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Drug targets exploited in *Mycobacterium tuberculosis*: Pitfalls and promises on the horizon

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ABSTRACT

Tuberculosis is an ever evolving infectious disease that still claims about 1.8 million human lives each year around the globe. Although modern chemotherapy has played a pivotal role in combating TB, the increasing emergence of drug-resistant TB aligned with HIV pandemic threaten its control. This highlights both the need to understand how our current drugs work and the need to develop new and more effective drugs. TB drug discovery is revisiting the clinically validated drug targets in *Mycobacterium tuberculosis* using whole-cell phenotypic assays in search of better therapeutic scaffolds. Herein, we review the promises of current TB drug regimens, major pitfalls faced, key drug targets exploited so far in *M. tuberculosis* along with the status of newly discovered drugs against drug resistant forms of TB. New antituberculosis regimens that use lesser number of drugs, require shorter duration of treatment, are equally effective against susceptible and resistant forms of disease, have acceptable toxicity profiles and behave friendly with anti-HIV regimens remains top most priority in TB drug discovery.

1. Introduction

Tuberculosis (TB) [1] is a leading cause of death worldwide from a single infectious agent, *Mycobacterium tuberculosis* [2,3]. Predominantly it infects lungs (pulmonary TB) but can also infect any other part of body (extra-pulmonary TB); if left untreated it destroys the body tissue by chronic inflammation and may culminate in death [4–6]. The current globally recommended chemotherapy for the treatment of drug-susceptible TB (DS-TB) involves an intensive phase of four first-line anti-TB drugs (ATD's) those include Rifampin (RIF), Isoniazid (INH), Pyrazinamide (PYZ) and Ethambutol (EMB) administered for the first 2 months followed by a continuation phase of RIF and INH for the next 4 months under directly observed treatment short course (DOTS) strategy [7] (Table 1). Although DOTS strategy is labour intensive but it ensures high rates of patient treatment [8]. Treatment success rate of 85% or more for new cases are regularly reported by WHO [9]. Since 1995 up to 2009, 41 million lives were saved under DOTS and STOP TB strategy [10,11]. However owing to various challenges that include latent TB infection (LTBI), complex and lengthy duration of chemotherapy, emergence of drug resistance and HIV-TB coinfection, TB continues to be a major global health concern in the category of infectious diseases. The global incidence of TB is alarming as about one third of the world's population is harbouring the pathogen as asymptomatic LTBI [12] (Figs. 1 and 2).

The major drawback of the current chemotherapy is its long duration that lasts for 6–9 months for drug susceptible TB (DS-TB) and up to 2 years for DR-TB. This often leads to patient nonadherence, treatment failure and resurgence. WHO Global TB report of 2017 estimates 1.67 million deaths, 10.4 million developed active TB disease, 6,00,000 new cases of rifampicin resistance (RR-TB) out of which 4,90,000 had multi-drug resiatant (MDR-TB) with 6.3 million new TB cases reported alone in 2016 [9]. Worldwide spread of extensive drug-resistant TB (XDR-TB) with only 30% success rate of treatment reflects a dangerous senario [9]. HIV-TB co-infection is a challenging setback and people living with HIV (PLHIV) are the prime victims of TB as about 1.2 million new TB cases were found in HIV positive individuals (11% of total cases) in 2015. The success rates of TB treatment in HIV positive individuals are only 78% and 0.4 million such people died in 2015. HIV promotes TB infection by modifying clinical manifestations of TB, thereby delaying its diagnosis and early treatment [14–16].

A vision of transition from stopping TB to ending TB is turning bleak. However, advances in understanding the biology of *M. tuberculosis* along with availability of its complete genome sequence has provided researchers with a platform of wide range of novel drug targets

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Table 1
Mechanism of action of standard first line anti-TB drugs and their adverse effects.

Drug Discovery	Target	Mechanism of Action	Description	Adverse Effects
Rifampicin (RIF) (1963)	Bacterial RNA polymerase (RNAP)	Bactericidal-Inhibits Transcription RIF-inhibits bacterial DNA-dependent RNA polymerase by forming a stable enzyme-drug complex with the ß-subunit of RNA polymerase (RNAP-Rif), *rpoB* gene. Broad antibacterial spectrum, including activity against several forms of *Mycobacterium*.	RIF- Semi-synthetic; A member of the Rifamycin group of antibiotics produced from *Streptomyces mediterranei*. The most powerful anti-TB agent currently available.	Hepatitis, Joint pain, Fever, Flu syndrome Headache Haemolysis, Exanthema, Thrombocytopenia
Isoniazid (INH) (1952) (Prodrug Peroxidative activation by *M.tb* KatG)	InhA [Enoyl-(acyl-carrier-protein) reductase]	Bactericidal- Cell envelope disruption INH-Inhibits mycolic acid biosynthesis, an essential component of *M. tuberculosis* cell envelope. It specifically inhibits InhA, the enoyl reductase of *M. tuberculosis*, by forming a covalent adduct with the NAD cofactor. The INH-NAD adduct acts as a slow, tight-binding competitive inhibitor of InhA	INH-belongs to Pyridine- carboxylic class of drugs, containing a pyridine ring bearing a carboxylic acid group. Highly active against replicating but not dormant or near dormant bacilli	Psychiatric disorders Restlessness, Insomnia, Muscle twitching
Pyrazinamide (PYZ) (1954) (Prodrug- PZA converted by Pyrazinamidase (PZase) to POA)	S1 Component of 30S Ribosomal subunit	Bactericidal-Acidifies cytoplasm; Inhibits translation and trans-translation. The active moiety of pyrazinamide is pyrazinoic acid (POA). POA is thought to disrupt membrane energetics and inhibit membrane transport function at acid pH. Its analogs have been shown to inhibit the activity of purified FAS I.	Z- A pyrazine based compound active against tubercle bacilli in acidic inflammatory lesions	Elevated Uric acid, Gastrointestinal upsets, Anorexia, Arthralgia, Gout, Skin sensitivity to light
Ethambutol (EMB) (1961)	Inhibits Arbinosyl-Transferase	Bacteriostatic- Cell wall disruption Ethambutol disrupts arabinogalactan synthesis thereby preventing the interaction of 5'-hydroxyl groups of D-arabinose residues of arabinogalactan with mycolic acids that form mycolyl-arabinogalactan-peptidoglycan complex of *M. tuberculosis* cell wall	E- 1,2-Aminoalcohols based compound; Active during the early, intensive phase of treatment and may enhance the activity of other anti-TB agents by enhancing the mycobacterial cell wall permeability	Optic neuritis, Peripheral neuritis, Reduction in visual acuity, Low platelet count

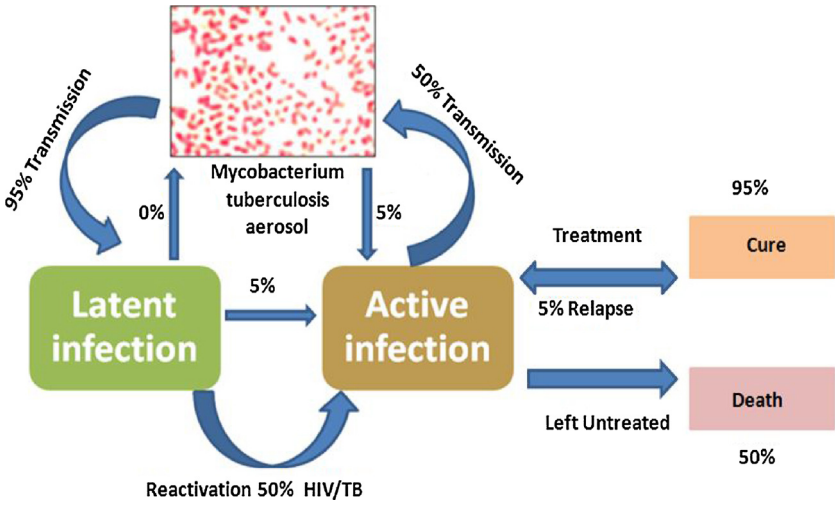

Fig. 1. Stages of *Mycobacterium tuberculosis* infection: *M. tuberculosis* aerosol transmission can lead to either latent-TB infection or progression to active-TB disease. In case of drug susceptible (DS-TB), 95% of patients can be cured upon treatment with 5% chances of relapse. However, high mortality takes place if left untreated. Latent-TB may reactivate into active TB years after the first exposure to the bacilli with higher chances of activation among immunocompromised individuals as in case of HIV patients.
Adapted from Anil Koul et al. [13].

