently monitor serum drug concentrations in individuals with HIV co-infection to optimize dosing.

HIV-infected individuals are already at increased risk of neuropathy related to HIV and ART. Therefore, in those taking isoniazid (INH), vitamin B6 supplementation is routinely used prevent additional neurologic toxicity from INH-associated neuropathy.

Recommendations

- **We strongly recommend a rifamycin (rifampin or rifabutin)-containing regimen for treatment of TB, despite the potential for drug-interactions with antiretroviral therapy** (*good evidence*).
- **We strongly recommend that TB treatment in human immunodeficiency virus co-infected individuals be administered daily throughout** (*good evidence*).
- **We conditionally recommend that, if a patient is not taking antiretroviral therapy, TB treatment be extended to 9 months** (*poor evidence*).
- **We conditionally recommend that, where available, serum TB drug concentrations be measured in people with human immunodeficiency virus co-infection and used to optimize TB drug dosing** (*poor evidence*).

2.2. Antiretroviral therapy in people with HIV and TB

ART is strongly recommended for all people with HIV who also have TB.[23] The optimal timing of ART initiation in people receiving TB treatment, balancing the risk of progressive HIV and TB disease with the risk of immune reconstitution inflammatory syndrome (IRIS), has been evaluated in nine randomized-controlled trials.[36–38] Two systematic reviews of these trials concluded that early initiation of ART, within 2 weeks of TB therapy initiation, reduces overall mortality and the incidence of additional acquired immunodeficiency syndrome (AIDS)-defining illnesses. The benefit of early initiation of ART was most apparent in patients with CD4 counts of $<50 \times 10^6$/L.

As an important caveat, early initiation of ART in cases of central nervous system (CNS) TB may be hazardous, probably because of the unique risks of IRIS reactions in the closed space of the cranium. One randomized study of TB meningitis compared immediate ART with a 2-month delay in ART initiation and found higher rates of severe adverse effects in the immediate ART group. However, the mortality rate, which was more than 50%, did not differ between arms.[39] Thus, in those with CNS-TB, the optimal time to initiate ART is not well-established. Delaying therapy at least 2 weeks after initiation of TB treatment appears to provide the best balance between avoiding cerebral complications of IRIS and improved TB treatment outcomes (see Chapter 7: Extra-pulmonary Tuberculosis).

In patients already receiving effective combination ART at the time of the TB diagnosis, ART should be continued. However, a change in ART regimen may be required to accommodate potential drug interactions with rifamycins. Note that when an ART dose adjustment is made to address an interaction with a rifamycin, the increased dose should

be maintained for 2 weeks after stopping the rifamycin to allow for the liver enzyme induction effect to wear off.

Recommendations

- **We strongly recommend initiating antiretroviral therapy within 2 weeks of starting TB therapy, provided there is no documented central nervous system TB** (*good evidence*).
- **We conditionally recommend delaying antiretroviral therapy (ART) initiation for at least 2 weeks after initiation of anti-TB treatment for those with central nervous system TB, although here the optimal time to initiate ART is less well-established and expert consultation is advised** (*poor evidence*).

2.3. Specific antiretroviral regimens in patients taking Rifamycin-containing TB treatment

Rifamycins are the only anti-tuberculous agents to exert clinically important interactions with antiretroviral drugs (see Table 1). Rifabutin is associated with weaker enzyme induction and thus has less potential for serious drug-drug interactions than either rifapentine or rifampin. However, there is less published clinical experience with rifabutin in the treatment of people with both HIV and TB, and rifampin is usually preferred in this population.[23,38]

Since rifamycin-based TB treatment is strongly recommended in people with HIV and TB (see recommendation in section 2.1), these drug-drug interactions substantially limit the number of compatible ART regimens available. Current recommendations from the World Health Organization (WHO) for people newly diagnosed with HIV and on treatment for TB is dose-adjusted dolutegravir plus 2 nucleoside analogues. An acceptable alternative is efavirenz plus 2 nucleoside analogues (see Table 1 for dosing for both regimens).[38]

The management of drug-drug interactions between ART and the rifamycin class is an area of active research and recommendations change frequently. Consultation with an experienced pharmacist and a regularly updated clinical drug-interaction resource is prudent (see section 13 on drug-drug interactions).

It is crucial that, while on TB treatment, ongoing monitoring of antiretroviral efficacy is performed. ART efficacy can be compromised in people with HIV and TB co-infection because of drug-drug interactions, reduced adherence related to increased pill burden or overlapping toxicity. Thus, we strongly advise close monitoring of plasma HIV ribonucleic acid (RNA) in people on TB treatment. Monthly testing is recommended until plasma viral load is no longer detectable and then, at minimum, quarterly testing while on TB treatment.

In patients with a suboptimal virologic response to ART in whom an interaction or decreased absorption is a possible explanation, measurement of serum antiretroviral concentrations should be considered, although clinical evidence to support this strategy is lacking. Adherence to ART should also be optimized and antiviral resistance excluded.

