REVIEW ARTICLE

What is New in Management of Pediatric Tuberculosis ?

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Tuberculosis continues to haunt mankind since its discovery more than a century ago. Although commendable advancements have been made in the diagnosis as well as treatment, especially in the last couple of decades, the healthcare burden of this disease worldwide is immense. Continuously evolving medical science has provided recent changes in national guidelines along with discovery of newer anti-tubercular drugs after many decades. In view of WHO declaring tuberculosis as a global health emergency and strong commitment being reflected by Government of India whereby National Strategic Plan aims to eliminate tuberculosis by 2025, it is high time that we work collectively on the goal of tuberculosis elimination. This article sums up the updates on newer anti-tubercular drugs as well as the recent changes adopted in Revised National Tuberculosis Control Program.

Keywords: *Anti-tubercular drugs, Mycobacterium tuberculosis, Treatment*

Tuberculosis (TB) continues to have a significant impact on healthcare worldwide. Despite availability of anti-tubercular treatment (ATT) available for more than last five decades, approximately one-third of total world's population continues to harbour tuberculosis infection. The emergence of multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) in the last decade has raised a global concern [1,2].

As per WHO estimates of 2015, there were an estimated 10.4 million new cases of TB worldwide, which included 1 million children. In the same year, 1.8 million people are estimated to have died from tuberculosis, of which 0.2 million were children. This is despite the fact that the number of TB cases fell by 22% from 2000 to 2015. Inequality in diagnosis and treatment access is evident from the fact that the case fatality ratio varies from 5% in developed countries to 20% in low- and middle-income countries [1]. In 2015, there were an estimated 480,000 cases of MDR-TB and an additional 100,000 cases of Rifampicin Resistant Tuberculosis (RR-TB), which are also eligible for treatment for MDR-TB. Only 20% of such eligible patients were started on second line ATT in the same year. In pediatric age group, MDR-TB is underestimated, and primary MDR-TB is reported as well [3,4]. Also, cases of XDR-TB have been on the rise in the last few years. A cure rate of meager 52% for MDR-TB and 28% of XDR-TB has been the real cause of worry and there is need of urgent and definitive measures to control tuberculosis [1].

Based on the current evidence, this review aims to apprise the readers about the newer drugs and the updated strategies to combat tuberculosis.

DRUGS FOR TUBERCULOSIS

The continuous need of newer drugs and combinations has always been felt as the disease has refused to die down over the last five decades. Many drugs are being tested, and are in various phases of development [5] (***Box* 1**). Efforts are being made to develop newer drugs, and also to develop newer regimens with the help of these drugs.

BOX 1: CLINICAL PIPELINE OF NEWER ANTI- TUBERCULAR DRUGS IN VARIOUS STAGES OF DEVELOPMENT

Pre-Clinical	*Phase II*
1. PTBZ 169	1. SQ 109
2. BTZ-043	2. Levofloxacin
3. Spectinamide 1810	3. Rifampicin (High Dose)
4. GSK 070	4. Nitazoxanide
5. TBA 7371	
Phase I	*Phase III*
1. TBI-166	1. Delaminid
2. Q-203	2. Bedaquiline
3. OPC 167832	3. Rifapentine
	4. Clofazimine

The newer drugs are broadly discussed as: (*i*) New application of existing drugs (***Table* I)**; and (*ii*) Newer drugs/research molecules (***Table* II**).

New Application of Existing Drugs

Rifamycins: The drugs in this group consist of Rifampicin, Rifabutin and Rifapentine.

It has been suggested that dosage of Rifampicin higher than routinely recommended 10 mg/kg may be needed to achieve reduction in treatment duration in new cases of tuberculosis. Some studies in mice models have yielded encouraging results to evaluate the role of high dose rifampicin (15-30 mg/day), especially in the intensive phase of ATT [6]. A phase II randomized trial comparing rifampicin in doses of 20 mg/kg/day and 15 mg/kg/day to the standard 10 mg/kg/day for first two months of ATT is ongoing [7]. Preliminary evidence suggests acceptable tolerance of higher dosage and proportionate increased serum concentration levels with increasing doses of Rifampicin [8]. Higher doses of Rifampicin have also been studied in adults as a part of standard ATT regime as well as when used in combination with other newer drugs such as Moxifloxacin and SQ-109 [9]. Current evidence suggests the potential for shortened treatment duration with such higher doses of rifampicin.