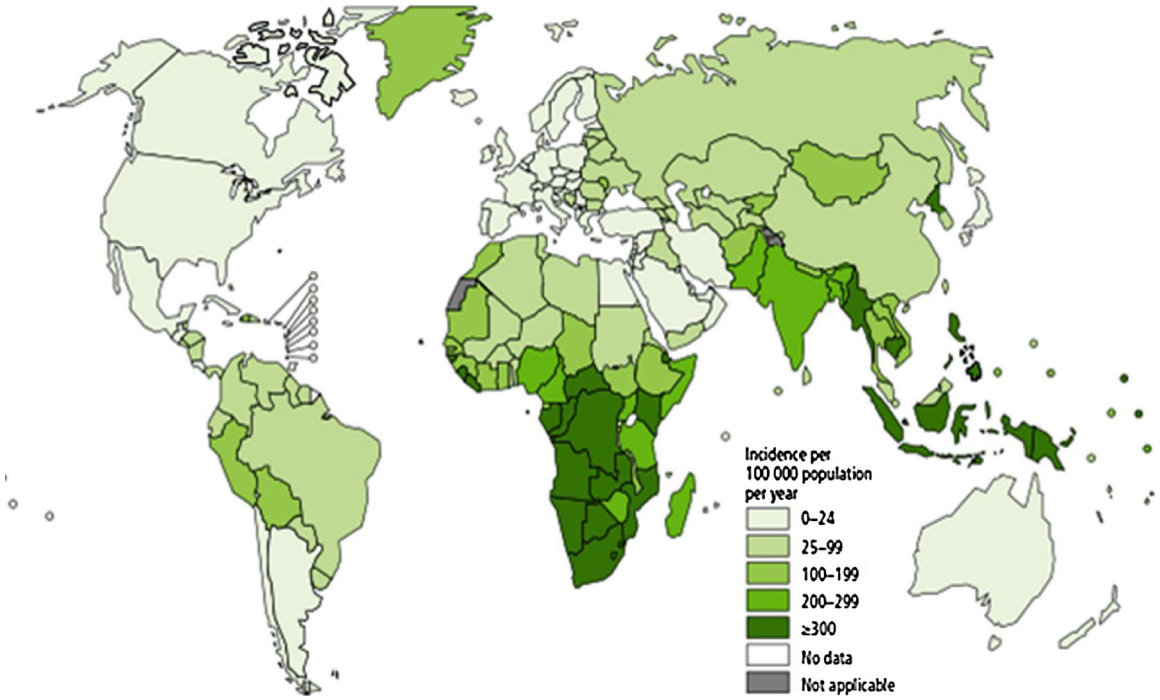

Fig. 2. Estimated TB incidence rates, 2016.
WHO Global tuberculosis report, 2017.

and regimens [17]. Gene products involved in controlling vital aspects of mycobacterial structure and metabolism *e.g.* Cell wall synthesis [18], DNA replication [19], RNA synthesis [20], protein synthesis [21], energy metabolism [22] and folate metabolism [23] are potential drug targets exploited in TB drug discovery in last forty years (Table 3).

Decades of research all around the globe has led to the discovery of new molecules with anti-TB potential that are being currently evaluated both in pre-clinical and clinical stages of drug development. However, as very few drugs make it to the market, it is need of an hour to search for new ATDs that can address the challenges associated current TB treatment. Innovation in search of new and effective ATDs will hopefully alleviate world's TB burden [24,25].

In this review, we begin by providing a brief overview of TB with an aim to highlight its global impact on human health. First, we directed our efforts to describe the implementation and success of current chemotherapy in combating TB. Next, we describe the major pitfalls or challenges in TB chemotherapy. The rest of the review provides the readers with in-depth details of the drug targets exploited in *M. tuberculosis* till date with updates about recently approved FDA drugs to strengthen the existing regimens with respect to their potency, bioavalibility and safety profile. Since, very few molecules make it through the stringent bottlenecks of TB drug discovery and development programme. This directs us towards the urgent need of discovery of new drugs that can completely target different enzymes and further expand the horizon of new drug targets to combat the ever evolving *M. tuberculosis*.

2. Treatment for tuberculosis

BCG (Bacillus Calmette Guerin) was the first vaccine to be developed over a period of thirteen years against TB (1908-1921). However, its limited efficacy and interference with the diagnosis of active TB restricted its use in the developed world [26]. Nevertheless, in developing countries the vaccine is still used in clinics to prevent childhood

TB but not reactivated pulmonary disease or HIV–associated TB. As the century progressed, preventive care was followed by various treatment strategies including surgical interventions, followed by the use of antibiotics. Chemotherapy for TB originated with the discovery of the first antibiotic effective against *M. tuberculosis*, *Streptomycin* isolated from *Streptomyces griseus* in 1944 [27,28]. However, the use of monotherapy using streptomycin eventually led to the development of resistance to this drug, culminating in treatment failure. With the introduction of para-aminosalicylic acid (PAS) [29] and isoniazid (INH) [30] in the early 1950's, the idea of concomitant administration of at least two drugs to treat TB was acknowledged globally as a way forward. Early clinical trials revealed the use of these drugs for a very long period of about 12–24 months to prevent recurrence. The introduction of rifampicin (RIF) in the early 1970's started the era of effective short-course chemotherapy reducing the duration of treatment to less than 12 months [31]. The use of pyrazinamide (PZA) enhanced the INH/RIF potency thereby making the use of 6 months treatment course as standard global chemotherapy [32]. The modern treatment short course for DS-TB evolved since 1940 and exploits four first-line ATDs (RIF,INH, PYZ and EMB); this regimen has significantly contributed to save human lives (just between 1995 to 2009, it saved 41 million lives) [7,10,11] (Figs. 3 and 4, Table 1).

Second-line drug regimens recommended by WHO for the treatment of MDR-TB include fluoroquinolones (ofloxacin ciprofloxacin, moxifloxacin, levofloxacin) [33], aminoglycosides (kanamycin, amikacin),capreomycin, cycloserine, para-aminosalicylic acid, and thioamides (ethionamide, prothionamide) [34]. Suitable drug regimens are ideally chosen by a stepwise selection process across the five categories of ATD's on the basis of their efficacy (resistant/susceptible), safety and cost (Table 2). The duration of the intensive phase of treatment is at least 6 months when an injectable drug is included or 4 months after culture conversion. The continuation phase without the injectable drug prolongs until 18 months after culture conversion. These drugs require at least 3-fold longer duration of administration than first-line drugs resulting in toxic side effects and loss of adherence besides lack of availability [35,36]. As such, it is need of an hour to address multiple challenges associated with the treatment of TB in order search for a reliable solution.

3. Pitfalls: challenges in treatment of tuberculosis

Despite availability of modern short course TB treatment (for DS-TB) and an armamentarium of second line ATDs (for DR-TB), TB continues to be the top most infectious killer in humans. This is due the fact that TB treatment faces certain issues those include LTBI; complexity and long duration of treatment; emergence and spread of drug resistance, HIV-TB co-infection and drug-drug interactions between ATDs and ARVs; these prevent treatment strategies to reach the desired level of success. [37–39].

One third of the world's population is harbouring *M. tuberculosis* as LTBI *i.e.* 2 billion individuals are infected [40]. People with LTBI are at a risk of developing active TB disease and therefore they act as a reservoir for the same; thus curing LTBI is a challenge for modern chemotherapy [12,25,41]. Existing health interventions for TB prevention are treatment of LTBI with particular attention focused on children aged less than five years. The targets of an 80% reduction in TB incidence by 2030 and a 90% reduction by 2035 to achieve the 'End TB Strategy' goals will require an unparalleled decline in TB incidence rates. This decline is possible only if the probability of progression from LTBI to active TB among 2 billion people is reduced to below the current life time risk of 5–15%. Unfortunately LTBI subjects owing to lack of symptoms do not adhere to current long duration treatment strategies. Therefore significant interventions are required to address this limitation of modern TB treatment.

