Current Prospects: Drug acting against resistant Tuberculosis

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Abstract: The most lethal disease tuberculosis is caused by Mycobacterium tuberculosis and the risk has worsened with the appearance of drug resistance, in particular multi drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Antimicrobial resistance (AMR), is one of the most dominant health hazard that has emerged in the 21st century. This review embrace the drug resistance in MTB and inclusive overview of present phenotypic and molecular approaches for drug vulnerability testing, with particular attention to the methods endorsed and recommended by the WHO. "Drug resistance is an unavoidable consequence of the use of drugs; however, the appearance of multi-drug resistance can be managed by accurate diagnosis and perfect regimens. Moreover, the discovery of new chemical entities targeting specific vulnerabilities in the M. tuberculosis bacterium has gained significant attention. Various drug candidates are in different stages of preclinical and clinical development. Additionally, combination therapy approaches involving multiple drugs with complementary mechanisms of action are being explored to overcome drug resistance and improve treatment outcomes In recent years, funded collaborative efforts of researchers from academia, not-for-profit virtual R&D organizations and industry have resulted in the continuous growth of the TB drug discovery and development pipeline. While substantial progress has been made in the field of drug development against resistant TB, several clinical trials. Nonetheless, the current prospects in drug development against resistant tuberculosis hold great promise for improving treatment outcomes, reducing transmission, and ultimately eradicating this devastating disease.

Keywords: Tuberculosis, anti-TB, Isoniazid, DOTS, Extensive Drug Resistant (XDR)-TB

INTRODUCTION

The world's worst infectious illness, tuberculosis (TB), which is caused by the bacteria Mycobacterium tuberculosis (MTB), has become more dangerous due to the advent of drug resistance, particularly extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB). In 2019, there were an estimated 10 million new incident cases of active TB disease worldwide [1]. Antimicrobial susceptibility testing is still not generally accessible or used, despite the World Health Organization's (WHO) End-TB Strategy's advocacy for its usage. Drug-resistant MTB strains may have some fitness costs due to resistance-related changes, but these costs may be offset by the occurrence of compensating mutations, which would restore growth fitness. Understanding these underlying pathways might offer crucial insights into the etiology of TB and forecast the global pandemic of MDR-TB in the future. India accounts for 25% of the global TB burden. Pulmonary TB is the most common site for pathological lesions but it also affects other sites, which is called extra pulmonary TB. The infection is usually due to inhalation of the infected droplet nuclei and the lung is generally the first organ to be affected. Pulmonary TB usually occurs after a period of dormancy in a previously infected individual. The onset is gradual but deceptive. Spread of pulmonary TB to the pleura results in pleural effusion as a part of inflammatory reactions. Later, the tubercular bacilli may disseminate and the hypersensitivity reaction to mycobacterial proteins may cause extensive tissue damage and virtually any organ of the body may be involved shown in Fig 1. Miliary tuberculosis is a massive dissemination of tubercle bacilli throughout the body including liver and spleen that do not have a high oxygen tension. [2]

Mycobacterium other than M. tuberculosis are called non tuberculous or atypical mycobacteria. These are present in the environment and can cause diseases similar to tuberculosis. Some of them are: M. Kanasii, which produces milder but chronic pulmonary disease resembling tuberculosis; M. marinum causes swimming pool granuloma:M. scrofulaceum, causes cervical lymphadenitis and M. Leprae, which causes leprosy. M. avium complex include both M. avium and M. intracellulare. MAC is common and important cause of disseminated TB type of pulmonary

disease seen most commonly in immunocompromised patients, e.g. those with AIDS. This review describes the drug resistance of TB with newest treatment approaches for MAC.

