Review Article

Adverse Drug Reactions in Anti-Tuberculosis Therapy with Special Emphasis on Rifampicin: A Review

Vaishnavi. V. Bhosale*, Nikita.C. Mohite, Omkar.A. Devade, Prakash. D. Jadhav, Sonali .T. Kolekar, Chaitali .S. Dalavi, Rahim .M. Shaikh
Yashoda Technical Campus, Faculty of Pharmacy, Satara, Maharashtra- India
***Corresponding author's E-mail:** vaishnavibhosale338@gmail.com

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ABSTRACT

Tuberculosis (TB) remains a significant global health burden, necessitating prolonged combination therapy with first-line anti-tuberculosis drugs (ATDs). Despite their efficacy, these drugs are frequently associated with adverse drug reactions (ADRs), which can negatively impact patient adherence and treatment outcomes. Among these, hepatotoxicity is one of the most serious and commonly reported complications, particularly associated with isoniazid and rifampicin. Isoniazid undergoes hepatic metabolism to form toxic intermediates that may induce liver injury. Rifampicin, a cornerstone of anti-TB therapy due to its potent bactericidal activity, is also associated with a wide spectrum of ADRs, including hepatotoxicity, hypersensitivity reactions, gastrointestinal disturbances, and significant drug–drug interactions due to enzyme induction. The occurrence and severity of ADRs are influenced by multiple factors such as age, comorbidities, nutritional status, alcohol consumption, and genetic variability. Pharmacogenomic insights have increasingly highlighted the role of genetic profiling in predicting susceptibility to ADRs and guiding individualized therapy. This review provides a comprehensive overview of ADRs associated with anti-tuberculosis therapy, with special emphasis on rifampicin. It discusses the underlying mechanisms, risk factors, and the role of genetic determinants in modulating drug response. Additionally, strategies for monitoring, early detection, prevention, and management of ADRs are emphasized. Early recognition and appropriate intervention are crucial for improving treatment adherence and achieving favourable clinical outcomes. Overall, integrating pharmacogenomic approaches with clinical monitoring may significantly enhance the safety and efficacy of TB treatment.

Keywords: Adverse drug reactions (ADRs), Anti-tuberculosis drugs (ATDs), Tuberculosis, Rifampicin, Prevention and Monitoring.

INTRODUCTION

Tuberculosis (TB) is a highly contagious infectious disease caused by *Mycobacterium tuberculosis* and remains a major global public health concern. According to the World Health Organization (WHO), TB ranks among the top ten causes of death worldwide and continues to be one of the leading infectious killers, second only to COVID-19 in recent years. In 2022, approximately 10.6 million individuals developed TB, and about 1.6 million deaths were attributed to the disease. TB is particularly prevalent in regions affected by poverty, malnutrition, overcrowding, and human immunodeficiency virus (HIV) co-infection, which significantly increase susceptibility to infection. TB primarily affects the lungs, accounting for more than 85% of cases, and is referred to as pulmonary tuberculosis. However, the infection can also involve extrapulmonary sites such as the spine, kidneys, brain, genital organs, and skin. Transmission occurs mainly through inhalation of airborne droplets from individuals with untreated or undiagnosed infectious TB, particularly those who are sputum smear-positive. Early diagnosis and effective treatment are therefore essential to control the spread of the disease.[1]

The treatment of TB relies on combination therapy with first-line anti-tuberculosis drugs (ATDs), including isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). These drugs are highly effective in curing TB and preventing transmission when administered appropriately. The Directly Observed Treatment, Short-course (DOTS) strategy, recommended by WHO, has proven to be one of the most effective approaches for TB control by improving treatment adherence, increasing cure rates, and reducing the emergence of multidrug-resistant TB.[2]

In India, TB control is implemented under a national program that provides free diagnosis and treatment to all patients. The Revised National Tuberculosis Control Programme (RNTCP), established to strengthen TB management, has developed standardized treatment guidelines that have been periodically updated to improve patient outcome. Despite their effectiveness, anti-tuberculosis drugs are associated with a wide range of adverse drug reactions (ADRs)[3]. The WHO defines ADRs as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function." Patients receiving ATD therapy may experience ADRs ranging from mild gastrointestinal disturbances to severe complications such as hepatotoxicity, hypersensitivity reactions, and neurological effects. These adverse effects can significantly affect patient tolerance, adherence to therapy, and overall treatment success. Effective management of ADRs requires a comprehensive understanding of the pharmacokinetics and pharmacodynamics of anti-tuberculosis drugs, including their mechanisms of action and toxicity. Clinicians must be able to identify both common and rare adverse reactions and recognize patient-related risk factors that may predispose individuals to an increased risk of toxicity.[4]

