CHAPTER 4: TUBERCULOSIS (TB) DISEASE

Chapter developed by: Prof Terry O'Connor[1], Prof Catherine Fleming[2], Dr Conor Grant[3], Dr Niamh Logan,[3] Dr James O'Connell[4] and Ciara MacKenna[5], in collaboration with the Guideline Development Group for the National Tuberculosis (TB) Guidelines and the Research and Guideline Development Unit (RGDU)[6]

1. Consultant Respiratory Physician, Mercy University Hospital, Cork
2. Consultant in Infectious Disease, Galway University Hospital, Galway
3. Respiratory Department, St James's Hospital, Dublin
4. Specialist Registrar in Public Health Medicine, Health Service Executive
5. Pharmacist, St James's Hospital, Dublin 8
6. HSE: Public Health, National Health Protection Office, Health Service Executive

This guideline chapter draws on NICE guidance © NICE (2016) Tuberculosis. Available from here. All rights reserved. Subject to Notice of rights. NICE guidance is prepared for the National Health Service in England. It is subject to regular review and updating and may be withdrawn. NICE accepts no responsibility for the use of its content in this publication

SUMMARY OF RECOMMENDATIONS

- In the context of suspected pulmonary TB (PTB), perform a chest X-ray. Further diagnostic investigations should follow if chest X-ray appearances suggest TB.
- Rapid nucleic acid tests (GeneXpert® MTB/RIF Ultra assay) and TB cultures should be carried out when a diagnosis of TB disease is suspected.
- Additional radiological examinations, biopsies and/or referral for specialist clinical input may be required for the diagnoses of extra-pulmonary TB (eTB). Please see section 4.2.2 for further detail.
- The clinician responsible for initial care should refer the person with TB to a clinician with training in, and experience of, the specialised care of people with TB.
- Multidisciplinary TB clinics should be developed, for provision of direct referral pathways for people with confirmed and suspected TB.
- All patients diagnosed with TB should receive directly observed therapy (DOTS) or video observed therapy (VOTS) especially in the early stages of treatment. Where resources are scarce priority for DOT/VOT should be given to those patients with drug resistant TB and/or those patients whose medical or social circumstances indicate that treatment adherence may be problematic.
- All patients diagnosed with TB should be tested for HIV coinfection.
- Standard therapy for TB disease that is genotypically rifampicin sensitive on PCR, and without CNS involvement, consists of 2 months Rifampicin, Isoniazid (with

pyridoxine), Pyrazinamide and Ethambutol, followed by Rifampicin and Isoniazid (with pyridoxine) for a further 4 months.

- Services should recognise special populations with a diagnosis of TB, including people who are pregnant or breastfeeding, people living with HIV, liver disease and renal disease (see section 4.7), and underserved populations such as Travellers, Roma, refugees and applicants seeking protection[1], people who are homeless, and other marginalised groups realising that additional medical, nursing and community support (including peer support), as well as translated resources and interpretive services may be required.

4.1 Introduction

TB disease (also referred to as active TB) is defined as infection with mycobacteria of the *M. tuberculosis* complex, where mycobacteria are multiplying and causing symptoms and signs of disease. This is distinct from TB infection (also known as latent TB infection -LTBI) where mycobacteria are present but are inactive and not causing symptoms of disease. The diagnosis of TB disease is made most often on the basis of positive cultures but approximately 15%-25% of cases are a clinical diagnosis on the basis of appropriate clinical, radiological and pathological presentation, as well as treatment response.

Although the incidence of TB is decreasing in Irish-born individuals, the risk of TB remains higher in people from higher incidence TB countries reflecting their country of origin, and among people who are immunosuppressed (1). See more information on the Health Protection Surveillance Centre (HPSC) website.

4.2 Diagnosing TB disease

TB should be considered especially in the setting of chronic cough (>3 weeks), loss of appetite and unexplained weight loss, or night sweats (2).

If TB is considered a possibility, microbiology staff should consider carrying out GeneXpert® MTB/RIF Ultra assay and/or culture on submitted samples, even if it is not requested.