Good practice statement

- **Close monitoring of plasma human immunodeficiency virus (HIV) RNA in people on treatment for both TB and HIV is suggested with monthly measurements until plasma HIV RNA is no longer detected, followed by quarterly testing during the course of TB treatment.**

2.4. Additional considerations in selecting a compatible antiretroviral regimen for people on TB treatment

There are no significant interactions between the nucleoside analogue class and the rifamycin class and these can be used together without dose adjustment. Tenofovir alafenamide serum concentrations are reduced with rifampin but intracellular concentrations of the active form of the drug appear adequate.[40]

All the other antiretroviral drug classes, including protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors (INI) and CCR5 receptor blockers, demonstrate major interactions with the rifamycins and caution is required.

Dolutegravir and raltegravir may be used with rifampin, provided doses are increased to account for the enhanced metabolism (see Table 1).[41–44] It should be noted, however, that twice-daily dosing of some components of an ART regimen adds significant complexity and pill-burden and that this can challenge consistent adherence to ART. In a recent randomized controlled trial involving people with HIV and TB receiving rifampin-based treatment, twice-daily raltegravir was less effective at controlling HIV than an efavirenz-based, once-daily regimen.[41] The difference was largely attributed to reduced adherence to the more complicated ART regimen in the raltegravir arm.[41] Although a single, small phase-one study suggests that dolutegravir can be given once daily with rifabutin, there is less published clinical experience with this regimen.[45] Other members of the integrase-inhibitor class — bictegravir and elvitegravir — cannot be used with the rifamycins.[23]

Extensive experience and a controlled trial has shown that the NNRTI efavirenz at standard dosing of 600 mg/day remains effective when used with rifampin, despite variable reduction in efavirenz serum concentrations.[46] An increase in dose of efavirenz to 800 mg has been used in patients with larger body mass or suboptimal viral suppression. Rilpivirine and doravirine are not compatible with rifampin but with dosage adjustment can be co-administered with rifabutin.[23]

No PI dosing regimen has been found to be safe and effective in combination with rifampin. Rifabutin can be substituted for rifampin in TB treatment to permit the use of PIs but is associated with higher rates of hematologic and ocular toxicity.[20,47] This is because rifabutin concentrations are increased by concomitant therapy with PIs. There is greater experience with ritonavir than cobicistat "boosting" of PIs.

Table 1. Summary of compatible rifamycin-based anti-tuberculous therapy and antiretroviral regimens (last updated September 2021).

Rifamycin	Anchor drug in antiretroviral regimen	Nucleoside analogue component of anti-retroviral regimen
Rifampin 600 mg daily	Efavirenz 600 mg daily[38,46] Dolutegravir 50 mg twice daily[41,43] Raltegravir 800 mg twice daily[42]	No clinically important interactions expected[23,38]
Rifabutin 150 mg daily	Ritonavir "boosted" protease inhibitor[23,48]	No clinically important interactions expected[23,38]
Rifabutin 300 mg daily	Dolutegravir 50 mg daily[45] Raltegravir 400 mg twice daily[42,49] Rilpivirine 50 mg daily[23] Doravirine 100 mg twice daily[23]	No clinically important interactions expected[23,38]

Note: Expert consultation is strongly advised when selecting antiretroviral therapy (ART) regimens in people on tuberculosis treatment.

2.5. Immune-Reconstitution Inflammatory Syndrome

IRIS is a frequent early complication of ART in people with HIV and TB. There are two types of IRIS. The first occurs during TB therapy, after ART initiation, and is known as paradoxical IRIS. The second occurs following ART initiation in patients with unrecognized TB, and is known as unmasking IRIS.[47,50,51]

IRIS has been reported with a frequency ranging from 8 to 43%.[52] IRIS usually presents as fever and disease progression at involved sites, for example as enlarging lymph nodes, worsening pulmonary infiltrates on chest radiograph or exacerbation of inflammatory changes at other sites. Mortality attributed to IRIS appears to be uncommon except in cases with CNS involvement. Most affected patients have low initial CD4 cell counts, typically 100×10^6/L or less. Onset has been described between 2 and 40 days after ART initiation.

Diagnosis of IRIS requires exclusion of other possible causes, including treatment failure due to drug resistance or development of a different opportunistic infection.[53]

Treatment of IRIS is not always required, as the condition is self-limited. However, if the symptoms are severe enough to warrant therapy, corticosteroids such as prednisone at doses in the range of 1 mg/kg of body weight, given over four weeks, have been shown effective in a randomized trial.[54] Most people can be managed successfully without interruption of ART or TB treatment and in any case, such interruption will not hasten resolution of IRIS.

A single randomized-controlled study has shown that a short course of prednisone given at the same time as ART initiation can reduce the frequency of symptomatic IRIS without increasing the risk of other opportunistic illness.[55] People who should be considered for this intervention are those at high-risk of paradoxical IRIS, defined by CD4 count less than 100×10^6/L. It is important to ensure that patients are responding to TB therapy prior to using preemptive prednisone and that rifampin resistance is excluded. The presence of Kaposi's sarcoma or active hepatitis B infection are additional contraindications.[55]

Recommendation

- **We strongly recommend, in people with HIV responding to TB therapy and who are about to initiate antiretroviral therapy, and whose CD4 count is less than 100 x106, prednisone 40 mg/d for 14 days followed by 20 mg/d for 14 days to reduce the risk of symptomatic immune reconstitution inflammatory syndrome, unless rifampin-resistance, Kaposi's sarcoma, and active hepatitis B infection are present as contraindications** (*good evidence*).

