



Journal of Interdisciplinary Science & Technology

The Enduring Shadow of Tuberculosis: A Comprehensive State-of-the-art-review

K. Ram Prasad¹, A. Durga², K. Harshavardhani¹, S.K. Sherley Sam¹
S. Vinisha¹, M. Dhanalakshmi²

¹SMVEC- School of Pharmacy, Madagadipet, Puducherry

²Dean, SMVEC- School of Pharmacy, Madagadipet, Puducherry

ramrampari23@gmail.com, durga91601@gmail.com, harshavardhanikumaran289@gmail.com, sherlysam2125@gmail.com,
vinishasenthilkumar2006@gmail.com, deanpharmacy@smvec.ac.in

Corresponding author- K. Ram Prasad

DOI: 10.5281/zenodo.23219794

Abstract: Tuberculosis remains a significant infectious disease worldwide and a considerable public health concern. Chemotherapy has gradually replaced prolonged treatment schedules with shorter, more effective multidrug regimens. This review summarizes the evolution of TB chemotherapy, emphasizing currently used first- and second-line anti-TB drugs, their mechanisms of action, adverse effects, and standard and shortened treatment regimens. The review also examines the emergence and development of drug resistance, with particular emphasis on multidrug-resistant tuberculosis. The review also examines major factors associated with poor treatment adherence, such as prolonged therapy, adverse effects, socioeconomic circumstances, and healthcare barriers, along with strategies to improve treatment completion. Therapeutic considerations for special populations and clinical conditions, including children, pregnancy, HIV co-infections, breastfeeding, renal dysfunction, diabetes, liver diseases, transplant recipients, and extrapulmonary tuberculosis, are also highlighted. Future strategies focus on developing shorter, safer treatment regimens, novel anti-TB drugs, host-directed therapies, and advanced drug-delivery systems.

Keywords: Treatment of chemotherapy, evolution of TB, emergence and development of drug resistance, factors associated with poor treatment, therapeutic considerations, future strategies, novel anti-TB drugs, advanced drug-delivery system

1 INTRODUCTION

Tuberculosis (TB) has been one of the oldest infectious diseases affecting human beings, and even today it is one of the greatest public health challenges in the world. It continues to spread in all corners of the globe [1]. Robert Koch (Father of TB) discovered the pathogen *Mycobacterium tuberculosis* (*M. tb*), a gram-positive, acid-fast bacillus, in 1882, and received the Nobel Prize in 1905 for his discovery [2]. After COVID-19, TB is the second leading cause of mortality; it is a highly contagious airborne disease and can also be spread by *M. bovis*, *M. microti*, *M. Africanum*, *M. Canettii*, and *M. pinnipedii* [3]. This continues to be the leading cause of death in the HIV infected population [4]. About one third of the world population is infected with this pathogen [5]. This bacterium mainly affects the lungs (pulmonary TB). It may also spread to other parts of the body, such as the kidneys, meninges, spine, bones and joints, genitourinary system, pleura, and lymph nodes (extrapulmonary TB) [6]. The major route of transmission is inhaling droplets from an

infected person that contain bacteria expelled during coughing, sneezing, singing, and speaking [7]. To effectively identify active tuberculosis cases, the healthcare system must use diagnostic procedures such as sputum culture, chest radiography, and the tuberculin skin test [8]. The likelihood of becoming infected with TB after exposure depends primarily on the infectiousness of the source case, the proximity of the exposure environment, and social and behavioural factors (e.g., smoking, alcohol, indoor air pollution). The transmission rate is higher in overcrowded areas, where social interaction is greater [9].

Tuberculosis treatment is lengthy; one of the challenges is that four drugs are used in treatment, which lasts a minimum of 6 months. If patients do not follow the regimen, treatment can fail, and bacteria can develop resistance to the drugs used [10]. Drug-resistant tuberculosis (DR-TB), which includes multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant (XDR-TB), is adding huge challenges to effective treatment and disease control. These forms of

resistance, compared to drug-sensitive tuberculosis (DS-TB), may need to be treated for a longer period of time with more expensive and potentially toxic therapeutic regimens [11].

Recent advances in tuberculosis treatment have focused on shortening treatment duration, improving tolerability, and developing more effective regimens for drug-resistant tuberculosis. The development and incorporation of newer anti-TB agents have further expanded therapeutic options, and these newer regimens offer the potential for shorter treatment and improved efficacy. Ongoing research on new drugs, shorter regimens, host-directed therapy, and advanced drug-delivery systems offers promising opportunities to further improve treatment outcomes. This review provides a comprehensive overview of tuberculosis chemotherapy, including current therapeutic approaches, drug resistance mechanisms, adherence strategies, special clinical situations, and future developments.

II. EVOLUTION OF DISEASE MANAGEMENT:

A. PAST:

Initial Studies;

Tuberculosis treatment became effective with the introduction of streptomycin in 1946. Patients treated with streptomycin showed a dramatic reduction in immediate mortality and a striking improvement in chest radiology and bacteriology. Still, the 5-year assessment showed that those who had received streptomycin continued to die in almost the same proportion and rate as those who had not received it, because streptomycin resistance emerged frequently.

When streptomycin was used with para-aminosalicylic acid (PAS, P), the frequency of streptomycin resistance was significantly reduced. In 1952, a new wonder drug, isoniazid (INH, H), was introduced. This reduced the MIC and had low toxicity. 200mg daily x 10 – effective dose, but expensive. After spending a year with PAS and SM.

The dropout rate was high: only 352 of 581 admitted patients completed their year of treatment, as it required at least 1 year of treatment in the hospital [14].

Tuberculosis treatment over the past few decades can be viewed in the historical context of the modern chemotherapeutic era, which began with streptomycin (STM) in 1943. The most important advance in tuberculosis treatment came with the introduction of isoniazid (INH) in 1952. The drug was used in combination with STM and para-aminosalicylic acid (PAS), and these medications cured over 90% of patients, but the treatment time was too long. In the 1960s, ethambutol (EMB) was introduced to replace the

poorly tolerated PAS, shortening the treatment period as shown in Table 1 and Figure 1 [16].

Table 1: Evolution of anti-tuberculosis treatment [16]

YEARS	DRUGS USED	LENGTH OF TREATMENT
1940S	STM+PAS	24 MONTHS
1950S	INH+STM+PAS	24 MONTHS
1960S	INH+STM+EMB	18 MONTHS
1970S	INH+RIF+EMB	9-12 MONTHS
1980S	INH+RIF+EMB+PZA	6 MONTHS
1990S	INH+RIF+PZA+?	6-? MONTHS

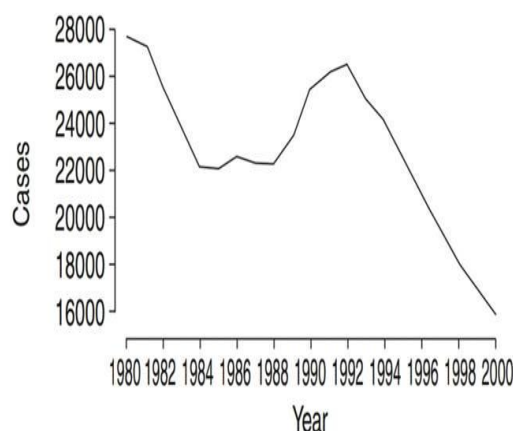


Figure 1: Reported tuberculosis (TB) cases in the USA between 1980 and 2000 [15].

The next major advance in therapy was the introduction of rifampicin (RIF) derived from *Streptomyces mediterranei*. The combination of INH, EM, EMB and RIF resulted in predictable cures in >95% of cases in just 8-9 months.

B. Present

Many countries' public health programs followed the World Health Organization (WHO) guidelines for treating TB until 2009 [13].