Appropriate microbiologic tests should always be obtained before commencing treatment for TB. However, if there are clinical signs and symptoms consistent with a diagnosis of TB and

[1] Refugees and applicants seeking protection include: Programme Refugees, Beneficiaries of Temporary Protection (BOTP) fleeing war in Ukraine, and International Protection Applicants (IPA)(*'asylum seekers'*)

following a risk assessment by the treating physician, TB treatment may be commenced pending culture results and/or if TB culture results are negative

Report results of all pathology or other diagnostic results suggesting TB to the patient's multidisciplinary team, and clinicians who ask for them.

All patients diagnosed with TB should be tested for HIV coinfection.

4.2.1 Diagnosing pulmonary (including laryngeal TB)

A chest X-ray should be performed if a clinical diagnosis of pulmonary TB is suspected. If chest X-ray appearances suggest TB, further diagnostic investigations should be carried out.

Occasionally a patient may have laryngeal TB in the setting of a normal CXR.

Send at least three separate respiratory samples (deep cough sputum samples) for TB microscopy and culture (3).

Samples should be obtained before starting treatment if possible or, failing that, within 7 days of starting treatment in people with life threatening disease.

Obtain spontaneously produced, deep cough sputum samples if possible, otherwise use induction of sputum following nebulisation of hypertonic saline or consider bronchoscopy and lavage and +/- CT Thorax if sputum is smear negative or not obtainable (3).

Send samples for TB culture from autopsy samples if pulmonary or laryngeal TB is a possibility.

Request rapid diagnostic nucleic acid amplification tests (GeneXpert® MTB/RIF Ultra assay) for the *M. tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum*) on specimens if there is clinical suspicion of TB disease (3, 4).

Interferon Gamma Release Assays (IGRAs) are of limited clinical utility in the diagnosis of TB disease (3).

4.2.2 Diagnosing extrapulmonary TB (eTB)

Discuss the advantages and disadvantages of both biopsy and needle aspiration with the patient, with the aim of obtaining adequate material for diagnosis.

Do not place part or all of any of the samples in formalin (or other fixative agent) when sending for TB culture.

While rapid diagnostic tests are useful if positive, they have a low sensitivity for detection of TB in pleural, ascitic, pericardial fluid and CSF samples.

Offer all patients presenting with suspected extrapulmonary TB a chest X ray and, if possible, culture of a spontaneously produced respiratory sample to exclude or confirm coexisting pulmonary TB. Also, consider site specific tests as described below to exclude or confirm additional sites of TB disease.

Refer to an expert for sites not listed here, including TB of the eye and other rare sites of disease.

4.2.2.1 Pleural TB

In patients with suspected pleural TB, take a chest X-ray and consider CT Thorax (5).

Ultrasound-guided pleural fluid samples should be sent for microbiological analysis (including GeneXpert® MTB/RIF Ultra assay), biochemistry (which may include adenosine deaminase), and cytology with differential cell count (3).

If suspected coexistent pulmonary TB, send three separate deep cough sputum samples for GeneXpert® MTB/RIF Ultra assay, TB microscopy and culture. Consider bronchoscopy if sputum negative or not obtainable.

Consider a pleural biopsy in cases where the above tests are non-diagnostic or if there is a concern for drug-resistant TB (3).

4.2.2.2 Lymph Node TB (including intrathoracic mediastinal lymphadenopathy)

Ultrasound (including endobronchial ultrasound), CT and MRI imaging should be used in suspected lymph node TB to obtain biopsy or aspiration samples for microscopy, culture, histology, cytology and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay).

Treat active peripheral lymph node TB in people who have had an affected gland surgically removed with the standard recommended regimen.

4.2.2.3 Bone and joint TB

In patients with suspected bone or joint TB, X-rays, CT and MRI may help to obtain biopsy or aspirates from a paraspinal abscess, biopsy of a joint or aspiration of joint fluid for microscopy,

culture, histology and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay) (3, 4).