Diagnostic considerations in people with both HIV and TB are discussed in Chapter 3: Diagnosis of TB disease and Drug-Resistant TB and Chapter 4: Diagnosis of TB Infection. Regimens used for treatment of latent TB infection in people with HIV are discussed in the Chapter 6: TB Preventive Treatment in Adults.

3. People who have undergone solid organ transplant

Recipients of solid-organ transplantation have a substantially elevated risk of TB that can range between 4 and 30 times that of the general population.[56] This is a result of the potent impact of anti-rejection medications on host T-cell function and cell-mediated immune response.[57] Most commonly, TB in this population represents reactivation of latent infection in the recipient. However, transmission of unrecognized infection in the allograft (donor-derived infection) and acquisition of new infection post-transplantation can also occur.

TB in transplant recipients is frequently atypical in its clinical presentation.[58–60] Disseminated disease is present in up to 15-30% at TB diagnosis and cavitary disease is less frequent in this population.[58,61] TB often occurs within the first year following organ transplantation, reflecting both reactivation of previous infection and the period of the most intense immune suppression. Donor-derived TB (ie, TB arising from the transplanted organ) typically presents within three months of organ transplantation.

TB treatment is more difficult and outcomes are worse in solid-organ transplant recipients compared to other populations.[58,62] Overlapping drug toxicity and drug-drug interactions lead to adverse events in nearly one-third of transplant recipients receiving TB therapy.[58,63] Graft dysfunction and organ rejection occur more frequently in transplant recipients with TB compared to those without TB; this is related in part to drug-drug interactions reducing the serum concentrations of immune-suppression therapies. Mortality from TB is higher in transplant recipients, with rates up to 20% in modern cohort studies.[58,63,64]

Drug-induced liver injury occurs frequently in transplant recipients, with rates especially high in liver recipients. INH

can still be included as part of a first-line regimen, provided liver enzymes and liver function are closely monitored. Pyrazinamide (PZA) should be avoided in liver transplant recipients.[59,63,65]

Despite potential for drug-interactions, most experts recommend rifamycin-based for treatment of TB in transplant recipients.[60,65–67] However, interactions between TB and immunosuppressive agents necessitates close collaboration with transplant physicians and pharmacists.[60,66]

Rifabutin, which exerts less potent drug-interactions than rifampin, is the preferred rifamycin for treatment of active TB in this population.[68,69] The efficacy of rifabutin against TB has been demonstrated in clinical trials (albeit in non-transplant recipients) and is considered comparable to rifampin[20,70–73] (see Chapter 5: Treatment of Tuberculosis Disease). Importantly, rifabutin use appears to lessen the risk of graft rejection in transplant recipients.[70] Regular therapeutic drug monitoring of anti-rejection medications is recommended while on a rifamycin-containing TB treatment.

Dose reduction of immune suppression in transplant recipients is not needed to achieve cure of TB when using rifamycin-based TB treatment regimens. Furthermore, aggressive dose reduction of anti-rejection medications could potentially lead to an inflammatory immune-reconstitution syndrome that in some cases can be severe or life-threatening.[74]

Mold-active azoles (eg, voriconazole, posaconazole) are used as prophylaxis against fungal infection in some transplant recipients. Serum concentrations of these agents are substantially reduced by rifamycins. There is also a bi-directional interaction with rifabutin, which risks potential rifabutin toxicity. In some centers, azole prophylaxis is avoided.

Therapeutic drug monitoring of anti-TB drugs is also commonly performed in recipients of solid-organ transplants, due to the potential for altered pharmacokinetics in these complicated populations.

TB drugs for solid-organ transplant recipients should be administered daily throughout the treatment course and these patients should be provided with directly observed therapy (DOT) and/or close supportive care. Treatment extension to nine months is endorsed for this population but direct evidence to support this is lacking.[67,75] Many experts recommend longer treatment courses in transplant recipients, reasoning that, as in untreated HIV infection, where there is also persistent cell-mediated immune dysfunction, treatment extension has been demonstrated in controlled trials to reduce relapse risk.[16]

Recommendations

- **We strongly recommend rifamycin-based therapy for optimal treatment of TB in solid-organ transplant recipients** (*good evidence*).
- **We conditionally recommend rifabutin over rifampin to reduce the risk of potentially severe drug interactions with anti-rejection medications** (*poor evidence*)**.**
- **We conditionally recommend, given the potentially severe risk of drug-drug interactions, regular therapeutic drug monitoring of anti-rejection medications** (*poor evidence*).
- **We conditionally recommend treatment extension to nine months for solid-organ transplant recipients** (*poor evidence*).

