Treatment Of Tuberculosis: Current Regimens And Future Directions

[1]Siddhanth Askok Kakde, [2]Mr. Kuldeep Sukhdeo Kanadje, [3]Dr. D.K. Vir, [4]Abhay Ramdas Kapse, [5]Vaishnavi Kachru Ghuge.

1) Student, 2) Associate professor,3) Principal, 4) Student, 5) Student
Department of Pharmaceutical Science and Technology.
Shree Goraksha College of Pharmacy & Research Centre, Chhatrapati Sambhaji Nagar, India

Abstract : Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, remains a leading global cause of mortality from a single infectious agent. The treatment landscape for TB is complex, divided into regimens for drug-susceptible (DS) and drug-resistant (DR) disease. The first-line treatment for DS-TB is a six-month, multi-drug regimen, while DR-TB requires longer, more toxic, and costly regimens. This review outlines the fundamental principles of TB treatment, the current drug protocols, and the significant challenges faced, including drug resistance, co-morbidities, and patient adherence. Furthermore, it explores the pipeline of novel drug candidates targeting new bacterial pathways, which are crucial for combating DR-TB and potentially shortening therapy duration. Adherence support and patient-centred care are emphasized as critical components of successful treatment outcomes.

Keywords: Tuberculosis, Drug-Resistant TB, MDR-TB, Treatment Regimens, DOTS, New Drug Targets.

1. Introduction

Tuberculosis (TB) is an ancient airborne infectious disease caused by *Mycobacterium tuberculosis* that continues to exert a profound impact on global health. Despite decades of progress in diagnostics, therapeutics, and public health strategies, TB remains one of the most persistent infectious threats worldwide. Although the disease is both preventable and curable, the global burden remains alarmingly high, with an estimated one-quarter of the world's population carrying latent tuberculosis infection (LTBI). Individuals with LTBI serve as a silent reservoir, posing the risk of reactivation and contributing to ongoing transmission, especially in regions with limited healthcare access or high prevalence of immunocompromising conditions.

The World Health Organization (WHO) reported that in 2021 more than 10 million people developed active TB, while approximately 1.6 million deaths were attributed to the disease, making TB one of the leading causes of mortality from an infectious agent. These statistics highlight that, even in the 21st century, TB continues to challenge global health systems. Its burden is disproportionately concentrated in low- and middle-income countries, where socioeconomic factors such as poverty, malnutrition, overcrowded living conditions, and inadequate healthcare infrastructure accelerate transmission and hinder timely treatment.

Complicating the situation further is the rise of drug-resistant TB forms, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). These strains arise from inadequate or incomplete treatment, poor drug adherence, misuse of antibiotics, and biological factors intrinsic to *M. tuberculosis*, which has an exceptional ability to survive under hostile conditions. Drug-resistant TB requires longer treatment durations, multiple drug combinations, higher toxicity, and significantly greater financial investment. As a result, MDR-TB and XDR-TB have become major barriers to achieving global TB elimination goals.

Co-infections, particularly with the human immunodeficiency virus (HIV), further aggravate the global burden. TB remains the leading cause of death among HIV-positive individuals, as immunosuppression dramatically increases susceptibility to active disease. The dual epidemic of HIV–TB poses unique therapeutic challenges, such as drug–drug interactions, increased risk of adverse effects, and diagnostic difficulties due to atypical clinical presentations.

In recent years, advancements in TB research have led to improvements in diagnostic tools, shorter and more effective treatment regimens, and the development of new drug candidates. Novel therapeutics such as bedaquiline, delamanid, and pretomanid offer hope in treating resistant forms of TB, while ongoing clinical trials continue to explore optimized combinations for both drug-sensitive and drug-resistant strains. Alongside pharmacological innovations, public health strategies focusing on early detection, preventive therapy, vaccination, and social support systems play an essential role in reducing transmission.

This review aims to provide a comprehensive synthesis of current TB treatment approaches, spanning traditional first-line therapies, newer antimicrobial agents, and emerging treatment strategies under investigation. It also highlights the ongoing challenges in combating TB, with particular emphasis on drug resistance, co-morbidities, and public health limitations. Through a detailed exploration of current evidence and future prospects, this review seeks to contribute to the broader understanding of TB management and the global efforts required to ultimately eliminate this ancient yet enduring disease.

2. Definition of Tuberculosis

Tuberculosis is an infectious disease caused by bacteria of the Mycobacterium tuberculosis complex. It primarily affects the lungs (pulmonary TB) but can also disseminate to other parts of the body (extrapulmonary TB), such as the lymph nodes, kidneys, bones, and brain. The disease manifests in two states: latent TB infection (LTBI), where bacteria are present in a dormant state within granulomas without causing symptoms, and active TB disease, which is contagious and characterized by clinical symptoms.