The first-line drug regimen for DS-TB is complex and excruciatingly of long duration owing to which majority of patients fail to complete the full course of chemotherapy. Non-adherence and suboptimal response in presence of partially suppressive drug concentrations provides ample opportunity for rise of mutants leading to the emergence of DR-TB [43]. Drug-resistant TB is a persistent threat, with 600,000 rifampicin resistant (RR-TB) cases in which 490,000 had MDR-TB in 2016 alone. The countries with the largest numbers of MDR/RR-TB cases (47% of the global total) were China, India and the Russian Federation. Treatment for RR-TB and MDR-TB is longer, requires more expensive and more toxic drugs; it is therefore more often associated with patient non-adherence and hence treatment failure [42]. This is evidenced by the staggering nature of DR-TB as 105 countries have confirmed cases of XDR-TB; the most challenging scenario [9].

The synergistic relationship between TB and HIV influences each other's progress leaving the host more vulnerable to death [46,47]. TB

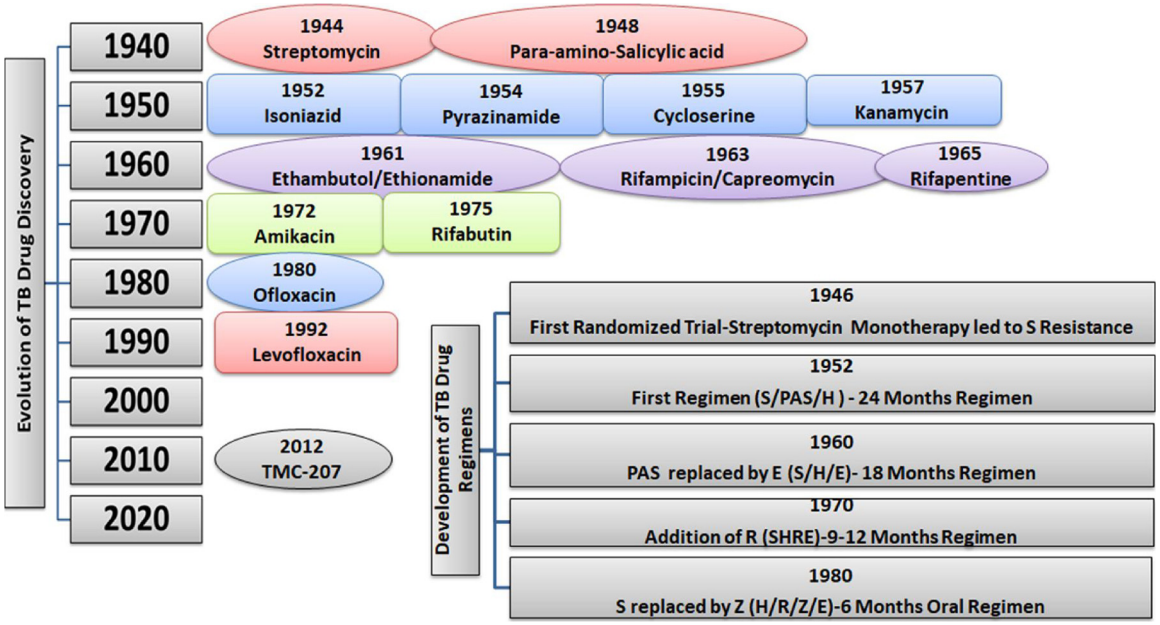

Fig. 3. The timeline and evolution of chemotherapy for tuberculosis.

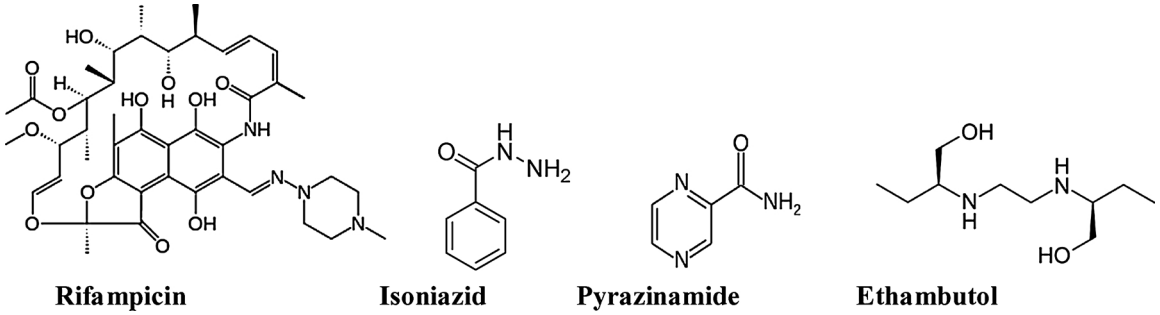

Fig. 4. Structure of standard first-line antituberculosis drugs.

is the most common opportunistic infection affecting HIV-positive individuals and leading cause of death in patients with HIV [15,16]. Parallel to it, HIV is the pre-eminent risk factor in the progression of LTBI to active TB disease [16]. On the other hand, the use of anti-retroviral drugs (ARV's) in HIV patients complicates the diagnosis and treatment of TB [48]. HIV patients with pulmonary TB are frequently sputum smear negative and up to 20% may have completely normal chest X-rays [49,50]. HIV-TB coinfected patients are exposed to increased pill burden with overlapping toxicities. ARV agents and TB drugs, particularly INH, RIF, and PYZ, can cause drug-induced hepatitis. As such they are more prone to nonadherence and treatment failure with higher risk of death during TB treatment. Many studies have shown that mortality rate has been consistently high with as many as 50% of HIV patients dying during the first two months of TB treatment [45,51–53]. Hence HIV-TB co-infection is a deadly duo as concurrent treatment of HIV and TB is complicated by many factors including, TB-associated immune reconstitution inflammatory syndrome (IRIS) [44]. These are the reasons that only limited success of TB treatment has been reported in HIV-TB coinfected patients [9,45].

Next, drug–drug interaction mainly between ARV's and Rifamycins (Rifampin, Rifabutin and Rifapentine) is a serious problem in itself. Rifamycins trigger overexpression of hepatic cytochrome CYP P450 and Uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes which lead to significant reductions in drug exposure and increased metabolism of ARV's [54]. The CYP3A4 isoform metabolises many drugs those include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), Maraviroc (MVC), and HIV Integrase inhibitors (IN) like Raltegravir. ARV's on the other hand nullify the effects of rifamycins (Rifampin is usually replaced with Rifabutin in most HIV-TB regimens as it is weaker inducer of cytochrome CYP P450) [55]. This undesired biological link between HIV and TB affects the distribution, progression and outcomes of both diseases that force the use of high dosage of multiple drugs with negative impact. Henceforth, the treatment for both the HIV patients infected with TB or vice-versa is a complex process that must address the selection of tailored ATD regimen and cocktail of ARV's with higher effectiveness, lower drug-drug interactions, and minimum complications related to IRIS [56].

Therefore, it is need of an hour to search for new ATD's that can address the current challenges posed by complexity of TB regimens, long treatment durations, emergence and world wide spread of drug resistance, LTBI treatment, co-morbidities due to coinfection with HIV [57], and other factors like diabetes [58],paediatric TB [59] and socio-economic determinants of TB [60].

4. Promises: drug targets exploited in TB drug discovery

Advances in understanding the biology of mycobacterium and decades of efforts directed on TB drug discovery with availability of its complete genome sequence has provided us with a platform of wide range of novel drug targets and regimens [17]. To address the above mentioned challenges for rapid and effective treatment of TB, there is a critical need of discovery and development of new ATDs [24,38]. The new drug should be effective against different forms of *M. tuberculosis* (DS-TB, DR-TB,MDR-TB and LTBI) with novel targets, better efficacy, minimum drug-drug interaction and least cytotoxicity [24,61]. Decades of extensive research all around the globe has led to the discovery of only few molecules that are being currently evaluated at later stages of clinical drug development [62]. Only two drugs, OPC and bedaquiline, formerly known as TMC207, is one of the rare examples of a new diarylquinoline antibiotic that has recently received accelerated approval for the treatment of pulmonary MDR-TB in adults [63–66].