4. People prescribed TNF-alpha inhibitors

TNF-alpha inhibitors (TNFi), including infliximab, adalimumab, etanercept, golimumab and certrolizumab, are associated with an elevated risk of reactivation of TB disease. Multiple registry analyses estimate the risk of TB to be more than twice that of patients with inflammatory disease not taking TNFi and up to 20 times higher than the general population.[76–79]

TB reactivation rates appear higher when TNFi therapy is given along with methotrexate or azathioprine.[80] Furthermore, within the TNFi class, infliximab and adalimumab appear to convey a higher risk of TB reactivation than etanercept.[81,82] The introduction of systematic screening for TB infection prior to initiation of treatment with TNFi appears to have reduced, but not eliminated, TB in people receiving these agents.[79,83,84]

TNF-a is a cytokine essential for the activation of macrophages and the formation and maintenance of granulomas.[85] The inhibition of TNF-a function leads to reduced immunologic containment of TB infection and can alter the clinical presentation of disease.

Indeed, people with TNFi-associated TB are more likely to have disseminated, meningeal and extra-pulmonary disease and less likely to have cavitary chest disease or sputum smear positivity.[86,87] This atypical presentation may delay TB recognition.[87,88] TB in patients treated with TNFi usually occurs within a median of 3 months after starting TNFi therapy.[87,89]

Sometimes, use of TNFi is delayed in patients who are under evaluation for possible TB before the diagnosis is confirmed, out of concern that the immune suppression may hasten disease progression or lead to dissemination before effective anti-TB therapy can be established.[90–92] However, it should be noted that abrupt TNFi withdrawal may be associated with exacerbation of TB disease despite anti-TB treatment, somewhat analogous to IRIS seen in HIV-coinfected patients.[93,94] Vigilance for this effect is prudent and re-introduction of TNFi has been reportedly effective in its management.[86,92,95,96] Small cohort studies and clinical experience suggest that TNFi can be safely administered once patient is established on effective TB therapy and provided that drug-resistance is not suspected.[95,97–100]

Despite lack of experimental data, many experts recommend longer treatment courses in patients receiving TNFi, reasoning that, as for people with untreated HIV infection, and thus persistent immune dysfunction, treatment extension may reduce relapse risk.[16] Relapse in people re-started on

TNFi therapy and completing standard TB treatment durations has been reported.[21,95]

Recommendations

- **We conditionally recommend that, where TNF-alpha inhibitors are stopped following the development of TB disease, it can be re-introduced once the patient is established on effective TB therapy** (*poor evidence*).
- **We conditionally recommend extending TB treatment to nine months in patients receiving TNF-alpha inhibitors** (*poor evidence*).

5. People with diabetes

Systematic reviews have estimated a three-fold increase in active TB in people with diabetes[101,102] and risk appears especially high in those with poor glycemic control, insulin dependence and higher Hba1c.[103–105]

The clinical manifestations of TB are altered by the presence of diabetes. Observational studies suggest people with diabetes are more likely to have cavitary and sputum smear-positive disease but less likely to have extra-pulmonary disease.[106–109]

Hyperglycemia and poorly controlled diabetes have also been correlated with worse TB treatment outcomes. Multiple retrospective studies observe that people with both TB and diabetes experience delayed sputum culture conversion and higher rates of treatment failure, relapse, mortality and acquisition of rifampin resistance.[107,110–114]

The prevalence of diabetes in people with newly diagnosed active TB can range up to 25% when routine testing is employed (see Chapter 1: Epidemiology of Tuberculosis in Canada, Figure 11). This has been demonstrated in both high TB-incidence and low TB-incidence countries.[115–119] In one Canadian study, diabetes was present in 19.7% of people with active TB.[120] Thus, screening for diabetes in patients with active TB is recommended and measurement of glycosylated hemoglobin A1C percentage is commonly used.[121–123]

Good practice statement

- **At the time of diagnosis of TB disease, routine screening for diabetes through measurement of glycosylated hemoglobin A1C percentage is suggested and those diagnosed with diabetes should be linked to a diabetes care provider.**

Optimization of glycemic control is associated with improved TB treatment outcomes.[109,111,124–126] People diagnosed with diabetes during their TB care should receive a referral to a diabetes care provider for long-term management.

Peak serum TB drug concentrations are frequently low in people with diabetes and this may contribute to the poorer TB treatment outcomes seen in this population.[3,28,29,33,127] It is not entirely clear how diabetes effects the pharmacokinetics of TB drugs, but increased body weight and gastroparesis with delayed absorption have been suggested as potential factors.[127–129] At least one observational study has linked the routine measurement of serum TB drug concentrations in diabetic patients with faster microbiological response to TB treatment.[130]

Longer treatment duration may be required in people with diabetes. In one large country-wide registry of people under treatment for pulmonary TB in Taiwan, higher relapse rates seen in people with diabetes was mitigated when TB treatment was extended to 9 months total.[107] However, the impact of treatment extension was small; of 12,688 people with diabetes and TB, relapse rates were 2.23% in those who received 6 months of treatment and 2.00% in those receiving 9 months (aHR 0.75 (95% CI, 0.59-0.97).

Recommendations

- **We conditionally recommend that for people with poorly controlled diabetes or evidence of gastroparesis, serum TB drug concentrations be used to optimize drug dosing** (*poor evidence*).
- **We conditionally recommend treatment extension to 9 months for those with diabetes and cavitary pulmonary or disseminated TB disease** (*poor evidence*).