2.1 Causes

TB is caused by inhaling aerosol droplets containing M. tuberculosis bacilli, which are expelled into the air when a person with active pulmonary TB coughs, sneezes, or speaks. Upon inhalation, the bacteria are phagocytosed by alveolar macrophages in the lungs. The host's immune response typically walls off the infection by forming granulomas, structures that contain but do not always eliminate the bacteria, leading to latent infection. Progression to active disease occurs in approximately 5-10% of infected individuals, a risk significantly heightened by immunosuppressive conditions such as HIV infection, diabetes mellitus, malnutrition, or immunosuppressive ther

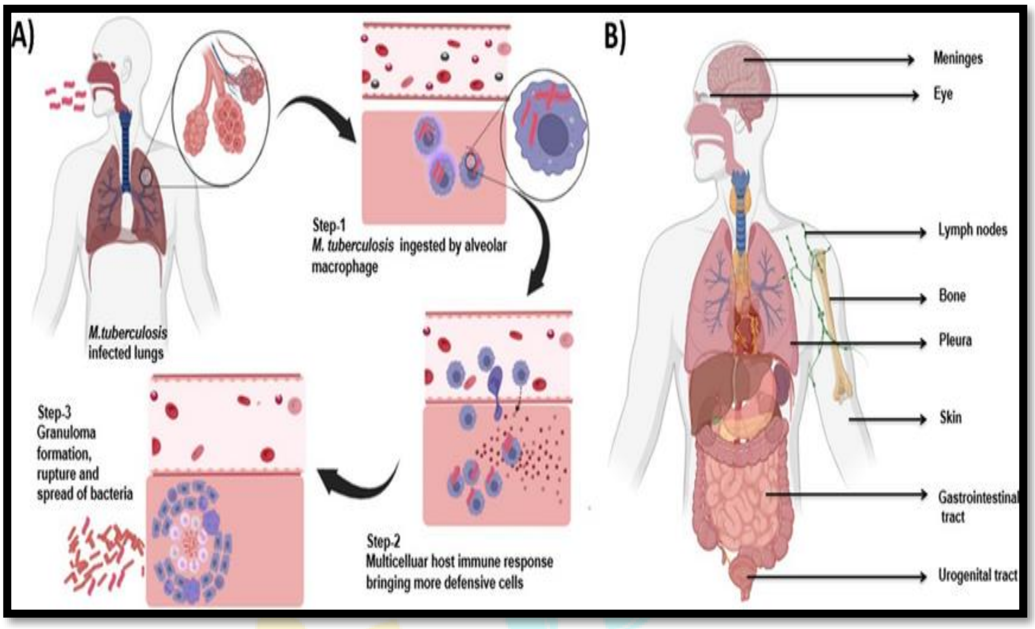

Figure 1 : A diagram illustrating the pathogenesis of TB, from inhalation to granuloma formation and cavitation.

2.2 Types

- TB can be classified based on anatomical site and drug susceptibility:
- Pulmonary TB: The most common and infectious form, affecting the lungs.
- Extrapulmonary TB: TB affecting organs other than the lungs.
- Drug-Susceptible TB (DS-TB): TB that is susceptible to all first-line anti-TB drugs.
- Drug-Resistant TB (DR-TB): A broad term encompassing various resistance patterns.
- Mono-resistant: Resistance to one first-line anti-TB drug.
- Poly-resistant: Resistance to more than one first-line drug (but not both isoniazid and rifampicin).
- Multidrug-resistant (MDR-TB): Resistance to at least both isoniazid and rifampicin.
- Extensively drug-resistant (XDR-TB): Resistance to isoniazid, rifampicin, any fluoroquinolone, and at least one second-line injectable drug.

2.3 Treatment

The treatment of TB is founded on several core principles: using drug combinations to prevent resistance, ensuring adherence through support programs, and tailoring therapy based on drug susceptibility test (DST) results.

2.3.1 Treatment of Drug-Susceptible T.B.

The standard first-line treatment for DS-TB is a six-month regimen divided into two phases:

Intensive Phase (2 months): Isoniazid (INH), Rifampin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB).

Continuation Phase (4 months): INH and RMP. - This regimen is highly effective, with cure rates exceeding 95% when adhered to fully. Ethambutol is included initially as a "protector" drug until DST confirms full susceptibility, at which point it can be discontinued. Therapy should be administered daily, especially in the initial phase.