Instead of Rifampicin, Rifabutin is generally recommended for patients of TB co-infected with HIV as it has lesser drug interactions and side effects [10]. The dose is 5 mg/kg in children and 150-300 mg/day in adults [11].

TABLE I NEWER APPLICATIONS OF EXISTING DRUGS FOR TREATMENT OF TUBERCULOSIS

Drug	*Class*	*Dose*	*Mechanism of action*	*Current indications*	*Side effects*
High dose Rifampicin	Rifamycins	15-35 mg/kg OD	Inhibition of RNA synthesis	Not currently approved in WHO/RNTCP guidelines	Fever, thrombo-cytopenia, acute renal failure
Rifabutin	Rifamycins	300 mg OD	Inhibition of RNA synthesis	Not currently approved in WHO/RNTCP guidelines, but widely recommended by experts and CDC	Nausea, vomiting May need to modify dosage as 150 mg BD
Rifapentine	Rifamycins	900 mg/week	Inhibition of RNA synthesis	Approved by CDC for treat-ment of latent TB infection	Nausea, vomiting, headache
Moxifloxacin	Flouro-quinolones	400 mg OD	Inhibition of DNA gyrase	Approved as core drug by WHO for drug resistant tuberculosis	QT prolongation, psychosis
Levofloxacin	Flouro-quinolones	750 mg OD	Inhibition of DNA gyrase	Approved as core drug by WHO for drug resistant tuberculosis	QT prolongation, psychosis
Cycloserine	Oxazolidinone	250-500 mg OD	Inhibition of RNA synthesis	Approved as core drug by WHO for drug resistant tuberculosis	Seizures, depression, vertigo, GI upset
Linezolid	Oxazolidinone	300-600 mg OD	Inhibition of RNA synthesis	Approved as core drug by WHO for drug resistant tuberculosis	Myelosuppression, GI upset, neuropathy, thrombocytopenia
Amoxicillin-Clavulanate	Beta Lactams	500-1000 mg and 125-250 mg TDS	Inhibition of cell wall synthesis	Enlisted as add on agent by WHO for drug resistant tuberculosis	Nausea, diarrhea
Meropenem	Carbapenems	500-1000 mg TDS	Inhibition of cell wall synthesis	Enlisted as add on agent by WHO for drug resistant tuberculosis	Intravenous injection related complications
Imipenem-Cilastin	Carbapenems	500 mg QID	Inhibition of cell wall synthesis	Enlisted as add-on agent by WHO for drug resistant tuberculosis	Intravenous injection related complications

OD: once daily; BD: twice a day; TDS: thrice daily; QID: four time a day; CDC: Centers for Disease Control; RNTCP: Revised National Tuberculosis Control Program; WHO: World Health Organization.

TABLE II NEWER DRUGS FOR TREATMENT OF TUBERCULOSIS

Drug	*Class*	*Dose*	*Mechanism of action*	*Current indications*	*Side effects*
Bedaquiline	Diaryl-quinolines	400 mg OD for 2 wks 200 mg TDS for 22 wks	Inhibition of ATP synthetase	WHO- and RNTCP-approved for MDR-TB when standard 2nd line regime cannot be used	Q_{TC} prolongation, arthralgia, myalgia, dark colored urine
Delaminid (OPC 67683)	dihydro-nitroimidazo-oxazole	100 mg BD for 6 mo	Inhibition of myco-bacterial cell wall synthesis	WHO-approved with conditional recommendation only in select patients	Q_{TC} prolongation, psychosis
Pretomanid (PA 824)	nitroimidazo-oxazole	100-1200 mg OD	Inhibition of myco-bacterial cell wall synthesis	Under trial only	Not significant so far, under trials
SQ-109	1,2 ethylene diamine	Under trial	-	Under trial	Under trial

OD: once daily; BD: twice a day; TDS: thrice daily; RNTCP: Revised National Tuberculosis Control Program; MDR-TB: multidrug resistant tuberculosis; WHO: World Health Organization.