The main problem is the long duration of treatment (the 6-month regimen), which provides opportunities to stop treatment, which may result in the development of drug resistance; the treatment is cumbersome for both the patient and the clinic. Secondly, the incidence of multidrug-resistant (MDR) strains of *M. tuberculosis* has risen, which are resistant to both RIF and INH.

Prevention of drug resistance

Anti-tubercular drugs become ineffective because mutations in the bacterial chromosomal DNA can confer resistance. In comparison, these mutations are rare events, as it should be possible to estimate the chances of spontaneous resistance arising during the simultaneous treatment with INH and RMP. Other proportions also lack bacteriological proof, but do provide diagnostic proof of disease [14].

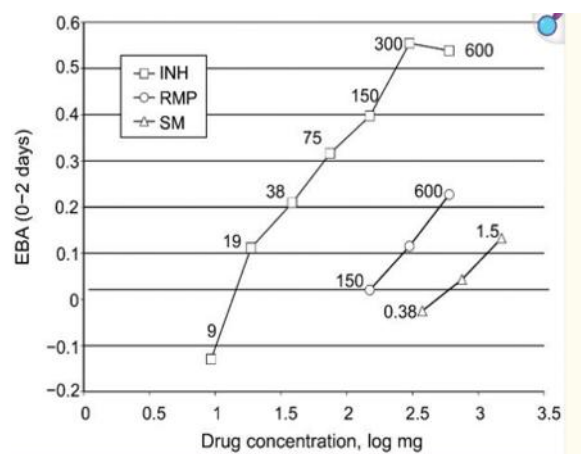


Figure 2: EBA during the first two days of treatment with a range of INH, RMP, or SM doses, including low doses that produce no EBA [15].

Current Treatment Regimens

As early as the 1980s, short courses of therapy (SCTs) were shown to be as effective as longer courses for pulmonary TB. Short courses of therapy (SCTs) have been as effective as long courses since the early 1980s. Plus, short courses lowered the expense associated with chemotherapy and encouraged patients to follow through with treatment because of their low toxicity. The standard treatment for pulmonary TB is to be HIV-negative and not resistant to the drugs, for 6 months.

Several regimens are used, with the most widely accepted being a combination of INH, RIF, and PZA taken once

daily for two months, then INH and RIF for a further two months, as daily for 4 other months [16].

FUTURE:

Until the discovery of streptomycin in 1944, chemotherapy for tuberculosis (TB) was not possible. Since the 1950s and 1960s, primary anti-TB chemotherapy has been based on the introduction of isoniazid.

Future improvements in tuberculosis treatment. The chemotherapy emphasis is on developing shorter, safer, and more effective regimens of treatment, especially one for multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. Ongoing studies focus on developing new anti-tubercular drugs, host-directed therapies, immunomodulators, optimized drug combinations, and targeted drug-delivery systems to improve treatment outcomes and minimize the risk of drug resistance.

Producing immunomodulators that strengthen host defense mechanisms and promote bacillus uptake and killing would be a valuable weapon, particularly against intracellular organisms.

In difficult cases, biological response modifiers, such as interleukin-2 or granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-related apoptosis-inducing ligand, and others, with antimicrobial activity, can help expand treatment options; the most important measures should be earlier diagnosis and immediate treatment for all patients, and the implementation and generalization of DOT programs [16].

II ANTI-TUBERCULOSIS DRUGS ARE CLASSIFIED AS FOLLOWS

A. FIRST-LINE DRUGS

The drugs used to treat tuberculosis at the beginning of treatment are called first-line drugs. They are usually used together to ensure effective therapy and to prevent development of resistance. The major first-line drugs include isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide, along with their mechanisms of action and classifications (depicted in Figure 3-6).

1. Isoniazid (IZH)

Isoniazid, also called nicotinic acid hydrazide, is one of the drugs used to treat drug-susceptible tuberculosis. It is

bactericidal and is active against actively multiplying tubercle bacilli [18,20].

It comes in 100 mg and 300 mg tablets to take by mouth. It is a prodrug and turns into an active drug in the body [21].

Mechanism of Action

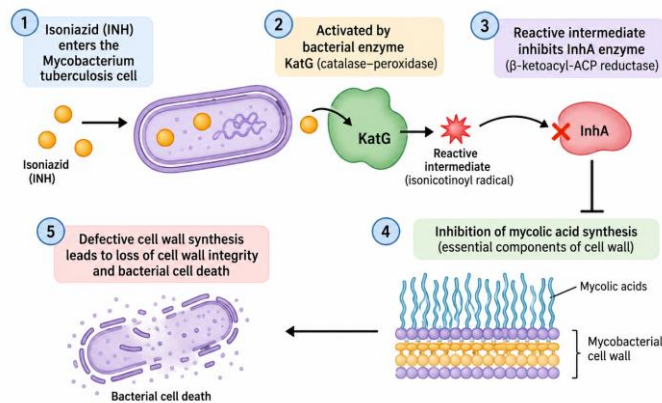


Figure 3: Molecular Level MOA of Isoniazid

Peripheral neuropathy, hepatotoxicity, GI disturbance, unusual bleeding, urine is dark yellow- orange, hypersensitivity are commonly seen with its use [17,20].

Uses

Isoniazid is used in combination with other medications for the treatment of active TB.

Isoniazid is used alone to treat latent TB and prevent it from becoming active TB due to the risk it poses to individuals. It kills the TB bacteria [18]

2. Rifampicin (RIF)

Rifampicin inhibits bacterial RNA synthesis by binding to the β-subunit of RNA polymerase, encoded by the *rpoB* gene. It blocks RNA synthesis initiation and prevents transcription of DNA into RNA [18].

Adverse Effects

Orange-red discoloration of urine, sputum, sweat, and faeces, thrombocytopenia, and acute renal failure [17,20].

Uses

Rifampicin is used in combination with other medications for the treatment of active TB and latent TB.

Mechanism of Action

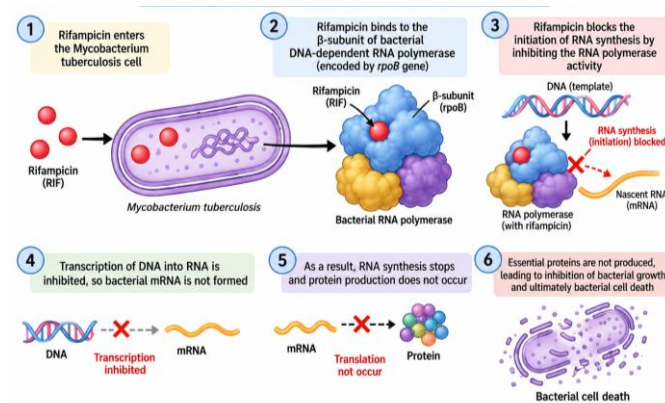


Figure 4: Mechanism of action of rifampicin (RIF) against *Mycobacterium tuberculosis*

3. Pyrazinamide (PZA)

Pyrazinamide is a unique anti-TB drug that helps shorten TB treatment. It works by blocking several bacterial targets, including energy production, trans-translation, and likely pantothenate or coenzyme A, which bacteria need to survive [3].