Global Burden

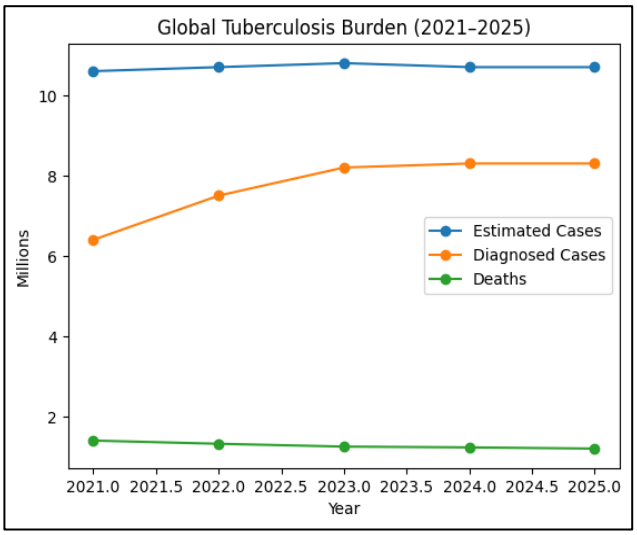

Figure 1: Global Tuberculosis Burden (2021-2025)

Among 2021 and 2025, the number of new cases of tuberculosis worldwide was projected to reach between 10 and 11 million. A significant percentage of cases go undetected, despite increases in diagnostic coverage increasing the number of recognised cases from over 6.4 million in 2021 to over 8.3 million in 2024. Although mortality has gradually decreased from roughly 1.4 million in 2021 to 1.23 million in 2024, TB remains one of the most common infectious agent-related causes of death. Nearly 87% of all cases worldwide occur in 30 high-burden nations, including India, Indonesia, China, the Philippines, and Pakistan. This indicates a highly concentrated disease burden.[5,6]

Adverse Drug Reaction [ADR]

The definition of adverse drug effects, undesirable drug effects or adverse drug reactions (ADR) has evolved over time. In the 80s it was defined by the World Health Organization (WHO) as any unintended noxious reaction that occurs at doses normally used in humans for prophylaxis, diagnosis or treatment or to modify physiological functions.[7]

Classification of Adverse Drug Reaction [ADR]

Table 1: Classification of Adverse Drug Effect (ADR)

Type of ADR	Characteristics	Examples (Anti-TB Drugs)
Type A (Augmented)	Dose-dependent; predictable; common; less severe; preventable by dose adjustment	Isoniazid – Peripheral neuropathy; Rifampicin – Hepatotoxicity, orange urine; Pyrazinamide – Hyperuricemia; Ethambutol – Optic neuritis
Type B (Bizarre)	Not dose-dependent; unpredictable; rare; serious; often immunological	Rifampicin – Flu-like syndrome, thrombocytopenia; Isoniazid – Drug-induced lupus; Streptomycin – Ototoxicity
Type C (Chronic)	Dose and time-related; long-term use; cumulative toxicity	Isoniazid – Chronic hepatotoxicity; Ethambutol – Vision impairment; Long-term ATT – Nutritional deficiencies
Type D (Delayed)	Occurs after long time or after stopping drug; rare but serious	Isoniazid – Carcinogenic potential; Rifampicin – Late hepatotoxicity
Type E (End-of-use)	Occurs after withdrawal; rebound effects	ATT withdrawal – TB relapse; Rifampicin withdrawal – Flu-like syndrome
Type F (Failure)	Unexpected treatment failure; due to interactions or resistance	Rifampicin – Enzyme induction reduces drug efficacy; MDR-TB due to poor adherence

Tuberculosis [TB]

Tuberculosis (TB), also known colloquially as the "white death", or historically as consumption, is a contagious disease usually caused by Mycobacterium tuberculosis bacteria.[8]

Classification of Tuberculosis [9]

Classification Based on Anatomical Site

Pulmonary Tuberculosis (PTB)

Pulmonary TB involves the lung parenchyma and is the **most common and infectious form** of the disease. It is transmitted via airborne droplets from individuals with active disease.