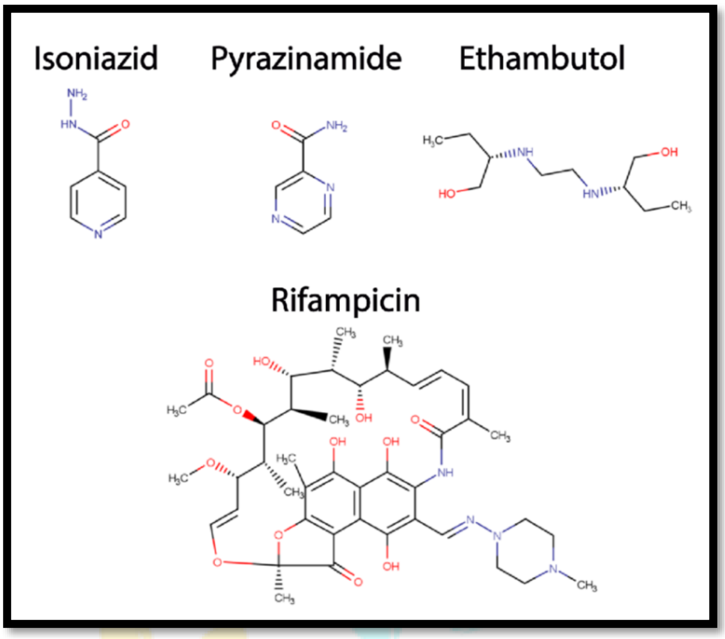

Figure 2 Chemical structures of the four first-line drugs: Isoniazid, Rifampin, Pyrazinamide, Ethambutol.

2.3.2. Treatment of Drug-Resistant TB

- Treatment of DR-TB is more complex and prolonged.
- Isoniazid-Resistant TB: Treated with a 6-month regimen of RMP, EMB, PZA, and a fluoroquinolone (e.g., Levofloxacin).
- MDR/XDR-TB: Requires specialized regimens lasting 9-20 months using second-line drugs. A typical longer regimen includes a combination of drugs from Groups A (e.g., Bedaquiline, Linezolid, Levofloxacin/Moxifloxacin), B (e.g., Clofazimine, Cycloserine), and C (e.g., Delamanid, Pyrazinamide, Ethambutol, Imipenem). The WHO also recommends a shorter (9-11 month) all-oral regimen for eligible MDR-TB patients. For XDR-TB, newer regimens like BPaL (Bedaquiline, Pretomanid, Linezolid) have shown promise.

2.3.3. The Role of Patient Support and Adherence

- Successful TB treatment requires more than just prescribing drugs. Comprehensive, patient-centred care is critical. This includes:
- Directly Observed Therapy (DOT): Having a healthcare worker observe the patient taking each dose to ensure adherence. Community-based DOT is preferred over clinic-based.
- Adherence Support: Using incentives (e.g., food vouchers, transport fares) and enablers (e.g., counselling, reminder systems, blister packs) to overcome barriers to adherence.
- Addressing Social Determinants: Linking patients to social, financial, and psychological support is essential, especially for marginalized populations.