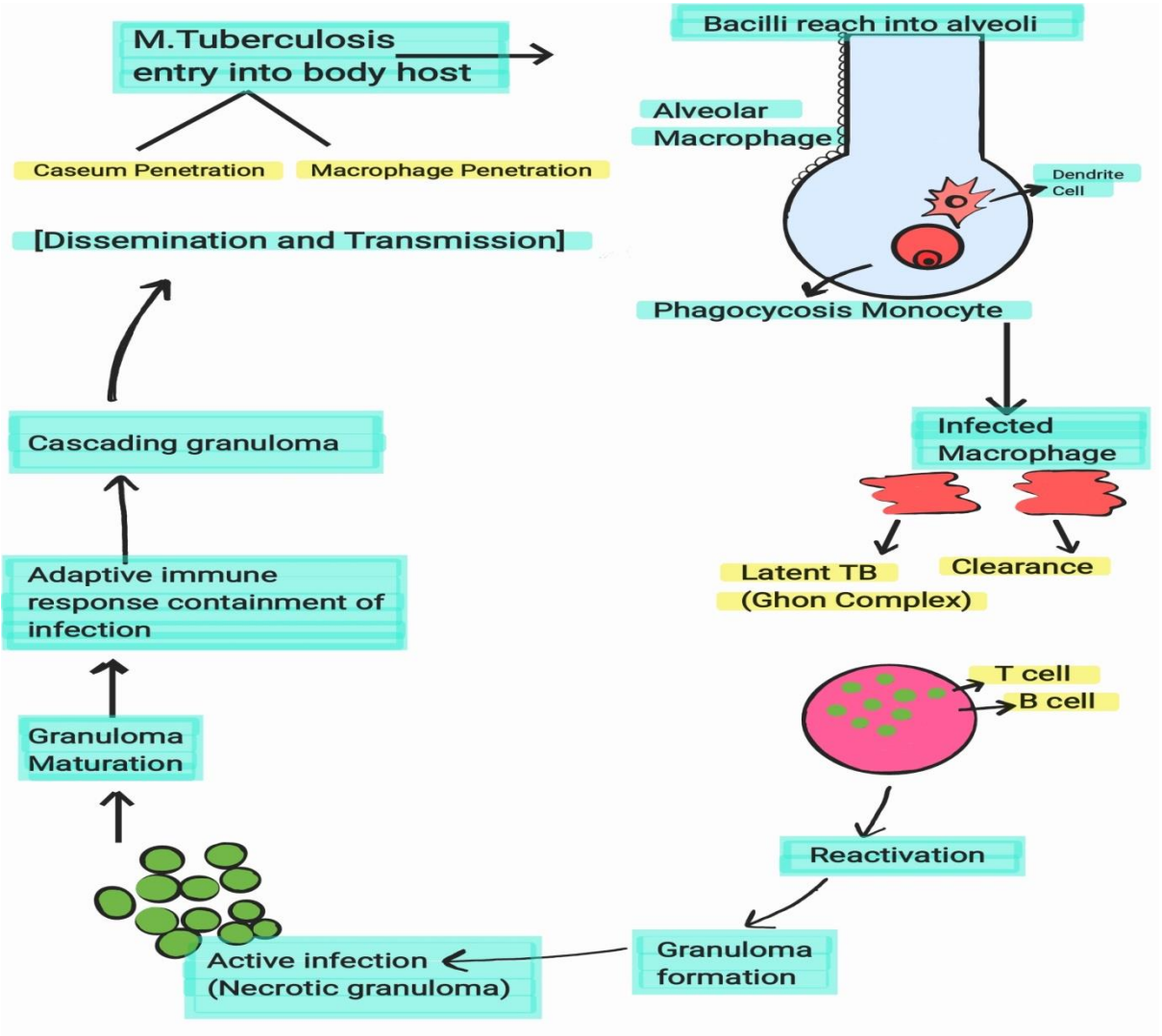


Figure 1: TB infection pathology invading humans

Since a major portion of the tubercle bacilli becomes intracellular and resides in the macrophages, it is inaccessible to the majority of antibiotics as these cannot penetrate easily. Moreover, the mycobacteria are well known for developing resistance to any single drug. Combination of the drugs are therefore needed to overcome resistance during the course of therapy. The answer as to why a multiple drug combination lowers the chances of development of resistance is simple. It is advisable to combine at least two or more anti-TB drugs to which the Mycobacterium is susceptible. Since the response of the therapy is also slow, the treatment must continue for months depending on the drug that has been used. The risk of adverse reaction is therefore a major concern in proper drug selection. The therapy must contain two or more drugs to avoid development of resistance, the drug must be taken regularly and the drug therapy must continue for a sufficient duration to achieve adequate therapeutic results. Traditionally, the drugs used in the treatment of TB are classified into first line drugs and second line drugs. In first line drugs, first line essential (Isoniazid Rifampicin, Pyarzinamide, Ethambutol) and first line supplemental drugs (Streptomycin) are found. The second line drugs include second line orally active agents [Fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin, ciprofloxacin), Ethionamide, Prothionamide, Para-aminosalicylic acid, Cycloserine, Terizidone, Thiacetazone, Rifabutin/Rifapentine) and second line injectable agents (Kanamycin/Amikacin, Capreomycin). Some newer anti- tuberculosis druds are Bedaquiline, Linezolid, Clarithromycin, Clofazimine, Amoxicillin-Clavulanic acid [3,4].