Clinical features:

- Persistent cough (>2–3 weeks)
- Haemoptysis
- Chest pain
- Fever, night sweats, weight loss

Public health importance:
PTB is the **primary driver of TB transmission**, making early detection and treatment crucial (WHO, 2023).

Extrapulmonary Tuberculosis (EPTB)

EPTB affects organs other than the lungs due to hematogenous or lymphatic spread.

Common forms:

- Lymph node TB
- Pleural TB
- Skeletal TB (e.g., spine – Pott's disease)
- Genitourinary TB
- TB meningitis

Classification Based on Bacteriological Status

Smear-Positive TB

- Presence of acid-fast bacilli (AFB) in sputum microscopy
- Highly infectious

Smear-Negative TB

- Negative sputum smear but clinical/radiological evidence present
- Less infectious but clinically significant

Culture-Positive TB

- Confirmed by culture methods (gold standard)
- Allows drug susceptibility testing

Classification Based on Disease Activity

Latent Tuberculosis Infection (LTBI)

- Infection without active disease
- Asymptomatic and non-infectious
- Diagnosed via tuberculin skin test or IGRA

Approximately 5–10% of LTBI cases progress to active TB during their lifetime

Active Tuberculosis

- Symptomatic and infectious (in pulmonary cases)
- Requires immediate treatment

Classification Based on Drug Resistance

Drug-Sensitive TB (DS-TB)

- Responsive to first-line drugs such as Isoniazid and Rifampicin

Multidrug-Resistant TB (MDR-TB): Resistant to at least isoniazid and rifampicin**,** Requires second-line therapy

Extensively Drug-Resistant TB (XDR-TB): MDR-TB plus resistance to fluoroquinolones and second-line injectable drugs

Rifampicin-Resistant TB (RR-TB)

- Resistance to rifampicin with or without resistance to other drugs
- Considered a surrogate marker for MDR-TB

Drugs used in treatment of Tuberculosis [10]:

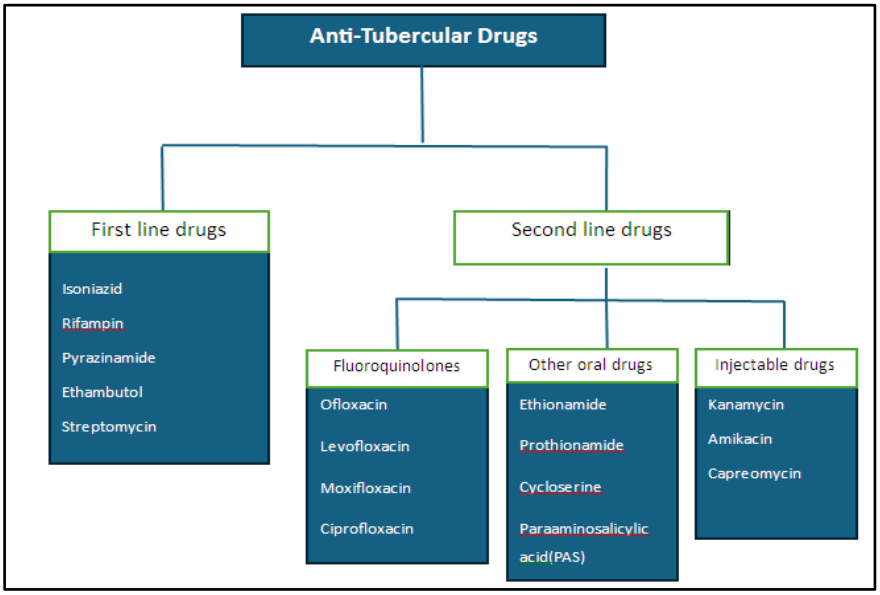

Figure 2: Classification of Anti-Tuberculosis Drugs

Pathophysiology of Tuberculosis

Mycobacterium tuberculosis, an aerobic, acid-fast bacillus with a lipid-rich cell wall containing mycolic acids that contribute to its virulence and resistance to host immunological defences, is the cause of tuberculosis, a chronic infectious disease [11]. Inhaling airborne droplet nuclei released by people who have active pulmonary tuberculosis is the main method of transmission [12]. The bacilli cause infection in the terminal alveoli after being breathed.