Gene products involved in controlling vital aspects of mycobacterial structure and metabolism like, DNA replication, RNA synthesis, protein synthesis, energy metabolism, cell wall synthesis and folate metabolism are attractive drug targets that can act as stepping stones in the discovery of new effective drugs [67]. Drugs that target different sites in *M. tuberculosis* are depicted in Table 3 and explained in detail in the text.

5. DNA replication

DNA replication refers to a biological process that produces identical copy of DNA from one original DNA molecule. For any organism to survive and propagate, faithful replication and maintenance of its genome are essential activities among its overall energy expenditure [68]. *M. tuberculosis* infects human population by successive cycles of

Table 2
Categories of anti-tuberculosis drugs.

Categories	Type	Names
Category 1	First-line oral drugs	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
Category 2	Fluoroquinolones	Levofloxacin, Moxifloxacin, Ciprofloxacin, (Ofloxacin)
Category 3	Injectable agents	Amikacin, Capreomycin, Kanamycin, Streptomycin
Category 4	Oral Bacteriostatic second-line agents	Ethionamide, Prothionamide, Para-aminosalicylic acid, Cycloserine, (Terizidone)
Category 5	Agents with efficacy that is not totally clear/certain (not recommended for routine use in treating patients with drug- resistant TB generally)	Isoniazid (high-dose: > 10 mg/kg), Linezolid, Clofazimine, Clarithromycin, Amoxicillin-clavulanate, Imipenem/cilastatin (+ clavulanate) Thiacetazone (Rifabutin)

Table 3
Drug targets exploited in *Mycobacterium tuberculosis*.

DNA Replication	RNA Synthesis	Protein Synthesis	Energy Metabolism	Cell Wall	Folic acid Metabolism	Multiple Targets
Fluoroquinolones	**Rifamycins**	**Streptomycin**	**Pyrazinamide (PYZ)**	**Isoniazid (INH)**	**p-Amino salicylic acid (PASA)**	**Nitroimidazoles**
Moxifloxacin (phase III)	*Rifampicin (RIF)*	**Oxazolidinone**	**Q-203**	**Ethambutol (EMB)**		*Delamanid* (phase III) (OPC-67683)
Gatifloxacin	*Rifapentine*	*Linezolid* (phase II)	**Diarylquinoline**	**Ethionamide (ETH)**		*Pretomanid* (phase III) (PA-824)
		Sutezolid (phase II) (PNU-100480)	*Bedaquiline* (phase II) (TMC-207)	**Ethylenediamine** *(SQ-109)*		
			Riminophenazine *Clofazimine(CLZ)*	**Benzothiazinones** *(BTZ043);(PBTZ169)*		
				Cycloserine (CS)		
				Capuramycin		

cell division and transmission of DNA in order to retain its foothold [19]. This makes DNA replication associated enzyme machinery critically important for nucleotide synthesis, initiation, unwinding and elongation of the DNA to be accessible to mycobacterium under the metabolic, immune, and antibiotic stresses of variable host environments [69]. As such, the process of DNA replication is a vital drug target in progressively evolving drug-resistant bacteria, including *M. tuberculosis*. Some of the main antibiotics targeting mycobacterial DNA replication are depicted in Table 3.

Fluoroquinolones are broad-spectrum antimicrobial agents [70] that also exert their action against *M. tuberculosis* [71]. They interfere with bacterial DNA replication and repair by targeted inhibition of two critical enzymes for bacterial viability, DNA gyrase (topoisomerase II) and topoisomerase IV. However, in *M. tuberculosis* only type II DNA gyrase is expressed and thus is the sole target of fluoroquinolone action [72]. DNA gyrase, encoded by gyrA and gyrB, expresses a tetrameric protein containing two α and β subunits that catalyzes the DNA supercoiling to relieve tension ahead of replication fork and ensures smooth DNA replication [73].

Chromosomal mutations in the quinolone resistance-determining region of *gyrA* or *gyrB* in *M. tuberculosis* are thought to be the main mechanism involved in development of fluoroquinolone resistance. The most frequent mutations of *gyrA are* found to be at position 90 and 94 but mutations at position 74, 88 and 91 have also been reported [74,75]. Interestingly, simultaneous occurrence of mutations T80A and A90G in *gyrA* has been reported to cause hypersusceptibility to several quinolones pointing towards the complex nature of fluoroquinolone resistance in *M. tuberculosis* [76]. Furthermore, the contribution of efflux pumps have also been reported as a possible mechanism for fluoroquinolone resistance in *M. tuberculosis* [77].

Fluoroquinolones are currently in use as second-line drugs in the treatment of MDR-TB [78]. Nalidixic acid, discovered as a by-product of the antimalarial chloroquine is a source of two vital synthetic derivatives of fluoroquinolones, ciprofloxacin and ofloxacin [79]. Moxifloxacin (MOX) and gatifloxacin, a new-generation quinolones are being evaluated in clinical trials with the purpose of shortening the TB treatment duration and proposed to be used as first-line antibiotics [80,81]. Moxifloxacin is an 8-methoxy-fluoroquinolone developed and marketed as Avelox [82]. It was approved to treat several acute respiratory and uncomplicated skin and soft tissue infections [82]. Moxifloxacin is widely used in countries all around the globe though rarely as a second-line TB drug. Furthermore, it does not have regulatory approval for use against TB or MDR-TB, although it was studied as part of the REMox TB trial and in the NC-005 trial. Moxifloxacin shows little interaction with the cytochrome P450 enzyme system, which is heavily involved in the metabolism of some of the antiretroviral drugs (ARVs) used to treat HIV/AIDS [83]. Therefore, moxifloxacin is an ARV-friendly TB drug candidate. Gatifloxacin-containing regimen of four months duration for the treatment of pulmonary tuberculosis is currently, undergoing trial to evaluate its efficacy and safety.

6. RNA synthesis

RNA synthesis or transcription is the primary step of gene expression, in which a particular segment of DNA is copied into RNA by the enzyme RNA polymerase (RNAP). During transcription, RNA polymerase reads a sequence of DNA to produce a complementary, antiparallel RNA primary transcript thereby regulating the whole biochemical setup of any cell. Bacterial RNAP is a well-recognized target for broad-spectrum antibacterial drugs [84,85]. Some of the main antibiotics targeting mycobacterial RNAP are depicted in Table 3.

Rifampicin (RIF) acting early in DNA transcription machinery, inhibits bacterial DNA-dependent RNA polymerase by forming a stable enzyme-drug complex with the ß-subunit (a rpoB gene product) of mycobacterial RNA polymerase [86]. This RNAP-RIF complex binds close to the RNA/DNA channel thereby physically blocking the transit of the growing RNA chain [87]. In *M. tuberculosis*, RIF displays bactericidal mode of action and exhibits very effective activity even against non-replicating persisters when used in higher dosage [88]. However its clinical utility is hampered by decreased binding of rifamycins to bacterial RNAP due to mutation in the gene encoding β-subunit of RNA Polymerase (rpoB gene) resulting in drug resistance [89,90]. RIF resistance is considered as a surrogate marker for MDR-TB as mono resistance to rifampicin is quite rare and almost all rifampicin-resistant strains are also resistant to other ATDs, especially to INH. Mutations in the *rpoB* gene that codes for the ß-subunit of the RNA polymerase lead to conformational changes within the enzyme resulting in decreased rifampicin affinity and development of drug resistance. This gene mutation is found in majority of rifampicin-resistant clinical isolates of *M. tuberculosis* [91]. The mutations in the rifampicin resistance-determining region or the hot-spot region comprising of 81-base pairs spanning 507–533 codons of the *rpoB* gene are found in about 96% RIF resistant isolates of *M. tuberculosis* [92]. In majority of studies, the most commonly associated mutations associated with rifampicin resistance are in codons 516, 526 and 531 [93]. However, the occurrence of mutations outside the hotspot region of *rpoB* gene has also been reported. Mutations with less frequency *e.g.* in 518 or 529 codons confer low-level resistance to rifampicin but are still susceptible to other rifamycins, such as rifabutin or rifalazil [94]. Such mutations have important implications for TB patients coinfected with HIV since they receive rifabutin, a lesser effective inducer of the cytochrome P450 CYP3A oxidative enzyme [95]. A recent 2-month study testing the safety of high doses of RIF together with standard treatment for DS-TB showed no significant increase in adverse events at doses of 10 mg/kg, 15 mg/kg and 20 mg/kg [9].