Drug Resistance

Drug resistance in clinical MTB strains is endorsed to chromosomal mutations. The main mechanisms of resistance leading to drug resistance consist of drug target modification, over expression of drug target, disruption of pro drug activation and the activation of efflux pump [5,6], Multidrug-resistant tuberculosis (MDR-TB) has become a big terrorize to global health. The current approach for management of MDR-TB and widespread drug resistant tuberculosis[7,8]. The goal of treatment of tuberculosis is to ensure high cure rates, prevent emergence of drug resistance, minimize relapses and cut the chain of transmission through early diagnosis and treatment. One of the main reasons for the therapeutic failure has been the patient's poor compliance after having a symptomatic relief. The Revised National Tuberculosis Control Programme (RNTCP), therefore has recommended the Directly Observed Therapy using Short course (DOTS) in 1997 based on the anti-TB treatment guidelines devised and advocated by the WHO in 1995 for adoption by the countries world over as per their local requirements.

In the last 20 years, the anti-TB treatment has undergone many changes. The old conventional 12-28 months long treatment was replaced in 1995 to a short 6-9 months treatment under DOTS on the recommendation of the WHO in the hope that administration of anti-TB medication under direct supervision of health professional will assure full compliance. As per these guidelines, the TB patients are divided into 4 categories and the treatment regimens have 2 phases: An initial Intensive phase followed by a Continuous Phase (CP). In IP 4-5 bactericidal drugs are used for a period off 2-9 months with the aim of rapidly killing the bacteria to bring about symptomatic relief/sputum conversion and to minimize the chances for developing resistance. The CP lasts for 6-24 months during which the remaining bacilli are eliminated to minimize the chances of relapse. The duration of IP and CP may vary according to the category of the patient. This resulted in not only an increase in the development of multi-drug resistant (MDR), but also extensive drug resistant (XDR) TB cases world over including India.

Resistant tuberculosis, also known as drug-resistant tuberculosis (DR-TB), is a form of tuberculosis (TB) that does not respond to standard antibiotic treatment. It is primarily caused by the improper use or misuse of anti-TB drugs. Here are some key factors that contribute to the development of resistant tuberculosis:

1. Inadequate treatment: One of the primary causes of drug-resistant TB is inadequate or incomplete treatment. TB treatment usually involves a combination of antibiotics taken for a specific duration. If the prescribed medication is not taken consistently or for the required duration, the bacteria may survive and become resistant to the drugs.
2. Inappropriate drug regimen: TB treatment typically involves a combination of several antibiotics. If the initial drug regimen is not appropriately chosen based on the drug susceptibility testing or if the drugs are not used in the correct combination, it can lead to the development of resistance.
3. Poor treatment adherence: Irregular or incomplete adherence to the prescribed TB treatment is a major factor in the development of drug resistance. Patients may stop taking their medication once they start feeling better, or they may have difficulty following the treatment regimen due to various reasons such as side effects, lack of awareness, or lack of access to healthcare.
4. Delayed diagnosis: Late or delayed diagnosis of TB can contribute to the development of drug resistance. When TB is not diagnosed promptly, the infection has more time to progress and spread, making it more challenging to treat effectively.
5. Transmission of drug-resistant strains: Drug-resistant strains of TB can be transmitted from person to person. If a person with drug-resistant TB infects others, it can lead to the spread of resistant strains in the community.
6. HIV co-infection: Individuals who are infected with both TB and HIV have a higher risk of developing drug-resistant TB. HIV weakens the immune system, making it more difficult to fight off TB infection and increasing the likelihood of treatment failure.
7. Overuse and misuse of antibiotics: Inappropriate use of antibiotics, such as using them without a prescription or not completing the full course of treatment, can contribute to the development of drug-resistant strains of TB.