Consider lumbar puncture in patients with active spinal TB who have neurological signs or symptoms, to assess central nervous system involvement.

TB medication is the first line of treatment for spinal TB. Additional interventions may be necessary based on the assessment of a multidisciplinary team. Do not routinely refer people with spinal TB for surgery to eradicate the disease. Refer people with spinal TB for surgical review of images/surgery if there is spinal instability or spinal cord compression.

4.2.2.4 Central Nervous System TB

In patients with suspected CNS TB, consideration should be given to CT and/or MRI of brain, biopsy of suspected tuberculoma and cerebrospinal fluid sampling for microscopy, culture, histology and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay).

Treatment for TB meningitis may be initiated if clinical signs and other laboratory investigations are consistent with the diagnosis, even if a rapid diagnostic test is negative.

Manage direct spinal cord involvement (for example, a spinal cord tuberculoma) as TB of the central nervous system.

Consider referring people with TB of the CNS for surgery as a therapeutic intervention only if there is evidence of raised intracranial pressure.

4.2.2.5 Localised tuberculous abscess

In patients with suspected localised tuberculous abscess (outside of the lymph nodes), ultrasound or other appropriate imaging can be used to obtain aspirate and biopsy material for microscopy, culture, histology and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay) (3, 4).

4.2.2.6 Disseminated TB

In patients with suspected disseminated TB, CT of the head, thorax, abdomen and pelvis, MRI or abdominal ultrasound may help to obtain biopsies from sites of disease such as lung, liver and bone marrow. Targeted samples such as bone marrow aspirates, bronchial washings and cerebrospinal fluid can be sent for microscopy, culture, histology and/or nucleic acid

amplification testing (GeneXpert® MTB/RIF Ultra assay) (3, 4). Blood cultures for TB can be diagnostic and should be sent.

Test people with disseminated (including miliary) TB who have neurological signs or symptoms for CNS involvement. If there is evidence of CNS involvement, treat as for TB of the CNS.

4.2.2.7 Pericardial TB

In patients with suspected pericardial TB, echocardiography should be used to guide consideration for pericardial fluid sampling or pericardial biopsy for microscopy, culture, histology, adenosine deaminase measurement and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay).

4.2.2.8 Gastrointestinal TB

In patients with suspected gastrointestinal TB, ultrasound, CT, endoscopy and laparoscopy may be used to obtain ascitic fluid, or biopsies of omentum, bowel and liver for microscopy, culture, histology, adenosine deaminase measurement and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay).

4.2.2.9 Genitourinary TB

In patients with suspected genitourinary TB, three early morning urine[2] samples over three consecutive days should be sent for TB culture. Ultrasound, intravenous urography, laparoscopy, hysteroscopy and cysto-ureteroscopy may help to obtain biopsies from the site of disease, such as endometrial curretting or renal biopsy for microscopy, culture, histology and/or nucleic acid amplification testing (GeneXpert® MTB/RIF Ultra assay) (3, 4).

4.2.2.10 Skin TB

In patients with suspected skin TB, biopsies from sites of disease can be sent for GeneXpert® MTB/RIF Ultra assay microscopy, culture, histology (3, 4).

[2] The Early Morning Urine (EMU) is the first urine passed (voided) after sleep; it is more concentrated urine and likely to yield better test results, as mycobacteria accumulate in the bladder overnight.

4.3 Managing TB disease in all age groups

Once a diagnosis of TB disease is made

- The clinician responsible for care should refer the person with TB to a clinician with training in, and experience of, the specialised care of people with TB.
- The principle of active case management should guide care and all patients should be assigned a nurse who is a point of contact for them (6). For the period of TB treatment, a multidisciplinary service should assist the patient in navigating all medical needs and psychosocial supports. Management of the patient with TB is not just a medical issue and the patient may need support from outside the medical system, e.g. housing, social welfare support, education etc.
- All patients diagnosed with TB should receive directly observed therapy (DOTS) or video observed therapy (VOTS) especially in the early stages of treatment. Where resources are scarce priority for DOT/VOT should be given to those patients with drug resistant TB and/or those patients whose medical or social circumstances indicate that treatment adherence may be problematic.
- Patients diagnosed with TB should be tested for HIV coinfection (3, 4).
- For patients with limited English skills, face to face interpretive services and translated information materials, should be available for all clinical encounters (3). For patients with low literacy, information materials in infographics and visual aids should be available.