6. People with chronic kidney disease

End-stage kidney disease requiring dialysis is a well-established risk factor for TB disease, with incidence rates 7 times higher than the general population.[131–133] Evidence is emerging to suggest that TB risk is also increased in people with earlier stages of chronic kidney disease (CKD), with risk rising as estimated glomerular filtration rate drops below 50 ml/min.[133–135]

Susceptibility to TB in CKD appears multifactorial.[136,137] People with CKD often have low 25-hydroxy vitamin D levels and higher rates of protein malnutrition. As uremic waste products accumulate in later stages of renal disease, a broad cellular immune dysfunction develops. The risk of TB may be compounded by associated co-morbid conditions such as diabetes and use of immune suppressive drugs.

The clinical presentation of TB in people with CKD is often insidious and atypical.[136] Systemic symptoms, such as fever, anorexia and weight loss, may mimic uremia and can result in a delay of diagnosis. People with CKD frequently have extra-pulmonary TB, rather than the more recognizable pulmonary disease.[138] Delayed recognition may contribute to the higher mortality rates seen in these populations.[136]

A special consideration in this population is to ensure renal-adjusted dosing for some TB drugs.[136] Rifampin and INH are primarily metabolized and excreted through the liver with little urinary clearance. Thus, dose adjustment of these agents is not required for patients with renal insufficiency.[138] Although PZA is also metabolized primarily through the liver, some of its metabolites are eliminated renally and so its dose should be adjusted in people with advanced CKD ((Stage 4/5, GFR < 30ml/min).[138,139] Ethambutol (EMB) is mostly excreted unchanged by the kidneys and people with advanced CKD have substantially reduced clearance of the drug.[140] Ethambutol-induced ocular toxicity is largely dose-related and so dose adjustment and regular visual acuity testing is necessary in those with advanced CKD.

Because therapeutic efficacy of both PZA and EMB appears dependent on peak concentrations, the dosing interval for both drugs should be extended in people with advanced kidney disease, rather than decreasing the dose administered.

There is insufficient evidence to guide dosing of people with moderate kidney disease (GFR 30-60mL/min). In this range, people should be monitored carefully for toxicity, and therapeutic drug monitoring might be necessary to guide appropriate dosing.

The mechanism of drug removal by peritoneal dialysis is not the same as by hemodialysis and so TB drug-dosing recommendations for people receiving hemodialysis may not necessarily apply. There is comparatively little clinical experience in TB drug-dose adjustment in people receiving peritoneal dialysis.[141,142] Thus, people receiving peritoneal dialysis should be monitored carefully for drug toxicity and therapeutic drug monitoring may be necessary.

Treatment extension solely based on CKD is not recommended, as neither slower response to treatment nor higher relapse rates have been reported in these patients.

Recommendation

- **We conditionally recommend, in people with advanced chronic kidney disease (Stage 4/5, GFR < 30ml/min), that dose intervals should be modified to three times weekly for pyrazinamide (25-30 mg/kg) and ethambutol (15-20 mg/kg)** (*poor evidence*).

Good practice statement

- **Pyrazinamide and ethambutol (and other first-line TB drugs) should be dosed after dialysis session in people on hemodialysis.**

7. People with liver disease

TB treatment in patients with underlying liver cirrhosis is challenging because with limited hepatic functional reserve, they are at particular risk of liver decompensation following drug-induced hepatotoxicity. For patients with liver cirrhosis of any stage, PZA and INH are best avoided[143] and establishing a hepatic-sparing TB regimen in consultation with a TB expert is recommended.

Although rifampin is associated with drug-induced liver injury, the risk is significantly lower than with either INH or PZA.[144] Furthermore, rifampin is considered crucial to achieving relapse-free (or long-term) TB cure. Thus, rifampin is often used in patients with compensated liver cirrhosis (Child-Pugh A) although is usually avoided in those with overt liver decompensation (Child-Pugh B or C).[143] Fluroquinolones, especially levofloxacin, are associated with low rates of hepatotoxicity and are sometimes used in people with decompensated liver cirrhosis.[145,146]

Serological screening for viral hepatitis infection should be a part of routine testing at the time of TB treatment initiation for all people with TB, regardless of whether liver disease is apparent on initial testing.[147,148] Viral hepatitis and TB share epidemiologic associations: both hepatitis B (HBV) and C (HCV) are more prevalent in people from Asian and African regions.[149,150] In Canada, HCV infection is prevalent in people who use drugs, those who are unstably housed and those born before 1965. Viral hepatitis is also a risk factor for drug-induced liver injury during TB treatment.[151–155]

Observational data has shown that antiviral treatment of active hepatitis B during TB therapy reduces the incidence of subsequent drug-induced liver injury and hospitalization. TB patients found to be seropositive for hepatitis B surface antigen at the time of TB diagnosis should be promptly referred for hepatitis B treatment.[156]

Currently recommended antiviral treatment regimens for chronic hepatitis C infection are considered incompatible with the rifamycin class because of significant drug-interactions.[157] Antiviral therapy for HCV is thus usually deferred until completion of rifamycin-based TB treatment. Collaboration with a hepatitis specialist is recommended.

Recommendation

- **We conditionally recommend routine serological screening for viral hepatitis at the time of TB treatment initiation** (*poor evidence*).