Mechanism of Action

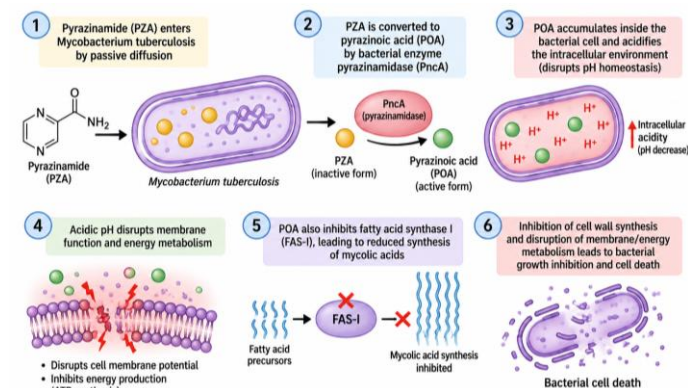


Figure 5: Mechanism of action of pyrazinamide (PZA) against *Mycobacterium tuberculosis*,

Figure 5 is depicting the conversion by pyrazinamidase (PncA) to the active form pyrazinoic acid (POA), disruption of intracellular pH and membrane/energy metabolism, inhibition of mycolic acid synthesis, and subsequent inhibition of bacterial growth and cell death

Adverse Effects

Hypersensitivity, hyperuricemia, yellow eyes or skin, hepatotoxicity, gout [17,20].

Uses

It is used in combination with other medications -Isoniazid, rifampicin, and ethambutol-to treat active TB [18].

4. Ethambutol

Ethambutol inhibits arabinosyl transferase, an enzyme that synthesizes arabinogalactan, an important component of the *Mycobacterium tuberculosis* cell wall [18].

Mechanism of Action

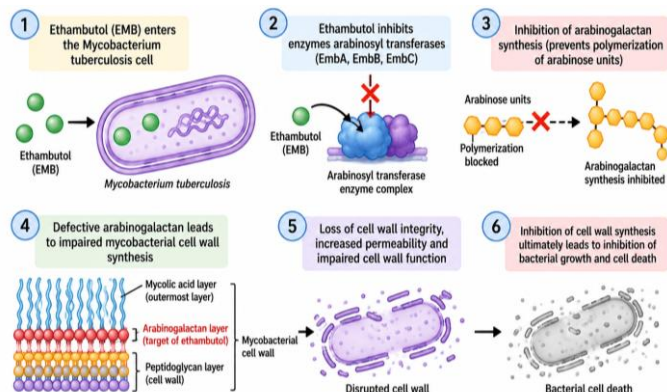


Figure 6: Mechanism of Action of Ethambutol (EMB) Against *Mycobacterium tuberculosis*

Adverse Effects

Arthralgia, optic neuritis, renal impairment, red-green blindness, gastrointestinal disturbance [17,20].

Uses

Ethambutol is used in combination with other medications - Isoniazid, rifampicin, and Pyrazinamide-to treat active TB [18].

B. Second Line Drugs

These drugs cause much more serious side effects than first-line drugs. They are mainly used to treat multidrug-resistant TB or intolerance. The main second-line drugs include fluoroquinolones, amino-salicylic acid, ethionamide, aminoglycosides, para-amino salicylic acid (PAS), streptomycin, and cycloserine (depicted in Figure 7-13) [17].

1.Ethionamide

Ethionamide is used with other medications to treat tuberculosis. It kills bacteria and inhibits their growth, and it is classified as an antibiotic. However, it does not treat colds, influenza, or other viral infections [19].

Adverse Effects

Gastrointestinal disturbances, hepatotoxicity, hypothyroidism, diarrhoea, abdominal pain [17].

Uses

Treatment of TB [17].

Mechanism of Action

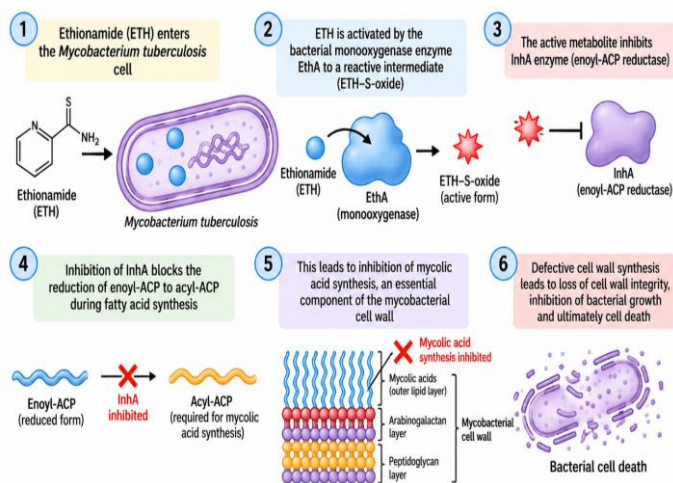


Figure 7: Mechanism of Action of Ethionamide (ETH) Against *Mycobacterium tuberculosis*

2.Fluoroquinolones

Examples: levofloxacin and moxifloxacin [17].

Mechanism of Action

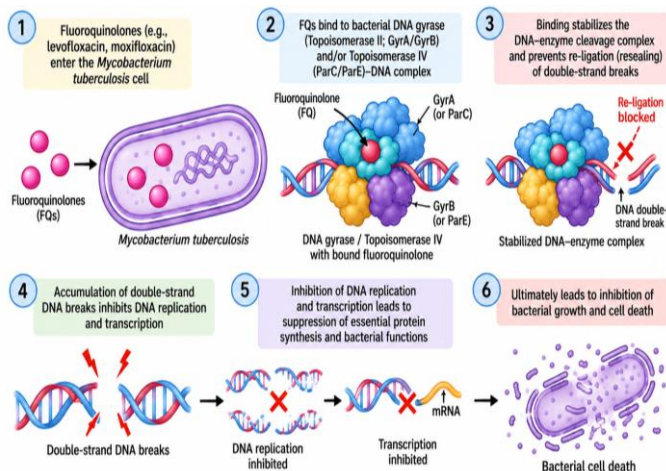


Figure 8: Mechanism of Action of Fluoroquinolones Against *Mycobacterium tuberculosis*

Adverse Effects

Tendinitis, QT prolongation, arthralgia, and skin swelling [17,19,22].

Uses

Levofloxacin: Used to prevent and treat plague [17].

Moxifloxacin: Used to treat pneumonia and plague, and for prevention [17].

3. Aminoglycosides

Examples: amikacin and kanamycin [17].

Mechanism of Action

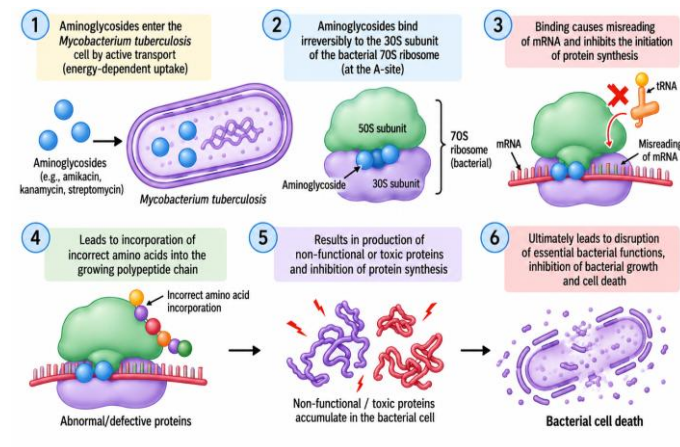


Figure 9: Mechanism of Action of Aminoglycosides Against *Mycobacterium tuberculosis*

Adverse Effects

Kanamycin: Auditory nerve damage, vertigo, and nephrotoxicity [19].

Amikacin: Nephrotoxicity and ototoxicity [22].

Uses

Treatment of meningitis, blood infections, and severe bacterial infections [17].