It is important to address these causes and implement proper TB control measures, including accurate diagnosis, appropriate treatment regimens, patient education, and support, to prevent the emergence and spread of drug-resistant TB [10].

Classification of drug resistance

- **Poly-drug resistant TB (PDR- TB).** Poly drug resistant TB in which patients have resistance against more than one first-line anti-TB drug.
- **Isoniazid-resistant TB :** In this patients resist to isoniazid and susceptible to rifampicin [11]
- **Mono-resistant TB (MR TB).** TB patient, whose biological specimen is resistant to one first- line anti-TB drug only [12]
- **Multidrug-resistant TB (MDR-TB).** Patients who are infected with strains resistant to isoniazid and rifampicin, called multidrug-resistant (MDR)
- **Rifampicin Resistance (RR)** Resistance to rifampicin detected using phenotypic or genotypic methods, with o without resistance to other anti-TB drugs excluding Isoniazid. Patients, who have any rifampicin resistance, should also be managed as if they are MDR-TB case.
- **Presumptive DR-TB.** Patient who is eligible for rifampicin resistant screening at the time of diagnosis OR/and during the course of treatment for DS-TB or H mono/poly DR-TB. [13]

Category	**National Strategic plan for TB control 2012-17**
New Cases	**IP- 2 HRZE daily** **CP- 4 HRE daily** **Duration- 6 months** **Comment- Optimum therapy**
Previously treated case **1. All Relapses** **2. Treatment defaults** **3. Treatment failures and others**	**IP- 2 HRZES daily+1 HRZE daily** **CP- 5 HRE daily** **Duration- 8 months** **Comment- These patients have low/medium risk of MDR-TB**
MDR-TB	**IP- 6-9 Km Lfx Eto Cs Z E** **CP- 18 Lfx Eto Cs Z E** **Duration- 24-27 months** **Comment- Treatment may be modified**
Rifampicin resistant Isoniazid sensitive or unknown	**IP- 6-9 Km Lfx Eto Cs Z E H** **CP- 18 Lfx Eto Cs E H** **Duration- 24-27 months** **Comment- Treatment may be modified**
Extensive Drug Resistant (XDR)-TB	**IP- 6-12 Cm, Mfx, PAS, High dose-H, Cfz, Lzd, Amoxi-Clav** **CP- Mfx, PAS, High dose-H, Cfz, Lzd, Amoxi-Clav** **Duration- 24-30 months**

Table: Dosage regimens/ Anti-TB Treatment for patients

-H,R,Z,E,S- Standard codes for isoniazid, rifampin, pyrazinamide, ethambutoland streptomycin respectively

- Km Lfx Eto Cs Z E- Standard codes for Knamycin, Levofloxacin, Ethionamide, Cycloserine+, Pyrazinamide, Ethambutol, Isoniazid respectively

- Cm, Mfx, PAS, High dose-H, Cfz, Lzd, Amoxi-Clav Standard codes for drugs: Injection Capreomycin, Moxifloxacin, Para amino salicylic acid, Isoniazid, Clofazimine, Linezolid, Amoxicillin-clavulinic acid respectively

Test to detect resistance

- **Genotypic tests**-Rapid molecular diagnostic method for Drug Resistance Testing (DRT)- These are genotypic tests that detect specific genetic mutations that are associated with drug resistance
- **Phenotypic tests** -Growth based Drug Susceptibility Testing (DST)

Where in bacilli are grown and subsequently tested for drug susceptibility using various drug containing and drug-free media

List of drug resistance-related genes against anti-TB drugs (miotto 2018)