Good practice statement

- **When initiating active TB therapy in people with liver cirrhosis, consultation with a TB expert is advised. A hepatic-sparing regimen, which might exclude pyrazinamide and isoniazid, may be required.**

8. Women who are pregnant and breastfeeding

8.1. TB and pregnancy

Population studies demonstrate an elevated risk of TB in pregnant and postpartum women, with incidence rates nearly twice that of women who are not pregnant.[2,158]

Pregnancy suppresses T-helper cell-mediated immune function, increasing susceptibility to TB infection and progressive disease.[159,160] However, immune suppression seen during pregnancy can also mask the symptoms of progressive disease, making recognition more difficult.[161] Furthermore, insidious symptoms of active TB may be attributed to pregnancy itself. Hesitancy to perform chest radiography may further delay diagnosis.[162] After delivery, T-helper cell suppression is immediately reversed and, in some cases, the symptoms of TB disease are exacerbated as a result.[159]

TB in pregnancy is associated with significant morbidity for both woman and their infants.[163,164] Pregnant women with TB have higher rates of miscarriage, cesarean sections, anemia, pre-term labor and mortality.[165,166] Infants born to mothers with active TB are more likely to be premature or low birthweight.[165] Thus, referral to an obstetrician for expert prenatal care is recommended for all pregnant women with TB.

Initiation of treatment for active TB in pregnancy should never be deferred, as the benefits of TB treatment greatly outweigh risks to mother and fetus. TB is not by itself an indication for termination of pregnancy. Treatment of TB in pregnant women is largely the same as in nonpregnant women.[162,167] Treatment failure and relapse are not more common in pregnancy and treatment extension is not necessary.[168,169] Dose adjustments are not required with advancing gestation as clinically significant changes to pharmacokinetics of the TB drugs have not been demonstrated.[170] Adverse effects from TB drugs, including drug-induced hepatitis, may be more common in pregnant women and careful monitoring is required.[171]

The first-line anti-TB drugs are all categorized as "Category C" by the US Food and Drug Administration. This classification reflects the lack of controlled studies in pregnant women and possible harm to fetus in animal reproductive studies. However, INH, rifampin and EMB have long track records of safety in pregnancy and are considered acceptable for first-line treatment.[167,172,173]

Because PZA is not absolutely necessary to cure TB, and because there is a lack of formal studies on the fetal safety of this drug, its inclusion in treatment regimens for pregnant woman is usually decided on a case-by-case basis. To date, no reports of PZA teratogenicity in humans have emerged despite a long history of use[21] and the WHO continues to recommend its use in pregnant women.[174] If PZA is not used, TB treatment is extended to nine months.

Fluroquinolone use in pregnancy has not been associated with adverse pregnancy outcomes.[175] However, larger studies that include pregnant women exposed to longer treatment durations are needed to better establish safety; at the present time. these drugs should be used only if there are no safer alternatives.

There is considerably less experience with second-line TB agents in pregnancy[167] (see Chapter 8: Drug-resistant Tuberculosis). Consultation with an expert in multidrug-resistant TB is recommended.

Recommendations

- **We strongly recommend using isoniazid, rifampin and ethambutol as initial treatment in pregnant women, as all 3 are considered safe in pregnancy** (*good evidence*).
- **We conditionally recommend adding pyrazinamide to the regimen in pregnant women with extensive disease, smear-positive pulmonary disease, disseminated TB or intolerance of any of the other first-line drugs** (*poor evidence*).

8.2. TB and breastfeeding

First-line TB drugs achieve only very minimal concentrations in breast milk and toxicity to infants has not been reported. TB transmission via breast milk has not been reported in the chemotherapeutic era.[176]

Good practice statements

- **Breastfeeding is to be encouraged in women taking first-line TB therapy.**
- **Pyridoxine supplementation for the breastfeeding infant is not necessary unless the infant is also taking isoniazid.**

See Chapter 9: Pediatric Tuberculosis for management of the neonate and peripartum periods.

9. People over 75 years of age with TB

In Canadian-born non-Indigenous and foreign-born Canadians, TB incidence rates are highest in those older than 75 years of age.[177] The higher rate of TB in older adults appears to be driven by a combination of higher prevalence of latent infection, increasing frequency of medical co-morbidities and, possibly, waning immunity.[178]

TB disease can be more difficult to recognize in older adults.[179] Chest radiographic patterns are often atypical, with older adults less likely to demonstrate cavitation or upper-lobe predominance of infiltrates. Older adults are also more likely to have smear-negative disease.[180]

Age over 75 years appears to be associated with poorer TB treatment outcomes, including higher mortality rates and lower completion rates.[180,181] Age over 75 years is also associated with more adverse events, including gastrointestinal upset, rash, drug interactions and drug-induced liver injury.[144,182–185] A systematic review demonstrated that the odds of drug-induced liver injury in active TB treatment was 30% higher in older people than in younger people.[185] In older patients with active TB, PZA is the most common cause of adverse events. However, these risks should be balanced with the benefit of PZA in people with high bacillary burden.

Recommendation

- **We conditionally recommend the routine use of pyrazinamide be avoided in older adults, particularly in those over 75 years of age** (*poor evidence*).