4. Para- Amino Salicylic Acid (PAS)

Mechanism of Action

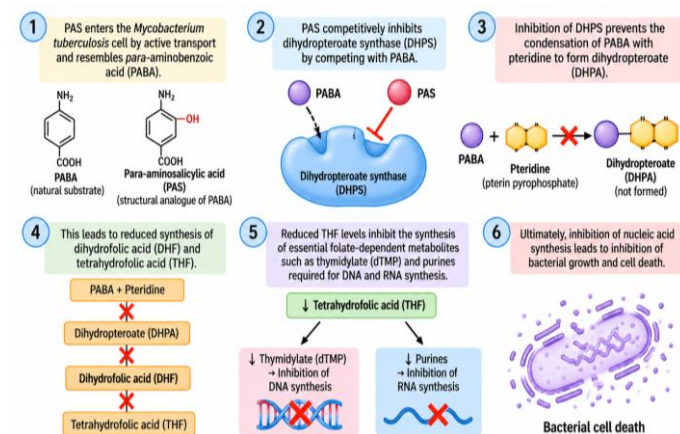


Figure 10: Mechanism of Action of Para- Amino Salicylic Acid (PAS) Against *Mycobacterium tuberculosis*

Adverse Effects

Hypersensitivity reactions, hepatotoxicity, hypothyroidism [22].

Uses

1. PAS is used in combination therapy for TB with other active ingredients.
2. It is most frequently used in patients with multidrug-resistant TB [17].

5. Streptomycin

Mechanism of Action

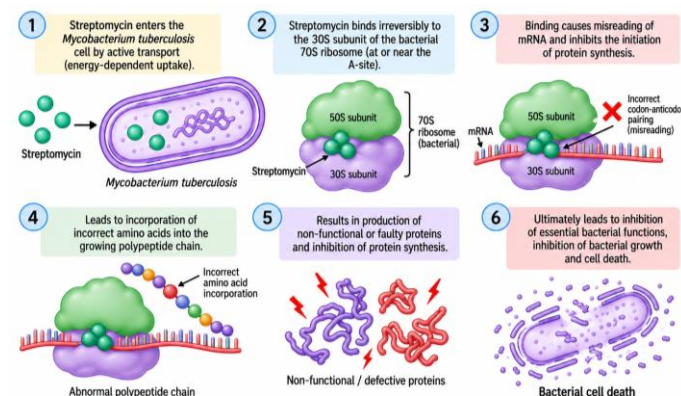


Figure 11: Mechanism of Action of Streptomycin Against *Mycobacterium tuberculosis*

Adverse Effects

Vestibular and auditory nerve damage, renal damage, and ototoxicity [19].

Uses

1. Streptomycin is currently used mainly with other medications to treat pulmonary tuberculosis.
2. It is the best recognized antibacterial treatment for tuberculosis [19].

6. Capreomycin

Capreomycin is a polypeptide antibiotic [17].

Mechanism of Action

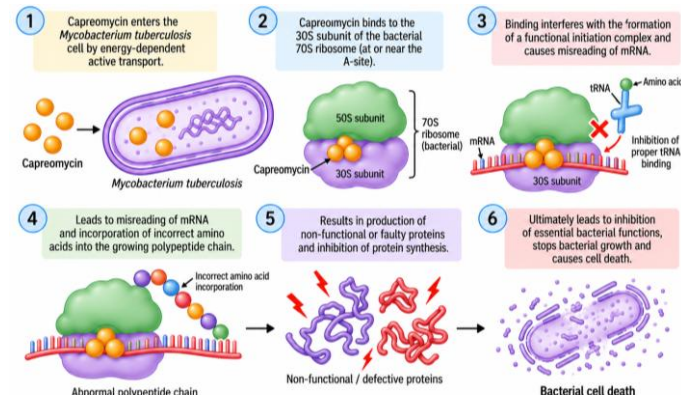


Figure 12: Mechanism of Action of Capreomycin Against *Mycobacterium tuberculosis*

Adverse Effects

Ototoxicity, nephrotoxicity, and optic neuritis [17,22].

Uses

Because of its toxicity, capreomycin is typically used to treat patients who are resistant to other medications [19].

7. Cycloserine

Mechanism of Action

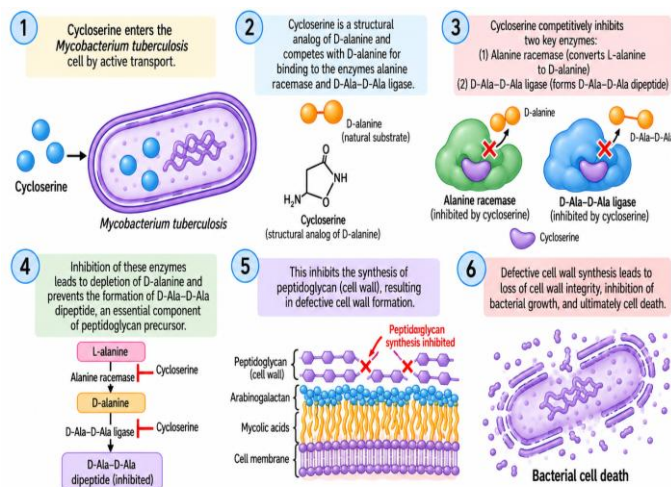


Figure 13: Mechanism of Action of Cycloserine Against *Mycobacterium tuberculosis*

III DRUG REGIMENS FOR TUBERCULOSIS: Standard and Short-Course Options

A. Standard Six-Month Regimen (2HRZE/4HR)

Intensive phase (2 months): isoniazid + pyrazinamide + ethambutol, given daily.

Continuation phase (4 months): isoniazid + rifampicin, given daily.

This regimen is the WHO reference standard for new, drug-susceptible pulmonary TB and is strongly recommended based on high-certainty evidence [23].

B. New Four-Month Regimen (2HPZM/2HPM)

First 2 months: isoniazid + rifampentine + pyrazinamide + moxifloxacin, given daily.

Next 2 months: isoniazid + rifampentine + moxifloxacin, given daily (pyrazinamide dropped).

Total duration is 17 weeks. This four-month regimen was found to work just as well as the standard six-month regimen in the study 31/A5349 phase 3 trial. WHO now endorses it (2022, conditional recommendation, moderate certainty), as does CDC (2022 interim guidance), for patients aged 12 and older with drug-susceptible pulmonary $\pm$ TB who are not pregnant [24,25,26]. It avoids the ocular toxicity risk of

ethambutol but requires monitoring for moxifloxacin-associated QT prolongation in at-risk patients [27].

C. Paediatric Four-Month Regimen (2HRZ(E)/2HR)

First 2 months: isoniazid + rifampicin+ pyrazinamide ($\pm$ ethambutol), given daily.

Next 2 months: isoniazid + rifampicin, given daily.

For children and adolescents aged 3 months to 16 years with non- severe TB (without suspected or confirmed MDR/RR-TB), this shortened regimen is strongly recommended by WHO based on moderate-certainty evidence. Note it uses standard rifampicin rather than rifapentine, unlike the adult four-month regimen above [23].

IV DRUG RESISTANCE

A. Genetic basis of isoniazid and rifampicin resistance

Isoniazid resistance most commonly arises from mutations or deletions affecting the *katG* gene, the *inhA* gene, or the alkyl hydroperoxide reductase gene, and roughly 15 % of isoniazid-resistant isolates examined were found to lack *katG* completely - a loss associated with high-level resistance at an MIC of 64 micrograms/ml or greater [28].

B. Four core resistance mechanisms identified

Diagnosis and treatment of MDR-TB states that resistance in *Mycobacterium tuberculosis* results from spontaneous, random chromosomal mutations rather than acquired resistance genes. It lists four specific mechanisms driving this resistance: activation of bacterial efflux pumps, alteration of the drug's target site, production of enzymes that inactivate the drugs, and disruption of the steps needed to activate certain prodrugs [29].

C. Efflux pumps and biofilm formation sustain MDR-TB

Drug delivery systems for MDR-TB point to genetic mutation, efflux pump activity, and biofilm formation as the three molecular mechanisms most responsible for resistance persisting despite treatment, framing them as the central obstacle that newer drug-delivery approaches are specifically being designed to overcome [30].