4.4 Drugs and dosing regimens

Please see **Table 4.1** for recommended dosing regimens.

Standard therapy for TB disease consists of combination therapy with Rifampicin, Isoniazid (with pyridoxine), Pyrazinamide and Ethambutol. Ideally this should only be started when rifampicin resistance is ruled out by GeneXpert® MTB/RIF Ultra assay. This is especially important if the patient has a risk factor for MDR TB such as prior TB treatment or is part of a group considered to be at higher risk for MDR-TB, for example from an area of the world with higher TB resistance rates.

Concomitant administration of pyridoxine with isoniazid is recommended to prevent neuropathy.

Daily dosing schedule is recommended over thrice weekly dosing regimens. This is due to higher risk of treatment failure, relapse and resistance associated with thrice weekly regimens.

Once drug susceptibility testing results are available, treatment should be modified to reflect any resistance patterns (see Chapter Five: Drug resistant TB).

Use of fixed dose combination tablets is preferred over separate drug formulations, based on evidence showing that compliance is higher with fixed dose combinations.

Table 4.1: Dosing regimen

	Dose	Dose adjustments
Rifater *(Rifampicin, isoniazid & pyrazinamide)* (7)	Adult dose *please see individual component recommendations below* 9-12 mg/kg Rifampicin 4-5mg/kg Isoniazid, and 23-30mg/kg Pyrazinamide Standard adult dose: Weight <40kg three tablets daily Weight 40-49kg four tablets daily Weight 50-64kg five tablets daily Weight >65kg six tablets daily	Renal impairment: pyrazinamide dose to be reduced as outlined below – Rifater combination product not suitable for daily administration Impaired liver function: dose of rifampicin should not exceed 8mg/kg/day – combination product may not be appropriate, may need to prescribe as separate components.
Rifinah *(Rifampicin & isoniazid)* (8)	Adult dose 10mg/kg OD rifampicin with 5mg/kg OD isoniazid Standard adult dose (9): Weight <50kg 150/100mg three tablets OD Weight >50kg 300/150mg two tablets OD Concomitant administration of pyridoxine 10mg OD recommended	Renal impairment: no dose adjustment Impaired liver function: dose of rifampicin should not exceed 8mg/kg/day – combination product may not be appropriate (8).
Rifampicin	Adult dose 8-12mg/kg OD Standard adult dose: Weight <50kg 450mg OD Weight ≥50kg 600mg OD	Renal impairment: no dose adjustment Impaired liver function: dose should not exceed 8mg/kg (10)

Isoniazid (with pyridoxine)	Adult dose 5mg/kg OD Standard adult dose: 300mg OD Concomitant administration of pyridoxine 10mg OD recommended	Renal impairment: no dose adjustment Impaired liver function: no dose adjustment (11)
Pyrazinamide	Adult dose 20-30mg/kg OD Standard adult dose: Weight <50kg 1.5g OD Weight ≥50kg 2g OD	Renal impairment (CrCl <30 ml/min): in severe renal impairment/dialysis dose adjustment required. 25-30mg/kg three times per week (post dialysis on dialysis days) (9) Impaired liver function: no dose adjustment (12)
Ethambutol	Adult dose 15mg/kg OD In obesity, consider use of lean body weight and therapeutic drug monitoring.	Renal impairment (CrCl <30 ml/min): in severe renal impairment/dialysis dose adjustment required. 15-25mg/kg (max 2.5g) three times per week (post dialysis on dialysis days) (6) Impaired liver function: no dose adjustment (13)

4.5 Duration of therapy

Standard duration of therapy for TB disease without CNS involvement;