Another drug from the same class is Rifapentine, which has a longer half life and has been studied more for latent tuberculosis infection (LTBI) than active tuberculosis. Once weekly prophylactic regimen of 300 mg Rifapentine and 900 mg Isoniazid for three months has been found to be equally effective as 9 months of 300 mg daily Isoniazid in adults [12]. In children, doses varying from 300-900 mg have been used with acceptable tolerance. Higher weight-adjusted doses are warranted in children to achieve systemic exposures that are associated with successful treatment of LTBI in adults [13].

Flouroquinolones: The key drugs in this group are Moxifloxacin and Levofloxacin, and their superiority over other quinolones is well proven [14]. There have been numerous trials with encouraging results to use quinolones along with other first line drugs with an aim to curtail the duration of ATT [15]. A standard ATT regimen was compared with a Gatifloxacin/Moxifloxacin-containing regimen in the intensive phase with an aim to reduce the treatment duration to four months but the latter resulted in higher relapse rates as compared to the former. Further, children less than five years of age are known to eliminate quinolones more rapidly in urine and achieve a lesser serum concentration than adults.There is lack of adequate pharmacokinetic data, especially in children less than five years of age. Hence it becomes more relevant to optimize their usage in children for prevention of drug resistance [14]. Traditionally, the use of quinolones has been restricted in children because of concerns about arthropathy but available data does not show any evidence of such side effects in either children or adults treated with long term quinolones.

Oxazolidinones: This class of drugs act via competitive inhibition of an enzyme involved in translation, and hence block protein synthesis [16]. Cycloserine was the first oxazolidinone that was used as an antitubercular drug but the most popular drug currently in use is linezolid. Two recent randomized control trials with linezolid showed improved rates of sputum conversion in patients of XDR-TB [17,18]. However, increased failure rates at lower range of dose (300 mg/day) and increased severity of adverse effects at higher range (600 mg/day) limit its long-term use. Peripheral neuropathy, gastrointestinal disorders and myelosuppression are common adverse effects [19]. As of now, both Cycloserine and linezolid are enlisted as core drugs by WHO for management of drug resistant tuberculosis. There is not much data available about their use in children as anti-tubercular agents.

Beta-lactams and Macrolides: Amoxycillin-Clavulanate, Imipenem-Cilastin and Meropenem are the drugs enlisted in WHO group D of drugs for treatment of drug resistant tuberculosis (***Box* 2)**. Meropenem and Clavulanate have potent synergistic *in vitro* activity against *M. tuberculosis* as Clavulanate inhibits the â-lactamase and potentiates the antibacterial activity of Meropenem [20]. A recent paper published encouraging data about triple therapy consisting of Amoxicillin, Clavulanate and Meropenem showing potential *in vitro* activity against tuberculosis bacilli [21]. Macrolides, especially Clarithromycin have been successfully used to treat non-tubercular mycobacteria in the past but the results in *M. tuberculosis* have been disappointing because of development of rapid resistance [22].

Newer Drugs

Bedaquiline: This particular drug has been the first anti-tubercular agent approved by the Food and Drug

BOX 2: NEWER CLASSIFICATION FOR MEDICINES USED FOR DRUG RESISTANT TUBERCULOSIS

A. Flouroquinolones·
- Levofloxacin (Lfx)
- Moxifloxacin (Mfx)
- Gatifloxacin (Gfx)

B. Second line injectable agents
- Amikacin (Am)
- Kanamycin (Km)
- Capreomycin (Cm)

C. Other core 2nd line agents
- Ethionamide/Prothionamide (Eto/Pto)
- Cycloserine/Terezidone (Cs/Trd)
- Linezolid (Lzd)
- Clofazimine (Cfz)

D. Add-on agents

(Not a core part of drug resistant anti-tubercular regimes)
- D1
  - Pyrazinamide (Z)
  - Ethambutol (E)
  - High Dose Isoniazid (H^h)·
- D2
  - Bedaquiline (Bdq)
  - Delaminid (Dlm)
- D3
  - Para-amino salicylic acid (PAS)
  - Imipenem-Cilastatin (Ipm)
  - Meropenem (Mpm)
  - AmoxicillinClavulanate(AmxClv)