Alveolar macrophages phagocytose Mycobacterium TB once it has been deposited in the alveoli. Nevertheless, the organism has defences against destruction, such as resistance to reactive oxygen and nitrogen intermediates

and prevention of phagosome–lysosome fusion [12]. The adaptive immune response is then triggered, especially cell-mediated immunity, which is crucial for managing infection. Antigen-presenting cells increase the bactericidal activity of macrophages by stimulating CD4+ T lymphocytes to generate interferon-gamma (IFN-γ) [13].

This permits intracellular survival and reproduction in macrophages, which eventually results in cell lysis and the dissemination of bacilli to nearby tissues . The development of the disease is largely dependent on the host immune response. The innate immune system first reacts by activating macrophages and releasing pro-inflammatory cytokines such interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), which attract more immune cells to the infection site. Granuloma development, an organised immune response intended to contain the infection, is a characteristic of tuberculosis. When host immunity is weakened, TB progresses from latent to active. Reactivation is greatly increased by conditions including immunosuppressive therapy, diabetes mellitus, HIV infection, and malnutrition. Granuloma integrity is compromised during active disease, which leads to bacterial growth, widespread tissue damage, and lung tissue cavitation. Crucially, the host immunological response rather than direct bacterial toxicity is responsible for a large portion of the tissue damage seen in tuberculosis [14].

In general, the intricate relationship between pathogen pathogenicity and host immune response is reflected in the pathophysiology of tuberculosis. Excessive or dysregulated immune responses greatly contribute to tissue damage and clinical symptoms, even though immunological systems are crucial for managing infection [15].

Signs and Symptoms of Tuberculosis:

- Fever
- Night sweats
- Unintentional weight loss
- Loss of appetite
- Fatigue and weakness

Special Emphasis of Rifampicin in Treatment of Tuberculosis

Rifampicin is an antibiotic used to treat various bacterial infections, especially tuberculosis. It belongs to the rifamycin group and works by inhibiting RNA production in bacteria.

Mechanism of Action:

Rifampicin gives strong bactericidal activity against both intracellular and extracellular Mycobacterium tuberculosis, rifampicin, a first-line antitubercular antibiotic in the rifamycin class, is widely recommended by the World Health Organization and the Central TB Division India for the treatment of drug-susceptible tuberculosis as part of combination therapy. Its mechanism of action involves inhibiting bacterial DNA-dependent RNA polymerase, which results in the rapid killing of actively dividing bacilli and sterilising activity against semi-dormant organisms.