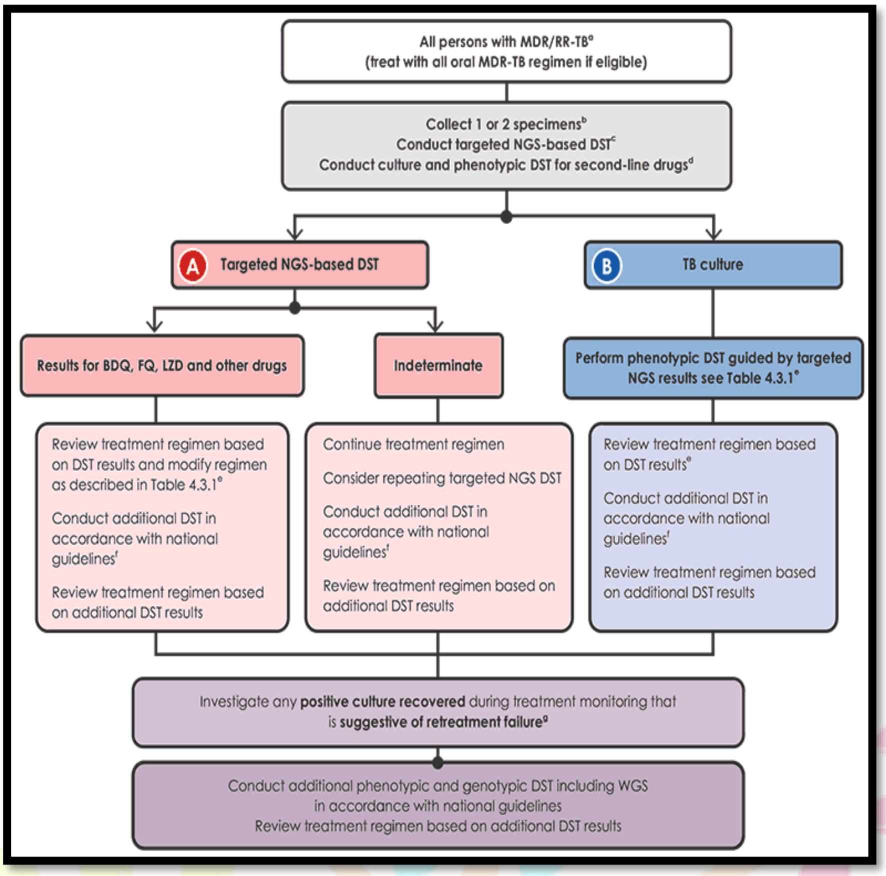

Figure 3 A flowchart algorithm for managing TB based on DST results.

3. Pathogenesis and Types of Tuberculosis

3.1 Pathogenesis

Tuberculosis begins when *Mycobacterium tuberculosis* (M. tuberculosis) bacilli are transmitted through airborne droplets released by individuals with active pulmonary TB during coughing, sneezing, speaking, or even breathing. Once inhaled, these droplets reach the alveoli, where the bacilli encounter the host's first line of defense—alveolar macrophages. The bacteria possess several virulence factors, such as lipoarabinomannan and secretory proteins, that enable them to survive intracellularly by inhibiting phagosome–lysosome fusion and neutralizing reactive oxygen species.

Inside macrophages, the bacilli may either multiply unchecked or trigger the recruitment of additional immune cells, including monocytes, neutrophils, dendritic cells, and T lymphocytes. This cellular aggregation leads to the formation of a granuloma—a hallmark of TB infection. Granulomas function as containment structures designed to limit bacterial spread. They consist of a central core of infected macrophages surrounded by epithelioid cells, multinucleated giant cells, fibroblasts, and lymphocytes.

In many individuals, the immune system successfully contains the infection, leading to a latent state where the bacteria remain viable but dormant within granulomas. This condition, known as latent TB infection (LTBI), can persist for years without causing symptoms. However, if the host's immunity declines due to factors such as malnutrition, HIV infection, diabetes, aging, or immunosuppressive therapy, the granuloma structure may break down. This allows dormant bacilli to reactivate, spread, and cause active TB disease. Reactivation typically occurs in the upper lobes of the lungs due to higher oxygen tension, which favors the growth of *M. tuberculosis*.

3.2 Types of Tuberculosis

Tuberculosis manifests in several clinical forms depending on host immunity, site of infection, and drug susceptibility profile. These types can be classified into the following categories:

3.2.1 Pulmonary Tuberculosis

- Infection primarily affects the lungs.
- Represents the most common and most contagious form of TB.
- Symptoms include persistent cough, hemoptysis, chest pain, fever, night sweats, and weight loss.
- Pulmonary TB is responsible for the majority of transmission in communities.

3.2.2 Extrapulmonary Tuberculosis

- Occurs when infection spreads beyond the lungs to other organs.
- Common sites include lymph nodes (lymphadenitis), pleura, bones and joints (Pott's disease), genitourinary tract, gastrointestinal system, skin, and central nervous system (tuberculous meningitis).
- More prevalent in immunocompromised individuals, especially those with HIV infection.
- Symptoms vary depending on the organ involved and may lead to severe complications if untreated.

3.2.3 Latent Tuberculosis Infection (LTBI)

- Characterized by the presence of viable but dormant bacteria without clinical symptoms or radiological disease.
- Individuals with LTBI are non-contagious.
- Approximately 5–10% of infected persons progress to active disease during their lifetime, with higher risk among immunocompromised populations.
- Diagnosis is based on tuberculin skin test (TST) or interferon-gamma release assays (IGRAs).

3.2.4 Drug-Susceptible Tuberculosis (DS-TB)

- Caused by strains of *M. tuberculosis* that are responsive to all first-line anti-TB drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol.
- Standard treatment regimens are highly effective when adhered to properly.