D. Global drug-resistance TB burden

By 2023, 10 % of global TB cases were classified as drug-resistant, with both multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) cases showing rising prevalence; treatment of drug-resistant TB remains complicated by long regimen duration, severe side effects, and high overall cost factors linked directly to poor patient

adherence and treatment failure; however, newer agents such as bedaquiline, linezolid, and meropenem have improved outcomes when used in combination regimens like BPaLM [31].

E. Nature Reviews Disease Primers on MDR-TB mechanisms and epidemiology

MDR-TB occurs in *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin, posing a major global public health challenge [32].

F. Regional treatment barriers in Central Asia

In Central Asia, control of MDR-TB is limited by delayed diagnosis, inadequate infection control, and insufficient health care resources. The predominance of the Beijing lineage of *M. tuberculosis* further contributes to the spread of drug-resistant TB in the region [33].

V. ENSURING ADHERENCE TO ANTI-TB DRUGS

Adherence to anti-tuberculosis treatment is often difficult because TB therapy may include multiple drugs, prolonged treatment duration, and tolerability issues. Inadequate adherence can negatively affect treatment outcomes and result in unsuccessful treatment, recurrence of TB, and increased risk of drug resistance [34].

The term “compliance” is increasingly being replaced by “adherence” because treatment completion is seen as an active decision by the patient. Currently, concordance emphasizes communication, negotiation, mutual understanding, and collaboration between the patient and health care professionals [35].

A. Factors Contributing to Anti-TB Medication Adherence

1. Patient- related Factors

Several patient factors can influence adherence to anti-TB therapy. Demographic characteristics such as young age, male gender, and marital status have been associated with difficulties in maintaining medication adherence. On the other hand, lifestyle-related behaviours, including alcohol consumption and cigarette smoking, may also contribute to non-adherence to TB medication. In Addition, psychological and cognitive factors such as (forgetfulness, poor understanding of treatment, perceived barriers, psychological distress, and stigma) can interfere with regular medication use. In contrast, patients with a higher level of educational background tend to have better adherence to TB treatment.

Poor mental health may further reduce both adherence and regular follow-up visits [38].

2. Socioeconomic Factors

Several studies have shown that low social support can significantly contribute to poor adherence to TB treatment. In particular, absence of assistance from family members and neighbours in reminding the patients to take their medications, as well as lack of food and financial support, has been identified as an important factor associated with non-adherence. Among people with TB-HIV co-infection, encouragement and support from family, friends and health care professionals can improve adherence to Isoniazid Preventive Therapy (IPT). TB most commonly affects low socioeconomic groups, including people who are homeless, unemployed, or living in poverty. Moreover, poor socioeconomic conditions may enhance exposure to TB risk factors such as malnutrition, overcrowded housing, and unsafe working environments [38].

3. Health System Factors.

Poor communication and weak relationships between healthcare providers and patients are important factors that influence non-adherence to TB medication. Studies show that healthcare providers' attitudes and behaviours can influence patients' attitudes and medication-taking behaviour. Maintaining empathetic relationships may be difficult when healthcare providers lack adequate training in an overburdened health system. Furthermore, insufficient supervision and the inability of healthcare providers to effectively manage a patient's illness have been reported as factors contributing to treatment interruption and default from TB therapy [38].

4. Therapy-Related Factors.

Adverse effects associated with anti- TB drugs are the major therapy-related reasons for poor medication adherence. Some other factors that may contribute to non-adherence include a high pill burden, HIV co-infection, the presence of multiple comorbidities, and concurrent use of antiretroviral therapy (ART). In addition to this, the complex treatment regimens and medication-related side effects can further reduce adherence. Anti-TB treatment may cause various side effects, including Gastrointestinal disturbances (18.4%), Psychiatric disorders (5.5%), Arthralgia (4.7%), Acute liver injury (3.9%), Peripheral neuropathy (3.1%), Thyroid disorder (2.3%), Epilepsy (2.0%), Skin disorder (2.0%), hearing problems (1.6%), and Kidney injury (1.2%) [36].

B. Methods for Ensuring Adherence to Anti-TB Therapy

Self-administered therapy (SAT) and directly observed therapy (DOT) are the two principle approaches used in anti-TB treatment. When SAT is employed, fixed-dose combinations (FDCs) should be used to reduce the risk of monotherapy; however, this requires regular monitoring to ensure treatment adherence. The WHO has recommended DOT as a key element of the DOTS strategy since 1993, aiming to improve adherence and achieve better treatment outcomes. Enhanced DOT incorporates patient-centered care by providing supportive incentives, such as food, accommodation, clothing, and medical care, to encourage patients to complete treatment. By integrating TB care with TB/HIV, MDR-TB, and other relevant health services, it improves patient support and continuity of care. Treatment literacy is a key factor that supports better adherence and promotes the successful completion of tuberculosis treatment [13].

VI. SPECIAL POPULATION

Special groups, particularly children and pregnant women, have received insufficient attention during the development of tuberculosis medicines. In developing countries, these patients are often underrepresented in pharmacological studies, while post-marketing pharmacovigilance systems are generally limited. There is an ethical need to produce evidence at an early stage to ensure the most appropriate treatment for these special populations, as well as for patients with common coexisting conditions such as diabetes and human immunodeficiency virus (HIV) infection. A sufficiently broad range of drug formulations should be made available for patients who cannot receive standard treatment approaches. Since genetic differences can affect an individual's response to tuberculosis therapy, depending on the population being treated, collecting and preserving biological samples for future pharmacogenetic research during clinical trials is also important [39].

A. Children with Tuberculosis

Children, especially infants and those living with HIV, have an increased risk of developing active tuberculosis and more severe forms of the disease after primary infection. Therefore, age-specific dosing, child-friendly drug formulations, and pharmacokinetic studies are necessary to ensure that anti-tuberculosis treatment is both safe and effective for paediatric patients [39].

B. Pregnant women with Tuberculosis

Tuberculosis occurring during pregnancy, when not treated, can lead to increased illness and complications for both the mother and the foetus. Therefore, early detection and timely initiation of suitable anti-tuberculosis treatment are important for better maternal and neonatal outcomes. Since physiological changes during pregnancy may affect the pharmacokinetics and pharmacodynamics (PK/PD) of anti-TB medicines, treatment should be individualized, with close monitoring to maintain maternal safety and promote fetal well-being [41].

C. Co- Infection with Human Immunodeficiency Virus

Pregnant women who are living with HIV should undergo early screening for tuberculosis and receive timely management. Treat both active TB and latent TB infection according to current treatment guidelines. Management can be challenging because the anti-TB drugs may interact with antiretroviral therapy (ART). Therefore, treatment should be individualized and carried out under appropriate specialist supervision [40].

D. Postpartum and Breastfeeding

Informing the paediatric care team about the mother's tuberculosis status is essential to ensure appropriate assessment and care of the infant. Untreated active tuberculosis is a contraindication to breastfeeding. However, breastfeeding is encouraged once the mother has received first-line anti-TB treatment for at least two weeks and is no longer infectious. Pyridoxine (vitamin B6) supplementation should be provided to all breastfeeding mothers taking isoniazid, and their infants should be carefully monitored for the development of jaundice [40].

E. Renal Dysfunction

In patients with renal impairment, pyrazinamide (PZA) and ethambutol (EMB) may require dose modification and should be administered after haemodialysis in end-stage renal disease. Dose adjustment is generally achieved by reducing the frequency of administration rather than decreasing the individual dose. Isoniazid (INH) and rifampicin (RIF) usually do not need dose adjustment. Therapeutic drug monitoring may also be considered when clinically required [43].

VII. PRINCIPLE AND GOALS OF ANTI- TB DRUGS

A. Principles of Anti-TB Drugs

The main goals of tuberculosis (TB) treatment are to achieve favourable patient outcomes, minimize disease transmission, and prevent drug resistance. Prompt initiation of an effective

treatment regimen rapidly lowers the bacillary burden and infectivity, with a reduction of more than 90% within two days and over 99% within 14-21 days. Among active TB cases, pulmonary TB is the most common [43].