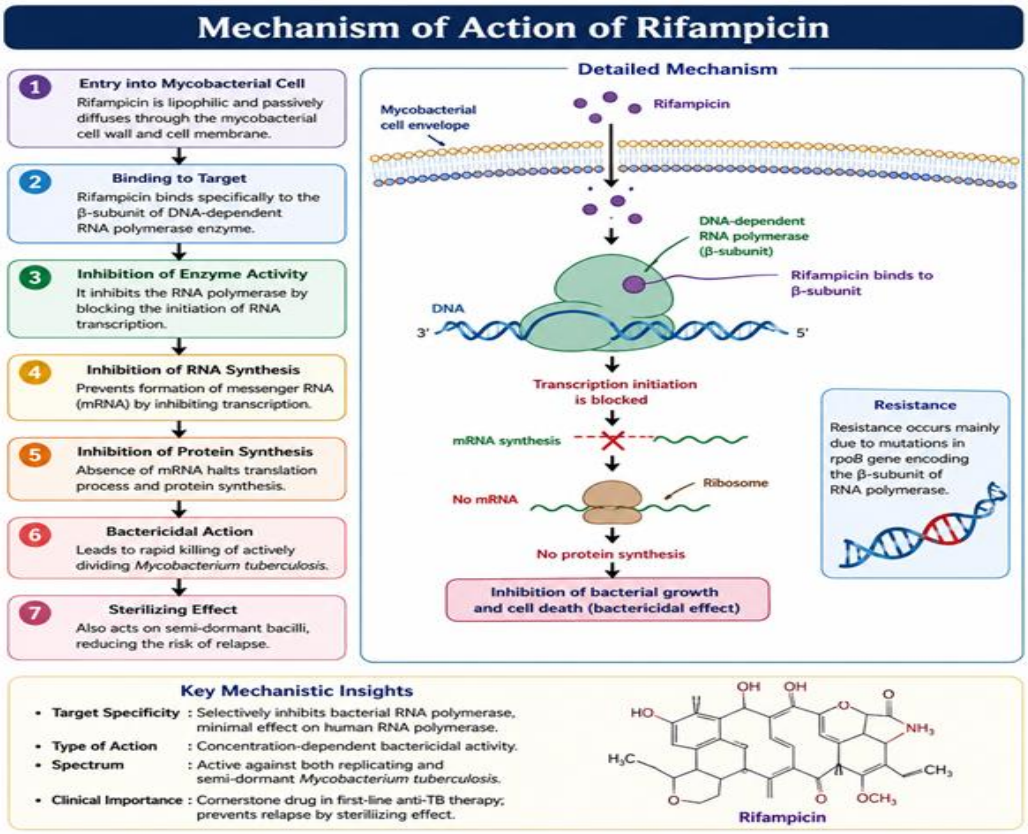

Figure 3: Mechanism of Action of Rifampicin [16,17]

Pharmacokinetics:

Absorption:-

- Rifampicin is well absorbed orally.
- Bioavailability ≈ 60–90%.
- Absorption is reduced by food, so it is usually taken on an empty stomach.
- Peak plasma concentration occurs within 2–4 hours.

Distribution: -

- Widely distributed throughout the body.
- Penetrates well into: Lungs, Liver, Kidneys, Bone
- Can cross: Blood-brain barrier (especially in inflamed meninges), Placenta
- Protein binding: ~80%
- Colour body fluids (urine, sweat, tears) orange-red.

Metabolism: -

- Metabolized in the liver.
- Undergoes deacetylation to an active metabolite.
- Rifampicin is a potent inducer of liver enzymes: Cytochrome P450 (CYP450 system)
- This leads to: Increased metabolism of many drugs (drug interactions)

Elimination: -

- Mainly excreted through: Bile → feces (major route), Some excreted in urine, Enterohepatic circulation occurs.
- Half-life: 3–5 hours (may decrease with repeated dosing due to enzyme induction).

Adverse Drug Reactions of Rifampicin [18-23]:

Hepatotoxicity

Includes: Elevated liver enzymes (ALT, AST), Hepatitis, Rarely fulminant liver failure

- Incidence: Clinical hepatitis occurs in 1–3% of patients
- Onset: Usually within 2–8 weeks of therapy
- Mechanism: Induction of hepatic enzymes via pregnane X receptor (PXR), Increased oxidative stress and toxic metabolite formation, Endoplasmic reticulum stress in hepatocytes
- Risk increases when combined with: Isoniazid, Pyrazinamide

Immunoallergic Reactions

- More common with intermittent dosing
- Includes: Flu-like syndrome (fever, chills, myalgia) ; Hypersensitivity reactions
- Severe reactions: Thrombocytopenia, Haemolytic anaemia, Acute renal failure, Shock (rare but serious), Mechanism: Antigen–antibody complex formation (immune-mediated)

Gastrointestinal Effects

- Common but usually mild
- Includes: Nausea, Vomiting, Abdominal pain, Loss of appetite
- Clinical impact: May reduce patient compliance

Dermatological Reactions

- Includes: Rash, Pruritus, Mild hypersensitivity reactions
- Usually: Self-limiting, Reversible on drug discontinuation

Discoloration of Body Fluids (Characteristic Effect)

- Causes orange-red discoloration of: Urine, Sweat, Tears, Saliva
- Due to: Chromophore nature of rifampicin
- Clinical importance: Harmless but important for patient counselling

Drug Interactions

- Rifampicin is a potent inducer of CYP450 enzymes
- Leads to: Increased metabolism of many drugs
- Affects: Oral contraceptives, Antiretroviral drugs, Anticoagulants, Antiepileptics
- Clinical outcome: Reduced drug efficacy, Possible treatment failure

Haematological Effects

- Less common but significant
- Includes: Thrombocytopenia, Leukopenia, Haemolytic anaemia
- Mechanism: Immune-mediated destruction of blood cells

Renal Toxicity

- Rare but serious
- Includes: Acute tubular necrosis, Interstitial nephritis
- More common with: Intermittent therapy
- Mechanism: Hypersensitivity reactions affecting kidneys

Cholestatic Effects

- Includes: Cholestatic jaundice, Hyperbilirubinemia

- Mechanism: Interference with bile secretion and bilirubin transport

Risk Factors for ADRs

- Advanced age
- Malnutrition
- Alcohol consumption
- Pre-existing liver disease
- HIV infection
- High doses of rifampicin
- Genetic polymorphisms affecting metabolism

Prevention and Monitoring of Tuberculosis [24-32]

Prevention of Tuberculosis

Vaccination

- BCG vaccine (Bacillus Calmette–Guérin) is used for TB prevention.
- Provides protection mainly against severe forms of TB in children (e.g., TB meningitis, miliary TB).
- Included in national immunization programs in many countries.