Administration (FDA) recently, after almost four decades. It inhibits the proton pump required for ATP synthesis and inhibits the metabolism of the mycobacterium [22]. Bedaquiline should be used only when the standard MDR regimen cannot be designed because of reasons such as; *in vitro* resistance to these drugs, known adverse drug reaction, poor tolerance or contraindication to any component of the combination regimen. As per WHO guidelines, it can be used as a part of second line ATT only in patients older than 18 years. However, it has been found to be effective and safe in children and adolescents in the same dosage as recommended for adults [25]. The dose is 400 mg once a day for two weeks followed by 200 mg thrice a week for remaining 22 weeks to complete six months, maximum time period for which bedaquiline can be given. Revised National Tuberculosis Control Program (RNTCP) of India is introducing this drug via a conditional access program throughout the country. Known, adverse effects associated with bedaquiline include nausea, vomiting, dizziness, arthralgia, myalgia, increased serum amylase and transaminase levels, QT prolongation and dark urine. Drugs which inhibit liver function via CYP3A4 metabolism (*e.g*., ketoconazole, ritonavir) increase blood levels of bedaquiline, and hence its toxicity [26].

Delamanid and Pretomanid: Both these drugs belong to the class of nitroimidazoles, which act by inhibition of mycobacterial cell wall synthesis [27,28]. Delamanid has been much more extensively studied than pretomanid. WHO recommends the use of delamanid only for six months of intensive phase in a dose of 100 mg twice a day in patients with MDR-TB/XDR-TB having high baseline risk for poor outcomes [29]. Increased rates of sputum conversion as well as decreased mortality have been docmented when delamanid was used in addition to an optimized background regimen in patients with drug-resistant tuberculosis [30]. Pretomanid, however, is a prodrug that requires bio-reductive activation of an aromatic group to exert an anti-tubercular effect. It has also shown substantial bactericidal activity both during intensive and continuation phases of treatment in experimental mice model of tuberculosis [28]. In 2016, WHO issued guidelines for use of delamanid in children and adolescents, which mentioned that children with MDR-TB with resistance to quionolones or second line injectables (or both) should be the candidates for this drug. In children, this drug should be used as an add-on drug in longer MDR-TB regimens (18-24 months) rather than as a part of shorter MDR-TB regimens launched by WHO in 2016 [31]. Bedaquiline, delamanid and pretomanid have revolutionized the management of not only drug-resistant tuberculosis but also HIV-TB co-infection.

Other Drugs: SQ-109 is a 1, 2 ethylenediamine, an ethambutol analogue. After having shown significant results in both *in vitro* and *in vivo* mice model of tuberculosis, this compound is currently undergoing trials in humans [32]. SQ-109 has been shown to have synergistic action with isoniazid, rifampicin and streptomycin. SQ-109 lowers the Minimum inhibitory concentration (MIC) of Rifampicin and this synergy may have a significant role in patients with Rifampicin resistant tuberculosis [33].

There are some other drugs in the preclinical phase.

- Pyrroles: BM 212 and LL3858 are the most potent pyrroles described so far. Synergistic activity with other first line ATT drugs has been noted in murine model [34].

- Benzothiazinones: this new class of drugs acts by inhibition of mycobacterial cell wall synthesis [35]. Primary evidence suggests activity against both drug-susceptible and drug-resistant strains.

Recently, WHO has approved a 9-12 month short regimen for uncomplicated MDR-TB patients (Bangladeshi Regimen). It consists of 4-6 months of Intensive phase of Kanamycin,Moxifloxacin, Prothionamide, Clofaziminie, High dose Isoniazid, Pyrazinamide and Ethambutol followed by 5 months of continuation phase which consists of moxifloxacin, clofazimine, pyrazinamide and ethambutol [36].

RNTCP: REVISED AND REVISITED

There have been numerous changes and updates in the new guidelines issued by the government of India [37,38]. Highlights are summed up in ***Table* III**.

New Definitions

'Presumptive Pulmonary TB' refers to condition in a person with any of these symtoms: cough and/or fever of >2 weeks, significant weight loss, hemoptysis or any chest radiograph abnormality. In pediatric patients, loss of body weight is defined as >5% weight loss in the last three months. 'Presumptive Drug Resistant TB' refers to in a condition any patient who has failed treatment with first line ATT, pediatric TB non-responders, contacts of drug-resistance TB, previously treated TB cases, TB patients with HIV co-infection or TB patients found positive on follow-up examination during treatment with first line ATT.