10. People with alcohol-use disorder

Excessive alcohol use is a well-established risk for TB. A systematic review found that people who drink more than 40 g of alcohol per day or who have a diagnosed alcohol-use disorder are at a 3-fold higher risk of TB disease compared to people with lower alcohol use.[186–188]

Alcohol likely exerts a direct toxic effect on the cellular immune system, increasing susceptibility to TB.[188] Furthermore, people with alcohol-use disorder experience higher rates of social marginalization, homelessness, micro- and macronutrient deficiency and incarceration, all of which are associated with elevated rates of TB infection and reactivation.[188]

Alcohol-use disorder has been associated with delay in diagnosis of TB and a higher likelihood of sputum-smear positivity at diagnosis.[189,190]

People with heavy alcohol use have nearly double the risk of treatment failure and have elevated TB-related mortality.[191–193] These adverse outcomes are only partly explained by loss to follow-up; high rates of adverse events, intermittent nonadherence and severity of initial disease also contribute. In people

with alcohol-use disorder, community-based, rather than clinic-based, DOT is preferred.[191,194]

Good practice statement

- **People with an alcohol-use disorder should receive supportive care, including community-based direct observed therapy, to ensure optimal adherence, and should be linked to alcohol counseling and support services while undergoing TB therapy.**

11. People who inject drugs

Although precise estimates are not available, people who inject drugs appear to have a higher risk of TB infection and disease than the general population.[195–198] This susceptibility is likely mediated by several factors, including co-morbid HIV infection, tobacco use and undernutrition, as well as increased risk of exposure related to homelessness and incarceration. The presentation of TB is not evidently altered by injection drug use itself, absent co-morbid, immune-altering conditions.

Injection drug use has been associated with reduced adherence to, and lower rates of, TB treatment completion.[199] However, enhanced adherence supports such as provision of monetary or material treatment incentives, peer support, integration with opiate agonist therapy and DOT can improve adherence to TB treatment and monitoring.[195,200,201] Several studies have highlighted that, with adequate adherence support, high treatment completion rates and good outcomes can be achieved in people who inject drugs.[195,202,203]

Co-morbid liver disease is common in people who inject drugs and screening for viral hepatitis and close treatment monitoring is prudent.[195]

Rifampin substantially reduces serum concentrations of methadone and buprenorphine, and this can precipitate opiate withdrawal syndrome.[204] Furthermore, once rifampin is stopped, hepatic enzyme induction will wear off, usually over a period of about 2 weeks, and opiate serum concentrations can then increase, risking opiate toxicity. Rifabutin exerts less of an effect on the metabolism of these drugs and is not usually associated with withdrawal symptoms.[205,206] Hydromorphone does not interact with the rifamycin drug class and dose adjustment is not necessary.

Given these clinically important drug-drug interactions, dosage adjustment of opioid agonist therapy and close monitoring is required throughout TB therapy. It is important that TB treatment providers alert opioid agonist providers prior to initiating rifamycin therapies and that an opiate monitoring strategy is in place. A notification to the opiate prescriber when the rifamycin is soon to stop is also strongly advised.

For patients who may not tolerate any change to opiate-agonist therapy, rifabutin can be substituted for rifampin in the TB treatment regimen.

Good practice statements

- **People with drug-use disorders should receive supportive care, including community-based directly observed therapy, to ensure optimal adherence, and should be linked to drug-use counseling and support services while undergoing TB therapy.**
- **In patients receiving treatment for TB with rifamycin-based regimens who are also on opioid agonist therapy, it is important to adjust opioid agonist therapy in close collaboration with provider at both initiation and completion of the TB treatment course.**

12. People who smoke tobacco

People who smoke tobacco are at increased risk of TB infection and progression to active TB, likely due to biologic impacts on innate immune responses and social factors related to exposure.[207,208] Recent systematic reviews estimate the risk of TB disease to be twice as high in people who smoke compared to nonsmokers.[207,209]

Smoking may also affect the clinical presentation of TB. Large patient registries from Spain and Hong Kong have demonstrated that people who smoke are more likely to have pulmonary disease, lung cavitation and sputum-smear positivity and are more likely to require hospitalization for TB treatment than are nonsmokers with TB.[210,211]

Smoking is also associated with worse TB treatment outcomes, including a higher risk of recurrence and increased mortality.[211–213] One cohort study found those who smoke more than 10 cigarettes per day are twice as likely to relapse as those who do not currently smoke.[214] Additionally, TB is associated with an increased incidence of airway disease after treatment completion, which may compound the adverse effects of smoke exposure and existing airway disease.

TB patients are engaged into medical care for several months and have frequent visits with nursing staff, pharmacists and physicians. This represents a good opportunity to offer help in smoking cessation. A systematic review demonstrated that smoking cessation interventions appear effective in people receiving treatment for TB.[215] No controlled trials have examined the impact of smoking cessation interventions affect TB treatment outcomes.[216]

Good practice statements

- **People with TB who smoke tobacco should be offered tobacco cessation interventions during TB therapy.**
- **People with pulmonary TB who smoke tobacco should be offered pulmonary function testing at the end of treatment.**

13. Drug-drug interactions

A complete medication review with assessment for potential drug interactions and need for dose adjustments of concomitant medications is recommended for all patients at initiation of TB treatment. Any adjustments of doses of these medications should be reconsidered within 2 weeks of stopping TB treatment.[217–219]