In first-line chemotherapy, isoniazid (INH) produces strong initial bactericidal activity. Rifampicin (RIF) and pyrazinamide (PZA) play a major role in eliminating bacteria during the intensive phase. During the continuation phase, rifampicin is particularly effective against dormant or slowly metabolizing bacilli. Standard treatment using INH and RIF is generally completed within six months, whereas the omission of either drug can extend the duration of therapy to 12-18 months [13].

B. Goals of anti-TB Drugs

The main objectives of anti-TB chemotherapy are to achieve complete cure without relapse, reduce deaths and complications, stop the transmission of the disease within the community, and prevent the development of drug-resistant strains. Long-term treatment using a combination of anti-TB drugs is necessary to achieve these goals. Active tuberculosis should not be treated with a single drug alone. Similarly, adding only one drug to a treatment regimen that is failing should be avoided, as this may result in the emergence of multidrug-resistant tuberculosis (MDR-TB). As recommended by the WHO, the management of tuberculosis, including drug-resistant TB, requires the use of multi-drug therapy, comprising:

- The initial intensive phase consists of Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PYZ), and Ethambutol (ETB), which are administered daily for two months.
- The continuation phase involves treatment with Rifampicin and Isoniazid for an additional four months. These medicines may be given daily or three times a week, according to the recommended treatment schedule [44].

VIII. SPECIAL SITUATIONS IN ANTI-TB DRUGS

A. Diabetes mellitus

Standard recommended anti-tuberculosis chemotherapy should be followed in patients with diabetes mellitus. Maintaining strict control of blood glucose levels is also important. Because rifampin can interact with oral hypoglycaemic drugs, an increase in their dosage may sometimes be necessary. In addition, prophylactic pyridoxine

at a dose of 10mg per day is recommended to help prevent peripheral neuropathy caused by isoniazid [13].

B. Pre-existing liver disease

Firstly, patients with pre-existing liver disease may have a greater risk of developing drug-induced hepatitis. Secondly, drug-induced hepatitis can have severe and potentially fatal consequences in individuals with limited hepatic reserve. Thirdly, detecting and monitoring drug-induced hepatitis may be challenging because underlying liver disease can cause fluctuations in liver function test results [42].

C. Treatment in unconscious patient

For patients receiving nutrition through a nasogastric or gastrostomy tube, routinely prescribed anti-tubercular drugs can be powdered and administered through the tube. Feeding should be withheld for approximately 2-3 hours before and after drug administration. In patients who have undergone an enterostomy or are receiving parenteral nutrition, intramuscular streptomycin and intravenous quinolones may be administered. Once oral feeding is resumed, treatment can be switched back to oral anti-tubercular therapy [13].

D. Post-transplant patients and other special situations.

Tuberculosis may develop several months or even years following transplantation. Affected Patients may show the usual clinical features of TB, while others may present with typical, unusual, or nonspecific manifestations. The management of TB in transplant recipients can be challenging because of potential drug-drug interactions with immunosuppressive therapy. In post-transplant patients, treatment regimens containing rifampin are generally avoided because rifampin increases the clearance of cyclosporine, which may reduce its therapeutic effect [13].

E. Extra Pulmonary Tuberculosis

Tuberculosis has the potential to affect almost any organ or tissue in the body, and extrapulmonary involvement is seen more commonly in children and persons with impaired immune function. The diagnosis of extrapulmonary tuberculosis requires the collection of appropriate specimens from the affected site, including pleural fluid, pericardial fluid, peritoneal fluid, and peritoneal biopsy specimens; lymph node tissue; and bone marrow, blood, urine, brain, or cerebrospinal fluid should be obtained for AFB staining, mycobacterial culture, and drug susceptibility testing. The fundamental principles used to treat pulmonary tuberculosis also apply to extrapulmonary forms of the disease [47].

IX. FUTURE PROSPECTS AND CURRENT DEVELOPMENT:

Approximately 2 billion people worldwide are estimated to be infected with *Mycobacterium tuberculosis*. The future development of chemotherapy in tuberculosis is mainly focused on overcoming major limitations such as prolonged treatment duration, multidrug resistance, adverse drug reactions, poor adherence, and eliminating dormant *Mycobacterium tuberculosis*. The drug-sensitive treatment regimen consists of ethambutol, isoniazid, rifampicin, and pyrazinamide in the intensive phase, followed by rifampicin and isoniazid in the continuous phase. Tuberculosis chemotherapy mainly focuses on shorter, safer, and more effective treatment regimens. A mA prolonged multidrug regimen can cause adverse effects and poor patient compliance. Therefore, shortening the duration while maintaining therapeutic efficacy is an important goal in tuberculosis treatment [48, 52, 54].

The development of new anti-tuberculosis drugs has provided more options, particularly for multidrug-resistant tuberculosis. New drugs such as bedaquiline, delamanid, and pretomanid have been introduced as new treatments for MDR-TB. Another important development is the reuse of existing drugs and the development of new drug combinations. Fluoroquinolones such as Moxifloxacin, norfloxacin, and gatifloxacin have been introduced to improve treatment outcomes and shorten the treatment duration. This approach is mainly important for MDR-TB; multidrug treatment often takes a long time and is associated with toxicity [48, 51, 52, 53, 54].

In the future, chemotherapy is increasingly focused on targeting long-lasting and non-replicating tuberculosis, because the bacilli can survive conventional treatment and contribute to death. Host-directed therapy is another promising approach that aims to enhance the defensive immune response and improve bacterial clearance. Appropriate dosage selection and safety of host-directed therapies still require further clinical studies [48,52,54].

Nanotechnology-based nanomedicines and advanced drug delivery systems also represent future approaches. Nanoparticles can provide targeted and controlled drug delivery systems that can reduce drug doses and adverse drug reactions while improving treatment adherence. There are various approaches for the administration of drugs to the body. For example, an inhalation-based drug delivery system may also deliver the drug directly to infected lung macrophages. Future chemotherapy for tuberculosis is expected to focus on novel drug targets, multidrug treatment,

direct host-targeting therapy, nanomedicine, and personalized therapy [48, 51, 52,54].

X. STATISTICAL METHODS:

Statistical methods play an important role in tuberculosis chemotherapy by allowing researchers to compare different regimens, identify statistically significant differences, and assess factors associated with treatment success or failure. These methods evaluate the safety, effectiveness, and treatment outcomes of tuberculosis chemotherapy [55, 56, 57].

A. Treatment Success:

Kaplan-Meier analysis is used to study time-to-event outcomes such as sputum culture, treatment failure, and death.[56]

Shorter regimen- 83%

Longer regimen-73.2%

The student's t-test is used to compare continuous variables, and the chi-square test is used to compare categorical variables. Treatment success is important for chemotherapy outcomes in tuberculosis; it may include cure and treatment completion. Treatment success is used to compare treatment regimens and determine which regimen provides better outcomes [56,57].

B. Cure and Mortality:

Shorter regimen- Cure (79.9%), Mortality (9.9%)

Longer regimen- Cure (70.9%), Mortality (18.3%)

This method is also used to evaluate the adverse effects of chemotherapy in tuberculosis, especially for drug-induced liver injury. Predictive models, frequency comparisons, and logistic regression are also used to identify patients at increased risk of adverse drug reactions. These statistical methods are essential for the safety and effectiveness of chemotherapy in tuberculosis. Appropriate statistical analysis provides evidence for selecting effective and safe tuberculosis treatment regimens [56,57].