Changes in Diagnostic Algorithms

In a patient with presumptive pulmonary TB, smear examination and chest radiograph both have been given importance now. All these patients undergo two sputum smear examinations. If the first smear is positive for AFB, the patient is labelled as microbiologically confirmed TB. If the first smear is negative, the second sample is simultaneously subjected to smear and Cartridge Based Nucleic Acid Assay (CBNAAT). On the basis of CBNAAT, the patient is diagnosed either as drug sensitive TB or Rifampicin resistant TB. An indeterminate result calls for an additional CBNAAT for a valid result, and in case of a second inderterminate result, the specimen is to be sent to an accredited laboratory for culture and drug sensitivity testing.

In a patient with presumptive extrapulmonary TB, appropriate specimen from the involved site should be collected and subjected directly to CBNAAT (except for urine, stool and blood). Based on a positive CBNAAT or a positive culture (where CBNAAT is negative), the patient is classified as microbiologically confirmed extrapulmonary TB. If the patient is diagnosed as having extrapulmonary TB, based on clinical suspicion or other diagnostic tools, he/she can be classified as clinically diagnosed TB.

Similarly, for a presumptive pediatric pulmonary TB patient, CBNAAT should be straightaway performed on sputum sample or on gastric lavage if sputum is negative but chest radiograph is suggestive. If both these arms are not clinically relevant, further course of action should be

TABLE III HIGHLIGHTS OF CHANGES BETWEEN NEW AND OLD RNTCP GUIDELINES FOR MANAGEMENT OF TUBERCULOSIS

Old RNTCP Guidelines	*New RNTCP Guidelines*
No role of Nucleic acid amplification assay (CBNAAT) in diagnosis, only for diagnosis of drug resistance	Upfront use of CBNAAT in smear negative PTB cases, extra pulmonary TB, pediatric TB and HIV patients for diagnosis of TB
Alternate day drug delivery	Daily drug delivery
Continuation phase of Category II only included ethambutol	Continuation phase of both Category I and Category II now includes ethambutol
Intensive phase extended by one month if sputum positive at end of intensive phase	No need of extension of intensive phase irrespective of sputum result at 2 months
No fixed dose combinations	Fixed dose combinations available
Limited weight band options with no provision of dispersible tablets for children	Multiple weight band options with provision of dispersible tablets for children
No provision/importance on long term follow- up of DOTS patients after completion of treatment	Follow up of minimum two years required for DOTS patients after completion of treatment

based on the combination of chest radiograph and Mantoux test.

Changes in Treatment Approach

Principles of TB treatment have changed from intermittent to daily treatment with administration of daily fixed dose combinations (FDCs). The FDCs now consist of four weight bands in adults (25 kg to >70 kg) and six weight bands in children (4 to 39 kg) with dispersible tablets. This has created a lot of flexibility in drug dosages in both adults and children. For new TB cases, Intensive phase now consists of 8 weeks of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol followed by 16 weeks of three drugs Isoniazid Rifampicin and Ethambutol. For previously treated cases, intensive phase is recommended to be of 12 weeks where streptomycin is stopped after 8 weeks and remaining four drugs are given in daily dosage as per weight band for another 4 weeks. At the start of Continuation Phase (CP), pyrazinamide is stopped and rest of the three drugs are given for 20 weeks. In both new and previously treated cases, Intensive Phase is not recommended to be extended now. In extra pulmonary tuberculosis, continuation phase can be extended for 3-6 months in certain scenarios based on clinical decision.

Changes in Follow-up

A clinical monthly follow-up should be done whereby either the patient may visit the clinical facility or the medical officer may visit the patient's house. In the previous guidelines, sputum smear examination was done at 2, 4 and 6 months in new cases and at 3, 5 and 8 months in previously treated cases. In newer gidelines, sputum smear examination is recommended only at the end of intensive phase and at the end of treatment. Long-term follow-up is now recommended with evaluation at 6, 12, 18 and 24 months after completion of treatment, which was not recommended earlier.