- 2 months Rifampicin, Isoniazid (with pyridoxine), Pyrazinamide and Ethambutol
- Followed by Rifampicin and Isoniazid (with pyridoxine) for a further 4 months

For TB disease with CNS involvement;

- 2 months Rifampicin, Isoniazid (with pyridoxine), Pyrazinamide and Ethambutol
- Followed by Rifampicin and Isoniazid (with pyridoxine) for a further 10 months

For TB disease with bone or spinal involvement but no evidence of CNS involvement;

- 2 months Rifampicin, Isoniazid (with pyridoxine), Pyrazinamide and Ethambutol
- Followed by Rifampicin and Isoniazid (with pyridoxine) for a further 7-10 months (3).

For TB disease with evidence of cavitation on initial chest x-ray and persistent positive sputum cultures after 2 months of treatment a longer duration of treatment is recommended (9 months total);

- 2 months Rifampicin, Isoniazid (with pyridoxine), Pyrazinamide and Ethambutol
- Followed by Rifampicin and Isoniazid (with pyridoxine) for a further 7-9 months (5).

Longer durations of treatment (e.g. 9 to 12 months total) may be considered for patients at higher risk of treatment failure. Additional risk factors for treatment failure include diabetes, HIV, smokers, low BMI, extensive TB disease on imaging and immunosuppressed individuals (6).

While the published evidence does not support the general use of Therapeutic Drug Monitoring (TDM) for all patients on treatment for TB disease, clinicians may find TDM useful in specific circumstances. Such circumstances include but are not limited to:

- Patients with a BMI of >30 or <18.5
- Advanced chronic kidney or liver disease
- Malabsorptive conditions, when significant drug-drug interactions are expected.
- Delayed sputum conversion or treatment failure in the absence of another explanation
- Disseminated TB

4.6 Adjunctive corticosteroids

Adjunctive high dose steroids are indicated in the treatment of CNS TB. Dexamethasone or prednisolone should be commenced at the start of treatment and tapered over 4-8 weeks.

Consider the use of corticosteroids in those with pericardial TB with risk factors for inflammatory complications (3).

4.7 Special populations

4.7.1 Pregnancy and breastfeeding

Untreated TB poses a significant risk to the mother and foetus, and deferral of TB treatment until after delivery is not recommended (14).

The standard regimen for drug sensitive TB as outlined above is recommended for pregnant women.

There is a paucity of clinical trial data on treatment of TB in pregnant women as they are largely excluded from clinical trials. Although first-line anti-tuberculous drugs do cross the placenta there does not appear to be any associated teratogenicity.

Small concentrations of these anti-tuberculous drugs have been measured in breast milk but have not been shown to cause toxic effects to the infant. Therefore, breastfeeding is encouraged for women with TB who are deemed non-infectious (14).

The concentration of drugs in breast milk should not be considered as a marker of effective treatment for TB disease or TB infection in the nursing infant (6).

Isoniazid is excreted in breastmilk and consideration should be given to the prescription of prophylactic pyridoxine to the nursing infant. Whenever isoniazid is given to a pregnant or nursing woman, supplementary pyridoxine, 25–50 mg/day, is prescribed (6)

4.7.2 HIV

HIV testing should be performed in all patients diagnosed with TB disease. HIV and TB co-infection should be managed by multidisciplinary teams with expertise in managing both TB and HIV.

The standard regimen for drug sensitive TB, consisting of rifampicin (R), isoniazid (I), pyrazinamide (P) and ethambutol (E) or 'RIPE', is recommended for those living with HIV co-infection (14, 15). However, HIV is a risk factor for drug-resistant TB.

A number of drug interactions exist between TB therapies and anti-retroviral therapy, particularly associated with rifampicin. A detailed drug interaction check should be completed prior to commencing therapy and discussion with a multi-disciplinary team with expertise in TB and HIV co-infection.

Patients with newly diagnosed or untreated TB and HIV co-infection should commence antiretroviral therapy alongside anti-tuberculous therapy except in cases of CNS TB (see below). Commencing antiretroviral therapy at the beginning of TB therapy is associated with a significant reduction in morbidity and mortality.