S.no	Drug	MOA	Resistance-related genes	Gene function	Reference
1.	Rifampicin	RNA synthesis inhibition	Rpo B 95–99	polymerase subunit	14,15
2.	Isoniazid	Mycolic acid biosynthesis inhibitor and effects on DNA, lipid, carbohydrate, and NAD metabolism	katG	Isoniazid Catalase-peroxidase 8,9 inhA 8–43 Promoter region for 2-trans-enoyl-acyl carrier protein reductase	16,17
3.	Ethambutol	Arabinogalactan biosynthesis inhibition	embB	Arabinosyltransferase 5-Phospho-α-d-ribose-1-diphosphate: Decaprenylphosphate 5-phosphoribosyltransferase	18 19
4.	Streptomycin	Protein synthesis inhibition	rpsL rrs gidB	Ribosomal protein S12 16S rRNA Putative 16S rRNA methyltransferase	20,21 20 22
5.	Quinolones	DNA gyrase and topoisomerase IV inhibitor	gyrA gyrB	DNA gyrase subunit A DNA gyrase subunit B	23 24
6.	Aminoglycosides	Protein synthesis inhibition	rrs eis	16S rRNA Aminoglycoside acetyltransferase	25 26
7.	Pyrazinamide	Not fully resolved, may include membrane potential	pncA rpsA	Amide conversion S1ribosomal protein	27

		disruption	panD clpC1	Aspartate decarboxylase Protease	
8.	Cycloserine	Peptidoglycan biosynthesis inhibition	Ald	L-alanine dehydrogenase	28
9.	Para-aminosalicylic acid	Folic acid and iron metabolism inhibition	folC dfrA e thyA	Dihydrofolate synthase Dihydrofolate reductas Thymidylate synthase	29 29 30
10	Linezolid	Protein synthesis inhibitor (50S subunit)	rplC rrl	50S ribosomal protein L3 23S rRNA gene	31,32
11	Clofazimine	Release of Reactive Oxygen Species (ROS) and cell membrane disruption	rv0678 rv1979c rv2535c	Transcriptional regulator to repress the expression of multisubstrate efflux pump MmpL5 Possible permease	33,34
12	Bedaquiline	Inhibition of mitochondrial ATP synthase	rv0678	Transcriptional regulator to repress the expression of multisubstrate efflux pump MmpL5	35,36
13	Delamanid	Mycolic acid biosynthesis inhibition	ddn fgd1 fbiA fbiB fbiC	Deazaflavin-dependent nitroreductase Glucose-6-phosphate dehydrogenase Protein FbiA for flavin cofactor F420 biosynthesis Protein FbiB for flavin cofactor F420 Protein FbiC for flavin cofactor F420 biosynthesis	37 38 39 40 41

				biosynthesis	
14	Clarithromycin	Protein synthesis inhibition (50S subunit)			
15	Amoxicillin clavulinic acid	Cell wall disruption via peptidoglycan modulation			