Rifapentine belonging to the class of rifamycins that has shown potential in the treatment of TB [96]. Rifapentine is generally more active against *M. tuberculosis* than RIF, but strains resistant to rifampicin

are usually cross-resistant to rifapentine [97]. Rifapentine is highly protein bound in blood, but the free, unbound drug is the microbiologically active fraction [98]. Recent animal studies have shown that increasing the frequency of rifapentine administration could shorten treatment times for both latent and active TB infection. However, these results were not replicated in a subsequent human clinical trial [99]. Rifapentine results in the inhibition of bacterial DNA dependent RNA polymerase.It is among the three approved or repurposed drugs undergoing further testing besides rifampicin and linezolid [9]. It is in phase III clinical trial for the possible potential to shorten treatment duration of DS-TB. TBTC Study 31/A5349 is investigating the possibility of shortening treatment of drug-susceptible pulmonary TB to 4 months by using rifapentine, with or without moxifloxacin [9]. The trial began in January 2016 in Uganda. The Phase 2 clinical trial for treatment shortening of drug-susceptible TB treatment is evaluating the antimicrobial activity and safety of an experimental intensive phase (first 8 weeks of treatment) TB treatment regimen in which several doses of rifapentine are substituted for rifampin [100].

7. Protein synthesis

Protein synthesis (translation) is a biosynthetic pathway whereby viable cells assemble amino acids at ribosomes to generate new proteins essential for cell survival. Disruption of ribosomal assembly or any step from initiation to formation of proteins in mycobacteria presents a viable target for drug discovery. Some of the main antibiotics targeting mycobacterial protein synthesis are depicted in Table 3. Streptomycin (STM), originally isolated from the soil microorganism *Streptomyces griseus*, was the first antibiotic to be successfully used against *M. tuberculosis* [101]. It is active against rapidly growing mycobacterial bacilli. STM is an aminocyclitol-glycoside that acts by inhibition of initiation step of protein synthesis. STM specifically binds to 30S subunit of mycobacterial ribosome at two sites, the ribosomal protein S12 and the16S rRNA coded by *rpsL* and *rrs* genes respectively [102,103]. As result of being administered as monotherapy, unfortunately, soon resistance to STM started to emerge. The major mechanisms of resistance to STM that account for 60%–70% of the resistance are mutations found in *rpsL* and *rrs* genes [104,105]. The most commonly reported mutation in *rpsL* gene is substitution in codon 43 from lysine to arginine that results in high-level resistance to STM. While as in *rrs* gene, the most common mutations occur around nucleotides 530 and 915. However, there remains a vast percentage of strains resistant to STM that lack mutations in either of above two genes thereby suggesting alternate mechanisms of drug resistance. A study reported that mutations in *gidB* gene that codes for conserved 7-methylguanosine transferase (7-MGT) specific for the 16S rRNA are responsible for low-level resistance to STM [106,107].

Linezolid, a member of the oxazolidinone class of drugs was discovered in the 1990s and is the first oxazolidinone to be developed and approved by the FDA for use in 2000 to treat single or multiple-resistant Gram-positive disease causing bacterial infections [108]. It is active against most Gram-positive bacteria including *M. tuberculosis*, streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) [109]. As a protein synthesis inhibitor, linezolid is amongst the very few artificial antibacterials targeting the 50S ribosomal subunit in *M. tuberculosis*, thereby disrupting its protein production and ultimately halting its growth [110]. The mechanism of action of this bacteriostatic agent appears to be unique in that it blocks the early step of initiation compared to other protein synthesis inhibitors that usually target the later stages of mycobacterial protein synthesis machinery. Linezolid in combination with other drugs in two recent clinical studies, successfully treated most MDR-TB patients [111–113]. However its long term use usually resulted in significantly higher toxicity accompanied by forbidding side effects like peripheral neuropathy and anemia [114,115]. Although bacterial resistance to linezolid has remained very low, but one study revealed the presence of about 1.9% linezolid resistant strains after analyzing 210 MDR-TB strains [116]. Further analysis of *in vitro* selected linezolid-resistant mutants with mutations in the 23S rRNA displayed minimum inhibitory concentration (MIC) values in the range of 16–32 μg/mL when compared to MIC value of 4–8 μg/mL in normal susceptible strains [117]. In a recent study involving *in vitro* selected mutants and clinical isolates of *M. tuberculosis* resistant to linezolid, T460C mutation was found in *rplC* gene that codes for 50S ribosomal L3 protein using next-generation sequencing technique [118]. The possible involvement of efflux pumps in rendering *M. tuberculosis* resistant to linezolid have also been suggested in previous studies [77].

Sutezolid (PNU-100480) is a thiomorpholinyl analog of linezolid. The anti-TB activity of sutezolid was first reported in 1996 [119]. Williams et al. showed that in contrast to linezolid, sutezolid is more potent and has better activity profiles when subjected to either *in vitro* testing or in murine models of TB [120,121]. Sutezolid is bactericidal in action through limiting protein synthesis in mycobacteria and has been established to be secure and well accepted [119]. Sutezolid is under efficacy and safety study of phase II to characterize its effects for the treatment of both DS and DR-TB. Standard multiple ascending dose Phase I study evaluating PK and safety is reported recently [120]. It is an efficacy and safety study to characterize the effect of PNU-100480 when given for 14 days to treatment-naive patients with drug-sensitive pulmonary TB. 14 day dose-escalation is complete and 28 day study in healthy volunteers was also completed by May 2010 [122].

8. Energy metabolism

All bacteria require energy to maintain their viability. In our quest to discover novel and sterilizing drugs to combat emerging forms of TB, energy metabolism in mycobacteria has emerged as a subject of intense research investigation in the form of a novel drug target [123]. Targeting components of respiratory ATP production is a viable option for exploitation Oxidative phosphorylation, a pathway for generating ATP acts as attractive drug target for interference with different elements of energy metabolism. As such they are highly active in combating dormant or latent mycobacteria with a possibility to shorten the duration of TB chemotherapy. Some of the main antibiotics targeting mycobacterial energy metabolism are depicted in Table 3. Pyrazinamide (PZA), a frontline anti-TB drug that is majorly active against non-replicating persisters acts by disrupting membrane potential and depleting energy reserves in *M. tuberculosis* [124]. Another drug, Q203 belongs to a promising class of imidazopyridine amide (IPA) compounds which has displayed a promising potential against *M. tuberculosis* [125]. The discovery of Q203, a drug candidate that disrupts the cytochrome-*bc* complex is a good example that highlights the potential applications of inhibiting energy metabolism [125]. Q203 blocks *M. tuberculosis* growth by targeting the *cytochrome bc1* complex of respiratory chain thereby limiting its ability for synthesis of ATP and disable the energy generating machinery [125]. Under *in vitro* conditions using culture broth medium, Q203 inhibited the growth of MDR and XDR clinical isolates of *M. tuberculosis* within nanomolar range of drug concentration while as in a mouse model of TB, it was efficacious at a dose below 1 mg per kg of body weight [126]. In addition, using once-daily dosing, Q203 displayed compatible pharmacokinetic and safety profiles.