Early Detection and Treatment

- Prompt diagnosis and initiation of therapy reduce transmission.
- Screening methods: Sputum smear microscopy, Chest X-ray, Molecular tests (e.g., GeneXpert)

Infection Control Measures

- Proper ventilation in homes and healthcare settings
- Use of masks (especially in high-risk settings)
- Isolation of infectious patients during early treatment phase
- Cough hygiene and respiratory etiquette

Chemoprophylaxis (Preventive Therapy)

- Given to high-risk individuals: Close contacts of TB patients, HIV-positive individuals
- Common regimen: Isoniazid preventive therapy (IPT)

Public Health Programs

- Implementation of Directly Observed Treatment, Short-course (DOTS) strategy: Ensures supervised drug intake, Improves adherence and cure rates
- In India, TB control is under National Tuberculosis Elimination Programme (NTEP) (formerly RNTCP)

Addressing Risk Factors

- Improve nutrition
- Control HIV infection
- Reduce overcrowding
- Avoid smoking and alcohol abuse

Monitoring of Tuberculosis

Clinical Monitoring

- Regular assessment of: Symptoms (cough, fever, weight loss); Weight gain (indicator of recovery)
- Evaluation of treatment adherence

Bacteriological Monitoring

- Sputum examination: At baseline, During treatment (e.g., 2 months, end of treatment)
- Conversion from positive to negative indicates treatment success

Radiological Monitoring

- Chest X-ray used to: Assess disease progression, Monitor response to treatment

Monitoring of Adverse Drug Reactions (ADRs)

- Regular evaluation for side effects of anti-TB drugs: Hepatotoxicity, Peripheral neuropathy, Skin reactions
- Liver function tests (LFTs) for high-risk patients

Treatment Adherence Monitoring

- Direct observation under **DOTS strategy**
- Use of digital adherence tools (SMS reminders, apps)
- Counselling and patient education

Drug Resistance Surveillance

- Detection of multidrug-resistant TB (MDR-TB)
- Use of molecular diagnostic tools
- Adjust treatment based on resistance pattern

Special Population Monitoring

- Extra care in: Children, Elderly, Pregnant women, HIV patients
- Dose adjustment and closer follow-up required

CONCLUSION

Tuberculosis remains a major global health concern requiring prolonged combination therapy. Although drugs like rifampicin are highly effective, they are commonly associated with adverse drug reactions (ADRs), particularly hepatotoxicity, which can affect treatment adherence and outcomes. Early detection, proper monitoring, and management of ADRs are essential for ensuring safe and

effective therapy. Additionally, pharmacogenomic approaches and strengthened pharmacovigilance can help in minimizing risks and improving individualized treatment. Overall, a comprehensive approach is necessary to enhance treatment success and patient safety in tuberculosis management.

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REFERENCES

1. Puspita Das Roy, Mousumi Majumder & Bidyut Roy. Pharmacogenomics of Anti-TB Drugs-Related Hepatotoxicity Pages 311-321.

2. Madhukar Pai, Michael A. Behr, David Dowdy. Tuberculosis. The Lancet Infectious Diseases. 2016;16(6):117–131.

3. Singh, K. P. Carvalho , A .C. Centis , R. D. Ambrosio , L. Migliori , G. B .Mpagama , S.G. Nguyen , B. C. Aarnoutse, R .E .Aleksa , A. Van Altena. Clinical standards for the management of adverse effects during treatment for TB. Int. J. Tuber. Lung Dis. 2023, 27, 506–519

4 . Tripathi, K.D., 2013. Antitubercular Drugs. Essential of Medical pharmacology, seventh edition. Jaypee Brothers Medical Publishers (P) Ltd, India. Essentials of Medical Pharmacology. pp. 765

5. WHO Global Tuberculosis (TB) Report 2024. Available from: https://share.google/yciYVujzw29VAhgCr

6. WHO Global Tuberculosis (TB) Report 2025. Available from: https://www.drishtiias.com/daily-updates/daily-news-analysis/who-global-tuberculosis-tb-report-2025

7. Rashmi R. Udaykumar, P. B. Bairy, R. K. Vidyasagar. Adverse drug reaction monitoring and reporting systems: a review. International Journal of Pharmaceutical Sciences Review and Research. 2015;31(2):172–179.