Treatment approaches

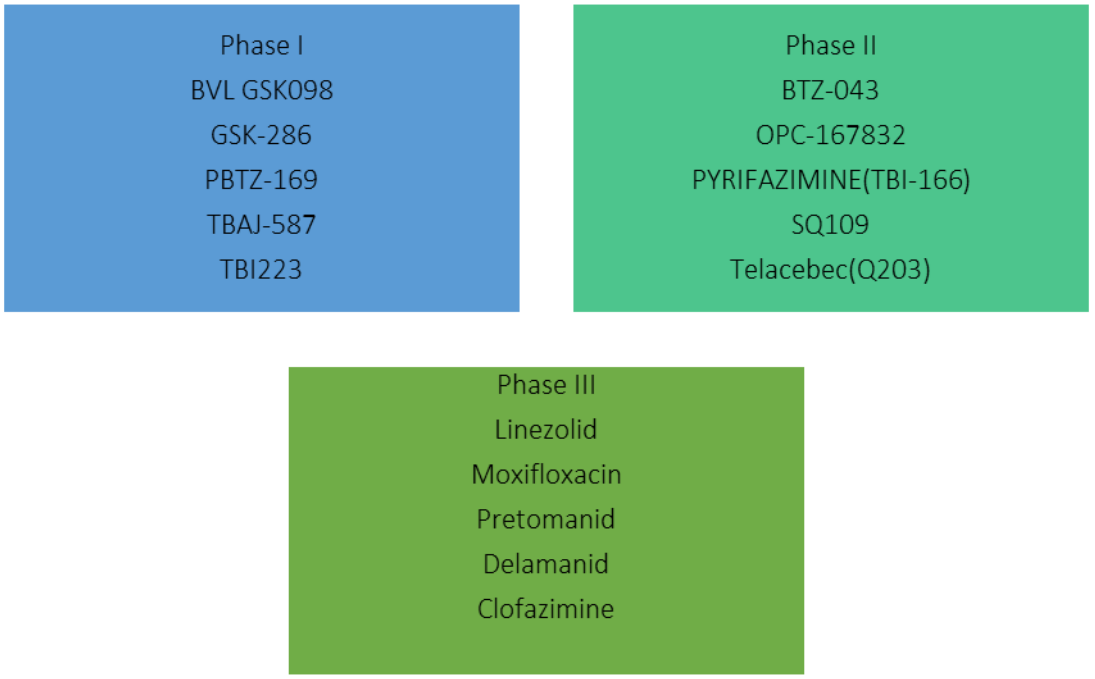
When managing multi-drug resistant tuberculosis (MDR-TB), obtaining a comprehensive past history of TB treatment is critical (42). This is mainly significant for patients with multiple treatment courses with first- or second-line anti-TB drugs. In cases where a patient has acknowledged previous treatment with ethambutol or pyrazinamide as part of a failed first-line regimen, it is not advisable to consider these drugs as likely to be effective (43). The reason behind this is that the development of drug resistance may render these medications ineffective in treating MDR-TB. By gathering detailed information about the patient's prior treatment regimens, healthcare providers can assess which drugs may still be effective and tailor the management approach accordingly. This helps to optimize treatment outcomes and minimize the risk of further drug resistance development (44).

Pyrazinamide, ethionamide, or PAS (para-aminosalicylic acid) which are Laboratory resistance, combined with a history of use in a failing regimen, strongly suggests that these drugs are ineffective in the treatment of MDR-TB (45). In the management of MDR-TB, it is recommended to include at least four second-line anti-TB drugs that are likely to be effective. These regimens typically consist of a later-generation fluoroquinolone, such as levofloxacin or moxifloxacin, a second-line injectable drug, and other oral second-line drugs. The inclusion of pyrazinamide is also considered unless there is a contraindication, such as a history of drug allergy, or evidence suggesting its ineffectiveness against the patient's specific strain of TB (46) (e.g., a clear history of failing to respond to a pyrazinamide-including regimen and drug susceptibility testing indicating resistance). It is worth noting that in resource-limited settings where drug susceptibility testing (DST) for pyrazinamide may not be readily available, pyrazinamide is often included in MDR-TB regimens as a routine practice. These recommendations are supported by a large meta-analysis of individual data from over 9000 patients, indicating the effectiveness of these combination regimens in managing MDR-TB (Ahuja et al., 2012). It's important to keep in mind that TB treatment guidelines may evolve over time, so it's always advisable to consult the most current guidelines and recommendations from reputable sources for up-to-date information (47).

The dosing of anti-TB drugs is typically based on the weight of the patient. Commonly used dosing tables use a few weight bands for simplicity. However, it's important to adjust the drug doses when adults gain weight or move into a higher weight band. This ensures that patients receive the appropriate amount of medication for effective treatment (48). While anti-TB drugs are generally administered once a day to improve peak-dependent killing, some second-line drugs, due to their side effects, may benefit from divided dosing. For instance, drugs like ethionamide and cycloserine are traditionally given in two divided doses to reduce side effects. However, if the once-daily dosing is well-tolerated, it can be acceptable (49). In the case of extensively drug-resistant tuberculosis (XDR-TB), a similar approach to designing a regimen may be used, but with some important considerations. In patients with a chronic history of multiple failed treatment courses, it may not be possible to have a minimum of four likely effective second-line drugs available (50). In such cases, the XDR regimen may include drugs that are resistant on drug susceptibility testing (DST) but have never been used, or drugs that have been used but are still susceptible on DST. Clinicians may opt to use a later-generation fluoroquinolone, like moxifloxacin, even in the presence of documented resistance to an early-generation fluoroquinolone, such as ofloxacin (51). If an injectable drug is still likely to be effective, clinicians may consider using it for a longer duration, such as 12 months or even for the entire treatment duration. New drugs that have demonstrated efficacy, such as bedaquiline or delamanid, should be strongly considered. In cases of localized disease, resective surgery may also be an option.