Bedaquiline (Sirturo) formerly known as TMC207 or R207910 is a member of diarylquinoline class of antibiotics [65]. In a whole-cell based assay Andries et al., identified this lead compound after screening a library of about 70,000 molecules against *M. smegmatis* by high-throughput screening [64,65]. *In vitro* studies have revealed TMC207 to be bactericidal in nature with potent activity against both replicating and nonreplicating strains of mycobacteria [127]. As such it bears high potential in shortening the duration of TB treatment. TMC207 displayed activity against both DS and MDR-TB strains of *M. tuberculosis* with a very low MIC [128,129]. In preclinical studies, TMC207 displayed

activity against *M. tuberculosis* clinical isolates resistant to RIF, INH, EMB, PZA STM, and MOX under *in vitro* conditions with zero cross-resistance against any drug. *In vivo* studies have shown that TMC207 has superior bactericidal and sterilizing activity in the murine model of tuberculosis when compared to that of INH or RIF [65,130]. This potent *in vitro* and *in vivo* activity against *M. tuberculosis* led to its entry into clinical trials against drug susceptible and MDR-TB. It received fast track approval in 2012 by the US FDA [66]. Bedaquiline is a highly lipophilic medication metabolized by cytochrome P450 (CYP) 3A4 to a less-active M2 metabolite. Its terminal half-life is extremely long (5–6 months). Its metabolism is complicated by drug–drug interactions with increased susceptible to CYP3A4 degradation particularly when triggered by the inducer, RIF [131–133]. Bedaquiline displays a unique mechanism of action as a completely new target for any anti-mycobacterial drug. It selectively inhibits ATP synthase enzyme of *M. tuberculosis* Table 3 [134]. ATP synthase is used in the process by which *M. tuberculosis* generates its energy supply. It selectively inhibits the proton pump of ATP synthesis machinery by binding to its oligomeric and proteolipic subunit c, thereby leading to depletion of ATP molecules that finally culminates in bacterial death [65,135,136]. The mode of action was discovered by analyzing *M. tuberculosis* and *M. smegmatis* mutants resistant to bedaquiline. By comparative genome sequencing of susceptible strains with respect to the mutant strains, the only mutation found was in the *atpE* gene. This gene encodes for c part of the F0 subunit of ATP synthase, a complex enzyme that generates the ATP needed by the mycobacterial cell. Bedaquiline has a favored specificity towards mycobacterial ATP synthase compared to its eukaryotic mitochondrial counterpart [135]. In bedaquiline resistant mutants, the most prevalent mutation in the *atpE* gene found is A63P. However in some other mutant strains, I66M type has also been found that introduces a modification which prevents the proper binding of bedaquiline to its target [137]. To further assess the mechanisms of resistance to bedaquiline in *M. tuberculosis,* a study conducted on 53 resistant mutant strains revealed that only 15 had mutations in *atpE gene* while the majority 38 strains lacked mutations in *atpE* or even in the F0 or F1 operons, thereby suggests that other mechanisms of resistance may also be in play [138].

Based on the results of two phase II clinical trials, in addition to the current second-line treatment regimen, bedaquiline received conditional approval by the US FDA for the treatment of MDR-TB under the trade name *Sirturo*. After approval bedaquiline has been introduced in several countries for the treatment of severe forms of MDR-TB on the condition of interim guidance accompanying the authorization issued by the WHO's interim policy guidance on its use in June 2013. Recently first two XDR-TB cases were treated with both bedaquiline and delamanid [139]. In yet another recent study, bedaquiline was found to inhibit the growth of total drug resistant *M. tuberculosis* strains (TDR-TB), with MIC values ranging from 0.125 to 0.5 mg/L [140]. Compared with the current standard of care recommended by WHO, the safety and efficacy of bedaquiline as part of short MDR-TB regimens of 6 and 9 months duration is now under investigation in the second stage of the Phase III STREAM trial that started recruitment in March 2016. The first results are expected towards the end of 2020.

Clofazimine (CFZ) is a riminophenazine based derivative that was synthesized by Barry et al. [141]. It was discovered in 1954 through structural modifications of a compound diploicin that was extracted from *Buellia canescens* [142]. Riminophenazines have displayed activity against several mycobacterial infections and used particularly *against M. leprae* to treat leprosy since 1962 [143]. However, initial research on CFZ showed it to be inactive in guinea pig and monkey models of TB resulting in delayed development of this valuable compound against *M. tuberculosis* [144]. With the emergence of MDR-TB, renewed interest in persuing phenazines as possible new anti-TB agents was on rise. CFZ exhibited MIC value of 0.12 μg/ml against DS-TB strain whereas 0.108–0.240 μg/ml against a panel of MDR and XDR strains *M. tuberculosis*. CFZ on testing proved to be active in animal models infected with MDR *M. tuberculosis* strains [145]. High early bactericidal activity and earlier lung culture conversion within 3 months compared to 5 months in clofazimine-containing first-line treatment was observed in mouse models of *M. tuberculosis* infection [146]. Reassessment of clofazimine in combination with gatifloxacin, ethambutol, pyrazinamide, prothionamide, kanamycin and high-dose isoniazid for 9 months, resulted in treatment of 88% of MDR-TB patients [147]. As a result of this research, investigation of clofazimine's potential to shorten treatment for DS-TB commenced. However, CFZ accumulates within cells and tissues to high concentrations leading to undesirable side-effects [148,149]. The exact mode of action of CFZ was unclear until recently. However, renewed interest in deciphering the possible target of CFZ have pointed its mode of action towards outer membrane [150]. Another study revealed that in the presence of mycobacterial enzyme NADH-quinone oxidoreductase type II (NDH-2), clofazimine is reduced and subsequently after spontaneous reoxidation liberates bactericidal levels of reactive oxygen species (ROS) most likely O^{-2} [151,152]. Furthermore, it is also suggested that CFZ may cause interference with bacterial potassium transport by induction of mycobacterial phospholipase A2 activity to reduce ATP production [153]. Resistance to CFZ has not yet been fully understood; however, recent study reveals the main mechanism of CFZ resistance to be linked to mutations in a transcriptional regulator, Rv0678 [154]. The resulting mutation cause up-regulation of a multi substrate efflux pump (MmpL5), which causes resistance not only to CFZ but also to bedaquiline (BDQ) [155,156]. Recently, in *PepQ* gene (*Rv2535c*) coding for putative Xaa-Pro aminopeptidase, loss-of-function mutations was reported to confer low level of CFZ and BDQ cross-resistance [157]. CCFZ is currently comprised in the WHO Group 5 list of the second-line ATD's and is used for treating MDR and XDR patients who run out of other available choices [158,159]. Recently, CFZ displayed *in vitro* synergism with other ATD's against MDR-TB isolates [160]. CFZ was also reported to shorten the duration of first-line treatment regimen for experimental chemotherapy of TB [161].

9. Cell wall

The cell wall of *M. tuberculosis* has uniquely intriguing architecture dominated by high content of a variety of lipids and carbohydrates that functions as cache of impermeable barrier against hydrophilic antimicrobial agents. As mycobacterial porin proteins are inefficient in allowing the permeation of solutes, hydrophilic agents cross the cell wall very rarely [162]. Indeed antibiotics active against other microbes fail to cross mycobacterial cell wall and thus make it a focus for TB drug discovery programme [163]. This large macromolecular peptidoglycan-glycolipid complex structure, termed as mycolyl-arabinogalactan-peptidoglycan complex is composed of mainly three distinct layers, peptidoglycan, arabinogalactan and mycolic acids that play a crucial role in cell growth, survival, virulence and permeability to antibiotics [164]. Fatty acid biosynthesis represents a validated and yet relatively unexploited target for the discovery of new anti-mycobacterial agents. Recent insights in the biosynthesis of peptidoglycan enable the entire biosynthetic pathway to be reconstituted for high-throughput inhibitor screening [165]. A joint course of action between fatty acid synthases (FAS) and a modular polyketide synthases (PKS) leads to the construction of extremely complex lipids of mycobacterial cell wall [166]. The last enzyme in the fatty acid elongation cycle, known as enoyl-acyl carrier protein reductase (ENR), is of prime interest mainly due to the target specific activity of a variety of both synthetic and natural antibacterial compounds against this enzyme. Some of the main antibiotics targeting mycobacterial cell wall are depicted in Table 3. Isoniazid (INH) and Ethambutol (EMB), is few of the representative mycobacterial cell wall inhibitor as components of first line ATD's.