XI. RECENT ADVANCES IN TB CHEMOTHERAPY:

Chemotherapy for tuberculosis has advanced significantly, with the development of more effective, safer, and better-tolerated drugs. Recent research mainly focuses on shorter drug treatment to improve patient adherence and to prevent the development of drug resistance. Recent advances in

tuberculosis chemotherapy include a four-month regimen for selected susceptible drugs. The regimen contains rifapentine, isoniazid, moxifloxacin, and pyrazinamide, which can shorten treatment duration while maintaining effective outcomes [59]. For drug-resistant tuberculosis, newer drugs such as bedaquiline, pretomanid, and linezolid, with moxifloxacin, are used to shorten the treatment to about six months, compared with much longer regimens [58]. Another approach to treatment is adjunctive or host-directed therapies, which are used to support recovery by modifying inflammation and abnormalities during anti-tuberculosis treatment. The main goal of chemotherapy in tuberculosis is to develop safer, more effective oral regimens that improve adherence, reduce treatment duration, and prevent resistance [58-60].

XII. CONCLUSION:

Over the years, tuberculosis chemotherapy has developed from lengthy treatment using early anti-tuberculosis medicines to combination regimens that provide improved therapeutic effects within shorter treatment periods. The conventional six-month regimen continues to be an important strategy for drug-susceptible tuberculosis. However, prolonged treatment, adverse drug reactions, interruption of therapy, poor adherence, and drug resistance remain important barriers to successful treatment. The increasing occurrence of MDR-TB and XDR-TB has created a greater need for effective drug combinations and newer therapeutic approaches. Recent developments, such as four-month treatment regimens and newer drugs including bedaquiline, pretomanid, and linezolid, have introduced additional options for selected patients.

Along with drug development, improving treatment adherence through patient-centered support, proper education, fixed-dose combinations, and regular monitoring is important for reducing treatment failure and resistance. Patients with special clinical conditions may need individualized treatment because physiological factors, co-infections, and drug interactions can influence therapeutic response. Future advances should focus on developing shorter, safer regimens; improving targeting of persistent bacilli; exploring host-directed therapies; using advanced drug-delivery systems; and implementing personalized treatment strategies. Continued research and clinical evaluation of these approaches are needed to improve TB treatment, reduce mortality and transmission, and support effective global TB control.

XIII REFERENCE

- [1] Davidson G, Davidson DU, Okoye OK, Mensah LS, Ukaegbu EC, Agbor DB, Adegbola MO, Eneyo US, Osuluku BA, Dinyain TO, Okeke AA. Overview of tuberculosis: causes, symptoms and risk factors. *Asian Journal of Research in Infectious Diseases*. 2024 Aug 20;15(9):8-19.
- [2] Alsayed SS, Gunosewoyo H. Tuberculosis: pathogenesis, current treatment regimens and new drug targets. *International journal of molecular sciences*. 2023 Mar 8;24(6):5202.
- [3] Bhanu ML, Kumari MP, Begum TM. Anti-tuberculosis drugs and mechanisms of action: review. *IJ Infectious Disea*. 2023;4(2):1-7.
- [4] Sandhu GK. Tuberculosis: current situation, challenges and overview of its control programs in India. *Journal of global infectious diseases*. 2011 Apr;3(2):143.
- [5] Sudre P, Ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. *Bulletin of the World Health Organization*. 1992;70(2):149.
- [6] Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. *Indian Journal of Tuberculosis*. 2020 Jul 1;67(3):295-311.
- [7] Al-Karawi AS, Kadhim AA, Kadum MM. Recent advances in tuberculosis: a comprehensive review of emerging trends in pathogenesis, diagnostics, treatment, and prevention. *International Journal of Clinical Biochemistry and Research*. 2023;10(4):262-9.
- [8] Suárez I, Fünfer SM, Kröger S, Rademacher J, Fätkenheuer G, Rybniker J. The diagnosis and treatment of tuberculosis. *Deutsches Aerzteblatt International*. 2019 Oct 25;116(43):729.
- [9] Narasimhan P, Wood J, MacIntyre CR, Mathai D. Risk factors for tuberculosis. *Pulmonary medicine*. 2013;2013(1):828939.
- [10] Lopes SR, Marcal M, Fernandes N, Silva F, Barbosa P, Vieira M, Ramos JP, Duarte R. Update in tuberculosis treatment: a scoping review of current practices. *Breathe*. 2025 Jan;21(1):240232.
- [11] Rabello E, de-Paris F. Tuberculosis Diagnostic Methods: Clinical Applicability, Implementation Challenges, and

Integrated Testing Strategies. *Pathogens*. 2026 Jan 28;15(2):142.

[12] Nuermberger EL, Spigelman MK, Yew WW. Current development and future prospects in chemotherapy of tuberculosis. *Respirology*. 2010 Jul;15(5):764-78.

[13] Joshi JM. Tuberculosis chemotherapy in the 21st century: Back to the basics. *Lung India: Official Organ of Indian Chest Society*. 2011 Jul;28(3):193.

[14] Mitchison DA, Davies G. The chemotherapy of tuberculosis: past, present and future. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2012 Jun;16(6):724.

[15] Iseman MD. Tuberculosis therapy: past, present and future. *European Respiratory Journal*. 2002 Jul 1;20(36 suppl):87S-94s.

[16] Collazos J, Mayo J, Martínez E. The chemotherapy of tuberculosis--from the past to the future. *Respir Med*. 1995 Aug;89(7):463-9. doi: 10.1016/0954-6111(95)90121-3. PMID: 7480975

[17] Krishna RG, Boddu SL, Damera S, Kadapa AK, Dharmareddy KM, Katha C. Advances in anti-tubercular agents: a comprehensive review.

[18] Khartode Pravin, Rushikesh Takale, Ritesh Deshmukh and Rahul Gawade. A review: first line used drugs in tuberculosis. *Int J Sci Technol (IJSAT)*. 2025;16(2):1-4.

[19] Sreelatha M, Naveena B, Prapurna Chandra Y. A review study on safety and efficacy on second line anti tubercular drugs. *Int J Exp Biomed Res*. 2023;2(3):132-138.

[20] Mereskeviciene R, Danila E. The adverse effects of tuberculosis treatment: a comprehensive literature review. *Medicina*. 2025 May 17;61(5):911.

[21] Dinesh Kumar, Adverse Drug Reactions Associated with Isoniazid in Tuberculosis Patients: A Review Study, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 4, 2822-2843,

[22] Prasad R, Singh A, Gupta N. Adverse drug reactions with first-line and second-line drugs in treatment of tuberculosis. *Annals of the National Academy of Medical Sciences (India)*. 2021 Jan;57(01):15-35.

[23] WHO consolidated guidelines on tuberculosis: Module 4: treatment - drug-resistant tuberculosis treatment, 2022

update [Internet]. Geneva: World Health Organization; 2022. PMID: 36630546.

[24] Dorman SE, Nahid P, Kurbatova EV, Phillips PP, Bryant K, Dooley KE, Engle M, Goldberg SV, Phan HT, Hakim J, Johnson JL. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *New England Journal of Medicine*. 2021 May 6;384(18):1705-18.

[25] Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022 Feb 25;71(8):285-289. doi: 10.15585/mmwr.mm7108a1. PMID: 35202353.

[26] WHO consolidated guidelines on tuberculosis: Module 4: Treatment and care [Internet]. Geneva: World Health Organization; 2025. Chapter 1, Drug-susceptible TB treatment.

[27] Dall C. New guidelines expand recommendations for shorter, all-oral TB treatments [Internet]. Minneapolis: Center for Infectious Disease Research and Policy, University of Minnesota; 2025

[28] Ohno H, Koga H, Kohno S. Multidrug-resistant tuberculosis. 2. Mechanisms of drug-resistance in *Mycobacterium tuberculosis*--genetic mechanisms of drug-resistance. *Kekkaku: [Tuberculosis]*. 1998 Nov 1;73(11):657-63.