Changes in Management of Drug-resistant TB

There is no major change in treatment of MDRTB/RRTB patients, which includes 6-9 months of intensive phase with Kanamycin, Levofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cycloserine, and 18 months of continuation phase with Levofloxacin, Ethambutol, Ethionamide and Cycloserine. However, the newer drugs for drug resistant tuberculosis have been reclassified into four different groups (***Box* 2**). Bedaquiline is being introduced in the RNTCP program in proven pulmonary MDR-TB patients >18 years of age with an aim to improve culture conversion time. In cases of INH resistance, the use of INH depends on the results of Line Probe Assay (LPA) or culture and sensitivity testing. If LPA reports INH resistance by *Kat G* mutation, INH is omitted whereas if the culprit is *INHA* mutation, high dose INH is added. In cases of polydrug resistance pattern, regimen designing or modification will be the prerogative of drug-resistance TB center committee.

CHALLENGES AND FUTURE PERSPECTIVES

Numerous challenges have been coming in way of development of newer ATT options. The socioeconomic factors that underlie the huge global burden of tuberculosis cannot be rectified in a short span of time. The unique ability of this organism to persist in the host environment and potential to acquire drug resistance is another daunting task needing urgent and effective addressal. Molecular mechanisms responsible for this dormancy and persistence are still not fully understood [39]. The funding for tuberculosis research, though has increased recently remains inadequate in proportion to the burden of this disease. The required timeline for clinical trials in developing these regimens is often very long, and there is a paucity of such expensive and specialized facilities [40]. There is an urgent need for widespread and fully committed involvement of governments, pharmaceutical industries and policy makers to deliver optimal future treatment options for tuberculosis [41]. An effective collaboration should ensure access to the best treatments for all those in need. It is of paramount importance to spend time and money for identifying more targets in this bacterium's pathophysiology so as to develop better treatment options, including those for drug-resistant organisms.

REFERENCES

1. World Health Organization: Global tuberculosis report 2016. Available from: *Error! Hyperlink reference not valid.www.who.int/tb/publications/global_report/en/.* Accessed June 2, 2017.
2. TB India 2016: Revised National Tuberculosis Control Programme 2016, Annual Status Report. Available from: *http:// www. tbcindia.nic.in* Accessed June 2 , 2017.
3. Smith SE, Pratt R, Trieu L, Barry PM, Thai DT, Ahuja SD, *et al*. Epidemiology of pediatric MDR tuberculosis in the United States, 1993-2004. Clin Infect Dis. 2017;16: 1437-43.
4. Yadav S, Rawal G. Primary Extrapulmonary Multidrug resistant tuberculosis in an immunocompetent child presenting with pleural effusion. Transl Pediatr. 2017;6:72-5.
5. Working group on new TB Drugs. Clinical Pipe line. Available from: http:// *www.newtbdrugs.org/pipeline/ clinical /.* Accessed December 25, 2017.
6. Lienhardt C, Vernon A, Raviglione MC. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. Curr Opin Pulm Med.