Isoniazid (INH), also known as isonicotinic acid hydrazide was introduced in 1952 as an anti-TB agent that remains till date a member of four drug regimen implemented globally for DS-TB [167]. However, the

metabolism of INH has been associated with INH-induced liver injury that may even culminate in liver failure. [168]. INH is a pro-drug that is activated by *M. tuberculosis* catalase-peroxidase (encoded by KatG gene) [169]. Once activated, it generates a flare of reactive oxygen species (ROS) and other free radicals that primarily attack nicotinamide adenine dinucleotide (NAD) to form a covalent adduct. This adduct inhibits the enoyl-ACP reductase, InhA (encoded by *InhA* gene), an enzyme involved in the synthesis of very long chain fatty acids that are used to form mycolic acids of *M. tuberculosis* cell wall [170,171]. This dependence of INH for activation by KatG is easily bypassed by KatG mutant strains resulting in INH resistance [172]. Although INH bears simple chemical architecture; resistance to this drug is not uncommon. Mutations in several genes, such as *katG*, *inhA*, *ahpC*, *kasA* and *ndh* have been associated with INH resistance [173]. Machado et al. investigated the mechanism of emergence of isoniazid drug resistance verses overexpression of efflux pumps. Their results showed that activity of efflux pumps allows the maintenance of an isoniazid resistant population in a sub-optimally treated patients [174]. Their results supported the concept that in order to prevent the emergence of drug resistance, efflux pump inhibitors can be considered as one viable drug target for developing new therapeutic strategies.

Ethambutol (EMB) is an oral medication primarily used to treat DS-TB [175]. It is usually given in intensive phase of first-line drug regimen along with as isoniazid, rifampicin and pyrazinamide. It may also be used to treat *Mycobacterium avium* complex and *Mycobacterium kansasii*. Ethambutol was discovered in 1961 and since has remained on the WHO's List of Essential Medicines. Ethambutol is bacteriostatic agent active against drug susceptible replicating mycobacterium bacilli. Its mechanism of action is to disrupt arabinogalactan synthesis by inhibiting the enzyme Arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of mycolyl-arabinogalactan-peptidoglycan (mAGP) complex and thus leads to increased permeability of the cell wall [176]. Ethambutol resistance is primarily associated with missense mutations in the *embB* gene.

Ethionamide (ETH) belongs to thioamides class of compounds that is specifically used along with other second-line antituberculosis drugs to treat active MDR-TB. Ethionamide, discovered in 1956 was approved for medical use in the United States in 1965 and since remains on the WHO's List of Essential Medicines. ETH is a structural analogue of INH and both are pro-drugs that need to be activated by mycobacterial enzymes [177]. The disruption of mycolic acid synthesis is thought to be the mechanism of action. ETH, a prodrug is dependent on the enzyme ethA for activation leading to the formation of an oxide metabolite that has considerably better activity than the parent drug [178]. The ethA, a monooxygenase controlled by the transcriptional repressor EthR binds NAD + to form adduct that leads to inhibition of InhA in a way similar to isoniazid. Resistance to ETH has been reported to result from various mechanisms, including mutations altering the NADH dehydrogenase encoded by *ndh*, and the MshA enzyme, involved in mycothiol biosynthesis [179]. Mutations in the *ethA* or *ethR* gene (a repressor that can be overexpressed to repress *ethA*) can result in the emergence of drug resistance [180]. Another route for emergence of resistance is the mutations in *InhA* gene itself or its promoter by changing the binding site or overexpression. Enhancing the expression of the *ethA* gene by suppressing its transcriptional repressor ethR is a well suited target for developing EthR inhibitors.

SQ609 was identified from a series of dipiperidine derivatives by Bogatcheva et al. [181,182]. SQ609 showed greater than 90% growth inhibition of intracellular *M. tuberculosis* at the concentration of 4 μg/ml in J774A infected macrophage cells without any toxicity. Furthermore, mice infected with *M. tuberculosis* when administered with SQ609 showed a prolonged therapeutic effect extended by 10–15 days with no weight loss. Precise mechanism of action is still unknown. However, it is proposed to act by inhibiting the biosynthesis of mycobacterial cell wall [181]. SQ609 is currently being assessed in preclinical studies.

Benzothiazinones (BTZ), represented by BTZ043, is a highly bactericidal agent that is active within nanomolar concentrations against tubercle bacilli. It has been shown to kill *M. tuberculosis in vitro*, *ex vivo*, and in mouse models of TB [183]. BTZ043 interferes with biosynthesis of mycobacterial cell wall by targeting DprE1, a flavoenzyme that catalysis a crucial step in the synthesis of D-arabinofuranose, a component of arabinogalactan and arabinomannan [183]. First, DprE1 reduces BTZs to generate electrophiles that reacts in a near-quantitative manner with the active-site of DprE1 itself and lead to its inactivation [184]. The interaction studies of BTZ043, with several ATD's or drug candidates against *M. tuberculosis* strain H37Rv (RIF, INH, EMB, TMC207, PA-824, MOX) with or without clavulanate, and SQ-109 revealed no antagonism and most of the interactions were purely additive [185]. DprE1 mutant enzymes isolated from BTZ-resistant strains neutralize the BTZs to inert metabolites while avoiding covalent inactivation [184]. PBTZ169, a piperazinobenzothiazinone based derivative is optimized by medicinal chemistry from its closest congener of electron deficient nitroaromatic compound, BTZ043 [186]. PBTZ169 were shown to be more potent compared to its parent compound with several other advantages like ease of chemical synthesis (as it lacks chiral centers) and better pharmacodynamics. Within the zebrafish model, in contrasted to BTZ-043, it exhibited an enhanced potency, security and competency profile. It has *in vivo* action within in murine models, and has displayed additive effect with several ATDs and possible synergistic effect when administered along with bedaquiline [187]. The target of action of PBTZ169 is similar to that of BTZ043. PBTZ169 covalently inhibits DprE1, an enzyme essential for the biosynthesis of key cell wall components [188]. However, PTBZ169 seems to be more stable due to the presence of cyclohexyl moiety which protects it from nitroreductase assault compared to its counterparts. The Innovative Medicines for Tuberculosis (iM4TB) foundation is leading PBTZ169 development. iM4TB was planning a Phase I study to start in Switzerland in 2017. In April 2017, The Bill & Melinda Gates foundation awarded EPFL-based non-profit iM4TB $2.45 million to take their innovative anti-tuberculosis drug PBTZ169 into clinical trials.

Cycloserine (CS) is an oral antimycobacterial agent that is specifically recommended by the WHO as a second-line anti-TB agent used as a last resort for the treatment of MDR-TB. Cycloserine was discovered from a kind *of Streptomyces* in 1954 and now features in the WHO lList of Essential Medicines. D-Cycloserine (D-CS) interferes with the formation of peptidoglycan biosynthesis by acting as a competitive inhibitor of alanine racemase (Alr) and D-alanine-D-alanine ligase (Ddl). As a cyclic analogue of D-alanine, Cycloserine inhibits two essential enzymes that are important in the cytosolic stages of peptidoglycan synthesis [189]. The first is a pyridoxal 5'-phosphate (PLP)-dependent enzyme, alanine racemase (Alr), which converts the L-alanine to the D-alanine form. The second is D-alanine-D-alanine ligase (Ddl) that is involved in joining two D-alanine residues together by catalyzing the formation of the ATP-dependent D-alanine-D-alanine dipeptide bond between the resulting D-alanine molecules. Being less potent than INH and streptomycin, it is also associated with many safety concerns that have impeded its uptake by many national TB programmes [190]. However, one advantage of D-CS is that emergence of drug-resistance is less reported when compared to first-line ATD's such as INH and RIF. Since it is able to penetrate into the central nervous system (CNS), Cycloserine shows various neurological side effects like headaches, drowsiness, depression, dizziness *etc.* [191].

Capuramycins is a class of antibiotics that have a uracil nucleoside structure tethered to a caprolactam substituent. Using adsorption and partition column chromatography, Capuramycin was isolated from the culture filtrate of *Streptomyces griseus* 446-S3 [192]. Capuramycins were discovered in a screening programme to identify inhibitors against bacterial translocase I (TL-1), an enzyme essential in peptidoglycan cell wall biosynthesis [193]. Capuramycin and its analogs are considered to be important leads for development of new drug for MDR-TB.