8. Lawn SD, Zumla AI. Tuberculosis. *Lancet*. 2011; 378:57–72.

9. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res*. 2004;120(4):316–353

10. Tripathi, K.D., 2013. Antitubercular Drugs. Essential of Medical pharmacology, seventh edition. Jaypee Brothers Medical Publishers (P) Ltd, India. Essentials of Medical Pharmacology, Pg no. 765.

11. Flynn JL, Chan J. Immunology of tuberculosis. *Annu Rev Immunol*. 2001; 19:93–129

12. Kumar V, Abbas AK, Aster JC. *Robbins Basic Pathology*. 10th ed. Elsevier; 2018.

13. World Health Organization. Global Tuberculosis Report 2024. Geneva: WHO; 2024.

14. Kumar V, Abbas AK, Aster JC. *Robbins Basic Pathology*. 10th ed. Elsevier; 2018.

15. http://www.optimabloem.co.za/world-tuberculosis-day/tb-signs-and-symptoms/

16.Campbell EA, Korzheva N, Mustaev A, et al. Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. Cell. 2001;104(6):901-912.

17. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. McGraw Hill; 2018

18. Girish Singla, Surendra K. Sharma, V. Mohan. Adverse effects of antituberculosis drugs. Expert Opinion on Drug Safety. 2010;9.553–566.

19. K. Ramappa , G. Aithal. Hepatotoxicity related to anti-tuberculosis drugs. Journal of Clinical and Experimental Hepatology. 2013;3.37–49.

20.S. K. Sharma,A. Mohan, K. Kadhiravan. Hepatotoxicity due to antituberculosis drugs. Indian Journal of Medical Research. 2012;136.780–790.

21.A. Yee, R. Valiquette, M. Pelletier. Incidence of serious side effects from first-line antituberculosis drugs. American Journal of Respiratory and Critical Care Medicine. 2003; 167:1472–1477.

22. M. T. Nafade , Madhukar Pai, K. Satyanarayana. Adverse drug reactions in tuberculosis treatment. Public Health Action. 2017;7(1):14–19.

23...R. S. Jindal, Ashok Kumar, S. K. Jain. Hepatotoxicity due to antituberculosis therapy. Indian Journal of Tuberculosis. 2012;59 :79–84.

24. Madhukar Pai, Michael A. Behr, David Dowdy. Tuberculosis. The Lancet Infectious Diseases. 2016;16(6):117–131.

25.World Health Organization. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. Geneva: World Health Organization; 2018.

26.Charles R. Horsburgh, Edward A. Rubin, Cynthia E. Barry. Latent Tuberculosis Infection Treatment and Control. Clinical Microbiology Reviews. 2015;28(3):669–705.

27.Madhukar Uplekar, Diana Weil, Christopher Lonnroth. WHO's End TB Strategy. International Journal of Tuberculosis and Lung Disease. 2015;19(9):1045–1046.

28.Gregory J. Fox, Justin T. Denholm, Ben J. Marais. Preventive therapy for latent tuberculosis infection. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2017; 7:6–12.

29.Christopher R. Horsburgh, Jeremiah M. Farley, Lee B. Reichman. Treatment of Tuberculosis. New England Journal of Medicine. 2015;373(22):2149–2160.

30.Jerome Chakaya, Alimuddin Zumla, Mario Raviglione. Global Tuberculosis Report 2020 – Reflections on the global TB burden. The Lancet Respiratory Medicine. 2021;9(10):1081–1083.

31.Guy B. Marks, Paul M. Griffin, Ben J. Marais. Ending tuberculosis globally. The Lancet. 2019;393(10178):1260–1262.

32.Soumya Swaminathan, K. Dheda, R. Wallis. Drug-resistant tuberculosis: challenges and opportunities. Clinical Infectious Diseases. 2017; 65:1105–1111.