3.2.5 Drug-Resistant Tuberculosis (DR-TB)

Drug resistance occurs when TB bacteria acquire genetic mutations that reduce drug efficacy. DR-TB is classified into the following subtypes:

- **Mono-resistant TB**
  Resistance to a single first-line anti-TB drug.
- **Poly-resistant TB**
  Resistance to more than one first-line drug, but not the combination of isoniazid and rifampicin.
- **Multidrug-resistant TB (MDR-TB)**
- **Extensively drug-resistant TB (XDR-TB)**

4. Current Treatment Regimens

4.1 Treatment of Drug-Susceptible Tuberculosis (DS-TB)

The treatment of drug-susceptible *Mycobacterium tuberculosis* infection follows standardized protocols recommended by the World Health Organization (WHO). The current global standard is a **6-month short-course chemotherapy regimen**, widely recognized for its high efficacy, cost-effectiveness, and feasibility in resource-limited settings.

4.2 Standard 6-Month Regimen

The regimen is divided into two distinct phases:

4.2.1 Intensive Phase (First 2 Months)

Patients receive a four-drug combination consisting of:

- **Isoniazid (H)** – inhibits mycolic acid synthesis; bactericidal to rapidly dividing bacilli.
- **Rifampicin (R)** – suppresses RNA polymerase; key sterilizing agent.
- **Pyrazinamide (Z)** – active against dormant intracellular bacilli within acidic environments.
- **Ethambutol (E)** – prevents emergence of resistance before susceptibility is known.

4.2.2 Primary Objectives:

- Rapidly reduce the bacterial load
- Prevent transmission by converting patients to smear-negative
- Reduce the likelihood of acquired drug resistance

4.3. Continuation Phase (Next 4 Months)

Consists of:

- **Isoniazid (H)**
- **Rifampicin (R)**

4.3 Treatment of Drug-Resistant Tuberculosis (DR-TB)

Drug-resistant TB includes **MDR-TB**, **pre-XDR TB**, and **XDR-TB**, all of which require prolonged, less tolerable, and more expensive therapies. Treatment outcomes depend on resistance patterns, bacillary load, patient adherence,and comorbidities such as HIV.

4.4 Longer All-Oral MDR/XDR-TB Regimen (18–20 Months)

According to WHO guidelines, a fully oral regimen consisting of three priority groups is recommended:

- **Group A (Highest Priority Drugs)**

These drugs form the core of DR-TB treatment due to strong bactericidal and sterilizing activity:

- **Bedaquiline (Bdq)**
- **Linezolid (Lzd)**
- **Fluoroquinolones (Levofloxacin/Moxifloxacin)**

- **Group B (Additional Effective Agents)**

Used when Group A alone is insufficient:

- **Clofazimine (Cfz)**
- **Cycloserine / Terizidone (Cs/Trd)**

➢ **Group C (Supplementary Agents)**

Used to complete the regimen when options from Groups A and B are limited:

- **Delamanid (Dlm)**
- **Ethambutol (E)**
- **Imipenem–Cilastatin**
- **Amikacin (Amk)** – used only when no oral options remain, due to toxicity risks

➢ **Advantages of All-Oral Therapy:**

- Avoids injectable drugs and their severe ototoxicity
- Improves patient comfort and adherence
- Provides better long-term outcomes compared to older injectable-containing regimens

4.5 Shorter MDR-TB Regimen (9–11 Months)

This regimen is suitable for eligible patients **without resistance to fluoroquinolones** and with no previous exposure to second-line drugs.

Typical components include:

- **Bedaquiline**
- **Levofloxacin**
- **Clofazimine**
- **Pyrazinamide**
- **Ethambutol**
- **Linezolid**

➢ **Benefits:**

- Reduced treatment duration
- Improved adherence
- Lower toxicity and cost
- Rapid culture conversion

Studies have shown that shorter regimens are effective for a large proportion of MDR-TB patients when used appropriately.

4.6 Novel Regimen for XDR-TB: The BPaL Regimen

For extensively drug-resistant TB, the breakthrough **BPaL regimen** offers a promising alternative.

➢ **Composition:**

- **Bedaquiline (B)**
- **Pretomanid (Pa)** – newly approved nitroimidazole with strong sterilizing activity
- **Linezolid (L)**

➢ **Key Features:**

- **Shortened duration** of 6–9 months
- **High efficacy**, even in difficult-to-treat cases
- Potential to replace toxic injectable regimens
- Recommended for XDR-TB and treatment-intolerant or non-responsive MDR-TB

Clinical trials like **Nix-TB**, **ZeNix**, and **TB-PRACTECAL** have demonstrated cure rates above 85% in selected populations, marking a major advancement in global TB therapy.