[29] Jang JG, Chung JH. Diagnosis and treatment of multidrug-resistant tuberculosis. *Yeungnam University journal of medicine*. 2020 Oct 31;37(4):277-85.

[30] Omoteso OA, Fadaka AO, Walker RB, Khamanga SM. Innovative strategies for combating multidrug-resistant tuberculosis: advances in drug delivery systems and treatment. *Microorganisms*. 2025;13(4):722. doi:10.3390/microorganisms13040722

[31] Michalik M, Lorenc T, Marcinkowski K, Muras M, Mikszta N, Mikszta J, Kantor K, Marcinkowska J. Advances and prospects for treatment strategies of drug-resistant tuberculosis: a review. *GMS hygiene and infection control*. 2025 Jun 26;20: Doc33.

[32] Dheda K, Mirzayev F, Cirillo DM, Udwadia Z, Dooley KE, Chang KC, Omar SV, Reuter A, Perumal T, Horsburgh Jr CR, Murray M. Multidrug-resistant tuberculosis. *Nature Reviews Disease Primers*. 2024 Mar 24;10(1):22.

- [33] Kozhamkulov U, Iglíkova S, Rakisheva A, Almazan J. Multidrug-resistant tuberculosis in Central Asia and predominant Beijing lineage, challenges in diagnosis, treatment barriers, and infection control strategies: an integrative review. *Antibiotics*. 2025 Jul 2;14(7):673.
- [34] Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, Nahid P. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLoS medicine*. 2018 Jul 3;15(7):e1002595.
- [35] Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. *Bmj*. 1997 Nov 29;315(7120):1403-6.
- [36] Sazali MF, Rahim SS, Mohammad AH, Kadir F, Payus AO, Avoi R, Jeffree MS, Omar A, Ibrahim MY, Atil A, Tuah NM. Improving tuberculosis medication adherence: the potential of integrating digital technology and health belief model. *Tuberculosis and respiratory diseases*. 2022 Dec 23;86(2):82.
- [37] Lawal A, Hussein A, Tiberi S, Kunst H. Barriers to and enablers of adherence to the treatment of active drug-sensitive tuberculosis in people living with HIV: a mixed method systematic review. *BMC Public Health*. 2025 Nov 29;26(1):39.
- [38] Nezenega ZS, Perimal-Lewis L, Maeder AJ. Factors influencing patient adherence to tuberculosis treatment in Ethiopia: a literature review. *International journal of environmental research and public health*. 2020 Aug;17(15):5626.
- [39] McIlleron H, Abdel-Rahman S, Dave JA, Blockman M, Owen A. Special populations and pharmacogenetic issues in tuberculosis drug development and clinical research. *The Journal of infectious diseases*. 2015 Jun 15;211(suppl_3):S115-25.
- [40] Miele K, Morris SB, Tepper NK. Tuberculosis in pregnancy. *Obstetrics and gynecology*. 2020 Jun;135(6):1444.
- [41] Lima T, Trigo S, Silveira E, da Silva GJ, Domingues S. Navigating Tuberculosis in Pregnancy and Lactation: A Review of Maternal and Neonatal Considerations. *Diseases*. 2026 Mar 11;14(3):102.
- [42] Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM. Official American thoracic society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clinical infectious diseases*. 2016 Oct 1;63(7):e147-95.
- [43] Dobbs TE, Webb RM. Chemotherapy of tuberculosis. *Microbiology Spectrum*. 2017 Apr 30;5(2):10-128.
- [44] Du Toit LC, Pillay V, Danckwerts MP. Tuberculosis chemotherapy: current drug delivery approaches. *Respiratory research*. 2006 Sep 19;7(1):118.
- [45] Dhiman RK, Saraswat VA, Rajekar H, Reddy C, Chawla YK. A guide to the management of tuberculosis in patients with chronic liver disease. *Journal of clinical and experimental hepatology*. 2012 Sep 1;2(3):260-70.
- [46] Epstein DJ, Subramanian AK. Prevention and management of tuberculosis in solid organ transplant recipients. *Infectious Disease Clinics*. 2018 Sep 1;32(3):703-18.
- [47] Blumberg HM, Burman WJ, Chaisson RE, Daley CL. American thoracic society/centers for disease control and prevention/infectious diseases society of America: treatment of tuberculosis. *American journal of respiratory and critical care medicine*. 2003 Feb 15;167(4):603.
- [48] Zhao CY, Song C, Lu YB, Huang AC, Zeng CM, Liu RH, Li WW, Xie ZH, Zhu QD. A new era in tuberculosis prevention and treatment: breakthroughs in drug development and future prospects. *Infectious Diseases and Therapy*. 2025 Oct;14(10):2205-19.
- [49] Zhuang L, Ye Z, Li L, Yang L, Gong W. Next-generation TB vaccines: progress, challenges, and prospects. *Vaccines*. 2023 Jul 31;11(8):1304.
- [50] Borah Slater K, Kim D, Chand P, Xu Y, Shaikh H, Undale V. A current perspective on the potential of nanomedicine for anti-tuberculosis therapy. *Tropical medicine and infectious disease*. 2023 Feb 3;8(2):100.
- [51] Kotadiya M, Andriambololona ON. Recent advances in tuberculosis drug development. *International Journal of Pharmacy Research & Technology (IJPRT)*. 2018;8(2):1-3.
- [52] Zumla AI, Gillespie SH, Hoelscher M, Philips PP, Cole ST, Abubakar I, McHugh TD, Schito M, Maeurer M, Nunn AJ. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *The Lancet infectious diseases*. 2014 Apr 1;14(4):327-40.

[53] An Y, Ni R, Zhuang L, Yang L, Ye Z, Li L, Parkkila S, Aspatwar A, Gong W. Tuberculosis vaccines and therapeutic drug: challenges and future directions. *Molecular biomedicine*. 2025 Jan 22;6(1):4.

[54] Dover LG, Coxon GD. Current status and research strategies in tuberculosis drug development: miniperspective. *Journal of medicinal Chemistry*. 2011 Sep 22;54(18):6157-65.

[55] Chang VK, Imperial MZ, Phillips PP, Velásquez GE, Nahid P, Vernon A, Kurbatova EV, Swindells S, Chaisson RE, Dorman SE, Johnson JL. Risk-stratified treatment for drug-susceptible pulmonary tuberculosis. *Nature communications*. 2024 Oct 30;15(1):9400.

[56] Wahid A, Ghafoor A, Khan AW, Al-Worafi YM, Latif A, Shahwani NA, Atif M, Saleem F and Ahmad N (2022) Comparative effectiveness of individualized longer and standardized shorter regimens in the treatment of multidrug resistant tuberculosis in a high burden country. *Front. Pharmacol*. 13:973713. doi: 10.3389/fphar.2022.973713

[57] Xiao Y, Chen Y, Huang R, Jiang F, Zhou J, Yang T. Interpretable machine learning in predicting drug-induced liver injury among tuberculosis patients: model development and validation study. *BMC Med Res Methodol*. 2024;24:92. doi:10.1186/s12874-024-02214-5.

[58] Larkins-Ford J, Aldridge BB. Advances in the design of combination therapies for the treatment of tuberculosis. *Expert opinion on drug discovery*. 2023 Jan 2;18(1):83-97.

[59] Singh V. Tuberculosis treatment-shortening. *Drug Discovery Today*. 2024 May 1;29(5):103955.

[60] Perumal D, Vaithiyalingam M, Dharanitharan K, Dinesh B, Kumar MS, Rahmathullah A, JK R. Neuro-Symbolic AI in Drug Discovery: Combining Deep Learning with Logical Reasoning Systems. In *Revolutionizing Drug Research and Personalized Medicine Through AI and Machine Learning 2026* (pp. 307-332). IGI Global Scientific Publishing.