There are several freely available online drug interaction resources that we suggest can be helpful to guide this assessment:

- Medscape (https://reference.medscape.com/drug-interactionchecker)
- University of Liverpool HIV Drug Interactions (https://www.hiv-druginteractions.org/checker)
- HIV/HCV Drug Therapy Guide from Toronto (https://hivclinic.ca/wp-content/plugins/php/app.php)

Rifampin is a well-documented potent inducer of hepatic and intestinal cytochrome P450 (CYP) enzymes, as well as the P-glycoprotein (P-gp) transport system. The onset of induction effects is gradual, with maximal effects on metabolizing enzymes and drug transporters by about two weeks. Induction can last for up to 4 weeks after stopping rifampin.[220]

Rifabutin is a less potent inducer of CYP P450 then rifampin. However, unlike rifampin, rifabutin is also a substrate of CYP3A4 and, therefore, can participate in bi-directional interactions, meaning that the metabolism of rifabutin can be altered by other drugs.[68,221]

Rifapentine, when dosed weekly, exerts less induction of CYP P450 then does rifampin. However, when rifapentine is dosed daily, it appears to have an even greater inductive effect than standard-dosed rifampin.[222] Rifapentine is not a substrate for CYP3A.

Isoniazid is primarily metabolized via N-acetylation and is an inhibitor of several CYP450 isoenzymes. Isoniazid may inhibit the metabolism of concomitant agents, including some antiepileptics or benzodiazepines.[223,224]

The absorption of quinolones is significantly affected when administered at the same time as antacids and minerals containing multivalent cations, such as aluminum, magnesium or iron. Separating administration times by at least 2 hours is recommended.[21]

EMB and PZA have a low risk of drug-drug interactions.

Good practice statement

- **Drug-drug interactions and altered pharmacokinetics of TB drugs are frequently encountered in people with HIV co-infection, organ transplantation, medical co-morbidities, liver disease, renal dysfunction, and advanced age. Consultation with an experienced pharmacist is recommended when treating TB in these populations.**

Disclosure statement

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Table 2. Common drug-drug interactions with Rifamycins (Last updated Dec 2021).

Drugs/Drug Classes Impacted	Potential Mitigation Strategy
Anticoagulants Warfarin Apixaban, dabigatran, edoxaban, rivaroxaban	Continue warfarin with frequent INR monitoring while on rifampin and for 4 weeks after stopping rifampin. Alternatively, could change to LMWH injection. [225,226] Avoid use of direct-acting oral anticoagulants with rifampin. Rifabutin may be used with dabigatran.[227–231]
Anticonvulsants carbamazepine, phenytoin, lamotrigine	Consult with neurologist to discuss the possibility of using alternative anti-epileptic agent. Levetiracetam is a preferred anticonvulsant when taking rifamycins as there are no clinically relevant interactions. Alternatively, therapeutic drug monitoring of these anti-epileptic agents with subsequent dose adjustment is required.[232–235]
Antidiabetics agents	More frequent blood glucose monitoring recommended. Potential for decrease in drug concentration of most oral antidiabetic agents in patients on rifamycins and potential for increased blood glucose levels. Dose adjustment of antidiabetic agents may be required,[236–243] No significant interaction with metformin or insulin.[243]
Antifungals Azoles (itraconazole, fluconazole, posaconazole, voriconazole, isavuconazole)	Subtherapeutic azole concentrations may occur when used with any of the rifamycins.[244–248]
Antihypertensives	Increased BP monitoring recommended with most antihypertensives. Rifampin has a strong interaction with calcium channel blockers and clinicians may be required to increase dose of the calcium channel blocker or change/add an alternate antihypertensive agent (consult provider). Rifabutin has a less potent interaction as compared to rifampin.[249–252]
Antiretroviral agents	See Text and Table 1.
Corticosteroids dexamethasone, methylprednisolone, prednisone	Monitor clinical response. May require increase in dose of corticosteroids.[253–255]
Immunosuppressive agents cyclosporine, tacrolimus	Rifabutin use is preferred over rifampin to minimize impact on concentrations of calcineurin inhibitors and to reduce the risk of allograft rejection. Monitor calcineurin inhibitor concentrations and adjust dose as required.[256–260]
Levothyroxine	Continue both agents but monitor TSH monthly. May require increase in dose of levothyroxine with rifamycins. Monitor TSH after stopping rifamycins.[261–263]
Opiate agonist therapy methadone, buprenorphine/naloxone (Suboxone)	Methadone and buprenorphine serum concentrations decrease substantially with rifampin and precipitation of withdrawal symptoms is frequent. May need preemptive OAT regimen dosage adjustment in addition to close monitoring. Discuss OAT with provider.[204,264,265] Rifabutin has much less impact on methadone and buprenorphine serum concentrations and is not associated with withdrawal symptoms.[205,206]
Oral hormonal contraceptive ethinyl estradiol, norethindrone, etc	Add a barrier method of contraception when taking a rifamycin with oral hormonal contraceptives.[266]

Abbreviations: INR, international normalized ratio; LMWH, Low molecular weight heparin; BP, blood pressure; TSH, thyroid-stimulating hormone; OAT, opiate agonist therapy.

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