Table 1 : Challenges in TB Management and Potential Solutions

Key Challenge	Impact on TB Control	Potential Solution	Supporting Strategy
Drug Resistance (MDR/XDR)	Treatment failure, prolonged therapy	Shorter oral regimens (e.g., BPaL, BPaLM)	Policy support & global access programs
Treatment Toxicity	Poor adherence and dropouts	Nanoparticle-based formulations	Therapeutic drug monitoring
Slow Diagnosis	Delayed treatment initiation	Advanced molecular tests (WGS, LAMP)	Strengthening lab capacity
Patient Non-Adherence	Higher risk of relapse and resistance	Digital adherence tools, DOT alternatives	Patient-centred care
Limited Access to New Drugs	Geographic and economic barriers	Global procurement and subsidies	International collaborations

5. Novel and Emerging Therapeutic Strategies

Rapid advancements in drug discovery, nanotechnology, and personalized medicine are reshaping future TB management. These innovations aim to overcome drug resistance, improve treatment outcomes, and reduce toxicity.

5.1 New Anti-TB Drugs and Molecular Targets

Several new compounds with novel mechanisms are under development:

- **Bedaquiline** – Inhibits ATP synthase, improving outcomes in MDR-TB.
- **Delamanid** – Blocks mycolic acid synthesis, weakening the bacterial cell wall.
- **Pretomanid** – Disrupts cell wall formation and energy generation; key drug in the BPaL regimen.
- **DprE1 Inhibitors (BTZ-043, OPC-167832)** – Target arabinan synthesis crucial for cell wall integrity.
- **MmpL3 Inhibitors (SQ109)** – Prevent transport of mycolic acids needed for cell wall construction.
- **QcrB Inhibitors (Telacebec/Q203)** – Interfere with the cytochrome bc1 complex, blocking ATP production.

These agents show strong activity against both drug-sensitive and drug-resistant strains.

5.2 Nanoformulations in TB Therapy

Nanotechnology enhances drug delivery and reduces toxicity.
Recent studies (Ezeqbe et al., 2025) demonstrate that **chitosan-coated isoniazid nanocapsules** improve drug stability, cellular penetration, and sustained release, resulting in lower MIC values.

Benefits of nano-drug delivery:

- Better penetration into macrophages and granulomas
- Controlled release
- Less systemic toxicity
- Increased patient adherence

5.3 Host-Directed Therapies (HDTs)

HDTs aim to enhance the host immune response rather than directly kill bacteria. Promising agents include:

- **Metformin** – Stimulates autophagy and boosts bacterial clearance.
- **Vitamin D analogs** – Enhance innate immunity via antimicrobial peptides.
- **Statins** – Possess anti-inflammatory effects and restrict bacterial survival pathways.

These therapies may shorten treatment duration and improve outcomes in drug-resistant cases.

5.4 Pharmacogenomics and Personalized Medicine

Genetic variations influence TB drug metabolism and toxicity.

- **NAT2** genotypes determine isoniazid acetylation rate; slow acetylators risk hepatotoxicity.
- **CYP2E1** variants modulate susceptibility to INH-induced liver injury.

Studies (Thomas et al., 2024) support **genotype-guided isoniazid dosing**, enabling safer and more effective personalized therapy.

Table 2 : Emerging Innovations in Tuberculosis Diagnosis and Treatment

Category	Innovation	Purpose/Benefit	Current Status
Molecular Diagnostics	GeneXpert, Whole-Genome Sequencing (WGS)	Rapid detection of TB and drug resistance	Widely adopted, expanding in LMICs
Pharmacogenomics	Genetic markers for drug metabolism (e.g., NAT2)	Personalized dosing, reduced toxicity	Under research, limited clinical use
Nanomedicine	Nanocarriers, liposomes	Targeted delivery, improved drug bioavailability	Pre-clinical to early clinical stages
Host-Directed Therapies	Immunomodulators, autophagy enhancers	Reduce inflammation and improve immune	In trials
AI / Machine Learning	Predictive models for drug resistance and outbreak surveillance	Improved accuracy and early intervention	Emerging application

6. Future Directions

The evolving landscape of tuberculosis research highlights several promising avenues aimed at improving treatment outcomes, reducing resistance, and strengthening global TB control efforts.

6.1 Development of Shorter, Safer, and Cost-Effective Oral Regimens

Future research is focused on identifying potent drug combinations that can shorten therapy duration while maintaining high cure rates. All-oral regimens using newer agents like bedaquiline, pretomanid, and linezolid hold potential to replace older, toxic injectable drugs and improve patient adherence.