Commencing antiretroviral therapy during TB therapy does increase the risk of immune reconstitution inflammatory syndrome (IRIS) which manifests as transient worsening of TB signs and symptoms in response to therapy. IRIS is more common in those with earlier initiation of antiretroviral therapy (i.e. within 2 weeks) and CD4+ lymphocyte counts <50 cells/μL.

The majority of cases of IRIS are mild to moderate in severity and can be managed symptomatically with non-steroidal anti-inflammatories. More severe cases can be managed with high dose steroids with a gradual wean.

The development of IRIS is not associated with worse treatment outcomes. The exception to this is in CNS TB. In the case of CNS TB antiretroviral therapy should not be commenced until 4-8 weeks of TB therapy has been completed. Early initiation of antiretroviral therapy in patients with CNS TB has been associated with fatal neurologic complications. There is a need, therefore, for a high index of suspicion and a low threshold to investigate for possible CNS involvement, which may present with subtle symptoms (14).

4.7.3 Liver disease

Many anti-tuberculous drugs can cause hepatotoxicity. Those with underlying liver disease, liver transplant and hepatitis C are at increased risk of drug induced liver injury when commenced on TB therapy. These patients should undergo increased monitoring throughout treatment.

Testing for hepatitis B and C is indicated for all persons starting TB treatment.

For those with advanced liver disease and an ALT >3 times the upper limit of normal at baseline (not due to hepatic tuberculosis) treatment regimens with fewer hepatotoxic agents are selected. However, where possible regimens including rifampicin and isoniazid should still be used.

Pyrazinamide is often associated with hepatotoxicity. An example regimen for those with underlying liver disease and sensitive TB could consist of; rifampicin, isoniazid and ethambutol for 2 months followed by rifampicin and isoniazid for 7 months (6, 16).

For those with an acute liver injury with a rise in ALT >3 times the upper limit of normal (if symptomatic) and > 5 times the upper limit of normal if asymptomatic, anti-tuberculous therapy should be interrupted. Every effort should be made to identify the causative drug. Treatment should recommence once liver enzymes have returned to baseline, or ALT returns to <2 x ULN. Drugs should be reintroduced in sequential fashion starting with the least hepatotoxic. (6, 16). Expert opinion from specialists in TB management should be sought in patients with liver disease or hepatotoxicity on anti-tuberculous therapy.

4.7.4 Renal disease

Patients with chronic renal disease have worse outcomes with TB disease and so enhanced monitoring of renal function is recommended.

For patients with chronic renal disease dose adjustments may be necessary. The interval between drug doses should be increased instead of dose reductions for patients with a creatinine clearance of <30 mL/minute and those receiving haemodialysis (6, 14). See **Table 4.1** for dosing regimens.

Serum concentrations of drugs may need to be monitored during treatment.

For patients who are on dialysis, post-dialysis administration of TB medications is preferred to facilitate directly observed therapy (DOT) and avoid increased drug clearance (6, 14).

REFERENCES

1. Health Protection Surveillance Centre (HPSC). Tuberculosis in Ireland: Provisional trends in surveillance data. 2024. Available from: https://www.hpsc.ie/a-z/vaccinepreventable/tuberculosistb/tbdataandreports/20240320_2019-2023_TB_Trends_Slideset%20v1.0.pdf.

2. Leila Barss, William J. A. Connors & Dina Fisher (2022) Chapter 7: Extrapulmonary tuberculosis, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6:sup1, 87-108, DOI: 10.1080/24745332.2022.2036073.