According to provisional guidance from the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), bedaquiline may be used for MDR-TB patients in whom treatment options are limited (52). It should be added to a conventional MDR or XDR regimen as designed previously. However, there are still uncertainties about the risks and benefits of bedaquiline, and it should be administered within a program that can closely monitor for side effects. At the time of writing, delamanid does not have international recommendations or a published drug insert, indicating limited guidance available for its use (53). It's important to note that TB treatment guidelines may vary across different regions and evolve over time. Therefore, it is crucial to consult the most up-to-date guidelines and recommendations from authoritative sources, such as the CDC or WHO, for specific and current information (54).

New anti TB drugs [72-77]



Clinical evaluation

For the improved therapies for TB resistance drugs more efforts have been approached to create new drugs. More than 100 novel compounds are scheduled on the Working Group on New TB Drugs website [83-85]Some compounds are in early clinical development (Table 2). This challenge is not only for identification but also for better combination to provide better treatment and to minimize resistance. assay methodologies(*in vitro*) like Diamond have improved the capability to measure and mold the quantitative impacts of predetermined ratios of drugs in combinations on MTB grown in a variety of media environment that may better represent the various niches and growth states present in the clinical scenery [63], [64].[65]

S.no	Investigational compound	Advantages
1.	Sutezolid (PNU-100480)	➢ Potentially more effective than linezolid with improved therapeutic index for MPS-associated toxicity. ➢ Sutezolid at 600 mg twice daily and 1,200 mg daily was safe and well tolerated and readily showed significant bactericidal activity in sputum and blood in a Phase 2 EBA study [55].
2.	Delpazolid (LCB01-0371)	➢ It has enhanced safety profile vs. linezolid. ➢ the bactericidal action of delpazolid was comparable to

		linezolid in a Phase 2a EBA study. [56]
3.	BVL-GSK098	➢ It has reduced resistance to Eto. The combination of BVL-GSK098 could allow for lower dose of ethionamide or prothionamide improving safety and tolerability [57]
4.	GSK2556286 (GSK-286)	➢ It has more ability to penetrate TB lesions ➢ It reduce relapse rates in mice
5.	SPR720	➢ activity against fluoroquinolone resistant strains is Maintained[58][71]
6.	TBAJ-587	➢ It is potentially active against bedaquiline resistant strains [59] ➢ Safety profile.is improved[70]
7.	SQ109	➢ It is observed that in Phase 2b study activity is improved when added to MDR regimens [60, [61], [62]. Potential multi-targeting effects.[78-82]
8.	Macozinone (PBTZ-169)	➢ It is highly potent and novel cell wall inhibitor[66,67]
9.	OPC-167832	➢ It is Highly potent, novel cell wall inhibitorin Single dose and with combination EBA active, recruiting.[68,69]

Conclusion

In conclusion, the current prospects for drugs acting against resistant tuberculosis (TB) present both hope and challenges in the ongoing fight against this deadly disease. While the emergence of drug-resistant strains of TB poses a significant threat to global health, there have been notable advancements in the development of new drugs that target these resistant strains. In recent years, researchers and pharmaceutical companies have made considerable progress in identifying and testing novel compounds that show promise in combating drug-resistant TB. These drugs utilize innovative mechanisms of action to effectively kill the bacteria or inhibit their growth, overcoming the resistance mechanisms developed by the TB strains. Furthermore, advancements in genomics and molecular biology have provided insights into the genetic basis of drug resistance, enabling researchers to develop more targeted and effective treatment strategies.

Despite these encouraging developments, challenges remain in bringing these drugs to the patients who need them. The regulatory approval process, cost considerations, and the complexity of implementing effective treatment programs in resource-limited settings pose significant hurdles. Additionally, the continued spread of drug-resistant TB strains emphasizes the urgent need for a comprehensive approach that includes improved diagnostics, infection control measures, and patient adherence to treatment regimens. Collaboration and investment in research, development, and implementation are essential to ultimately overcome the challenges posed by drug-resistant TB and improve the prospects for effective treatment and control of this global health threat.

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