6.2 Integration of Whole-Genome Sequencing (WGS)

Whole-genome sequencing is emerging as a rapid and precise method for detecting drug resistance mutations. WGS can guide individualized therapy decisions, monitor transmission patterns, and support early identification of MDR/XDR-TB strains in both clinical and public health settings.

6.3 Nanocarrier and Liposome-Based Drug Delivery

Advanced delivery systems such as nanoparticles, polymeric carriers, and liposomes enable targeted transport of anti-TB drugs directly to infected macrophages and granulomas. This approach promises improved bioavailability, lower toxicity, and reduced dosing frequency.

6.4 Artificial Intelligence and Machine Learning in TB Research

AI-driven platforms are accelerating the discovery of new drug candidates by predicting molecular interactions, optimizing drug combinations, and analyzing vast genomic datasets. Machine learning models can also enhance diagnostics and digital adherence monitoring.

6.5 Expanding Global Access Through Policy and Health System Support

Equitable access to new TB treatments requires strong global policies, sustainable financing, and integration of new regimens into national TB programs. Strengthening supply chains, regulatory frameworks, and public health infrastructure will be essential for widespread adoption.

7. Summary –

Tuberculosis (TB) remains one of the world's leading infectious diseases, driven by high rates of transmission, the persistence of latent infection, and the growing challenge of drug-resistant strains. Standard treatment for drug-susceptible TB consists of a six-month regimen using isoniazid, rifampicin, pyrazinamide, and ethambutol, which is highly effective when adherence is maintained. However, multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB require longer, more toxic, and costlier therapies involving second-line drugs such as bedaquiline, linezolid, clofazimine, and fluoroquinolones. Emerging regimens—including the shorter all-oral MDR-TB regimen and the BPaL combination—show promise in improving outcomes and reducing treatment duration..

8. Conclusion

Tuberculosis continues to pose a significant global health challenge despite the availability of established treatment options. Persistent issues such as the emergence of multidrug-resistant and extensively drug-resistant strains, treatment-related toxicity, lengthy therapeutic regimens, and difficulties in patient adherence remain major barriers to effective disease control. However, recent scientific advancements are opening new pathways for strengthening TB management. Innovations in rapid molecular diagnostics and whole-genome sequencing have greatly improved early detection and drug-resistance profiling. Pharmacogenomic tools are helping tailor therapy to individual patient responses, while nanomedicine and novel drug-delivery systems such as liposomes and nanocarriers have shown potential in enhancing drug efficacy and reducing toxicity. In addition, host-directed therapies aim to modulate the immune system to better combat infection and minimize tissue damage. Integrating these emerging technologies into national TB control programs, supported by robust healthcare policies, improved accessibility to newer regimens, and patient-centred care approaches, will be essential for future progress. Strengthening global collaborations, ensuring equitable access to diagnostics and treatment, and promoting continuous research will further accelerate TB elimination efforts. With sustained innovation and coordinated action, the WHO's vision of ending TB by 2030 becomes an achievable.