10. Folic acid metabolism

Folate, forms of which are also known as folic acid and vitamin B9, belongs to the category of B vitamins. In prokaryotes and eukaryotes, the pathways involved in the synthesis of vital intermediates like methionine, *N*-formylmethionyl-tRNA, glycine, serine, pantothenate, purines, and thymidine require reduced folate species. These folate species serve as essential cofactors in the transfer step of one-carbon groups involved in the synthesis of above mentioned intermediates [194]. Microbes rely on *de novo* folate synthesis to support one-carbon metabolism and are unable to acquire folate from the external environment while mammals lack the *de novo* folate biosynthesis pathway and must obtain this nutrient from their diet [195]. This contrast along with structural differences in key enzymes of folate utilization makes this pathway an ideal target for the development of antimicrobial agents [196,197]. The folate biosynthetic pathway of *M. tuberculosis* begins with the synthesis of para-aminobenzoic acid (PABA) and 7,8-dihydropterin pyrophosphate (DHPPP) and interference at any step can halt the growth of *M. tuberculosis*.

Para-amino salicylic acid (PAS) is a prodrug targeting folate metabolism of *M. tuberculosis* [198], Table 3. Its antitubercular mode of action was subject of multiple hypotheses since discovery. However, recent studies have revealed that it mimics the substrate *p*-aminobenzoate (PABA) thereby inhibiting dihydropteroate synthase (DHPS) [23]. This leads to poisoning of folate metabolism in *M. tuberculosis* and eventually death. Folate-dependent thymidylate synthase encoded by *thyA* gene is involved in folate metabolism and loss-of-function mutations in this gene was found to confer resistance to PAS thereby backing up the mechanism of PAS [199].

11. Multi-target drugs

Delamanid, previously known as OPC-67683, is a derivative of nitro-dihydro-imidazooxazole with activity against *M. tuberculosis*. Delamanid was shown to have potent *in vitro* and *in vivo* activity against drug-susceptible and drug-resistant *M. tuberculosis* [200]. It showed potent *in vitro* and *in vivo* activity with significant early bactericidal activity (EBA) in adult cases affected by pulmonary TB.When compared to rifampicin, it displays good early bactericidal activity [201]. Very recently, a study showed that delamanid kills dormant *Mycobacteria in vitro* and in the guinea pig model of TB [202]. OPC-67683 is a mycolic acid biosynthesis inhibitor that specifically inhibits methoxy and ketomycolic acid synthesis only in contrast to isoniazid that inhibits the synthesis of all mycolic acid subclasses that form the essential components of the *M. tuberculosis* cell envelope. [200,203]. OPC-67683 requires reductive activation by *M. tuberculosis* to exert its activity. Mutations in the mycobacterial *Rv3547* gene found in experimentally generated delamanid-resistant mycobacteria suggest its role in the activation of the drug [200]. Delamanid is currently undergoing clinical evaluation in a phase III trial [81]. Recently its safety and efficacy in a clinical evaluation was showed against MDR-TB [204]. European Medicines Agency (EMA) granted a conditional marketing authorization for delamanid for the treatment of pulmonary MDR-TB in adult patients “when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability” in April 2014. WHO issued an interim guidance on the use of delamanid in October of same year. As an addition to an optimized background regimen (OBR) for the treatment of MDR-TB in adults, the follow-up stage of a Phase III trial of the safety and efficacy of delamanid was recently completed. It is anticipated that results will be published in 2018. In children, the use of delamanid in addition to OBR for treatment of MDR-TB is being investigated in Phase I and II trials. Partial results were presented in 2015.

Pretomanid, a bicyclic derivative of nitroimidazopyran, belongs to a novel class of anti-bacterial agents, Nitroimidazoles. PA-824 has many attractive characteristics. It displays narrow spectrum of activity specifically against *M. tuberculosis* with no significant activity against a broad range of Gram-positive and Gram-negative bacteria [205]. It has displayed potent activity not only against all tested drug-resistant clinical isolates under *in vitro* conditions but has shown to be a potent bactericidal and a sterilizing agent in mice [206,207]. Furthermore, in a standard battery of genotoxicity studies, the compound has shown to be safe and well tolerated with no evidence of mutagenicity or any significant interaction with cytochrome P450 [208]. PA-824 display multitarget mechanism of action where it inhibits the mycobacterial protein synthesis and also disrupts its cell wall lipid biosynthesis. However, to exert its activity, it first needs to be activated by a nitroreductase [205]. The most common mechanism of resistance to PA-824 has been shown to be associated with loss of a specific glucose-6-phosphate dehydrogenase or the dezaflavin cofactor F420 [209]. More recently, minor structural changes in the drug caused by a nitroimidazo-oxazine-specific protein has also been identified [210]. Pretomanid has been developed by TB Alliance and is a potential cornerstone of future TB treatment regimens that is currently in phase II clinical trials. It is being tested as part of three potential combination regimens for the treatment of both drug-susceptible and drug-resistant TB. It is a part of the promising PaMZ (*Pretomanid* + *moxifloxacin* + *pyrazinamide*) regimen in clinical trials. “BPaZ” is another promising TB treatment regimen in phase II that consists of bedaquiline (B), pretomanid (PA-824) and pyrazinamide (Z), which is an established drug regimen that shows promise to reduce TB treatment to as little as three months. This is an oral regimen with impressive performance that nullifies the need for injectable agents as part of MDR-TB treatment and also cost effective than current MDR-TB therapy.

12. Need for new drugs

TB as a global agenda was utterly neglected for a period of at least four decades that generated a climate of indifference to the need for fresh drugs. As a result of this apathy, funding and interest for TB control and TB related research dried up as it was no longer considered a threat to the developed countries. The interest and concern over TB only renewed in the mid-1980’s as a result of dramatic surge in the incidence of HIV-TB co-infection, diabetics and an alarming rise in MDR-TB cases in the developed world. This led to refocused attention towards TB as a serious global concern particularly when dealing with drug resistant cases that are responsible for about 0.5% of the global economy’s output [9,38]. In 1993, WHO took an unprecedented decision and declared TB as a global health emergency and even today it seems not only to remain the same but much worse [211].

In order to achieve global control of TB epidemic, there is an urgent need to improve treatment by either improving the application of existing anti-TB agents or searching new drugs with a number of expectations [212]. An ideal new drug should (a) improve the treatment of latent TB; (b) avoid interactions with HIV medications without compromising efficacy; (c) shorten duration, simplify treatment and require low dosing frequency (for example, a once-weekly regimen) d) target MDR and/or XDR strains with high tolerability profiles; (e) be orally bioavailable with acceptable pharmacokinetic and pharmacodynamic profiles and (f) have improved safety. However, there are many challenges that impede the progression of drugs from the discovery up to developmental stage; (a) the biological mechanisms of mycobacterial persistence and latency still awaits to be fully established and till date no effective drugs are yet available against persistent bacilli; (b) there is lack of validated animal models that can reliably predict the precise treatment with newly identified drugs; (c) given the excruciatingly lengthy clinical trials and lack of reliable surrogate biomarker, it is extremely difficult to predict the efficacy of any new drug regimen; (d) scarcity of trial sites with enhanced capacity to conduct clinical trials in high TB burden countries [61,213–215]; and (e) lack of investment in TB drug discovery programmes due to insufficient profit return opportunity.

13. Conclusion

Discovery and development of current TB treatment regimens represent an unparalleled success story of modern medicine by which innumerable human lives have been saved. However, TB bugs have evolved multifaceted strategies against these regimens and are challenging them in many ways upto the extent that TB still remains top most infectious killer. Therefore global efforts against TB to eradicate this historicallly worse human enemy completely from the world map are going on. Advances in understanding the biology of *M. tuberculosis* along with the availability of its complete genome sequence have provided insights for a number of drug targets. Gene products involved in controlling vital aspects of mycobacterial structure and metabolism like cell wall synthesis, DNA replication, RNA synthesis, protein synthesis, energy metabolism, folate metabolism are the major targets that are being exploited for the discovery of new chemical entities to deal with emerging challenges in TB drug discovery and development. Future belongs to those regimens which are simple, require significantly lesser treatment durations, are effective against resistant forms of disease, exhibit nominal toxicities and interact least with anti-HIV regimens.

Conflict of interest

All authors declare that there is no conflict of interest.

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