3. Marcel A. Behr, Simon Grandjean Lapierre, Dennis Y. Kunimoto, Robyn S. Lee, Richard Long, Inna Sekirov, Hafid Soualhine & Christine Y. Turenne (2022) Chapter 3: Diagnosis of tuberculosis disease and drug-resistant tuberculosis, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6:sup1, 33-48, DOI: 10.1080/24745332.2022.2035638

4. David M. Lewinsohn, Michael K. Leonard, Philip A. LoBue, David L. Cohn, Charles L. Daley, Ed Desmond, Joseph Keane, Deborah A. Lewinsohn, Ann M. Loeffler, Gerald H. Mazurek, Richard J. O'Brien, Madhukar Pai, Luca Richeldi, Max Salfinger, Thomas M. Shinnick, Timothy R. Sterling, David M. Warshauer, Gail L. Woods. ATS/CDC/IDSA Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. 2017. Available from: https://www.idsociety.org/practice-guideline/diagnosis-of-tb-in-adults-and-children/#ExecutiveSummary.

5. Richard Long, Maziar Divangahi & Kevin Schwartzman (2022) Chapter 2: Transmission and pathogenesis of tuberculosis, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6:sup1, 22-32, DOI: 10.1080/24745332.2022.2035540

6. Payam Nahid, Susan E. Dorman, Narges Alipanah, Pennan M. Barry, Jan L. Brozek, Adithya Cattamanchi, Lelia H. Chaisson, Richard E. Chaisson, Charles L. Daley, Malgosia Grzemska, Julie M. Higashi, Christine S. Ho, Philip C. Hopewell, Salmaan A. Keshavjee, Christian Lienhardt, Richard Menzies, Cynthia Merrifield, Masahiro Narita, Rick O'Brien, Charles A. Peloquin, Ann Raftery, Jussi Saukkonen, H. Simon Schaaf, Giovanni Sotgiu, Jeffrey R. Starke, Giovanni Battista Migliori, Andrew Vernon. ATS/CDC/IDSA Guidelines for Treatment of Drug-Susceptible Tuberculosis. 2016. Available from: https://www.idsociety.org/practice-guideline/treatment-of-drug-susceptible-tb/#OrganizationandSupervisionofTreatment.

7. Electronic Medicines Compendium. Rifater 50mg/120mg/300mg Tablets. 2024. Accessed on: 24 September 2024. Available from: https://www.medicines.org.uk/emc/product/1596/smpc.

8. Electronic Medicines Compendium. Rifinah 300mg/150mg Tablets. 2024. Accessed on: 24 September 2024. Available from: https://www.medicines.org.uk/emc/product/6124/smpc.

9. British National Formulary (BNF). British National Formulary, NICE. Accessed on: 24 September 2024. Available from: https://www.nice.org.uk/bnf-uk-only.

10. Online MI. Rifadin (Sanofi) 150mg Capsules: Summary of Product Characteristics. 2024. Accessed on: 22 May 2024. Available from: https://www.medicines.ie/medicines/rifadin-150mg-capsules-33602/spc.

11. Electronic Medicines Compendium. Isoniazid 50mg Tablets BP: Summary of Product Characteristics. 2023. Accessed on: 22 May 2024. Available from: https://www.medicines.org.uk/emc/product/9138/smpc#gref.

12. Electronic Medicines Compendium. Zinamide (pyrazinamide) 500mg Tablets: Summary of Product Characteristics. 2020. Accessed on: 22 May 2024. Available from: https://www.medicines.org.uk/emc/product/5273/smpc#gref.

13. Electronic Medicines Compendium. Ethambutol 100 mg Tablets: Summary of Product Characteristics. 2022. Accessed on: 22 May 2024. Available from: https://www.medicines.org.uk/emc/product/9345/smpc#gref.

14. Ryan Cooper, Stan Houston, Christine Hughes & James C. Johnston (2022) Chapter 10: Treatment of active tuberculosis in special populations, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6:sup1, 149-166, DOI: 10.1080/24745332.2022.2039500

15. World Health Organization (WHO). Consolidated Guidelines on Tuberculosis Module 6: Tuberculosis and comorbidities 2024. Available from: https://iris.who.int/bitstream/handle/10665/376584/9789240087002-eng.pdf?sequence=1.

16. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. American Journal of Respiratory Critical Care Medicine. 2006;174(8):935-52.