9. References

1) Kaufmann, S.H.; Schaible, U.E. 100th anniversary of Robert Koch's Nobel Prize for the discovery of the tubercle bacillus. Trends Microbiol. 2005, 13, 469–475.
2) World Health Organisation. Global Tuberculosis Report 2022; World Health Organization: Geneva, Switzerland, 2022; Licence: CC BY-NC-SA 3.0 IGO; Available online: https://www.who.int/publications/i/item/9789240061729 (accessed on 1 February 2023).
3) Flynn, J.L.; Chan, J. Tuberculosis: Latency and Reactivation. Infect. Immun. 2001, 69, 4195–4201.
4) World Health Organisation. Global Tuberculosis Report 2020; World Health Organization: Geneva, Switzerland, 2020; Licence: CC BY-NC-SA 3.0 IGO; Available online: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf (accessed on 1 February 2023).
5) Philips, J.A.; Ernst, J.D. Tuberculosis Pathogenesis and Immunity. Annu. Rev. Pathol. Mech. Dis. 2012, 7, 353–384.
6) Acharya, B.; Acharya, A.; Gautam, S.; Ghimire, S.P.; Mishra, G.; Parajuli, N.; Sapkota, B. Advances in diagnosis of Tuberculosis: An update into molecular diagnosis of Mycobacterium tuberculosis. Mol. Biol. Rep. 2020, 47, 4065–4075.
7) Leung, A.N. Pulmonary Tuberculosis: The Essentials. Radiology 1999, 210, 307–322.
8) Luies, L.; du Preez, I. The Echo of Pulmonary Tuberculosis: Mechanisms of Clinical Symptoms and Other Disease-Induced Systemic Complications. Clin. Microbiol. Rev. 2020, 33, e00036-20.
9) Schluger, N.W. The pathogenesis of tuberculosis: The first one hundred (and twenty-three) years. Am. J. Respir. Cell Mol. Biol. 2005, 32, 251–256.
10) Russell, D.G.; Cardona, P.-J.; Kim, M.-J.; Allain, S.; Altare, F. Foamy macrophages and the progression of the human tuberculosis granuloma. Nat. Immunol. 2009, 10, 943–948. [Google Scholar] [CrossRef] [PubMed]
11) Huszár, S.; Chibale, K.; Singh, V. The quest for the holy grail: New antitubercular chemical entities, targets and strategies. Drug Discov. Today 2020, 25, 772–780.
12) Chai, Q.; Zhang, Y.; Liu, C.H. Mycobacterium tuberculosis: An Adaptable Pathogen Associated With Multiple Human Diseases. Front. Cell. Infect. Microbiol. 2018, 8, 158. Marrakchi, H.; Laneelle, M.A.; Daffe, M. Mycolic acids: Structures, biosynthesis, and beyond. Chem. Biol. 2014, 21, 67–85.
13) Peyron, P.; Vaubourgeix, J.; Poquet, Y.; Levillain, F.; Botanch, C.; Bardou, F.; Daffe, M.; Emile, J.F.; Marchou, B.; Cardona, P.J.; et al. Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for M. tuberculosis persistence. PLoS Pathog. 2008, 4, e1000204.
14) Grosset, J. Mycobacterium tuberculosis in the Extracellular Compartment: An Underestimated Adversary. Antimicrob. Agents Chemother. 2003, 47, 833–836.
15) Gengenbacher, M.; Kaufmann, S.H. Mycobacterium tuberculosis: Success through dormancy. FEMS Microbiol. Rev. 2012, 36, 514–532.

16) Dorhoi, A.; Kaufmann, S.H. Pathology and immune reactivity: Understanding multidimensionality in pulmonary tuberculosis. Semin. Immunopathol. 2015, 38, 153–166. [Google Scholar] [CrossRef] [PubMed]

17) Hunter, R.L. Pathology of post primary tuberculosis of the lung: An illustrated critical review. Tuberculosis 2011, 91, 497–509. [Google Scholar]

18) Reece, S.T.; Kaufmann, S.H. Floating between the poles of pathology and protection: Can we pin down the granuloma in tuberculosis? Curr. Opin. Microbiol. 2012, 15, 63–70.

19) Zumla, A.; Nahid, P.; Cole, S.T. Advances in the development of new tuberculosis drugs and treatment regimens. Nat. Rev. Drug Discov. 2013, 12, 388–404.

20) Rawat, R.; Whitty, A.; Tonge, P.J. The isoniazid-NAD adduct is a slow, tight-binding inhibitor of InhA, the Mycobacterium tuberculosis enoyl reductase: Adduct affinity and drug resistance. Proc. Natl. Acad. Sci. USA 2003, 100, 13881–13886. [

21) Campbell, E.A.; Korzheva, N.; Mustaev, A.; Murakami, K.; Nair, S.; Goldfarb, A.; Darst, S.A. Structural Mechanism for Rifampicin Inhibition of Bacterial RNA Polymerase. Cell 2001, 104, 901–912.

22) Louw, G.E.; Warren, R.M.; van Pittius, N.C.G.; Leon, R.; Jimenez, A.; Hernandez-Pando, R.; McEvoy, C.R.E.; Grobbelaar, M.; Murray, M.; van Helden, P.D.; et al. Rifampicin Reduces Susceptibility to Ofloxacin in Rifampicin-resistant Mycobacterium tuberculosis through Efflux. Am. J. Respir. Crit. Care Med. 2011, 184, 269–276.

23) Zhang, Y.; Mitchison, D. The curious characteristics of pyrazinamide: A review. Int. J. Tuberc. Lung Dis. 2003, 7, 6–21.

24) Goude, R.; Amin, A.G.; Chatterjee, D.; Parish, T. The Arabinosyltransferase EmbC Is Inhibited by Ethambutol in Mycobacterium tuberculosis. Antimicrob. Agents Chemother. 2009, 53, 4138–4146.

25) Chiang, C.-Y.; Centis, R.; Migliori, G.B. Drug-resistant tuberculosis: Past, present, future. Respirology 2010, 15, 413–432.