2010;16:186-93.
7. Milstein M, Lecca L, Peloquin C, Mitchison D, Seung K, Pagano M, *et al*. Evaluation of high-dose rifampin in patients with new, smear-positive tuberculosis (HIRIF): Study protocol for a randomized controlled trial. BMC Infect Dis. 2016;16:453.
8. Peloquin CA, Velasquez GE, Lecca L, Calderon RI, Coit J, Milstein M, *et al*. Pharmacokinetic evidence from the HIRIF trial to support increased doses of rifampin for tuberculosis. Antimicrob Agents Chemother. 2017;25;61. pii:e00038-17.
9. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, *et al*. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: A multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis. 2017;17:39-49.
10. Horne DJ, Spitters C, Narita M. Experience with rifabutin replacing rifampin in the treatment of tuberculosis. Int J Tuberc Lung Dis. 2011;15:1485-90.
11. Moultrie H, Mcllleron H, Sawry S, Kellerman T, Weisner L, Kindra G, *et al*. Pharmacokinetics and safety of rifabutin in young HIV infected children receiving rifabutin and lopinavir/ritonavir. J Antimicrob Chemother. 2015;70:543-9.
12. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, *et al*. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365:2155-66.
13. Weiner M, Savic R M, Kenzie W R, Wing D, Peloquin CA, Engle M, *et al*. Rifapentine pharmacokinetics and tolerability in children and adults treated once weekly with rifapentine and isoniazid for latent tuberculosis infection. J Pediatric Infect Dis Soc. 2014;3:132-45.
14. Thee S, Garcia-Prats AJ, Donald PR, Hesseling AC, Schaff HS. Fluroquinolones for the treatment of tuberculosis in children. Tuberculosis (Edinb). 2015;95:229-45.
15. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, *et al*. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371:1577-87.
16. Mohan A, Kumar DP, Harikrishna J. Newer anti-TB drugs and drug delivery systems. Medicine update. New Delhi: Jaypee Brothers Medical Publishers (for The Association of Physicians of India). 2013:388-92.
17. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, *et al*. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012;367:1508-18.
18. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, *et al*. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015;45:161-70.
19. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, *et al*. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015;7:603-15.
20. D'Ambrosio L, Centis R, Sotgiu G, Pontali E, Spanevello A, Migliori GB. New anti-tuberculosis drugs and regimens: 2015 update. ERJ Open Res. 2015;1:00010-2015.
21. Gonzalo X, Drobniewski F. Is there a place for â-lactams in the treatment of multidrug-resistant/extensively drug resistant tuberculosis? Synergy between meropenem and amoxicillin/clavulanate. J Antimicrob Chemother. 2013;68: 366-9.
22. Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL, and on behalf of the Efficacy Subgroup, RESIST-TB. World Health Organization group 5 drugs for the treatment of drug-resistant tuberculosis: unclear efficacy or untapped potential? J Infect Dis. 2013;207:1352-8.
23. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. WHO; 2013. Available from: *http://www.who.int/en/*. Accessed September 6, 2017.
24. Guidelines for use of bedaquiline in RNTCP PMDT India. Available from: *http://www.tbcindia.nic.in*. Accessed August 30, 2017.
25. Achar J, Hewison C, Cavalheiro AP, Skrahina A, Cajazeiro J, Nargiza P, *et al*. Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2017;23:1711-13.
26. Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J. 2017;22;49.
27. Xavier AS, Lakshmanan M. Delamanid: A new armor in combating drug-resistant tuerculosis. J Pharmacol Pharmacother. 2014;5:222-4.
28. Diacon AH, Dawson R, Hanekom M, Narunsky K, Maritz SJ, Venter A, *et al*. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrob Agents Chemother. 2010;54:3402-7.
29. World Health Organization. The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance. WHO; 2013. Available from *http://www.who.int/en/*. Accessed September 6, 2017.
30. Gupta R, Geiter LJ, Wells CD, Gao M,Cirule A, Xiao H. Delamanid for extensively drug resistant tuberculosis. N Engl J Med. 2015;373:291-2.
31. World Health Organization: The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. World Health Organization; 2016 . Available from: *http://www.who.int/en/*. Accessed April 15, 2018.
32. Chen P, Gearhart J, Protopopova M, Einck L, Nacy CA. Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs in vitro. J Antimicrob Chemother. 2006;58:332-7.
33. Nikonenko BV, Protopopova M, Samala R, Einck L, Nacy CA. Drug therapy of experimental tuberculosis (TB): improved outcome by combining SQ109, a new diamine antibiotic, with existing TB drugs. Antimicrob Agents Chemother. 2007;51:1563-5.

34. Arora S. Eradication of Mycobacterium Tuberculosis in 2 months with LL3858: a preclinical study. Int J Tubercl Lung Dis. 2004;8:S29.
35. Lechartier B, Hartkoorn RC, Cole ST. In vitro combination studies of benzothiazinone lead compound BTZ043 against Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2012;56:5790-3.
36. Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, *et al*. Int J Infect Dis. 2017; 56:190-3.
37. Revised National TB Control Programme: Technical and Operational Guideline for Tuberculosis Control in India 2016. Available from: *http:// www.tbcindia.gov.in*. Accessed April 10, 2018.
38. Chaudhari AD. Recent changes in technical and operational guidelines for tuberculosis control programme in India-2016: A paradigm shift in tuberculosis control. J Assoc Chest Physicians. 2017;5:1-9.
39. Zhang Y. Persistent and dormant tubercle bacilli and latent tuberculosis. Front Biosci. 2004;9:1136-56.
40. Ginsberg AM, Spigelman M. Challenges in tuberculosis drug research and development. Nat Med. 2007;13:290-4.
41. Lienhardt C, Vernon A, Raviglione MC. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. Curr Opin Pulm Med. 2010;16:186-93.